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Nancy S. Berg reflects on her first 100 days as ISPE's new leader and summarizes her plans to build Member value and reenergize the Society's focus on Regulatory Affairs.

ISPE's President and CEO: Building Member Value with a Renewed Focus on Regulatory Affairs

In joining your Society as the new President and CEO, my primary goal has been to be a student of ISPE. My first 100 days focused on meeting Members, observing the operation, reviewing strategic and business plans and organizational performance, and getting to know industry leaders and staff. During this time, I have met and interviewed more than 500 Members, industry and regulatory leaders from North America, Europe, Asia-Pacific, the Middle East, Africa, South America, and China, and pharmaceutical trade media—all in effort to understand their views on industry direction and trends, their company and agency challenges, and how ISPE can increase its value to our Members and their organizations. I found it overwhelmingly positive that Members and industry support an active and vibrant ISPE, and that Members and non-members alike express a willingness to volunteer their knowledge, experience, time, and resources to advance the Society and its mission.

In meeting with Members and industry, I also noted many common challenges and concerns across companies and countries—not surprising; these were related to quality, compliance, process and performance improvement, and maintaining product integrity in budget-challenging times. As companies continue to be pressured to improve performance, they look to ISPE for help in learning about best practices from other pharmaceutical companies and from outside our industry, too. Members and companies also look to ISPE for help in building and sustaining a culture of compliance where compliance is a positive value, rather than a costly "requirement." Companies have asked ISPE to help initiate discussions on how they can be better prepared for inspections and how they can better understand how to improve regulatory relationships overall.

ISPE plays a vitally important role in creating and sustaining progressive dialog around global harmonization and regulatory affairs among regulatory agencies, members, and their companies. Industry looks to ISPE to help them establish organizational standards leading to quality and performance improvements—and better results. Regulators, in turn, tell me they are interested in helping companies achieve the same positive, cost effective outcomes, and in my view, regulators have a clear desire to work closer with industry in realizing process improvements and better results. Admittedly, it may oftentimes be difficult for companies to ask regulators for help (and in turn, potentially raise complicated concerns) but fortunately, this is where ISPE can lead—and this is where we are leading. As a global association, we are the bridge to unbiased discussions and instrumental in providing meaningful, high-value education and publications that lead to better performance and smart results.

We're doing this because you've asked more of ISPE. In our most recent Member survey, Members were consistent in their suggestions that ISPE take a more visible and active approach to regulatory affairs, and that ISPE be a more contemporary and influential voice in regulatory education and discussions. (See sidebar for more information.)

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Enlightened regulatory affairs have been an important part of my forward agenda and we have been responding in three ways: 1) relationship building with regulators, 2) engaging regulators in ISPE Member groups, and 3) securing regulator participation in ISPE events. Following are some successes:

Action #1: Regulatory Relationships and Meetings

Since the beginning of the year, my team and I have met with and/or hosted a number of regulatory meetings. ***Renewing and advancing ISPE's presence with global regulators is one of our key priorities as we continue to build Member value.*** In addition to my direct involvement, ISPE regulatory affairs activities are also supported by a Member-led Regulatory and Compliance Committee made up of leaders from global manufacturing and supply companies as well as ISPE's regulatory affairs staff that includes Bob Baum (recently retired Executive Director, CMC, Pfizer), Bryan Wright, staff Advisor (retired MHRA, UK), and Bob Tribe, staff Advisor (retired TGA, Australia).

The following is a sampling of our many recent meetings:

2012 January	Regulatory leader participation as speakers and in meetings during ISPE's Tampa Conferences. Extensive meetings were held with the FDA (USA) to co-create the new FDA-ISPE Co-Sponsored Conference on CGMP (4-5 June, Baltimore – see additional details later in this article.)
2012 Jan-April	Meetings and discussions with EU regulators took place in conjunction with DIA's Euro Conference in Copenhagen and at ISPE's meeting in Japan and China (Hiroshima, Japan and Beijing, China respectively).
2012 March	Regulators participated in ISPE's Frankfurt Conferences (Germany).
2012 May	ISPE met with regulators participating at the Interphex show in New York, NY (USA) and is meeting with PIC/S leaders during the PIC/S – PDA meeting in Geneva, Switzerland.
2012 June	ISPE will present a FDA-ISPE Co-Sponsored event in Baltimore featuring heavy participation by the FDA and attendance by global agencies. (See additional details later in this article.)

ISPE Member Survey Excerpts

Respondents across all demographics (region, length of industry experience, company type) ranked "Practical Solutions to Regulatory Requirements" as their top priority, showing how essential this area of focus is to the members and their companies.

- 82% ranked "practical solutions to regulatory requirements" as important or very important to their own career development.
- 72% ranked "practical solutions to regulatory requirements" as something in which their company was likely or very likely to invest.
- 51% said they would be likely or very likely to invest personal funds and time to develop skills in this area.

Action #2: Engaging Regulators in ISPE Member Groups

ISPE is uniquely positioned to engage regulatory agencies in discussions on relevant issues and problem solving through its many established Member groups and networks. For example, a number of regulators have recently joined ISPE's Communities of Practice (COP) Council as well as individual COPs in order to take advantage of the connections, relationship building, and technical knowledge sharing that takes place in COP meetings and online discussions. Regulators are also supporting ISPE Chapters and Affiliates worldwide as speakers, active Members, and advisors. Members and regulators are working together to gain a better understanding of technology trends and best practices, including networking to achieve more successful outcomes. Increasing active regulatory involvement in ISPE Member groups responds directly to our strategic objectives to build regulatory dialog among Members and agencies.

Action #3: Collaborating with Regulators on Events

ISPE is more actively partnering with regulatory agencies on all of its events. For example, this June, the FDA and ISPE are co-sponsoring a new "mega" event entitled Redefining the "C" in CGMP – Creating, Implementing and Sustaining a Culture of Compliance (4-5 June, Baltimore, MD (USA)). At this event, the FDA will communicate its vision for quality in the 21st century, share views on global quality and its future vision for the Office of Compliance. In addition, MHRA (UK) will offer an international regulatory perspective and company experts will discuss quality, risk management, CAPA, flexible manufacturing, PAI, and regulatory success in a cloud environment, among many other issues. Registration for this

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Continued.

Some of the participants at the ISPE's Japan Affiliate Annual Meeting held in April.

conference is now open and limited, so please register early to ensure your seat at this "must attend" program (www.ISPE.org/2012CGMP).

We are also developing a top flight Global Regulatory Forum and an Executive Day (with regulatory discussions throughout) during ISPE's Annual Meeting (11-14 November, San Francisco, CA (USA)). Promotion for this event has been mailed to Members early as we anticipate a record attendance in our California location – the birthplace of biotechnology.

More News

ISPE's recent meetings and conferences in Japan and China also included major regulatory participation. At ISPE's Japan Affiliate Meeting (April 2012, Hiroshima, Japan), Shingo Sakurai, PhD, Director, Office of GMP/QMS, PDMA (Japan), presented a Keynote Session along with Helena Baiao, Chairman of PIC/S (Japan has recently applied for membership in PIC/S to join more than 40 PIC/S member authorities dedicated to harmonized GMP standards among their member authorities and countries), and FDA's Ilisa Bernstein, Acting Director, Office of Compliance, CDER, FDA, via video link. The Japan Affiliate Annual Meeting attracted some 300 participants who joined the group in celebrating its 10th anniversary as an ISPE Affiliate organization.

The following week, ISPE's China Annual Meeting again attracted a record number of regulators from around the world, and nearly 500 attendees from Chinese national and Multi-National Companies (MNCs) doing business in China. Participants learned about SFDA's (China) new GMP regulations from SFDA representatives. During the meeting, ISPE hosted noted regulators as panelists and keynote speakers including Mr. Xinyu Weng, Director, Division of Drug Manufacturing Supervision, Department of Drug Safety and Inspection, SFDA, Gerald Heddell, Director of Inspection, Enforcement and Standards, MHRA (UK), Helena Baiao, PIC/S (Portugal), Ilisa Bernstein, FDA (USA), and many agency representatives from central and provincial regulatory agency departments in China.

In both Japan and China, more than 75 attended the first Asia meetings of the International Leadership Forum (ILF), the global strategic Member group supporting ISPE and industry in the development of directional strategy. The ILF meeting featured a number of sessions and panels led by global regulators and industry executives and ILF members discussed their Global Positioning Strategy document (under development) which may be viewed at www.ispe.org/ilf.

Being at the epicenter of regulatory relationships and in front of regulatory trends and issues is core to building ISPE Member value – and successful education and training programs for industry. This has been just a sampling of our high energy efforts in this area of ISPE. In the next issues of *Pharmaceutical Engineering* I will describe our Professional Development and Knowledge Management strategies and how Members can positively impact ISPE's influence and growth. We need your voice and ideas. Let us hear from you.

ISPE's China Affiliate Annual Meeting included noted regulators as panelists and keynote speakers.

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Identifying Counterfeit Medicines with Industry-Suitable Technologies

by Dr. Fred Jordan and Dr. Martin Kutter

This article presents the latest pharmaceutical anti-counterfeit technology developments and describes different criteria which will help readers select those that best safeguard patient safety and the integrity of valuable pharmaceutical brands and products.

Introduction

This article investigates the latest security technologies available to branded pharmaceutical manufacturing companies to verify the authenticity of medicines. The authors argue that while serialization in pharmaceutical and medical device packaging may be appropriate to identify or recall medicines with manufacturing or distribution problems, it cannot prevent the introduction of falsified medicine into the legal supply chain. By contrast, the authors contend that, in order to increase reliability in the supply chain, digital authentication technologies that incorporate covert (invisible) security features provide a higher level of security than those with overt (visible) features; are easier and more cost-effective to deploy than those based on consumables; do not require any specific training, only a step-by-step process; and are more reliable than human sensory perception-based verifications. The article finally forecasts that while the newly adopted European directive 2011/62/EU calls on pharmaceutical companies and any actors involved in the manufacturing or distribution of medicinal products to verify the authenticity of medicines,[1] innovations in smartphone technology, including better image capabilities and increased computing power, will accelerate the need to develop a suitable, easy-to-use, and reliable product authentication process at the patient level.

When looking at the product security market, there are more than 100 security technologies (holograms, digital watermarks, DNA taggants, serialization, etc.) used to combat counterfeiting of primary or secondary packaging and of solid or flexible components, such as liquids, powders, and tablets. For a branded pharmaceutical manufacturing company, however, it is challenging to understand the scope and role of each of these technologies, especially when considering the cost of the technology feature itself and its nationwide or worldwide deployment. This article presents the latest pharmaceutical anti-counterfeit technology developments and describes different criteria which will help readers select those that best safeguard public safety and the integrity of valuable pharmaceutical brands and products.

Answering a Basic Question: Should We Leave it to Patients to Identify Counterfeit Medicines?

This question is a very topical issue both in developing and in industrialized countries, because consumer goods, including medicines – notably those not reimbursed by health insurance companies and those issued without a prescription, e.g., Over The Counter (OTC), are increasingly purchased via the internet. However, a study carried out by the European Alliance for Access to Safe Medicines found that 62% of medicines ordered on the internet were substandard or counterfeit. Of these, 68% were unlicensed imitations and the rest were counterfeit branded medicines.[2]

The question therefore arises as to the patient's responsibility in determining the authenticity of medicines. Today, a number of track and trace applications (e.g., serialization, bar codes, RFID Tagging, etc.) are used in the pharmaceutical industry to prevent falsified medicinal products from entering the legal supply chain. According to the World Health Organization, "These involve assigning a unique identity to each stock unit during manufacture, which then remains with it through the supply chain until its consumption."[3] Using any cell phone, a patient can identify and send the unique serial number printed on secondary packaging via SMS text message to a central database. The serial number is then automatically confronted with a free or already used position. The diagnostic

will be "authentic" if the number was never sent before or possibly "fake" if already checked. If the outcome is "fake," the secondary packaging is either a counterfeit or a second use of the original packaging, filled with highly probable fake medicine.

With this technology, the patient is given full responsibility for verifying the authenticity or not of the medicine. The success of this procedure must first rely on access to and utilization of mobile authentication devices, which could be problematic for elderly patients, people with motor restrictions, or who are visually impaired, and patients affected by socio-cultural and economic inequalities, for example. It is then based on the impossibility of transferring the verification process to a pseudo-server in the hands of counterfeiters. In other words, Man-In-The-Middle (MITM) attacks. Finally, it depends on the reliability and accuracy of the written code sent by the patient via text message, provided that patients systematically check the serial number position. If not, genuine positions remain unchecked and vulnerable to counterfeiting. Given these risks, patients should not bear the responsibility for uncovering fake medicine.

What is the Drug Manufacturer's Role in Verifying the Authenticity of Medicinal Products?

The next question arises as to the drug manufacturer's liability in the event of a "false positive." A false positive occurs when a counterfeit medicine is authenticated as genuine by the verification process, an outcome that might in turn affect a patient's health. It is quite easy to imagine how such a false positive could be generated with this serial number verification: a batch of genuine medicine is hijacked somewhere in the supply chain and while the genuine tablets are removed and sold in bulk, the genuine packaging is filled with fake medicine. Or imagine the following scenario: leaks, corrupt or coerced players in the supply chain create fake replications of medicine. In these cases, fake medicine will be authenticated as genuine and inadvertently reach the patient.

Claims that tracing the secondary packaging of medicine all along the supply chain – in other words, creating its e-pedigree – would prevent counterfeited medicine from entering the legitimate supply chain, are once again highly unrealistic. No major European pharmaceutical industry player today would vote for such a complex tracking and tracing solution, because it would require "…major packaging line changes and investments"[4] and true interoperability between medicine manufacturers, wholesalers, and prescription deliverers. Although creating an e-pedigree does provide valuable data on the history of a particular batch of drugs, it does not prevent fraudulent players in the supply chain from substituting genuine products with fakes and patients from purchasing them in turn.

One possible solution to combating counterfeit medicines lies in the newly adopted European directive 2011/62/EU, relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products. This directive clearly states that, for the purposes of patient safety, the "manufacturing authorization holder" shall:

- verify the authenticity of the medicinal product
- identify individual packs
- verify whether the outer packaging has been tampered with[5]

To this end, the European Parliament and the Council are calling for new measures, including the introduction of safety features on individual packs (these features will be decided at a later stage by the Commission, via delegated acts) and stricter rules on inspections and controls of all actors involved in the manufacturing and supply of medicinal products, among others. Per the Directive, focusing on authentication features rather than identification means could be the right industry-affordable answer to detecting counterfeit medicines, without having to rely on the hypothetical interoperability of non-compatible automated processes and ways of producing medicine by the various pharmaceutical industry players.

Identification and Authentication: Two Problems that Require Adapted Solutions

The original goal of batch or individual serialization was a means to identify and recall medicines with manufacturing or distribution problems. Although integral to patient safety, trying to change the primary purpose of serialization into an authentication process is problematic. Logistically speaking, this technology forces pharmaceutical companies to print a visible linear bar code on the packaging or label, which can sometimes be difficult given the variable size of the printable area and the code/substrate contrast. In addition, inspections and controls must be in place to ensure that a unique code is applied on each individual pack or label. Moreover, serialization requires adaptive hardware, software, and skills.

In the case of authentication, there are many security features available to brand owners and manufacturers capable of detecting counterfeits, not only with primary and secondary packaging, but also with dosage forms. The most efficient features are covert or invisible to the naked eye. According to the World Health Organization, "The purpose of a covert feature is to enable the brand owner to identify a counterfeited product. The general public will not be aware of its presence nor have the means to verify it."[6] These secret or covert procedures are widely available today and include invisible printing, embedded images, and digital watermarks, to name a few. These methods can help detect counterfeits by means of regular sample controls carried out at different points in the supply chain, even in the case of consumed or recovered packaging waste.

Some methods combine a human visual inspection with a device, such as the Raman Spectroscopy analyzer, which is capable of analyzing raw materials in medicinal and finished products, then comparing them with the analysis result of the correct chemical combination stored in the device. However, this device may cost dozens of thousands of dollars and require some training to properly manipulate. In addition, only a few

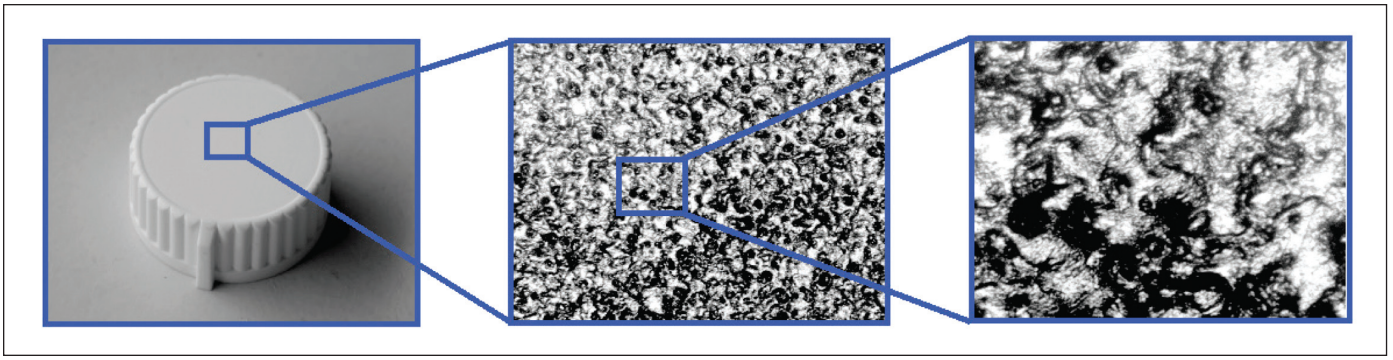

Figure 1. Details of a molded closure of a medicine jar showing microscopic differences, irregularities generated by the die cavity used to produce the part.

analyzers are generally available within a given company at a given time, forcing the manufacturer to send the suspected product to a dedicated lab.

Other more cost-effective, yet reliable technologies involve embedding an invisible marking on primary and secondary packaging using regular visible ink and standard printing processes, without having to change the packaging design or flow of production.[7] Another option involves using the intrinsic micro-differences present in a cavity mold[8] commonly used to create vials or medicine containers, capturing an image of the random pattern, and then storing it in a database - *Figure 1.*[9] In either case, the brand owner or manufacturer simply scans the item using a flatbed office scanner or an iPhone4 smartphone to receive a "genuine-or-fake" outcome.

As a consequence, while serialization may be appropriate to identify basic fraudulent actions, such as extension of the expiration date or market diversion, it is not suitable to determine the authenticity of a medicine. As we can see, checking a batch of drugs not equipped with reliable authentication features could prove costly, sometimes requiring a chemical analysis of the substance in question. Using industry-suitable invisible authentication security technologies instead can therefore help increase the number of controls at a very low cost and prevent the introduction of falsified medicine into the legal supply chain.

Can a Visual Inspection of Packaging by the Human Eye Help Identify a Well-Made Counterfeit?

Nothing looks more like a real medicine than a "well-made" counterfeit, which is sometimes virtually indistinguishable from the original.

This fact is particularly problematic for customs employees and other players in the supply chain, whose job consists in reading or visually inspecting a packaging, whose different elements may or may not be correctly replicated by counterfeiters. Some of these systems convert the object into a 3D representation displayed on a computer screen. Understandably, it would be challenging for anybody, even for customs or logistics employees to detect a real medicine from a fake. It is an either-or situation: either the replica is so poorly done (fake brand name, spelling mistakes, or other omissions) that there is no need to access the packaging information to determine that it is a counterfeit, or the replica is so well done that the visual inspection will lead to think that the packaging contains real medicine. A visual inspection of packaging by the human eye is unreliable in identifying counterfeits.

Visible (Overt) vs. Invisible to the Naked Eye (Covert) Security Features

Many pharmaceutical companies have added visible security features to their packaging to prevent counterfeiting. These include holograms, kinegrams, embossing, micro printing, moiré, or special ink, such as optical variable ink, to name a few. However, these visible features only provide minimum security and require training for effective authentication. By the same token, if a company suddenly decides to discontinue the use of visible security features, consumers might mistake a genuine product with a fake.

Today, counterfeiters have the best printing equipment and components at their disposal in order to perfectly replicate the visual aspects of a packaging, including its visible authentication features. By contrast, the use of "covert" features – security features that are invisible to the naked eye – provides a higher level of security, because counterfeiters will be unable to identify the presence of such features. For example, "good" counterfeit banknotes always include a replication of the visible security features, but not of the invisible ones. However, to prevent leaks, covert security features should never be disclosed. These features should only be shared with a limited number of trustworthy persons of the branded manufacturing company.

Anti-counterfeiting literature also suggests that a specialized scanner or a distinctive analysis is required in order to identify covert security features, making the "genuine-or-fake" verification a costly and time-consuming process. However, as in other industries, the digital or software revolution has opened up new and exciting possibilities. As we have seen, it is now possible to print digital security features using normal visible ink or varnish on primary or secondary packaging (e.g., folding boxes, blister packs, labels) to achieve invisible protection. In addition, these digital security features can be verified by means of an off-the-shelf office flatbed scanner or an iPhone4 smartphone device. While covert (hidden) features have traditionally required specialized knowledge, features, and means to verify them, drug manufacturers can now have

their printers or suppliers print invisible markings on primary and secondary packaging without using special inks, as well as perform product authentication using readily available consumer electronics - *Figure 2*.

Digital solutions for product authentication also have had a significant impact on the cost and wait time of implementing an anti-counterfeiting program for multi-brand companies using multiple production plants. For example, when deploying an anti-counterfeiting program, it is necessary to provide the various production plants with the right quantity of items in relation to the number of packaging elements to produce, plus extras for the overs. If poorly managed, this procedure can encourage theft during transportation and misuse of the overs to produce counterfeits. The use of security components also can affect the packaging printing equipment if special ink is used or if extra features such as holograms or taggants are inserted in the production run. By contrast, digital security features using normal ink will not alter the printing process or production speed; this is an important cost-saving benefit.

Human Sensory Perception-based or Machine-based "Genuine-or-Fake" Verification

When selecting a security feature, it is not only important to assess the cost of purchase, implementation, global deployment and management, and resistance to replication, but also how a "genuine-or-fake" verification is performed.

In this case, the various anti-counterfeiting features can be placed in two main categories:

- features which use human sensory perception
- features which are machine-readable

When using human sensory perception-based verification (visual, tactile, oral), a person will be required to undergo adequate training to be able to distinguish a genuine security feature from a fake replication, when displayed side-by-side. By contrast, when using machine-based verification, a person will only be required to follow a step-by-step process. If properly described, the latter can be performed by anyone without any specific knowledge or training.

As mentioned earlier, other visual features include the shape of the packaging and other printing details that counterfeiters may not have identified. A discrepancy between a genuine pack and a counterfeit can also be identified with the help of a detailed description, stored in and provided by an online database. But this data can only uncover counterfeits until attempts are made to remedy these discrepancies.

So, an important question arises as to the cost of performing a machine-readable "genuine-or-fake" verification. Because some existing digital authentication processes use off-the-shelf office scanners or iPhone-like devices to verify the authenticity of the packaging components (folding box, blister pack, or label) and because these supplies are often part of an office setting, performing a machine-readable verification using digital authentication processes result in virtually no added costs to the branded manufacturing company.

Local vs. Remote Verification Process

In order to perform a "genuine-or-fake" verification, there are two distinct methods: a local process using the appropriate hardware or a remote identification using an online server.

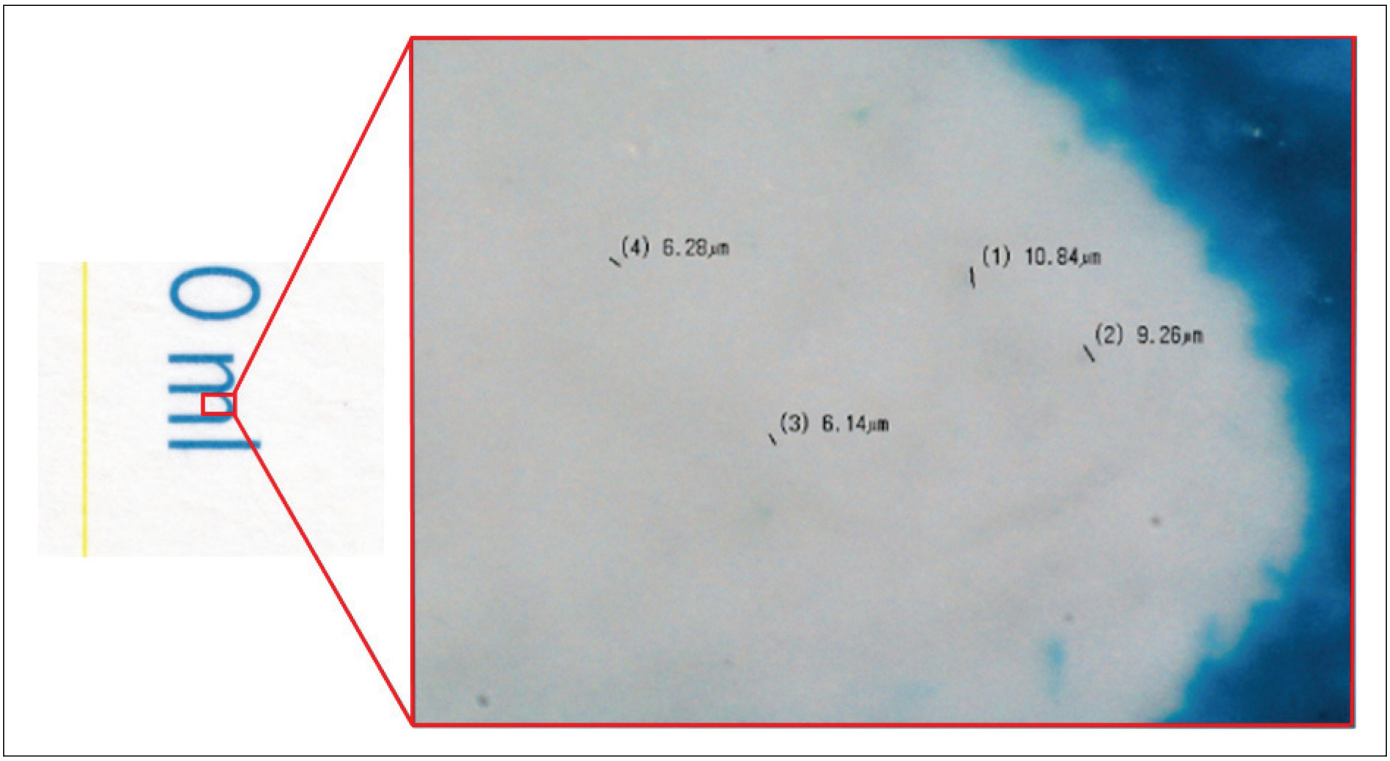

Figure 2. Example of a microscopic detail of invisible micro dots printed on the packaging thus generating a unique pattern that identifies the product as genuine.

Local verification could be seen as advantageous as it does not require any data connection. However, in the case of covert security features, using a local verification process requires that the equipment be rid of sensitive information, which, if stolen, could fall in the hands of counterfeiters. By the same token, if the pharmaceutical manufacturing company needs to carry out verifications at multiple locations, it will need to have the appropriate equipment, provide training, and perform maintenance and calibration onsite. These added costs should not be neglected, especially when taking into account employee turnover, and equipment upgrades and refills.

Because internet and mobile connections are widely available around the world today, a security feature enabling remote "genuine-or-fake" verifications via a central secure server is a major advantage. A remote verification process not only eliminates the need to share sensitive information with the operator, but also enables consolidation of all the verifications performed worldwide, thus facilitating the detection of any correlation between various fraudulent sources within the supply chain. As for all criminal acts, the quicker you uncover them the more you are well positioned to identify the criminal source to stop it.

Security Level and Protection Against Leaks

A recent FDA report[10] shows that organized crime is active in counterfeit medicine, as this industry represents a very lucrative and less risky criminal business compared to others. The use of corruption and coercion is therefore seemingly prevalent to obtain security features or programs. An important question then arises as to the number of people and companies that should be involved in the security chain. In the case of consumable security elements, suppliers are involved in the security chain on a recurring basis, exposing the recipient company to theft or misuse of the overs necessary to produce the secure packaging. Consequently, the less suppliers are involved in critical security elements, the less leaks.

Web-based Secure Server Solutions

There are two fundamental ways web servers can be used. The first approach consists in using the server as a data repository system. This method is used to detect the different anti-counterfeiting features used in a given packaging or production batch. For example, the IPM system – Interface Public-Members of the World Customs Organization[11] – is a secure communication tool for the exchange of information between Right Holders and customs administrations. By using the IPM system, field customs officers have access to the "genuine/fake" database to check imported goods for counterfeits.

The second approach uses the secure server to analyze different parameters of a packaging in order to automatically assess its authenticity[12] using a digital image captured with a regular office scanner, a digital camera, or even a smartphone device.

In this case, the secure server is also capable of managing the deployment of anti-counterfeiting features. Because these features are digital elements, there is no need to involve additional security suppliers in the security chain. The branded pharmaceutical manufacturing company has in turn full control over the generation of digital security elements and can allocate individual profile and password authorizations online to automate "genuine-or-fake" verifications worldwide.

This second approach appears to be the best protection against leaks, especially if very few high level employees are authorized to access critical security elements, such as an encryption key or security patterns. The security elements are then digitally routed via encrypted and secured data networks to local markets and their related production plants.

Of course, costs related to software licenses and software customization for the deployment of the application within an existing information technology environment, as well as royalties, have to be taken into consideration. However, if the web-based system is well conceived, access to a free Internet browser should only be necessary to use it. This approach also frees very large organizations from having to perform complex computer validation processes while updating local PCs with new pieces of software and, in turn, from disrupting the production of medicines.

Could Smartphones be Used to Uncover Fake Medicine at Various Stages of the Supply Chain, Including at the Patient Level?

Smartphones are continuously evolving with increased functionalities and computing power, as well as image and video capabilities. Smartphones can therefore benefit the development and expansion of digital authentication features based on invisible marking, allowing mobility and "on-the-fly" genuine-or-fake verification - *Figure 3*. However, these advancements do not mean that mobile verifications should be placed in the hands of patients, because of various unanswered questions raised at the beginning of this article.

First, it is totally different to equip an employee of the branded manufacturing company with an iPhone4 and the appropriate application than to make this application readily available online. Indeed, consumer equipment is often in very poor condition: dusty camera optic, partly damaged screen, or poor connectivity. By the same token, if an anti-counterfeiting

Figure 3. Smartphone genuine-or-fake verification example.

solution goes public, it is necessary to understand that it also will be available to the counterfeiters themselves. In this case, strict verification processes should be in place to detect attempts to tamper with the supply chain.

Today, the internet suffers from the fact that security elements were not considered at the early stages of its development. Indeed, the internet's original users were educated scientists whose minds were simply not attuned to its possible fraudulent uses. This mistake should not be repeated if patients or consumers are one day given the opportunity to perform product authentication.

In the interim, it might be interesting to invite frequent medicine consumers, who might not get reimbursed or might adopt a consumer-like attitude toward purchasing drugs, to test mobile verification, provided they are monitored and equipped with devices in good working condition. This study would allow a select number of consumers to perform and possibly legitimize the use of mobile verification in combating counterfeiting. The results from this first study also would allow to fine tune the service and extend it to a larger pool of users.

Several factors, such as the increasing use of smartphones; changing medication refund policies; the aging of the world population; the development of online commercial sites; and the reduction of door to door shipping costs will all accelerate the need to develop a suitable, easy-to-use, and reliable product authentication process at the patient level.

Summary

The following summarizes the key points made in this article:

- Patients should not bear the responsibility for uncovering fake medicine.
- Pharmaceutical companies and any actors involved in the manufacturing or distribution of medicinal products should oversee and manage the authentication process of medicinal products.
- Serialization and e-pedigree cannot prevent the introduction of falsified medicine into the legal supply chain.
- Identification and authentication are two different problems that require adapted solutions.
- Covert (invisible to the naked eye) security features provide higher security compared to overt (visible) ones.
- Digital solutions for product authentication are easier, faster, and more cost-effective to deploy compared to security consumable-based solutions, especially when considering large production volumes.
- Machine-readable security features are more reliable for authenticating genuine or fake items compared to human sensory-based features, as no specific knowledge is required, only a step-by-step process that, if well described, can be performed by anyone.
- Remote online verification using a web application does not require specific software at the verification side, only a free internet browser. This approach will reduce the risk of leaks, especially if very few people are involved in managing the sensitive security data elements.
- Future developments in the smartphone industry, including better image capabilities and increased computing power, might accelerate the need to develop a suitable, easy-to-use, and reliable product authentication process at the patient level.

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Risk and Reputation: A Science and Risk-Based Approach to Brand Protection

by Gary E. Ritchie, Emil W. Ciurczak, Sharon Flank, Stephen W. Hoag, and James E. Polli

This article presents an approach that incorporates real time monitoring that can be used as a quality and security measure, by establishing and monitoring a quality threshold.

Introduction

Economically motivated adulteration threatens the drug supply through counterfeiting, diversion, and tampering. Current approaches tend toward external protection mechanisms. This article shows an approach that incorporates real time monitoring that can be used as a quality and security measure, by establishing and monitoring a quality threshold. New data on the ease of incorporating a low cost, rapid, non-invasive, and non-destructive quality measurement system in real time, in the field at a pharmacy point of dispensing, is presented. A side benefit of the proposed science and risk-based approach is that brand protection expenditures may then be refocused on maintaining high product quality as a brand distinguishing feature.

Quality Beyond Manufacturing

There is increasing pressure on companies to answer questions about quality anywhere in the supply chain. Areas of concern also include contaminated and non-conforming raw materials. Optimally, existing quality processes could be leveraged as a predictor, monitor, and brand protection system.

Quality approaches focus on limiting cost and reducing waste by improving processes. These principles are not limited to the pharmaceutical industry; lean manufacturing and Six Sigma are now ubiquitous. Catching flaws as early as possible, preferably in the design stage, makes them inexpensive to fix. The simplest recitation of this rule is, perhaps, measure twice, cut once. In practice, this is taken to mean establishing a design space that embraces formulation composition.

Manufacturers who adopt quality-based brand protection gain better control of the supply and advance in competitiveness and quality, not only over their competitors, but over counterfeiters as well. Quality at delivery is what matters. If there are no defects in the product from the manufacturing site, but the customer receives a counterfeit or adulterated version, the quality process has failed, and the company may follow. Not only can quality be built in, but security can be built in too.

First, data are presented on existing variation in a commercial product, Norvasc. It is established that the current variability is low enough to permit exploration of intentional variation as a marking mechanism. Next, an efficient marking method is presented that allows for product, brand, and dose identification that can evolve in case of threat from counterfeiters and diverters. It uses data from the design space and shows how to exploit controlled intentional variation within the US Food and Drug Administration (FDA) Scale-Up and

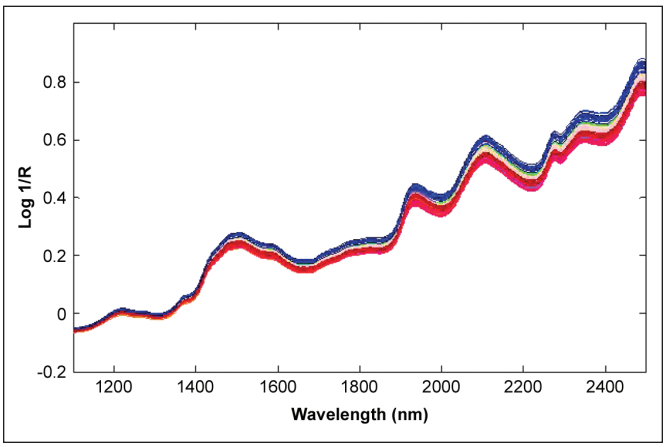

Figure 1. The Norvasc raw spectral plots (N = 150) show tight uniform spectra, indicative of very low variability of the commercial product.

Post-Approval Change (SUPAC) parameters. Finally, data from experiments in a retail pharmacy is presented, showing the practicality of real-time testing by non-experts, at the point of dispensing, using a portable spectrometer.

Spectral Fingerprinting

In order to use point-of-dispensing quality monitoring, a baseline must be established. The baseline is established by modeling the spectra from the existing product. Spectroscopy can be used to record a spectral fingerprint of that product and then check for identical spectral matches at the point of dispensing.

The first question to be addressed is that of commercial variation: is the quality control sufficient in the standard commercial product? How much variation across batches is seen in spectroscopic testing? For this study, 12 lots of Norvasc 10 mg were used, with 15 samples taken from each lot. This plot in Figure 1 shows five different lots of Norvasc, tested on Foss NIRSystems Rapid Content Analyzer. Samples were placed into sealed glass scintillation vials and scanned in reflectance mode; each sample was scanned 62 times and averaged into one spectrum; the wavelength range was 400 nm to 2500 nm with 2 nm spectral resolution. The raw spectral data were converted to log 1/R followed by 2nd derivative pretreatment using Foss's Vision software package.

Intentional Variation Experiments: Scale-Up and Post-approval Changes (SUPAC)

The FDA allows for a range of component and composition changes in the manufacturing of products, without onerous regulatory requirements. The Center for Drug Evaluation and Research (CDER) publishes a series of monographs in its "Guidance for Industry" series.[1] Its monographs "Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls: In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation" (SUPAC) deal with allowable changes in various dosage forms and reporting requirements.[2] Level 1 changes to excipients are those that are unlikely to have any detectable impact on formulation quality and performance; regulatory filing documentation of a Level 1 change is limited to the Annual Report. Level 1 changes are capped at 5%. Comparable European limitations on excipient changes (Type 1A) are 10%.[3]

In case of severe counterfeiting or diversion activity, or highly valuable product, an intentional variation fingerprint may be introduced for definitive identification. This fingerprinting method is optimized for today's contract manufacturing environment: it is possible to introduce a separate fingerprint or set of fingerprints for each contract location, making diversion easier to spot.

In the intentional fingerprinting experiments described, SUPAC Level 1 changes are used as a potential approach for tagging authentic product, in order to avoid counterfeiting and facilitate the detection of counterfeiting through spectroscopy. This approach avoids the use of a taggant that is fixed or one included in the formulation for the sole purpose as a taggant. The formulation-as-tag approach is less detectable, more nimble, and more cost-effective; it also avoids potential consumer concerns about ingesting nanoparticles or allergens.

Materials

The following drug substances and excipients were used as received: aspirin (Spectrum; Gardena, CA), prednisone (Sigma; St. Louis, MO), indomethacin (Spectrum; Gardena, CA), acyclovir (Spectrum; Gardena, CA), microcrystalline cellulose (Emocel 90M, Mendell; Patterson, NY), magnesium stearate (Spectrum; Gardena, CA), croscarmellose sodium (FMC Biopolymer; Princeton, NJ), starch (Lycatab C, Roquette; Lestrem, France), and lactose monohydrate (Super-tab, The Lactose Company; Hawera, New Zealand).

Component	Formulation A1 (mg/tab)	Formulation A2 (mg/tab)	Formulation A3 (mg/tab)
Aspirin	325	325	325
Microcrystalline cellulose	73	83	63
Magnesium stearate	2	2	2
Total Weight	400	410	390

Table A. Composition of Aspirin formulations.

Component	Formulation B1 (mg/tab)	Formulation B2 (mg/tab)	Formulation B3 (mg/tab)
Prednisone	5	5	5
Microcrystalline cellulose	94.5	94.5	94.5
Magnesium stearate	0.5	0.75	0.25
Total Weight	100	100.25	99.75

Table B. Composition of Prednisone formulations.

Component	Formulation C1 (mg/tab)	Formulation C2 (mg/tab)	Formulation C3 (mg/tab)
Indomethacin	25	25	25
Microcrystalline cellulose	71.5	74	69
Croscarmellose sodium	3	2	4
Magnesium stearate	0.5	0.5	0.5
Total Weight	100	101.5	98.5

Table C. Composition of Indomethacin formulations.

Component	Formulation D1 (mg/tab)	Formulation D2 (mg/tab)	Formulation D3 (mg/tab)
Acyclovir	200	200	200
Microcrystalline cellulose	113.26	120.26	106.26
Starch	35	27.99	41.99
Magnesium stearate	1.75	1.75	1.75
Total Weight	350	350	350

Table D. Composition of Acyclovir formulations.

Formulation Methods

Three tablet formulations were designed and evaluated for each of four drugs, such that 12 formulations were made. The four drugs were aspirin, prednisone, indomethacin, and acyclovir, and are denoted as drug A, B, C, and D, respectively. The drugs differ in their therapeutic uses, physicochemical properties, spectral properties, and dose ranges. For each drug, three tablet formulations were fabricated. Tables A to D describe the composition of the 12 formulations and refer to formulations A1, A2, A3, B1, etc. In each table, the first formulation is denoted the reference formulation (i.e., A1, B1, C1, and D1 are reference formulations). For each drug, the formulations were varied within the SUPAC Level 1 tolerance by varying one or more excipients, relative to the reference formulation, resulting in the second and third formulations (i.e., formulations A2 and A3 were variants for formulation A1; formulations B2 and B3 were variants for formulation B1). Second derivatives were plotted for Figures 2 to 5 to highlight the NIR differences in the formulations.

Variant formulations were attained through the following changes, relative to the reference. For aspirin, microcrystalline cellulose was increased and decreased. For prednisone, magnesium stearate was increased and decreased. For indomethacin, microcrystalline cellulose and croscarmellose sodium were simultaneously varied. For acyclovir, microcrystalline cellulose and lactose monohydrate were simultaneously varied. In some cases, the tablet weight changed.

Near-Infrared (NIR) Spectroscopy Methods

The formulations were scanned and analyzed by the Rapid Content Analyzer. The following test conditions were used. Samples were placed into sealed glass scintillation vials and scanned in reflectance mode; each sample was scanned 62 times and averaged into one spectrum; the wavelength range was

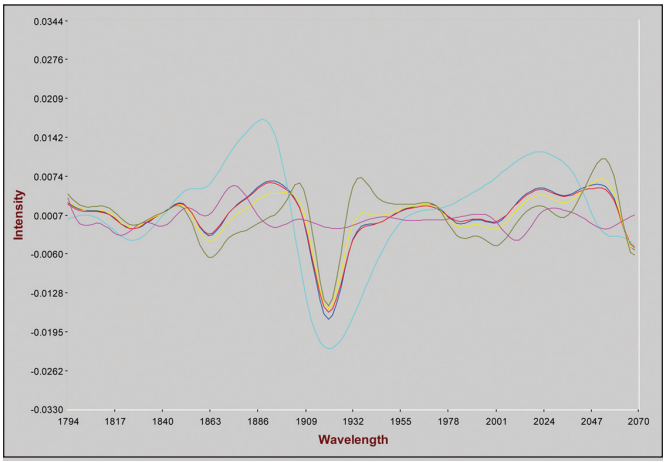

Figure 2. Second Derivative of Aspirin formulations where formulations A3 (yellow), Al (blue), and A2 (red) contained increasing amounts of microcrystalline cellulose; the intensities around 1995 nm and 2055 nm reflect NIR differences of the formulations.

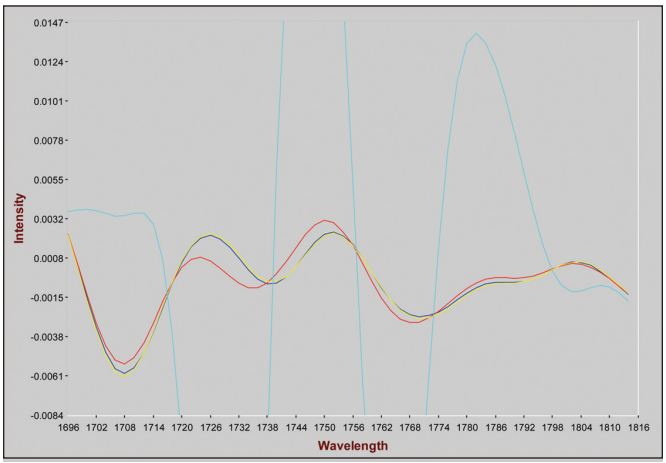

Figure 3. Second Derivative of Prednisone formulations where formulations B3 (yellow), Bl (blue), and B2 (red) contained increasing amounts of magnesium stearate; the intensities around 1705 nm as well as the regions between 1725 to 1735 and 1735 to 1790 nm reflect NIR differences of the formulations.

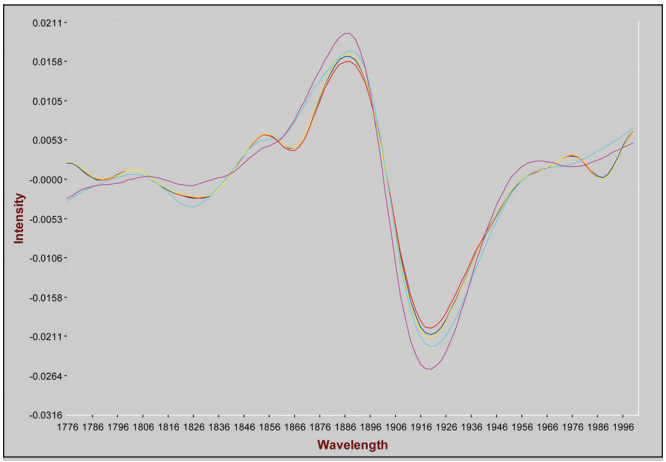

Figure 4. Second Derivative of Indomethacin formulations where formulations C3 (yellow), Cl (blue), and C2 (red) contained increasing amounts of microcrystalline cellulose; the intensities around 1890 nm and 1920 nm reflect NIR differences of the formulations.

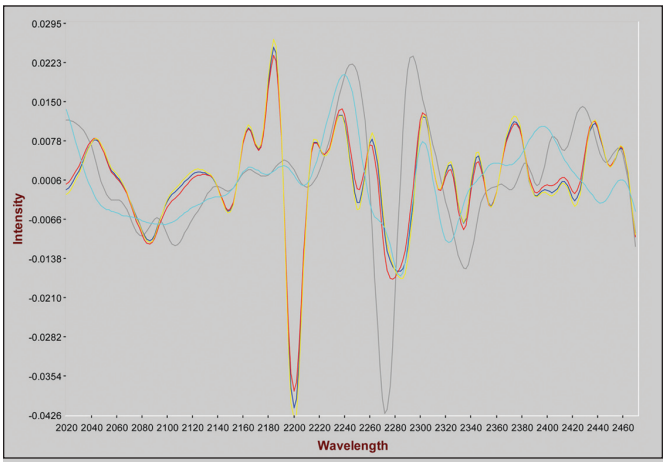

Figure 5. Second Derivative of Acyclovir formulations where formulations D3 (yellow), Dl (blue), and D2 (red) contained increasing amounts of microcrystalline cellulose as well as decreasing amounts of starch; the intensities around 2175 nm 2205, and 2225 nm reflect NIR differences of the formulations.

400 nm to 2500 nm with 2 nm spectral resolution. The raw spectral data were converted to log 1/R followed by 2nd derivative pretreatment using Foss's Vision software package.

Testing at the Point of Dispensing

Most manufacturers do not worry about counterfeits during the production process; however, the growth of contract manufacturing and other outsourcing suggests that it is prudent to verify incoming raw materials. Labeling errors highlight the importance of verifying the drug itself, not just the label: Pfizer's prostate cancer drug, Finasteride, was identified on some bottles as the anti-depressant Citalopram. Upsher-Smith's mislabeled Jantoven warfarin sodium was discovered by a retail pharmacist, who identified 10 mg tablets in a bottle labeled with the 3 mg dosage. Qualitest's hydrocodone bitartrate and acetaminophen tablets were found labeled as phenobarbital.[4]

There are several handoffs between production and the patient, and each of them provides an opportunity for counterfeiting and diversion. Even e-pedigree protects only the packaging, and it may be subject to bribery or blackmail. China Daily recently reported the sale of empty packages, complete with anti-counterfeiting, from hospitals, to be refilled with fakes.[5] There is an emerging consensus that the best protections are those that are closest to the consumer, preferably in the hands of a pharmaceutical professional. In a market with major counterfeiting issues, consumer verification (such as SMS codes to text to a central authority) may be useful. In the U.S., several major pharmacies (e.g. Target, Walmart, CVS) include a description of the dose form on the vial. In informal tests, less than 10% of the population is even aware those descriptions are there. Thus, American consumers are better protected by pharmacists than by even simple mechanisms that require their attention.

Experimental: Testing at the Point of Dispensing in a U.S. Pharmacy

As a policy matter, a national joint library of spectra would be useful, but would require a degree of coordination and disclosure that might be difficult to achieve in the short run. Spectra do not reveal quantitative formulation details, but manufacturers may be reluctant to endorse their release nonetheless. Other options include manufacturer-by-manufacturer tests, in which, say, Pfizer's field testers spot-check only their own products, including optional fingerprinting as described above. Alternatively, a single pharmacy, pharmacy chain, repackager, or hospital may test samples against its own library.

Method

At RiverRx, an independent pharmacy in Bethesda, Maryland, following the procedure standard in U.S. pharmacies, a pharmaceutical technician takes the prescribed drug from a supply shelf and fills a vial with the appropriate number of tablets or capsules. Filled prescriptions (the original large container, the prescription, and the vial to be dispensed) sit in a plastic basket for several minutes, waiting for verification by the supervising pharmacist. Those minutes constitute a theoretical time window for low-impact in-pharmacy testing. In that time, either the whole vial can be tested or as performed in this study, individual tablets/capsules can be retrieved from the vial. Sample presentation was studied by sampling directly or by the use of a variety of tablet holding mechanisms attached to the spectrophotometer, and it was concluded that a tablet holder enhanced results by reducing sampling variability.

The following test conditions were used: samples were tested using a sample holder and scanned in diffuse reflectance mode. The wavelength range was 1600 nm to 2400 nm, with pixel spacing of 8 nm and optical resolution of 11 nm. Thermo Scientific microPHAZIR software, version 1.0.3, was used to scan and monitor collection of the spectra. For chemometric analysis, Thermo Scientific Method Generator, version 3.101 R2, was used to model and predict spectra; Umetrics SIMCA-P+ 12, version 12.0.1.0, was used to investigate preprocessing of the spectra and create plots in conjunction with Method Generator.

	Dosage Amt (mg)	Manufacturer	Lot	Expiry Date
Ambien CR	12.5	Sanofi (France)	0T025	(Exp 09_2013)
Ambien	5	Sanofi (Hungary)	BC16H	(Exp 12_2012)
Atenolol	50	ZyGenerics	MK4431	(Exp 04_2012)
Ciprofloxacin	500	Ivax for Teva	BFB22A	(Exp 02_2012)
Lipitor	10	Pfizer (Puerto Rico)	V101739	(Exp 10_2013)
Lipitor	40	Pfizer	646090	(Exp 08_2013)
Lipitor	80	Pfizer (Puerto Rico)	V101145	(Exp 07_2013)
Lipitor	80	Pfizer (Puerto Rico)	V101719	(Exp 10)2013)
Methadone	10	Mallinckrodt	5771P77026	(Exp 08_2012)
Methadone	10	Mallinckrodt	5771P77093	(Exp 08_2012)
Methadone	10	Roxanne	064009A	(Exp 02_2013)
Omeprazole	20	Dr. Reddy	C006738	(Exp 09_2012)
Synthroid	100	Abbott	96010A8	(Exp 02_2012)
Synthroid	175	Abbott	92173A8	(Exp 11_2011)
Synthroid	200	Abbott	95222A8	(Exp 02_2012)
Synthroid	25	Abbott	81070A8A	(Exp 11_2010)
Synthroid	75	Abbott	96003A8	(Exp 02_2012)

Table E. Drugs tested at the retail pharmacy.

Instrument

The initial round of tests used a portable near-infrared spectrometer, the microPHAZIR from Thermo Scientific. Follow-on experiments are under way using a portable Raman spectrometer from Real-Time Analyzers as well, and preliminary results suggest high ease of use and good quality, with the exception of some laser damage on gelatin capsules. This can be ameliorated by investigating shorter acquisition times. Care must be taken in obtaining spectra, particularly with portable units, in order to minimize sampling variance and noisy spectra.

Samples

For testing at the pharmacy, tablets and capsules that RiverRx commonly dispensed were selected, with the focus on those which come in more than one dose or from more than one supplier. As shown in Table E, seven formulations were tested, covering 12 dosage levels and seven manufacturers. Three spectra were taken from each of 18 containers for a total of 54 observations; three outliers were discarded, yielding 51 observations. Figure 6 shows Savitsky-Golay Second Derivative Plots generated from those observations, and Figure 7 shows the overall success of the spectroscopic verification test.

Results

If quality is not confirmed near the customer, quality may not be delivered. The feasibility of point-of-dispensing testing is demonstrated by the RiverRx pharmacy study.

The testing should be a full profile, not a single-ingredient test that could be adulterated, as the scandals with diethylene glycol, melamine, and heparin remind us. It is believed that

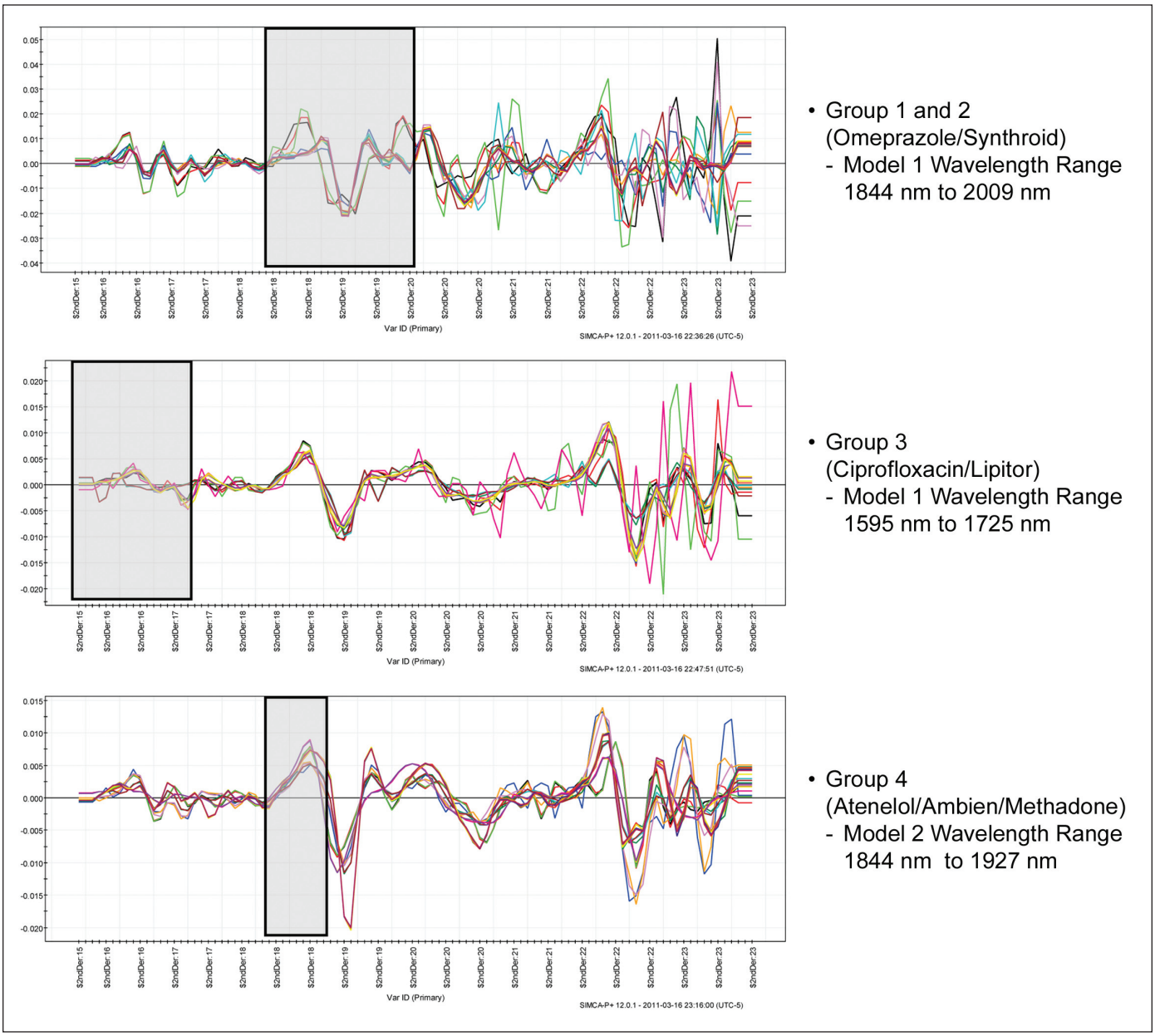

Figure 6. Savitsky-Golay Second Derivative Plots were generated, using nine point and five point second order polynomial and wavelength selection to preprocess the data for models 1 and 2 respectively.

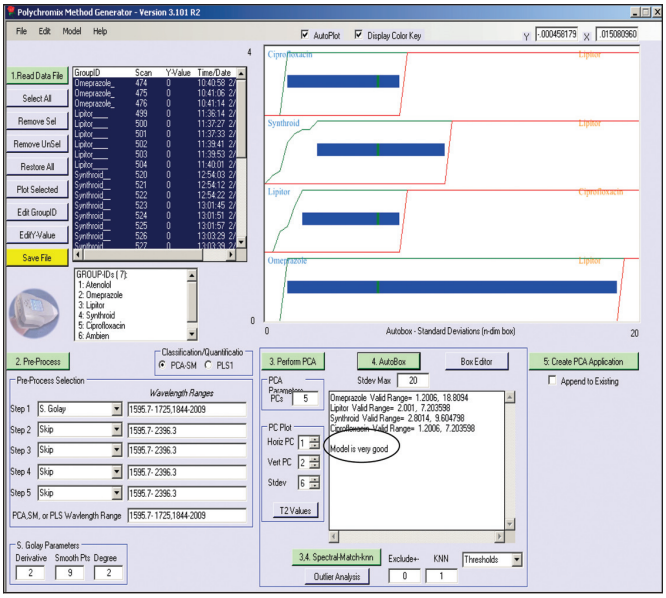

Figure 7. The pharmacy data illustrate that it is possible to distinguish right drug, right dose, with unintrusive spectroscopic tests performed within the workflow of a retail pharmacy.

the most secure method in the long run is unit dose testing at the point of dispensing via spectroscopic analysis. It offers the best protection to the patient for its ease of operation, speed and low cost, and for delivering a rapid, non-invasive, non-destructive chemical analysis of pharmaceuticals. The feasibility of intentional spectroscopic fingerprinting and analysis is demonstrated in the studies presented above.

Discussion

The situation with anti-counterfeiting and quality in 2012 appears to parallel the general manufacturing problems of a decade ago, outlined in Rathore and Winkle's exploration of science- and risk-based approaches and biologics:

"In 2000, the suboptimal state of drug manufacture and the FDA's outmoded review process had several undesirable consequences for drug regulation. As far as industry was concerned, although the quality of the products was adequate, there was a hesitation to implement new technologies because it was unknown how regulators would perceive such innovations. Many pharmaceutical companies also seemed to place little emphasis on manufacturing and its problems although the amount of product waste as a result of mistakes in manufacturing was high. In some cases, the waste was reported to be as much as 50% of the product manufactured. Also, much of the information developed or at least shared with the FDA was empirical. There appeared to be an inability to predict effects of scale-up on the final product as well as an inability to analyze or understand root causes for manufacturing failures. Furthermore, the industry had become much more global and the differences in how products were regulated from region to region lengthened preparation time and created additional paperwork to meet regulatory requirements."[6]

In fact, the approach presented in this article may be applicable to biologics as well. Counterfeit biologics have appeared in the marketplace, and doubtless we can expect more in the future. With biologics, the variability may come from the drug substance itself, not the formulation. Process control is harder to define, and quality attributes are defined later in the process.[7] Nonetheless, an end-to-end approach to quality may still offer rewards. Genentech, for example, recently noted that science- and risk-based approaches can help with approval time and inspections.[8]

Most manufacturers have already seen the advantages of spectroscopic testing for incoming raw materials since testing through the bin liner allows much faster results and avoids the need for a clean room process. As an aside, it should be noted that there is nothing inherent in spectroscopic quality monitoring that limits it to batch processing rather than continuous manufacturing. In-line use of spectroscopy for PAT helps reduce waste.

Quality production and point-of-sale verification are linked. However, the link has not extended from "We manufacture quality products," all the way to "We deliver quality products," focusing instead on separate, packaging-based anti-counterfeiting measures with separate costs.

Conclusion

If what the customer receives is inauthentic or mistreated product, it does not matter how good the manufacturer's quality processes are.

The last-mile problem affects every part of the supply chain. Manufacturers want control over distribution, but wholesalers and retailers stand between the manufacturer and the customer. The dispensing pharmacist is truly the guardian of the last mile. These experiments show that control can be provided to the pharmacist with a unique spectroscopic analytical model.

The pharmacist believes the label, believes in its quality promise. Our field results show added value to the pharmacy – no mixups, no tampering, no counterfeiting. The use of a rapid, non-destructive test has applications throughout the supply chain. Quality assurance procedures incorporate tested ingredients, verified suppliers, and the last mile. These results show the link between the manufacturer and quality: instant verification, linked back to the manufacturing database.

Quality optimization conflates two worthy goals: delivering the best possible product at the least cost with the least waste, and getting safe product all the way to the customer without problems or imposters in the supply chain. This conflation of benefits helps make the business case for science- and risk-based approaches to brand protection. Intentional variation as a marking mechanism can generate a quality fingerprint that is easily monitored throughout the supply chain. Furthermore, the science- and risk-based approach aligns anti-counterfeiting expenditures with current Good Manufacturing Practice (cGMP), enhancing return on investment.

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The Case Against Serialization

This article presents frank and objective reasons why this technology will never be implemented.

by James Robinson, P.E.

On 22 April 1987 during the 100th Congress, Public Law 100-293 was signed by then President Reagan. This law known as The Prescription Drug Marketing Act (PDMA) of 1987, was one of the most far reaching amendments to the Federal Food, Drug, and Cosmetic Act of 1938. Its primary focus was on protection of the pharmaceutical drug supply chain. 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. This act had four major sections.

Section 3 made it a crime to re-import drugs back into the US market. At the time, large amounts of exported drugs sold at a discounted price in a foreign country were being returned to the US market so that they could be sold at a profit. Many of these drugs were found to be counterfeit.

Section 4 set certain restrictions on sales of drugs including prohibiting sale of physician's samples. This "black market" was a very lucrative business for some doctors and pharmaceutical salesmen.

Section 5 put many controls over the distribution of physician drug samples. The existing system for providing drug samples to physicians through manufacturer's representatives had been abused for decades resulting in the sale to consumers of misbranded, expired, and adulterated drugs.

Section 6 focused on the control of drug wholesaler distributors where there existed a submarket commonly known as the "diversion market" which prevented effective control or even routine knowledge of the true sources of many of our prescription drugs. This section also had a pedigree requirement.

Most of the PDMA was successfully implemented and enforced. However, Section 6, the drug wholesale distribution section which included the requirement for a system for tracking drugs through the supply chain, has been delayed for years because prescription drug distributors challenged the scope of the pedigree requirements in court forcing the government to issue a stay on that part of the regulation. Many of the smaller drug distributors argued that the cost to implement a pedigree would make it difficult for them to compete with large wholesalers. The result was that Section 6 was never enforced. Wholesale distributors were free to continue to operate with very little control depending on individual state laws. In Florida, for example, a person could get a drug wholesaler's license without a background check.

This all came to light in 2005 when Katherine Eban's book *"Dangerous Doses: How Counterfeiters Are Contaminating America's Drug Supply"* was published. This book along with several well publicized counterfeiting incidents in the US including Lipitor and Viagra surprised everyone including our lawmakers and quickly prompted a series of congressional hearings, state legislation, and initiatives by pharmaceutical companies to protect them and their products from counterfeiters. During that period, pharmaceutical CEOs were constantly being asked by their stockholders what their companies were doing to protect their products from counterfeiters. Many considered counterfeit drugs the biggest threat to their business.

So, where are we today? Are we as consumers safe from the threat of counterfeit drugs? Of course, the answer is "no." Are we safer than we were 10 years ago? I think "yes." The pharmaceutical industry and the government have made great strides in protecting the supply chain against counterfeiters. New laws to prosecute drug counterfeiters have been enacted and existing laws are more strictly enforced with penalties increased significantly including jail

time. One of the enticements for criminals who previously were in the illegal drug business to get into counterfeiting legal drugs was that they could make more money and if caught the penalties were less severe. With more severe penalties and more aggressive investigations, today more criminals are being prosecuted and those convicted are spending more time in jail.

In the past seven years, most pharmaceutical companies have implemented programs to protect their products from counterfeiters. They have information on their websites to educate consumers about counterfeit drugs. Manufacturers have incorporated covert and overt features into their products and packages, and procedures have been put in place to monitor and control their supply chains. Vendors in every technical area of pharmaceutical packaging and logistics have been developing technologies and systems to improve the security of pharmaceutical products as they travel through the supply chain.

Since the pedigree requirement of the Prescription Drug Marketing Act of 1987 was never enforced, there is still no federal legislation approved for an e-pedigree. An e-pedigree requires a unique number on each package (serialization). The result, as documented in Katherine Eban's book, is that there is still a lack of control or even routine knowledge of the true sources of many of our prescription drugs. The diversion market which was the main objective of Section 6 of the PDMA still exists today. The only change is that the states like Florida have made the process of becoming a drug wholesaler more rigorous.

California took the initiative and passed a Pedigree Law in 2007. The California Pedigree Law requires a unique identifier on each package that would be stored in an interoperable database by the manufacturer. Every change of ownership requires the company that initiated the change of ownership to update the database until the package reaches the end consumer, i.e., pharmacists, clinic, hospital. At that point, the number would be retired and there would be a complete electronic record of each package with each change of ownership creating the pedigree for each package.

In 2007, the FDA endorsed RFID in a white paper as the technology of choice for that unique number. It was a new technology for pharmaceuticals that got a lot of interest and support from manufacturers, wholesalers, and technology suppliers. It could easily be read by inexpensive scanners and was already in use in other industries. Pfizer actually began serializing commercial packages of Viagra with an RFID tag inserted behind the label and continued doing that for several years. However, during several very comprehensive and well supported pilot programs, the RFID technology was proved unreliable and was abandoned.

In the US, the supply chain for drugs is very complex. A package can change ownership anywhere from five to as many as 12 times before it reaches the end customer. Outfitting the drug supply chain with RFID readers sounded simple at the time. Anyone who attended the public hearings in California in 2006 heard from vendors of RFID systems just how simple and inexpensive RFID would be to implement. That testimony had a big influence on the approval and the final details of the California Pedigree Law.

In the beginning, the biggest proponent of RFID technology for track and trace was the prescription drug wholesalers. They sponsored and participated in several pilots and actually challenged pharmaceutical companies to move faster with the technology. What was not mentioned was an underlying business objective that drove their interest. If they knew when they sold an individual package, they could rearrange their business model to reduce inventory costs by paying for their products only at the time they were sold. The cost to the large wholesalers to implement RFID readers was relatively small compared to the cost to the pharmaceutical manufacturer and packagers to incorporate RFID tags on their packages.

After the RFID technology was abandoned, the drug manufacturers switched to serialized 2D bar codes. Since the switch from RFID to 2D bar coding technology in the US, the drug wholesaler distributors have been very quiet. The reason is the high cost for a drug wholesaler to implement 2D bar code readers. To install line of sight 2D bar code scanners, drug wholesalers would need to totally redesign their pick and pack systems. That cost and the cost to pharmacies, clinics, hospitals, and the rest of the supply chain companies has not been identified. The cost would be much higher than readers for RFID tags which do not require line of sight.

When it comes to drug package serialization today, 2D bar coding dominates most discussions and seems to be the technology that is being used in every pilot program in the US, Europe, and now Latin America (Argentina, Brazil). It is a technology that is readily available by the vendors and the only technology that can be implemented since RFID failed to demonstrate reliability during the pilot programs. It is estimated that half of the pharmaceutical companies have active pilot programs. Since 2D bar coding is the technology already deployed in several European countries, it seems to make sense to have one system globally especially when many companies are supplying product globally. Or does it?

In Europe, several countries, e.g., Italy, Belgium, France, Turkey, have successfully implemented a system that uses printed bar codes on primary packages to authenticate those packages as a requirement for reimbursement by the government. These systems were implemented so that the dispenser can be reimbursed by the government who is paying for the drugs.

The US e-pedigree system is different from the reimbursement system in Europe. In the US, the objective is to use a track and trace system to develop an e-pedigree. In Europe, the objective is to have a bar code that can be read at the point of dispensing or point of use for authenticity so the dispenser can be reimbursed by the government. These are very different objectives that require different supply chain infrastructures.

A track and trace program requires one "interoperable electronic system," as it is called in the California Pedigree Law, that is used by every manufacturer, packager, wholesale distributer, pharmacy, and hospital, or clinic in the supply chain to update the transfer of the ownership as it occurs. Every

In the US, 2D bar coding is the technology being implemented by the pharmaceutical companies to meet California Pedigree Law by 2015. However, only pharmaceutical manufacturers and packagers are working on their part of the system which is to print a unique number on each package…
But the effort seems to stop with the pharmaceutical companies.

drug package would have a serial number entered into the database by the manufacturer. The system would have to be updated as the package moves through the supply chain from company to company to create the e-pedigree. Track and trace requires every pharmaceutical warehouse and every wholesaler in the supply chain to have the ability to read each individual bar code or case code as it arrives at their loading dock and as it leaves to the next company in the supply chain. It also requires every pharmacy, clinic, and hospital to read the bar code at point of dispensing to complete the cradle to grave e-pedigree. This system would create a supply chain control system of a scale the world has never seen and at a cost that has yet to be determined.

In Europe, the objective is authentication at point of use or point of dispensing for reimbursement by the government. The countries that have implemented it have a single payer, the government. Therefore, the 2D bar code is read only one time at the pharmacy and compared to a database that is managed by the government or its agent since they are the only payer. There is no requirement to put readers at wholesalers, distributors, or in any warehouse operations. The government provides, pays for, and manages the database that the pharmacy communicates with for verification.

In the US, 2D bar coding is the technology being implemented by the pharmaceutical companies to meet California Pedigree Law by 2015. However, only pharmaceutical manufacturers and packagers are working on their part of the system which is to print a unique number on each package. These companies are implementing pilot programs to serialize packages, cases, and pallets. But the effort seems to stop with the pharmaceutical companies. There is no activity by the drug wholesalers such as the pilot programs that were conducted with RFID several years ago. In those pilots, they not only placed RFID tags on packages and cases, but they actually tracked packages through the supply chain with all parties participating. The Healthcare Distribution Management Association (HDMA) has issued a position paper on the California Pedigree Law which is available on their website. (www.healthcaredistribution.org). HDMA represents 86% of the drug wholesalers in the US. In their position paper, they very carefully point out that RFID is preferred and that *"data matrix bar codes may travel at a much slower rate through the supply chain and incur higher labor costs because of the need to scan individual packages at each transaction point."* The average wholesaler processes more than 85,000 units per day. The cost to install line of sight readers and a system to track these serial numbers has not been discussed yet alone indentified.

Pharmaceutical companies have been keeping the system integrators, hardware vendors, IT consultants, and enterprise system engineers very busy over the past few years spending millions of dollars implementing pilot projects to print a unique serial number on individual packages. The common driver for these companies is to meet the California Pedigree Law by 2015 or a Federal Law if it happens prior to 2015. But where is the rest of the track and trace system partners who will, according to the California Pedigree Law, be required to read the 2D bar codes and update the database as ownership changes? Why haven't we heard the wholesale distributer trade groups or pharmacy trade groups? What happened to the pilot programs that we had with RFID where we actually shipped and tracked product through the supply chain? Why isn't there a "call for action" like the prescription drug wholesalers shouted for several years ago from the pharmaceutical companies when RFID was the technology? Are we seeing a "field of dreams" here where the attitude is to "put it on and they will read it?" Getting a serialized 2D bar code on a package achieves nothing if no one is equipped to read it. And where is the computer database system that is needed to track and trace these unique serialized numbers thought through the supply chain and be the source for the e-pedigree? Who will own that system? Who will validate it? How will it be used to insure against counterfeit product entering the supply chain? Who is responsible for maintaining the integrity of the data? Who is paying for its maintenance? The California Law did not address how to implement the "interoperable database." Why are there no articles describing the systems the prescription drug wholesalers and pharmacies are going to use to read these bar codes and update the database? Obviously, these details have not been addressed and there is no evidence of any plans for rest of the supply chain to comply with California law.

At a March 2012 Congressional Hearing on FDA User Fees, the National Association of Chain Drug Stores (NACDS), representing pharmacies that fill about 75% of all prescriptions, commented on the Pedigree Law. They said that "premature drug "track and trace" models would unnecessarily increase healthcare costs while imposing burdensome technologies that have not demonstrated an ability to enhance supply chain security. As lawmakers, we urge you to consider approaches that are feasible and workable for the supply chain, and to recognize the importance of not requiring untested costly mandates such as a prescription drug "track and trace" system for supply chain stakeholders. Such requirements would add billions in additional costs to the healthcare system and take time and resources away from pharmacies' ability to provide pharmacy services to their patients." Billions? Well that could be exaggerated, but given the number of manufacturers, packagers, repackagers, CMOs, wholesalers, clinics, hospitals, it may not be too far off. Nobody really knows.

With the current political climate on both sides of the aisle for "smaller government with fewer regulations," I do not see

the FDA taking any action in this area in the near future. No one would support a system that would add cost to our prescription drugs. And in 2015, if the California Pedigree Law becomes effective, my guess is that it will quickly be challenged in the courts by the wholesalers and pharmacies who will not have the infrastructure needed to read the 2D bar codes and the law will not become effective. This is what happened to the pedigree requirement in the PDMA in 1987.

So why are there millions of dollars being spent by pharmaceutical companies on converting their packaging lines to be able to print serialized 2D bar codes? First, the California Pedigree Law is still scheduled to become effective in 2015 and 2D is the only technology that can be implemented by manufacturers. Second, "inertia." This often happens to technology based projects like this. There was so much momentum created back in the RFID days with the open hearings in California, the FDA whitepaper, that it is hard to stop engineers from being engineers and solving problems. Third, is fear of negative public opinion. Pharmaceuticals are a $250 billion dollar business with a 17% profit margin and companies are concerned about their image. Protecting the public from counterfeit drugs is hard not to support even if there is no clear path to a workable solution. Pharmaceutical companies are basically spending money to look as if they are doing something to protect public health to protect their image. They don't seem to be concerned with the fact that none of their business partners in the supply chain will be ready to read the 2D bar codes and there will not be a centralized system to store the e-pedigree data.

So where do we go from here? Should the pharmaceutical manufacturers and packagers continue to spend on serializing packages when there will be no infrastructure to read the 2D bar codes and no database to create the e-pedigree? I say "no." Stop spending on 2D bar code serialization. Our supply chain partners will not have systems in place to read these bar codes. Let's ask PhRMA to be more active in lobbying against the California Pedigree Law. Let's ask the HDMA, National Pharmacy Association (NPA), and pharmaceutical manufacturers and packagers to partner together on solutions that will work; solutions that can be implemented and are cost effective; solutions that are not created by politicians but by industry.

One solution would be to track drugs with an e-pedigree using NDC and lot number. Wholesalers currently manage inventories using only NDC numbers. I am suggesting that they manage inventories with both lot number and NDC number therefore dividing up inventories into smaller groups. This would not require a unique identifier (serialized number) on individual packages. It would require a central database to track and keep a total number of packages by NDC and lot number. As packages change ownership, the e-pedigree would include the quantity of packages by lot number that was transferred. Therefore, at any time the total number of packages by lot of product and its location (owner) would be known. By tracking the total packages by NDC number and lot number through to the final customer, you would simply look for any increases in the inventories by lot number or any new lot numbers that were not assigned by authorized manufacturers or packagers as an alert that a counterfeit product may have entered the supply chain. This system would not be as effective as tracking individual packages, but it does not require any bar code reading systems anywhere is the supply chain and would be far less costly and much easier to implement. The Pharmaceutical Distribution Security Alliance (PDSA) has recently outlined a similar system with an implementation plan. NACDS has endorsed it already.

I am sure there are other solutions that could be effective, simple, implementable, and less costly. This is my "Call for Action."

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Veteran quality executive Martin VanTrieste provides a snapshot of the global and complex problem of counterfeiting. He explains his passion behind and the creation of Rx-360, an international consortium dedicated to increasing the security and quality of the pharmaceutical supply chain, and his candid thoughts on the importance of collaboration in a competitive industry.

PHARMACEUTICAL ENGINEERING Interviews

Martin VanTrieste, Senior Vice President, Quality, Amgen, and Founder, Rx-360

by Jeff Hargroves, Chair, ISPE *Pharmaceutical Engineering* Committee and Rochelle Runas, ISPE Technical Writer

Martin VanTrieste is the Senior Vice President of Quality at Amgen. He is responsible for all aspects of Quality Assurance, Quality Control, Compliance, Environment, Health and Safety along with Training at Amgen. Prior to joining Amgen, VanTrieste was with Bayer HealthCare's Biological Products Division as Vice President of Worldwide Quality and Abbott Laboratories as the Vice President of Quality Assurance for the Hospital Products Division (now known as Hospira). While at Abbott, VanTrieste held various positions in Quality, Operations, and Research and Development. He started his career at Abbott in 1983 after obtaining his Pharmacy degree from Temple University School of Pharmacy. VanTrieste has been actively involved with various professional and trade organizations, including United States Pharmacopeia (USP), Pharmaceutical Quality Research Institute (PQRI), Pharmaceutical Research and Manufacturers of America (PhRMA), and AdvaMed, and he is a member of the Board of Directors of the Parenteral Drug Association (PDA). He is the founder and first Chairman of Rx-360 and currently serves as Treasurer. Rx-360 is a nonprofit international supply chain organization that will enhance patient safety by increasing the security and quality of all parts of the supply chain.

Q You have long been a champion for quality in the pharmaceutical industry. Please tell us what sparked your interest (perhaps a defining moment) and consequently, your career, in quality?

A I can't really pick a defining moment in my life that enlightened me to become a quality professional. I began my career as a pharmacist and went to pharmacy school to serve patients. On my journey through my career I became a quality professional. It was not something that I sought or planned to do; it happened along the way. Prior to graduating from pharmacy school, I was given the opportunity to be an intern at a major pharmaceutical company. After that 12-week internship, I decided I wanted to work in industry, specifically in R&D as a formulation pharmacist. About eight years into my career path in R&D, I was given the opportunity to manage our product complaint department and this is where my passion for problem solving and continuous improvement began and was related to my desire to serve patients. That's the point where I think my career in quality was launched.

Q What is your definition of a supply chain and what are the key elements to it?

A I like to use the definition from Wikipedia, which basically says a supply chain is a system of organizations, people, technologies, activities, information, and resources involved in moving a product or service from a supplier to the customer. These supply chain activities transform natural resources, raw materials, and/or components into finished pharmaceutical products that we deliver to the patient.

Q What was the origin of the Rx-360 consortium?

A Rx-360 was formed in the aftermath of the heparin tragedy in 2007. I had the privilege to participate and speak at the first FDA/PDA supply chain workshop, which was inaugurated as a result of the heparin tragedy. During that workshop, Dr. Janet Woodcock of the FDA stated that heparin and the events surrounding it were a wake-up call for industry. She challenged everybody in the audience to act quickly and "Look at your supply chain and make sure this doesn't happen to you." That actual statement by Dr. Woodcock and her challenge – I'd almost say – was the birth of Rx-360.

After that meeting, I met with a small group of quality executives from the major pharmaceutical companies and we discussed a series of issues. First, we said that what happened to Baxter was very unfortunate and probably not a failure of any of their GMP systems. What happened with heparin was a result of criminal activity at the hands of some very unethical players. GMP systems are not really designed to catch criminals – they're designed to keep the honest people honest. We also said that while it was unfortunate these events happened at Baxter, we were fortunate that something similar didn't happen to us – almost as if we were lucky that none of our products were the first product to have this happen to. We then started to discuss how such events could be prevented by better detection, disruption, and deterrence. The more we talked about the situation and how to prevent it, I think the more scared we all became. That's because we realized that these criminals have entered the supply chain in an unprecedented manner and that it was a very global, complex problem that no one company, or person, or stakeholder, or regulator could solve all by themselves. Once we recognized that, we said, "Okay, if we can't do it ourselves, how are we going to be able to solve this problem? How can we protect the patients we serve from this ever happening again in our industry?" And it was at that point we said we are going to have to collaborate and work together to solve this problem. We agreed to collaborate and meet again later in that calendar year after we had time to talk to various stakeholders and collect their thoughts.

As I went away from that meeting, I started thinking of what we could do and writing it down on a piece of paper. Well, those thoughts, ideas, and interviews I conducted to try to figure out how we could solve this problem and results from talks with other industries about their strategies lead to a 27-page business plan for Rx-360 that I brought back to this group of executives. We reviewed that business plan, discussed its objectives and strategies, and basically at the end of that second meeting had an endorsement of the concepts we wanted to move forward with. If you look at the website, we focus on four things: technology, sharing of information, industry-wide surveillance, and sharing audit data. Those were the four concepts in our original business plan. That was the genesis behind Rx-360. We then formed working groups to determine how best to structure the organization. Finally, in June 2009, Rx-360 was formally incorporated as a legal entity in the state of Pennsylvania as a non-profit corporation.

Q What is the mission of the Rx-360 consortium?

A The mission of Rx-360 is to create and monitor a global quality system that meets the expectations of industry and regulators, that assures patient safety by enhancing product quality and authenticity throughout the supply chain.

Q Who can belong to the Rx-360 consortium?

A One of our tenets is transparency and openness, so we don't try to limit membership; we try to encourage as much membership as possible. We strongly believe that if we collaborate and focus all of our resources – who are subject matter experts – collectively on this problem, we'll be more successful than if we try to do it in various other mediums.

It's fairly simple (in regard to who can belong). If you're a pharmaceutical or biotech company or a supplier of raw materials, components, or services to the pharmaceutical industry, you can be a Member. We then open it up to Observers – regulators, legislators, policy makers, pseudo-government agencies, auditing companies, trade and professional organizations. Observers also include anyone who wants to join who doesn't fit into one of those categories; we explore how we can be more inclusive of them.

Q One of the activities of Rx-360 is sharing information, such as audits. Are there any concerns from prospective members regarding risks of joining?

A When we originally started the concept of Rx-360, we realized we would be sharing a great deal of information we've never shared before as an industry. Of course, that presented concerns to us, and most of those concerns came from a legal point of view (anti-trust, anti-competitive). We are a Washington D.C.-based organization. We chose this location because the US FDA is located there, as is the Secretariat of Rx-360, law firm Drinker Biddle & Reath LLP. We chose a law firm to act as our Secretariat to make sure we don't run afoul of any government regulations related to information sharing. We took it step further and filed a request with the SEC to get a formal opinion from them on our business plan. The SEC's basic ruling was, "If you follow this business plan, because you're doing this for the greater good of society and in the interest of patient safety, we would not take any antitrust actions against the organization if you agree to stick to your business plan." So we have that safe harbor created by the SEC for us. That clearly has allowed several members to join the organization who were a little tentative in the beginning.

Q Are you collaborating with any regulatory agencies, e.g., FDA, EMEA, or others? Are regulators involved in the development of Rx-360 Guidelines?

"I think there's great benefit from sharing best practices… You asked why people would do this. My response is simple. I know it would be very unwise not to share our best practices. Our industry has a privilege to serve patients and that privilege comes with responsibilities. The most important responsibility we have in our industry is to assure patient safety."

A We actively engage with regulators from around the world – the EMA, the FDA, WHO, EDMQ, and PIC/S – letting them know who we are, what we do, and ask them for advice and consent on what we should be working on and problems that should be addressed. We do all of that on a fairly routine basis. Since we're based in Washington D.C., we are close to the US FDA and the Agency does pay attention to what we do and looks at what we're writing. Many FDA employees are registered on our website and get our emails and flash reports. While they don't approve our documents, they do look at our drafts to gain any insights from our thinking and they provide us with their insights which we try to incorporate in those documents.

Q Do participating operating companies openly share best practices? Why is this a wise thing to do? How do participants balance open sharing with concerns over competitive advantage?

A It is amazing the level of openness to share best practices among our Members. If you think about our mission, which is aimed at protecting patients, so obviously this is where many of these best practices are shared – how to improve quality and the security of the supply chain. I can think of three very public and successful examples of sharing best practices at Rx-360.

There was a shortage a few years ago of the solvent acetonitrile, used extensively in the manufacturing of small molecule APIs and in laboratory analysis. During that shortage, people were concerned that some criminal or unethical players would somehow try to adulterate or substitute materials to take advantage of the higher prices being experienced in the acetonitrile market. We had companies work together to develop an analytical test method to detect for adulteration or counterfeits of acetonitrile. Consequently, our membership had 1) knew ahead of time of a shortage so they could prepare for it and 2) as they were building inventories of acetonitrile, had an analytical method they could use to test the acetonitrile to make sure it was authentic. That's the first example.

The second example was in reaction to the major earthquake in Japan that lead to a tsunami and some nuclear incidents at a power plant. We quickly formed a task force within a matter of a few days to ask, "How do we get our medicines into Japan and how do we get medicines and raw material out of Japan safely so that we can continue to serve patients?" We brought together experts on supply chain, quality, and even the nuclear industry. We had people who worked in our companies who were in the nuclear Navy and understood nuclear reactors and nuclear safety. We had people in our Environmental, Health, and Safety organizations who used to work for the nuclear industry who discussed nuclear safety and monitoring and how best to approach that. In a matter of a few days, we pulled all experts together. In a matter of a couple of weeks, we had a standardized protocol for our members to operate under. Instead of 27 different members trying to reinvent the wheel, we were acting in a unified way trying to help our suppliers in Japan versus pestering them with 27 different approaches. So, to me it was an effective way of getting together in a crisis, bringing the best and smartest minds together, and putting in place a process that regulators felt comfortable with. At that time, regulators around the world were imposing (policies) on manufacturers in their countries to deal with the Japanese situation. You didn't see that in Europe and the United States and I think a big part of that was because industry came together, shared these best practices, developed a highly effective protocol on how to deal with the situation, and the regulators felt comfortable that we were doing the right things. Then we shared that, and not just with our members. We published that information so it was available for everybody to use.

The last example occurred when the FDA in 2010 issued a letter to key stakeholders about the increasing threat of cargo and warehouse thefts. In a meeting between Rx-360 and the FDA, the FDA said, "If Rx-360 could do something in terms of a standard around how to prevent cargo theft, that would be very useful." So, we created a best practice document about how to prevent cargo theft, which is published on our website.

So, I think there's great benefit from sharing best practices because we can create industry wide standards and level that playing field, while making the system more effective and efficient. You asked why people would do this. My response is simple. I know it would be very unwise not to share our best practices. Our industry has a privilege to serve patients and that privilege comes with responsibilities. The most important responsibility we have in our industry is to assure patient safety. I remember when I was as kid, a Volvo automobile commercial that stated how Volvo invented and patented the seatbelt. That commercial went on to say that Volvo wanted to compete on features related to comfort, performance, price, etc., but that consumer safety was something too important to use as a competitive advantage and as such, Volvo would not enforce their patents and encouraged all automobile manufacturers to implement seatbelts in their designs. Now, I can't help but wonder how many thousands of lives have been saved by that decision. But I do know two lives that were saved by that decision – my two oldest daughters. They were in a massive car accident that totaled our car. It was horrific. But both of them are alive

today because they were wearing their seatbelts. So, when I think about our industry, we don't compete on patient safety and we don't compete because "I have a better supplier auditing function or I'm a better producer of drug x, y, and z." That's not how we compete as an industry. So, if that's not how we compete as an industry, it must not provide that much of competitive advantage. So, why don't we act more like Volvo? I think my colleagues throughout the industry agree with that. And that's why we share these best practices and why people aren't worried about the competitive disadvantage or advantage it may pose.

Q Can you give us a brief numerical overview of the size of the counterfeiting problem in the US/abroad?

A It's difficult to give an exact number because the data is hard to locate. And, of course, you only know what you catch; you don't know what gets by you. But the data does indicate that there are increasing trends of counterfeit activity. These (numbers) include tampering and illegal diversion and news and press estimates for final drug product counterfeiting: It ranges from one to five percent in developed countries and up to 30% in the emerging markets and there are even some estimates that in some parts of Africa it can be as high as 90%.

In the raw material space, we don't have any reported data, but we are aware of many incidents such as heparin, glycerin, and cough syrups in Panama, to tell us that that we have those types of problems. When people say, "Well, if it's only 1% or less in the United States, why should I, as an American, be concerned about that." Well, you know, if 90% of the malaria medicine in Africa is counterfeit/or substandard and the organism that causes malaria is developing resistance to legitimate malaria medicines in Africa, how long will it take for a resistance strain of malaria to get on an airplane and fly to south Florida, or to Texas, or to southern California and introduce an incurable disease into the United States? So, we need to be concerned about what's going on in the rest of the world because the world is becoming a much smaller place.

Q We understand you testified before Congress last year regarding supply chain issues. Can you tell us about this experience and any specific outcomes from that session?

A I was fortunate to be invited by the Senate Health, Education, Labor, and Pensions Committee to testify on the topic of securing the pharmaceutical supply chain. I testified on behalf of Rx-360 and it was a very positive experience for me, allowing me to share recommendations with the committee on ways to improve supply chain security. The Congress has been grappling with this complex issue and examining what kinds of policies should be adopted in an overall effort to protect patients from unsafe medicines.

In terms of specific outcomes, the committee recently released draft legislation that establishes new laws to help ensure the integrity of the supply chain. Some of these provisions included enhanced penalties for intentional adulteration and counterfeiting, risk-based inspections by the FDA of foreign manufacturers, registration of foreign and domestic establishments, accreditation of third party auditors, and requirements to implement oversight and controls over manufactured drugs to ensure quality. There is speculation that the Congress could pass these types of supply chain reforms this year as part of a broader legislation reauthorizing the Prescription Drug User Fee Act (PDUFA). Many of those provisions in the draft legislation (such as increased penalties for intentional adulteration and counterfeiting, risk-based inspections by the FDA of foreign manufacturers, and registration of foreign and domestic establishments) were provisions Rx-360 had recommended to the Health Committee.

Q In addition to Rx-360's efforts focusing on criminal activity causing harm to the pharmaceutical supply chain and thus patients, does Rx-360 also focus on quality issues (not criminally related) that can cause harm?

A Yes, we do. The entire auditing function and the sharing of audits and audit information is primarily focused on quality of raw materials and the quality culture of a supplier, so that is the point where we share more information around quality. We, of course, have common audit checklists, procedures, and protocols to follow and that's where most of that sharing of quality comes in.

Q What do you consider to be the best resources to help someone examine the robustness of their supply chain program?

A There are many places to go, but I would say that Rx-360 is a great source to do that and we have a workstream dedicated to just supply chain and supply chain controls. It's lead by Brian Johnson from Pfizer and Tim Valco from Amgen. That group is doing a lot in terms of conducting risk assessments of supply chains, determining the best mitigations to any risks that you identify in a supply chain, and coming up with series of best practices that they will be shortly sharing with their supply chain colleagues who are members and not members of (Rx-360).

Q How can ISPE help improve the management and control of our supply chains?

A We must collaborate and focus our resources to secure the supply chain. So, I would ask ISPE and other organizations not to initiate duplicate efforts that will only draw on the limited resources that industry has at its disposal to solve this very complex global problem. As such, I would ask ISPE to support ongoing efforts like Rx-360 and not to create competing initiatives that would only dilute our efforts to secure the supply chain.

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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.

Introduction

The cooling of a tank after steaming or after warm cleaning in place is a critical step. During the cool-down period, steam condenses into liquid water. A given amount of water vapor occupies 1000x more volume than the same amount of liquid water so an immense void volume is created when steam condenses. As more and more steam condenses, more and more thermal energy is released and the gas pressure in the tank lowers along with the partial pressure of the water vapor. When the pressure drops to a low enough level, a negative pressure (vacuum) is created.

Under vacuum conditions, it is entirely possible for a tank to implode due to the pressure difference between atmospheric pressure and the pressure in the inside of the tank, if the tank is not vacuum proof - *Figure 1*.

Figure 1. Imploded tank due to undersized venting filter.

In some cases, the tank also should be kept at overpressure in order to avoid any risk for contamination from eventual leaks. It would then be contradictory to allow for any negative pressure during cooling down regardless if the tank is vacuum proof or not.

In order to shorten the process down time, active cooling is often used, either by a cooling double envelope or in some cases a spray ball. Active cooling may in some cases generate such fast cooling that no realistic vent system may compensate the created vacuum.

For example, an insulated tank of 4.5 m^3 which is cooled down to 20°C by a spray ball after a CIP at 90°C will typically cool very fast, especially the first 10°C (from 90°C to 80°C). If cooling down from 90°C to 80°C takes three seconds, the required instant flow rate to compensate the vacuum is more than 1200 Nm^3/h due to water vapor condensation. Such a flow rate would still give a negative pressure of 70 mbar in the tank when having as many as seven sterilizing grade filters of 20" each in parallel, for a total membrane surface of 10.5 m^2 if no compressed air is used.

This should be compared to the required flow rate if the same insulated tank of 4.5 m^3 cools down naturally from 90°C to 20°C after a CIP. The instant flow rate in the beginning of the cooling down is only 35 Nm^3/h. A single sterilizing grade 10" cartridge (0.75 m^2 of membrane surface) would give less than 20 mbar of negative pressure within the tank if no compressed air is used.

The cooling down of tanks after steam sterilization is typically handled in one of the following ways:

1. Active cooling down compensated with compressed air
   a. Natural cooling down below 100°C followed by…

Pressure		Temperature		Surface		Volume		Absolute Humidity		Weight	
Mbar	Psi	°C	°F	m^2	ft^2	m^3	ft^3	g/m^3	grain/ US gallon	kg	pound
20	0.29	-20	-4	0.375	1.0	1.0	35.31	0.8	0.047	1.00	2.20
25	0.36	20	68	0.75	4.5	4.5	158.9	1.0	0.058	5.85	12.90
40	0.58	25	77	1.0	35	35	1236	2.24	0.13		
70	1.02	30	86	10.5	1,200	1,200	42,377	240	14.02		
168	2.44	40	104					1,300	75.94		
300	4.35	80	176					1,548	90.43		
500	7.25	90	194								
1,000	14.5	95	203								
1,300	18.85	100	212								
1,450	21.03	115	239								
1,500	21.76	130	266								
1,800	26.12										
2,800	40.61										

Table A. Conversion table for values appearing in the text.

   b. Active cooling down by cooling down the double envelope while compensating the generated vacuum with compressed air
2. Active cooling down without compressed air
   a. Natural cooling down below 100°C followed by…
   b. Active cooling down by cooling down the double envelope using an adequately sized vent filter not to go below the defined level of vacuum
3. Natural cooling down over night
   a. Natural cooling down below 100°C followed by…
   b. Natural cooling down over night, while compensating the generated vacuum with compressed air or without compressed air using an adequately sized vent filter not to go below the defined level of vacuum

Generally, reduced cooling down time would allow increased productivity of the tank and thereby the overall potential production capacity of a manufacturing area.

A robust and fast active cooling of production tanks without generating any vacuum allows the use of less expensive single round housings even for large volume tanks. Less important vacuum levels also allow the use of less expensive not fully vacuum rated tanks still maintaining process safety.

Materials - *Figure 2*

- stainless steel tank of 4.5 m^3 with cooling double envelope and sight glass
- supervising system
- vent filters (5" and 10")
- steam
- dry compressed air (-20°C of dew point corresponding to 0.8 g/m^3 of humidity at atmospheric pressure or 2.24 g/m^3 at 1.8 barg)

Existing Procedure of Steaming in Place

The tank is steamed via the valve C at a temperature of 130°C/1.8 barg (targeted temperature 127°C) for 30 minutes. Compressed air is injected via the valve A in order to pressurize the tank to 1.3 barg resulting in steam (at 1.8 barg) flowing out of the tank via the vent filter F until the pressure stabilizes at a pressure of 1.3 barg. The tank then cools down spontaneously to 95°C while the supervising system pressurizes continuously with compressed air at 1.3 barg. The spontaneous cooling down to below 95°C takes around two hours. Once at 95°C, the double envelope is cooled down with cold water in order to reach ambient temperature while the supervising system tries to maintain the tank at a pressure of 1.3 barg.

Consequences of Existing Procedure

As soon as the cooling of the double envelope starts, steam condenses on the inner surface. A clear dip of 300 mbar (from

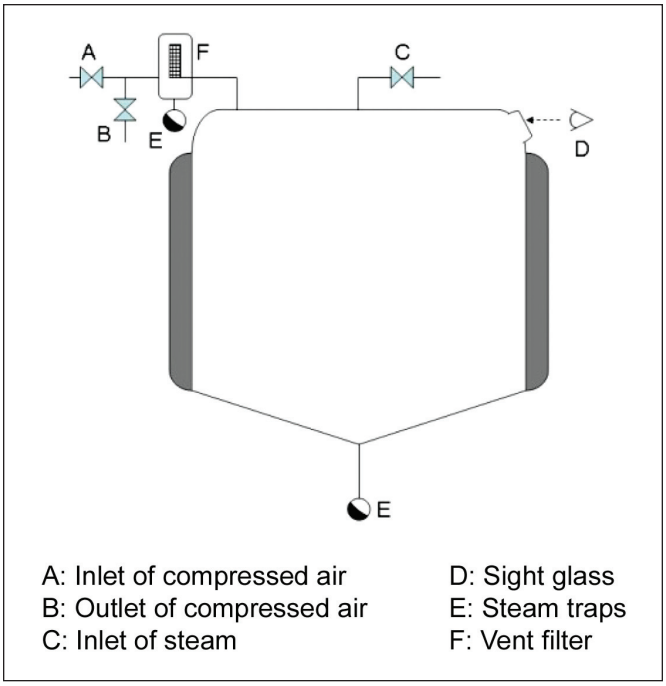

Figure 2. P&ID of the double jacketed vessel.

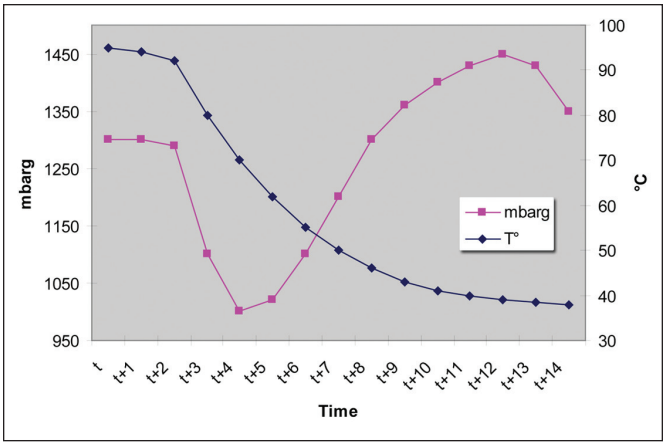

Figure 3. Pressure and temperature curve versus time for the original cooling process after steaming of the tank.

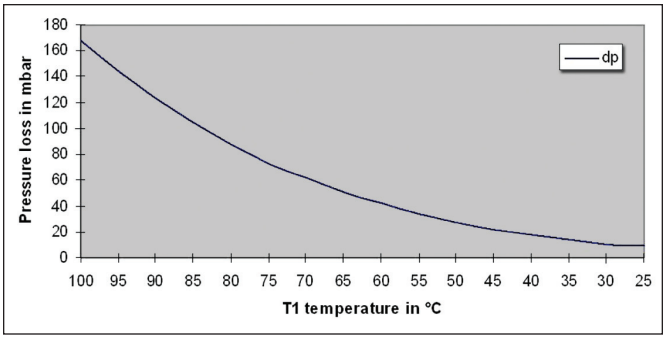

Figure 4. Illustrating the corresponding pressure drop due to vapor condensing when lowering the temperature from T1 to T1 - 5°C, e.g., when the temperature goes down from 100 to 95°C the generated pressure drop is 168 mbar regardless of tank size, if no air is injected.

1.3 barg down to 1 barg) can be seen on the pressure curve although the system tries to maintain the pressure at 1.3 barg as seen in Figures 3 and 4. Continuously pressurizing the system is not capable of delivering the required gas flow in order to remain at 1.3 barg as seen in Figure 3. This clearly shows the strong impact of condensation.

As the temperature goes down, the phenomenon of pressure drop per centigrade of temperature variation (mbar / Δ°C) is reduced as seen in Figure 4. The required airflow rate then gets smaller than the airflow capacity of the system and the pressure builds up again. The system then overcompensates to approximately 1.45 barg of overpressure seen in Figure 3 due to reading latency.

The active cooling down using the double envelope takes around 15 minutes to reach 40°C, another 15 minutes to reach 30°C and another 15 minutes to reach 25°C, for a total of three hours process time. In order to avoid down time, the steaming and cooling down of the tank is done over night.

Trials and Results

In order to speed up the cooling down process, we wanted to start the active cooling without waiting until the temperature had gone down below 100°C. Knowing that the pressure drop comes from the condensing of water vapor, as temperature goes down, the only way of avoiding an important vacuum was to get rid of most of the humidity before cooling down. Therefore, it was decided to perform the following sequences during the trials:

1. Steaming at 130°C for 10 minutes.
2. Depressurization from 1.8 barg down to 0.5 barg in order to exhaust some of the humidity and thereby also a lot of calories (461.5 J · kg^{-1} · K^{-1}). It was decided not to go below 0.5 barg in order to be sure to have a significant overpressure in case of condensation and thereby avoiding any vacuum inside the tank. As the temperature decreased with the expansion of the gas (pV = nRT) when depressurizing, the gas inside the tank became foggy because of it being saturated with steam.
3. Injection of compressed dry air. As the pressure progressively rose to about 1.8 barg, the fog disappeared due to reduction of the relative humidity.
4. Depressurization from 1.8 barg down to 0.5 barg. The appearing fog became less dense, clearly indicating that the humidity decreased within the tank.
5. Injection of compressed dry air. As the pressure progressively rose to about 1.8 barg, the fog disappeared more quickly than in step number 3.
6. Depressurization from 1.8 barg down to 0.5 barg. Hardly any fog could be seen.
7. Some trials were done by pressurizing the tank with dry air at 1.8 barg before cooling down the double envelope and some trials were done without pressurizing before cooling down the double envelope.

Water Vapor Removal

At the first depressurization, the absolute humidity inside the tank was reduced proportionally to the quantity of steam being expelled when depressurizing from p_1 to p_2. This reduction is expressed by the following equation:

$$H_{Abs0'} = H_{Abs0} \cdot \left(\frac{p_2}{p_1} \right)$$

Where:

H_{Abs0} = Absolute humidity in kg/m^3 at p_1 (in this case 1.548 kg/m^3)

$H_{Abs0'}$ = Absolute humidity in kg/m^3 at p_2

p_1 = Absolute pressure before depressurizing the tank (in this case 2800 mbara)

p_2 = Absolute pressure after depressurizing the tank (in this case 1500 mbara)

p_2/p_1 = The ratio of remaining level of H_{Abs0}

When re-pressurizing back to the initial pressure p_1 the water vapor inside the tank was mixed with air. As the injected air is not perfectly dry, the absolute humidity increases slightly although the relative humidity decreases. The absolute humidity increase inside the tank can be expressed by the following equation:

$$\Delta H_{Abs} = H_{AbsCA} \cdot \left(1 - \frac{p_2}{p_1} \right)$$

Where:

ΔH_{abs} = Absolute humidity change

H_{AbsCA} = Absolute humidity in kg/m³ of the compressed air at p_1 (in this case 0.00224 kg/m³)

p_1 = Absolute pressure after re-pressurizing the tank (in this case 2800 mbara)

p_2 = Absolute pressure before re-pressurizing the tank (in this case 1500 mbara)

$1 - p_2/p_1$ = The ratio of humidity coming from the injected compressed air

The estimation of the absolute humidity after one cycle of depressurization followed by re-pressurization (one full cycle) can be expressed by the following equation:

$$H_{Abs1} = H_{Abs0} \cdot \left(\frac{p_2}{p_1} \right) + H_{AbsCA} \cdot \left(1 - \frac{p_2}{p_1} \right)$$

Where:

H_{Abs0} = Absolute humidity in kg/m³ at p_1 before depressurizing (in this case 1.548 kg/m³)

H_{Abs1} = Absolute humidity in kg/m³ after depressurizing down to p_2 and pressurizing back to p_1

H_{AbsCA} = Absolute humidity in kg/m³ of the compressed air at p_1 (in this case 0.00224 kg/m³)

p_1 = Absolute pressure before depressurizing the tank (in this case 2800 mbara)

p_2 = Absolute pressure after depressurizing the tank (in this case 1500 mbara)

p_2/p_1 = The ratio of remaining level of H_{Abs0}

Then:

$$H_{Abs2} = \left(H_{Abs0} \cdot \left(\frac{p_2}{p_1} \right) + H_{AbsCA} \cdot \left(1 - \frac{p_2}{p_1} \right) \right) \cdot \left(\frac{p_2}{p_1} \right) + H_{AbsCA} \left(1 - \frac{p_2}{p_1} \right)$$

Then:

$$H_{Abs2} = H_{Abs0} \cdot \left(\frac{p_2}{p_1} \right)^2 + H_{AbsCA} \cdot \left(1 - \left(\frac{p_2}{p_1} \right)^2 \right)$$

Then:

$$H_{Absn} = H_{Abs0} \cdot \left(\frac{p_2}{p_1} \right)^n + H_{AbsCA} \cdot \left(1 - \left(\frac{p_2}{p_1} \right)^n \right)$$

Where:

n = Number of pulsations in full cycles

H_{Absn} = Absolute humidity in kg/m³ at p_1 after n pulsations

The corresponding graph as seen in Figure 5 illustrates the estimated reduction of the absolute humidity in kg/m³ as a function of the pulse cycles, based on equation number 3.

Quantifying the Energy Removal

As mentioned previously, when steam is replaced by compressed air, a great part of the energy is removed thus making the cooling down of the tank faster. The removal of 1.3 kg/m³ of water vapor in a tank of 4.5 m³ corresponds to 5.85 kg of water vapor. The average temperature according to the graph of the supervising system is approximately 115°C (388.15 K) during the depressurization cycles. As the specific gas constant for water vapor is 461.5 J · kg⁻¹ · K⁻¹ the removal of 5.85 kg of water vapor then corresponds to the removal of 1048 kJ from the tank:

$$461.5\ J \cdot kg^{-1} \cdot K^{-1} \cdot 5.85\ kg \cdot 3.8815\ K = 1048 \cdot 10^3\ J$$

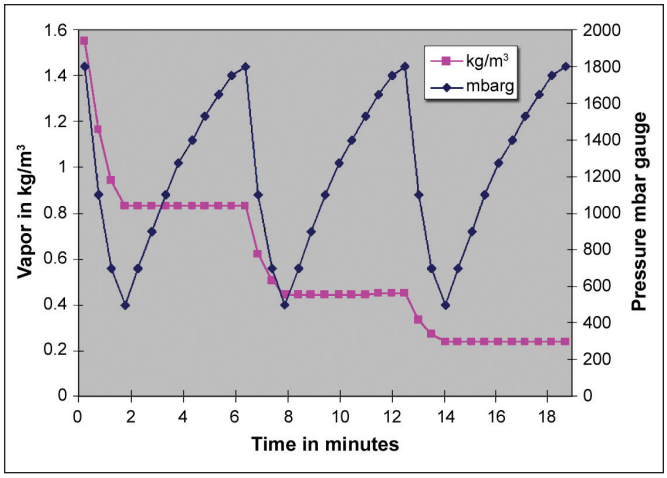

Figure 5. Illustrating the absolute humidity as a function of number of pulses. After the third pulse, the absolute humidity is 0.240 kg/m³ compared to 1.548 kg/m³ at the end of the steaming at 1.8 barg. The time line is taken from the trials with the 5" cartridge thus representing the longest time.

Level of Vacuum after Three Pulse Cycles

After the third depressurization, the tank was pressurized and maintained at 1.8 barg and the double envelope was cooled down with cold water. No clear pressure dip could be seen on the pressure curve thus indicating that the phenomenon of condensation was negligible in comparison to the compressed airflow capacity of the system.

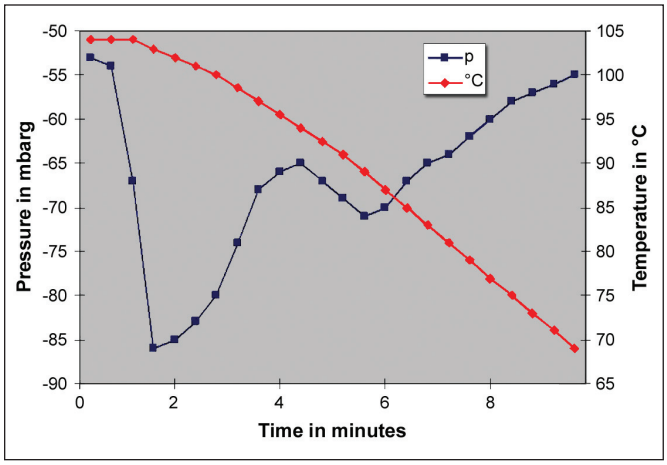

Figure 6. Three pulse cycles with compressed air followed by depressurizing and cooling without pressurization. The filter being used as vent filter is a 5" cartridge. The graph represents the cooling step.

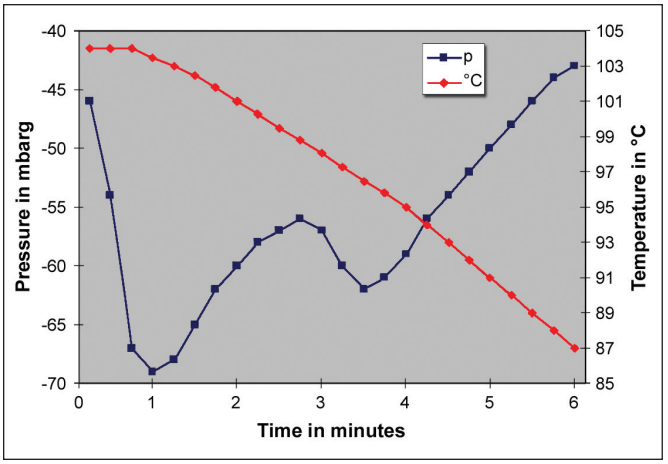

Figure 7. Three pulse cycles with compressed air followed by depressurizing and cooling without pressurization. The filter being used as vent filter is a 10" cartridge. The graph represents the cooling step.

In order to get a better visual on any condensation effect being masked by the compressed air, the same trial was performed, but after the third re-pressurization, the tank was depressurized all the way down to atmospheric pressure. The cooling down was done without pressurizing the tank and the pressure compensation was done spontaneously through the open vent filter. The observed pressure reduction in the tank during cooling was less than 40 mbar as shown in Figure 6 when using a 5" single layer sterilizing grade PTFE membrane filter.

When using a 10" single layer sterilizing grade PTFE membrane filter, the pressure reduction in the tank during cooling was less than 25 mbar as shown in Figure 7.

Discussion and Conclusion

The trials show that cooling cycles after SIP or CIP in general can be greatly optimized to reduce the downtime. Here the cooling cycle was reduced from three hours to only 30 minutes making it possible to perform the cooling during the day and not necessarily over night. On a general basis, the reduced cooling down time would allow increased productivity of the tank and thereby the overall potential production capacity of a manufacturing area. In this particular case, the existing one shift per day would not allow higher productivity. Two or three shifts per day would of course require appropriate downstream capacity to absorb the increased capacity of the tank. The use of disposable storage bags and filters would be an approach for increased downstream capacity.

Even if increased capacity is not the main goal, there are several benefits from the pressure pulse approach after a SIP/CIP:

1. The greatest part of water vapor is eliminated (three pulses reduced from 1.5 kg/m^3 to less than 0.3 kg/m^3) which reduces the vacuum effect when cooling down thus increasing process safety.
2. When eliminating the water vapor, a great part of energy is eliminated at the same time thus making the cooling down of the system faster, requiring less cold water through the double envelope.
3. Smaller vent filter can be used as smaller airflow rates are generated. Multiround housings can be avoided thus allowing the use of single round housings which can be reliably in-line water intrusion integrity tested.
4. The safety is increased for "one shift per day" production areas because the cooling down cycle is made during normal working hours with personnel available in case of an alarm.

Since this cooling approach with reduced cooling time did not require any hardware modification, the implementation could be done without any particular equipment qualification. The major objective was to make sure to avoid any higher differential pressure than 0.5 bar over the membrane during depressurization respecting the official mechanical resistance of the cartridge in terms of back pressure at high temperature.

A properly engineered system must take into consideration the mechanical resistance of the vent cartridge if the pulse approach is implemented so to not jeopardize the integrity of the sterilizing grade membrane.

The top of a tank is usually not double jacketed and therefore only cooled down by the surrounding air and by the heat transfer to surrounding stainless steel giving a much longer cooling down time. If the temperature probe inside the tank that monitors the cooling down is too close to the top, the apparent cooling down time would still be very long even when using the pulse approach as a certain temperature has to be reached for user safety and for process conditions. An additional temperature probe could inform the user about the temperature of the top or a mechanical protection could be used.

More than three pulse cycles would reduce the water vapor content even more and would allow an even smaller vent filter to be used. Nonetheless it should be taken into account that too small a filter surface or filter cartridges with limited flow capacity under humid conditions would require longer time to depressurize the tank thus increasing the process time. During these trials, the time to depressurize the tank from 1.8 barg to 0.5 barg was considered acceptable (2 min 30 sec) when using a 5" single layer sterilizing grade PTFE membrane cartridge (0.375 m^2 membrane surface). No significant pressure drop could be observed in the tank during active cooling cycle and there was no need to further reduce the filter size for economical reasons. Both cartridges used during these trials were integrity tested in order to validate the obtained results.

Keywords

Barg (bar gauge, bar of overpressure)
Bara (bar absolute pressure),
Vacuum, sterilizing grade vent filter
Steaming in place
Absolute humidity
Relative humidity
Differential pressure

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The purpose of this article is to recommend the formation of a standard(s) for extractables studies conducted on single use systems.

Standardization of Single Use Components' Extractable Studies for Industry

by Ekta Mahajan, Trishna Ray-Chaudhuri, and James Dean Vogel

Introduction

The use and implementation of single use technologies continues to grow in the biopharmaceutical industry. One of the key components to qualifying and implementing the use of single use technologies is the extractable and leachable profiles.

The definitions are referenced as follows from the Extractables and Leachables Subcommittee of the Bio-Process Systems Alliance.[1]

Extractables: chemical compounds that migrate from any product-contact material (including elastomeric, plastic, glass, stainless steel, or coating components) when exposed to an appropriate solvent under exaggerated conditions of time and temperature.[1,2]

Leachables: chemical compounds, typically a subset of extractables, that migrate into a drug formulation from any product contact material (including elastomeric, plastic, glass, stainless steel, or coating components) as a result of direct contact under normal process conditions or accelerated storage conditions. These are likely to be found in the final drug product.[2,3]

With the development of new single use technologies, systems and new suppliers, it is becoming more arduous in comparing the initial extractable profiles of similar types of components. There have been discussions and recommendations for bracketing the studies; however, every company and supplier follows a different protocol.

This article will list typical model solvents that are evaluated by end users, possible extraction conditions, and analytical techniques that should be considered in a standard. The identified extractable entities' levels should be analyzed and compared to standard guidelines such as the International Conference on Harmonization (ICH) Guidelines and European Pharmacopeia (EP) Monograms.

Recommendation for Model Solvent Approach

End users have received validation packages that are comprehensive, but differ significantly in protocol testing for the extractable studies. New suppliers are at times confused on what type of extractable studies should be run for their new single use system. Thus, common extractable study conditions that comprises the same sample surface area/volume ratio, storage extraction conditions (temperature, time and test points), model solvents, and the same analytical techniques are needed.

This will provide guidance to single use suppliers in performing a set standard of extractable studies. At the same time, the end-users will be able to compare single use components from various suppliers and

Model Solvent System	Reason
WFI pH 11-12 (0.5N NaOH)	Brackets high pH in up-stream and downstream processes processes
5M NaCl	Brackets salt in up-stream and downstream processes
PBS	Used typically in up-stream and downstream processes.
50% Ethanol	Brackets solvent in the processes in up-stream and downstream processes
WFI pH 2 (0.1M Phosphoric acid)	Brackets low pH in up-stream and downstream processes processes
20% Polysorbate 20	Brackets organic solvents in up-stream and downstream processes
WFI neutral	This is chosen as a control

Table A. List of solvents for extractable study.

The ISPE Disposables Community of Practice would like to suggest that a group of suppliers and critical end-users agree and formalize on a standard for extractable studies… Future developments and implementation of new single use systems in the biopharmaceutical industry will significantly benefit from the development of such a standard.

Model Solvent Solution	Storage Temperature
Time Point 0	25°C
Time Point 48 hours	40°C
Time Point 30 days	40°C
Time Point 4 months (120 days)	40°C

Table B. Temperature for extraction study.

be able to make an informed decision much more easily.

The ISPE Disposables Community of Practice (COP) Engineering Subcommittee has come together as a group of end users to propose the following model solvents, conditions, and the reasons for these choices - *Table A*.

Each type of single use system will need to be grouped by form, fit, and function. For example, bag assemblies as one group, aseptic connectors, components (hose barbs, reducers, quick disconnects, etc.), tubing, filters, and others.[4,5] It is suggested that a specific sample configuration be set for each group based on a set surface area/volume ratio.[6]

Storage conditions are critical to any extractable study. Table B shows suggested extraction conditions. Other storage temperatures may need to be considered depending on the single use system function.

The samples will be stored with the respective model solvents and stored at 40°C for accelerated aging condition. Storing test articles at elevated temperatures for short periods of time is known as accelerated aging and mathematically correlating increased temperature with time (known as the acceleration factor, Q_{10}).[7]

The FDA recommends Q_{10} is 1.8 for each 10°C increase over ambient temperature (25°C), to a maximum of 35°C above ambient. An Accelerated Aging Factor (AAF) calculated as Q_{10} is raised to the power of the storage temperature minus ambient temperature divided by 10, as seen below:

$$Q_{10} = 1.8$$

$$AAF = 1.8^{\left(\frac{T_{incubation} - T_{ambient}}{10}\right)} = 1.8^{\left(\frac{40 - 25}{10}\right)} = 2.415$$

The following analytical techniques should be considered for the standard and their respective tolerances for measurements:[8]

- pH measurements
- Conductivity Measurements
- Total Organic Carbon
- Screening of Metals
- Volatile Organic Compounds (VOC) with direct injection into gas chromatography/mass spectrometry (GC/MS)
- Semi-volatile compound analysis with extraction and GC/MS
- Non-volatile organic Compounds (NVOC) and organic acids by liquid chromatography/ mass spectrometry (LC/MS)
- Screening of Metals

Reporting the results (extracts) found in semi-volatile, volatiles, and non-volatile testing should be in accordance with the guidelines established by ICH[9] or the European Monograms.[10]

Path Forward

The ISPE Disposables Community of Practice would like to suggest that a group of suppliers and critical end-users agree and formalize on a standard for extractable studies. This standard will provide the test protocol, methodology, and data analysis for extractable studies conducted on single use systems. Future developments and implementation of new single use systems in the biopharmaceutical industry will significantly benefit from the development of such a standard.

Provide us your Feedback

The increasing interest in single use technologies has raised new challenges for pharmaceutical and equipment manufacturers. Different types of equipment present different challenges – different contact times, different construction methods, different functions, and equipment manufacturers have some tests to define the extractable and leachable profile for materials, but they are not standard. This article is intended to stimulate discussion and act as a catalyst for the formation of a group to develop standard protocols for these tests. What's your vision of this concept? Tell us by filling out the survey: http://SingleUseComponentsSurvey.questionpro.com.

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International

International GMP Collaboration Expanded[1]

The ongoing collaboration on Good Manufacturing Practice (GMP) inspections of active substance manufacturers between the European Medicines Agency and its international partners is to be expanded to include additional partners, according to new terms of reference.

The World Health Organization (WHO) has already become a new partner in this collaboration, through its Prequalification of Medicines Program. WHO's membership will contribute to its objective of there being safe and effective medicines for all.

The international collaboration initiative allows participants to share information on inspections, including planning, policy, and reports for manufacturers of active pharmaceutical ingredients that are located outside the participating countries. It also allows joint inspections to take place.

Global Drug Industry Tightens Anti-Corruption Code[2]

The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) reported that it had expanded and strengthened the code to ensure "the highest ethical and professional standards." The new IFPMA code extends the rules covering drug company behavior to also include interactions with medical institutions and patient organizations, as well as healthcare professionals, such as prescribing doctors. It also makes clearer the dividing line between promotional aid and items of medical utility which are allowed, and personal and cash gifts, which are not.

European Medicines Agency and European Commission Extend Confidentiality Arrangement with Japan[3]

The European Medicines Agency and the European Commission have extended their confidentiality arrangement with the Japanese medicines regulatory authorities for a year.

The extended arrangements allow the Agency to continue to exchange information on the regulation of human medicines with Japan's Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA) until February 2013.

The original confidentiality arrangement, established in 2007, has been extended after all parties found it to be a useful tool in regulatory cooperation. It allows exchange of:

- advance drafts of legislation and regulatory guidance documents
- scientific advice on medicine development
- assessments of applications for marketing authorizations
- information about the safety of marketed medicines

ICH

ICH E2C(R2) Reaches Step 2 of the ICH Process[4]

The ICH E2C(R2) Guideline on Periodic Benefit-Risk Evaluation Report reached Step 2 of the ICH Process in February 2012 and now enters the consultation period (Step 3).

The purpose of this revised guidance is to ensure that the periodic safety update reports for marketed drugs have the role of being periodic benefit-risk evaluation reports by covering: safety evaluation, evaluation of all relevant available information accessible to Marketing Authorization Holders (MAHs), and benefit-risk evaluation.

This Step 2 document marks the conclusion of the first phase of the E2C(R2) Expert Working Group's mandate. During the consultation period, the group will initiate the second phase of its mandate which is to conduct a gap and potential improvement analysis of ICH E2C, E2E, and E2F Guidelines.

PIC/S

PIC/S Recommendation: Model for Risk-Based Inspection Planning[5]

This PIC/S recommendation sets out a simple and flexible quality risk management tool that may be used by inspectorates when planning the frequency and scope of GMP. It is a methodology that is based upon the concept of rating manufacturing sites on the basis of an estimated risk that they may pose to patients, consumers, animals, and users of medicines. The methodology also takes into account the risk to product quality.

The methodology provides a simple two-page quality risk management worksheet that is designed to be completed by inspectors immediately following an inspection at the site. The worksheet is presented in Appendix 1 which can be found at http://www.picscheme.org/bo/commun/upload/document/pi-037-1-recommendation-on-risk-based-inspection-planning-copy2.pdf to this document and is designed to not require more than several minutes to complete.

Africa/Middle East

Saudi FDA Launches Code of Ethics[6]

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

Asia/Pacific Rim

Australia

Dr. Brian Richards named TGA's Acting Director[7]

Dr. Brian Richards is the Acting National Manager of the Therapeutic Goods Administration (TGA). Dr. Richards has extensive experience in the health sector, both in clinical practice and in health policy development and implementation. Dr. Richards has held a range of senior executive positions in the health portfolio since 1999, and has been responsible for providing policy advice to the Australian Government in the areas of health financing, primary and ambulatory care, e-health, chronic disease management, quality and safety of health care, information management, and health technology assessment.

China

SFDA Issues Work Plan for Electronic Supervision of Drugs[8]

The State Food and Drug Administration (SFDA) recently issued the 2011-2015 Work Plan for Electronic Supervision of Drugs. The plan defines the guidelines, objectives, main tasks, work arrangements, and guarantee measures for the electronic supervision of drugs.

SFDA Issues Work Plan for Nationwide Concentrated Rectification of Drug Production and Distribution[10]

To fight against illegal and criminal activities related to making or selling counterfeit and substandard drugs and regulate drug production and distribution order, the State Food and Drug Administration (SFDA) decided to conduct nationwide concentrated rectification of drug production and distribution, which will take four months from late February to late June 2012. SFDA recently issued the Work Plan for Nationwide Concentrated Rectification of Drug Production and Distribution. The Work Plan specifies the objectives, emphasis, procedures, and requirements of the concentrated rectification.

South Korea[11]

The Korean FDA announced its five main priorities of year 2012 are:

- tightened risk-based preventive measures
- enhancement of public assurance through preemptive response to vulnerable factors
- enhancement of competitiveness of healthcare industries including advanced bio-industry
- building public trust through communication and cooperation
- positive response to future environmental changes in food and drug industry

Vietnam

Vietnam Study Finds Bribes Dominate Medicine Prices[12]

Tuan Anh Nguyen, a researcher at Hanoi University of Pharmacy, broke down the different legal and illegal components that contribute to the cost of drugs in Vietnam, and found 40 to 60 percent of the final price could be spent to induce prescribers to use particular medicines, and to persuade procurement officers inside hospitals to buy them. The biggest share went to doctors.

Europe

European Union

European Medicines Agency Management Board Strengthens Conflicts of Interest Policies and Transparency[13]

Following its implementation in September 2011, the Management Board reviewed the initial experience with the Agency's revised policy on the handling of conflicts of interest for scientific-committee members and experts.

The Board endorsed a proposal from the Executive Director to further strengthen the policy taking into account the last six months' experience. The amendments clarify involvement in academic trials and in publicly funded research/development initiatives, align risk and related restrictions for the different roles in the scientific decision process, and tighten the rules in the case of grants from pharmaceutical industry.

The Board also endorsed proposals for additional measures to further increase the quality assurance, such as the introduction of a "breach of trust" procedure in case of incorrect or incomplete declarations of interests, and the introduction of ex-post cross checks on the correctness of the declared conflicts of interest, and of the risk mitigation measures.

The Board also adopted a revised policy on the handling of conflicts of interests for its members which follows largely the approach taken for the scientific committee members and experts while acknowledging the fundamentally different role of the Board. The new policy outlines specific restrictions when Board members do not take part in discussions and decision making. However, since the Board does not deal with product-specific topics, the type and the nature of restrictions differ from scientific committees. The new policy enters into force immediately.

European Medicines Agency Launches Call for Expression of Interest from Healthcare Professional Organizations[14]

The European Medicines Agency has launched a call for expressions of interest from European healthcare professional organizations interested in becoming involved in the Agency's work. The call follows the endorsement of the framework for interaction with healthcare professionals by the Agency's Management Board in December 2011. This framework sets out the Agency's plans for regular interaction with healthcare professional organizations. Organizations interested in becoming involved should complete the application form and send it to the Agency together with supporting information.

European Medicines Agency Increases Public Information on Conflicts of Interest of Experts and Management[15]

The European Medicines Agency has updated its list of European experts to display each expert's risk level. The Agency assigns a risk level to each expert in its 3500-strong list in line with his or her declared interests in the pharmaceutical industry. The Agency uses this risk level, together with the information in the declaration of interests, to determine each expert's permitted level of involvement in the Agency's activities.

A risk level of 1 indicates no interests in the pharmaceutical industry, level 2 represents indirect interests, and level 3 represents direct interests. Experts with a risk level of 3 have their activities restricted to the greatest extent in their work with the Agency. The risk level is based on the expert's interests within the past five years.

European Medicines Agency Releases Good Pharmacovigilance Practice Modules for Public Consultation[16]

The European Medicines Agency released the first batch of modules on good pharmacovigilance practices (GVP) for public consultation until 18 April 2012. Each of the seven modules released today covers one major process

in the safety monitoring of medicines. These are:

- Module I: Pharmacovigilance systems and their quality systems
- Module II: Pharmacovigilance systems master files
- Module V: Risk management systems
- Module VI: Management and reporting of adverse reactions to medicinal products
- Module VII: Periodic safety update reports
- Module VIII: Post-authorization safety studies
- Module IX: Signal management

Finland

New National Medicines Information Strategy for Finland[17]

For the first time, a national Medicines Information Strategy has been drawn up for Finland. The strategy brings together representatives of the healthcare and pharmaceuticals sectors. The strategy aims to safeguard efficient, safe, and economic medical treatment for citizens. The new strategy published by the Finnish Medicines Agency Fimea comprehensively describes the current situation regarding medicines information activities, the best practices of different parties, and the shortcomings and challenges of medicines information activities. The strategy was drawn up in cooperation with various parties within the healthcare and pharmaceuticals sectors.

The main objective of the strategy is to increase the amount of evidence-based, objective, and reliable information for the general population and healthcare professionals. The right information helps support the safe medical treatment of patients, and from the perspective of citizens, medicines information also can be considered a right that should be included as an essential part of providing medical treatments.

Netherlands

Dutch Medicines Evaluation Board Moves to Utrecht[18]

The Medicines Evaluation Board (MEB) has moved to Utrecht. As of 29 February 2012, MEB has a new address. The new visiting address is:

Graadt van Roggenweg 500
3531 AH Utrecht
The Netherlands
General telephone number: +31(0)88 2248000
General fax number: +31(0)88 2248001

The new postal address is:
P.O. Box 8275
3503 RG Utrecht
The Netherlands

United Kingdom

British MHRA's Red Tape Challenge – Medicines Regulations in the Spotlight[19]

The Medicines and Healthcare products Regulatory Agency (MHRA) is asking for views on the regulations that govern its work. For the next five weeks, through the Cabinet Office Red Tape Challenge website, the MHRA is inviting the public and businesses to suggest which existing regulations should be kept and which should be simplified or scrapped altogether. The Government's Red Tape Challenge aims to cut unnecessary and over burdensome regulations. Good regulation plays a vital role in protecting the public and employees. However, the Red Tape Challenge asks whether existing regulations are really providing the protection that is intended or are they unnecessary or overcomplicated and need to be improved or go altogether. Even where regulations are EU derived, as many of these regulations are, there may still be scope to improve implementation and enable greater efficiency.

Britain's MHRA Publishes 2011 Annual Report[20]

The MHRA published a sixth annual report "Delivering high standards in medicines advertising regulation." This covers the year 2011. It provides details of the activities of the Advertising Standards Unit, including vetting of advertising and complaints investigated and the development of guidance with self regulatory bodies to promote high standards.

European Medicines Agency Focuses on New Legislation[21]

This year, the European Medicines Agency's activities will concentrate on the implementation of the pharmacovigilance legislation and preparations for the new legislation on falsified medicines, according to the work program 2012, published last week.

The document, adopted by the Agency's Management Board at its meeting on 15 December 2011, forecasts a stable number of applications for marketing authorization for human and veterinary medicines in 2012.

It states that the Agency will continue to review its activities and processes so that it can identify areas where efficiency gains, re-allocation of resources, and reprioritization of activities may be possible. This should put the Agency in a position to manage its increased responsibilities with existing resources. In line with the road map implementation plan, the Agency will strengthen the quality and the regulatory and scientific consistency of its assessment process and its outputs where needed. The Agency also will increase its levels of transparency, advance its initiatives in the area of communication and interaction with stakeholders, deliver on public-health needs, support the availability of veterinary medicines, and support the review of veterinary legislation.

North/South America

United States

FDA Considers Expanding Definition of Nonprescription Drugs[22]

Getting medicines into the hands of consumers has become troublesome over the last few years. Research shows that for a variety of reasons, 20 percent of patients with prescriptions do not get them filled. In addition, the time or cost required visiting a doctor to receive a prescription or refill often stops patients. The Food and Drug Administration thinks that some of these doctor visits can be eliminated. It is exploring ways to make drugs for common conditions available as nonprescription products. Under this paradigm, the Agency would approve drugs – that would otherwise require a prescription – for Over-The-Counter (OTC) distribution, if certain conditions are followed.

The Agency is seeking input from consumers, pharmacists, members of the health care community, regulated industry, and insurers on the feasibility of this initiative, and what types of evidence would be needed to demonstrate that certain drugs could be used safely and effectively in an OTC setting.

FDA Amends Labeling Requirements in Drug GMP Regulation[23]

FDA amended the packaging and labeling control provisions of the current Good Manufacturing Practice (CGMP) regulations for human and veterinary drug products by limiting the application of special control procedures for the use of cut labeling to immediate container labels, individual unit cartons, or multiunit cartons containing immediate containers that are not packaged in individual unit cartons. FDA is also permitting the use of any automated technique, including differentiation by labeling size and shape, that physically prevents incorrect labeling from being processed by labeling and packaging equipment when cut labeling is used. This action is intended to protect consumers from labeling errors more likely to cause adverse health consequences, while eliminating the regulatory burden of applying the rule to labeling unlikely to reach or adversely affect consumers. This action is also intended to permit manufacturers to use a broader range of error prevention and labeling control techniques than permitted by current CGMPs.

FDA Issues Guidance on Direct to Consumer Television Ads[24]

This guidance is intended to assist sponsors of human prescription drugs, including biological drug products approved under section 351 of the Public Health Service Act, by describing how FDA plans to implement the requirement for the pre-dissemination review of direct-to-consumer television advertisements (TV ads) according to section 503B of the Federal Food, Drug, and Cosmetic Act (the FD&C Act). The guidance describes the types of TV ads that FDA intends to be subject to this provision, explains how FDA will notify sponsors that an ad is subject to the requirement of review under section 503B, and describes the general and Center-specific procedures sponsors should follow to submit their TV ads to FDA for pre-dissemination review in compliance with section 503B of the FD&C Act. The guidance can be found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM295554.pdf.

US Could Bring More Common Drugs Over the Counter[25]

Prescription drugs to treat some of the most common chronic diseases, such as high cholesterol and diabetes, may become available over the counter under a plan being considered by U.S. regulators. In what would be a major shift in policy if finalized, the Food and Drug Administration is seeking public comment on a way to make these medications more readily available.

Keeping the Focus on Scientific Integrity[26]

Dr. Jesse Goodman, Chief Scientist at FDA, discussed the efforts the Agency is making to enhance scientific integrity in a blog post. He detailed the following key principles:

- maintaining a firm commitment to science-based, data-driven decision-making
- shielding the Agency's science and its scientific staff from political influence
- facilitating the free flow of scientific and technical information;
- protecting the integrity of scientific data and ensuring its accurate presentation, including the underlying assumptions and uncertainties
- requiring a fair and transparent approach to resolving internal scientific disputes, including hearing and carefully considering differing views
- supporting whistleblower protections
- selecting and promoting scientists based on their knowledge, expertise, and integrity
- utilizing peer review of data and research used in decision-making, where feasible, appropriate and consistent with the law
- maintaining openness and selecting qualified advisory committee members based on expertise with transparency about conflicts of interest
- allowing FDA staff to communicate their personal scientific or policy views to the public, even when those views differ from official Agency opinions
- promoting the professional development of our scientists by encouraging publication in and editorial service to peer reviewed journals, presentations at professional meetings, and full participation in appropriate professional or scholarly societies and related activities that may benefit the public health

US Biologics Center Annual Report: Innovative Technology Advancing Public Health[27]

Some important efforts that are detailed in the report include a continued and sustained response to the H1N1 influenza pandemic as well as preparedness steps for potential future pandemics, intensive efforts to facilitate the development of medical countermeasures to combat bioterrorism and emerging infectious diseases, an increasingly robust international program rooted in international collaboration, and the successful initial implementation of a quality systems approach to CBER laboratories. CBER continued to perform its day-in, day-out workload of product reviews, risk assessments, compliance activities, and much more that assures the availability of safe and effective biological products to the American public.

FDA Sets Draft Rules for Biotech Drug Copies[28]

The Food and Drug Administration's long-awaited guidelines for the sale of lower-cost versions of biotechnology drugs leave open the possibility that some products might not need to be tested in humans.

FDA Office of Generic Drugs Releases Example of QbD for ANDAs[29]

This pharmaceutical development re-

port summarizes the development of Example Modified Release (MR) Tablets, 10 mg, a generic version of the Reference Listed Drug (RLD), Brand MR Tablets, 10 mg, indicated for therapeutic relief. FDA used a Quality by Design (QbD) approach to develop a tablet formulation and manufacturing process that ensures the quality, safety and efficacy of Example MR Tablets. The report can be found at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM286595.pdf.

FDA Commissioner Reflects on the History and Importance of Regulation in Blog Post[30]

On the 50 year anniversary of the Thalidomide incident, Dr. Margaret Hamburg wrote a blog entry reflecting on the importance of regulation. She stated: "Smart, science-based regulation instills consumer confidence in products and treatments. It levels the playing field for businesses. It decreases the threat of litigation. It prevents recalls that threaten industry reputation and consumer trust, not to mention levying huge preventable costs on individual companies and entire industries. And it spurs industry to excellence."

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In the Aftermath of the Earthquake

Lessons Learned in Disaster Recovery and Business Continuity

by the ISPE Japan Affiliate

The winter meeting of the ISPE Japan Affiliate was held 2 December 2011 at the Kyoto International Community House. The meeting theme was "Responsibility of Pharmaceutical Supply, Mastering Challenges – Lessons Learned from the Disaster." The event began with opening remarks by Tatsuo Miyagawa, Chairman of the Board, ISPE Japan Affiliate, followed by three general sessions and two special speeches. The event was attended by approximately 100 Affiliate members.

The objectives of the meeting were primarily to gain knowledge from pharmaceutical manufacturers and facility providers of the measures and actions taken to recover from the Great East Japan Earthquake that hit on 11 March 2011 followed by the significant incident at the Fukushima Daiichi Nuclear Power Plant, and to learn the systems and precautions we should take in the future to better prepare for potential disasters of this level. Additionally, special speeches were delivered on the CPIP certification and Japanese clinical testing environment. Reported here are the three sessions related to disaster recovery and business continuity.

"Recovery from the Disaster – Actions taken for Stabilizing Supply as a CMO"

by Toshiya Kai, President, Tohoku Nipro Co.

Toshiya Kai described the actions Tohoku Nipro took after the earthquake and how it resumed its supply in six months Tohoku Nipro is located approximately 200 km from the seismic center and was seriously damaged by the earthquake.

Kai indicated that damages spread to almost all areas of operations including utility, warehouse, quality control lab, formulation, and packaging areas. It was noted that the initial quake was followed by strong aftershocks, and above all, the Nuclear Plant accident. As a pharmaceutical supplier, Tohoku Nipro had to identify measures to maintain the pharmaceutical supply until their operations fully recovered. Kai described in detail how Nipro secured the supply by moving the products and people around within Nipro group plants and customers, while repairing the buildings and facilities. He especially stressed that a key success factor was ordering the analytical equipment immediately after the quake, which helped resume the in-house lab capabilities in a very short time. This made the method transfer unnecessary and accelerated the relocation of production. The highly engaged employees with a strong commitment to maintain the supply, collaboration within Nipro group, and proactive mental care to people enabled the prompt relocation of employees. Kai also explained that not only was the plant restored to the original state, but it was enhanced for better seismic protection.

"Utilize the lessons learned from this disaster and advance toward stable supply of medicines," said Kai.

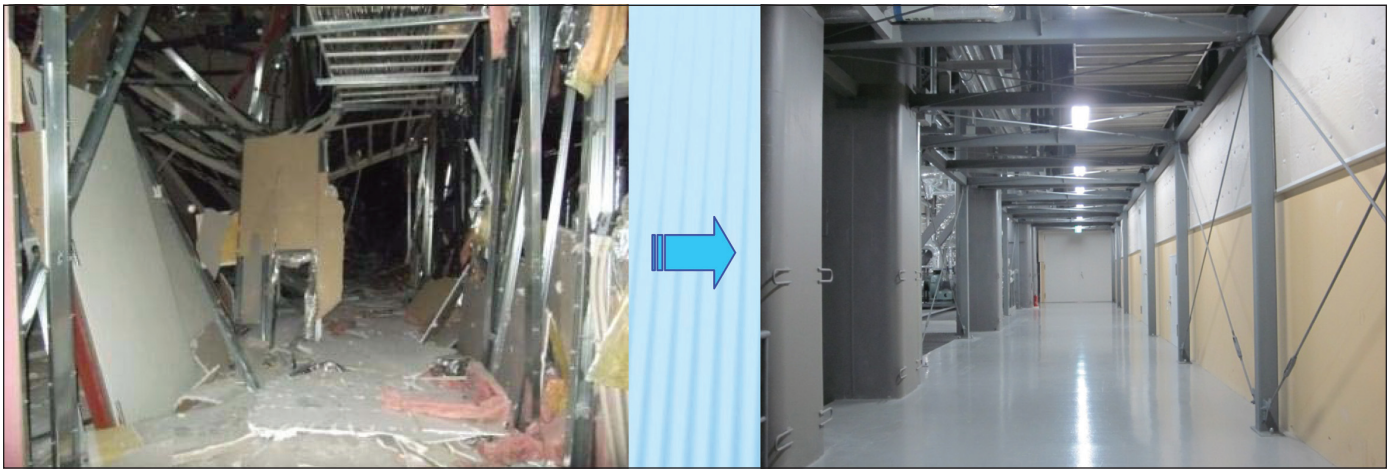
What made Tohoku Nipro resume operations in six months was, interestingly, declaring at an early stage that it would resume in six months. In the future, Tohoku Nipro will work toward establishing the coalition and back-up systems within the group by the commoditization of technologies and a mutual support system with vendors and suppliers utilizing an emergency contact system.

"Stand Against the Quake – Building Construction Technologies Supporting Earthquake Safety"

by Katsuto Ohata, Takenaka Corporation

Katsuto Ohata presented the proposal of assuring earthquake safety and its engineering solutions to realize the "Competitive Plant with Safety and Reliability."

"In Japan, which is the land of earthquakes, it is the highest priority to secure the earthquake safety of the construc-



Nipro machine room earthquake damage and recovery six months later.

Concludes on page 2.

In the Aftermath of the Earthquake

Continued.

tion that is the basis of social life in order to protect life and property," Said Ohata.

It was strongly emphasized that securing the safety of the employees and business continuity is the social mission of pharmaceutical companies, which have critical responsibility for maintaining and promoting people's health. The Great East Japan Earthquake resulted in huge losses of human lives mainly by the Tsunami. On the other hand, there were not many cases of building collapses directly caused by the quake. However, a number of manufacturing plants experienced extensive damages on manufacturing equipment and internal finishes, including walls and ceiling boards. In addition, the impact was expanded through the supply chain from the material and component suppliers and some pharmaceutical companies had to discontinue operations thus halting the business for a long time. With such background, it was indicated that a high level of true safety of the construction is required to ensure the safety of the facilities and equipment as well as human lives. Ohata compared three types of structural solutions against an earthquake, namely earthquake resistant structure, seismic isolation structure, and jolt-suppression structure, and concluded that seismic isolation is one of the most effective solutions available today to minimize the damage of medical and pharmaceutical facilities and properties as well as the building structure. He also explained the principles and merits of anti-seismic structure, typical project flow, methods for effectiveness verification, and the recent trend of anti-seismic construction.

"Actions Taken, Case of Foreign Based Pharmaceutical Company – Supply Chain and Radiation Measurement"

by Hirohito Katayama, Head of Product Supply Japan and Shiga Plant Manager, Bayer

Hirohito Katayama presented the activities for securing the supply chain and establishment of a radiation measurement scheme.

"As a global company, we have experienced changes through dynamic change-posture and diversity, which was well utilized in the flexible adaption to the environmental change this time," said Katayama.

The Great East Japan Earthquake was a fundamental testing event of preparation against an unanticipated, unprecedented situation. The systematic approach of a foreign-based pharmaceutical company was presented addressing the unclear and urgent challenges happening all at once by organizing information, prioritization, and resolution with limited resources. Immediately after the earthquake, the crisis management task force was launched, said Katayama.

First of all, the task force conducted the assessment of the impact including mechanical damages, power supplies, radiation, inventory of life saving drugs, and the supply situation of raw materials and packaging components. Then the task force implemented various countermeasures, namely, organizing a global level emergency team; coping with the domestic chaos; keeping the global team updated with the latest situation; and establishing the radiation testing capability for raw materials and products including those destined to overseas. All these were completed under a situation where multiple conflicting pieces of information on the nuclear power plant were confusing people. Katayama also explained the details of radiation control and the measurement results of packaging components and raw materials at the Shiga plant (all negative).

"…securing the safety of the employees and business continuity is the social mission of pharmaceutical companies, which have critical responsibility for maintaining and promoting people's health."

Katayama concluded with the following points:

- Distinct preparation (organization) and teamwork (information sharing) were the fundamentals of crisis response.
- Unexpected events will happen. Establish the rules for emergency organization and the information network. If you clearly define the emergency team organization and appropriately control the information, on-site teamwork will solve the problems.
- Brushing up the Japanese virtue of mutual cooperation will result in an organization very well prepared for crises.

In conclusion, the ISPE Japan Affiliate would like to thank the ISPE community for all the encouragement and support provided from around the globe. We also would like to report that the Japanese pharmaceutical industry has mostly recovered from the disaster and started moving forward. We would appreciate your continued support, and if there is any opportunity we would be happy to provide support back to anyone.

Thank you again.

Implementation of FDA's 2011 Process Validation Guidance for Industry

Report on the FDA's Presentation at ISPE Tampa Conference

by Dr. Kate McCormick

At the recent ISPE conference in Tampa on Lessons from 483s, FDA's Grace McNally spoke at the Process Validation (PV) track on 27 February 2012. Since the overview of PV had previously been given by Joanne Barrick from Lilly, McNally told delegates she would concentrate on three specific aspects: legacy products; commercial distribution; and warning letters relating to finalized revised process validation guidance issued in January 2011. However, she started by emphasizing that much of what she was going to address is not new. The 1987 PV guidance was a good start and agrees pretty well with the document, published last year. In particular, the use of objective measures and statistical tools is not new; it is just getting more attention. This is not an increased regulatory requirement; it's covered in the CGMP regulations. She also stated that PV guidance tracks well with both the ICH quality documents (ICH Q8, Q9, and Q10) and the CDER CGMPs for the 21st Century and QbD initiatives. It relates to risk management; even if the words are not found in CFR 210 and 211. Words such as "appropriate" or "suitable" imply assessment of risk.

For legacy products, McNally advised companies to take advantage of knowledge gained in their original validation. Concerns that the regulators would judge the original material to be out of date or inadequate are understandable, but not necessary. The quality of product being made now and in the future is what is relevant; what was made years ago is not (although evidence of lack of control should be of concern). If legacy process development is reviewed by regulators, it's from the point of view of understanding what's happening now. Regulators will rarely go straight to development work unless there is a concern.

McNally went on to tell delegates that the expectation for assurance in the manufacturing process prior to commercial distribution is not a new requirement; there was a similar requirement in the 1987 guidance. It is important to offer reasonable consumer/patient protection (which is more difficult to tell with pharmaceuticals than, e.g., with crisps) and the FDA believes that a manufacturer cannot experiment on the general public. There is no prescribed number of commercial scale batches process performance qualification. It's necessary to use risk assessment (including networking within the industry). A statistical basis for studies is implied although not stated or mandated. However, this is not a common non-compliance observed by the FDA so far.

Delegates heard that from the FDA's point of view, a company that understands its processes and can present them for review is preferable to a company that asks what they should do. Choices should make sense and companies should have the right people available at inspections to hold discussions and justify the approach taken. At the same time, the FDA has undertaken to train the investigators in PV.

In discussing requirements related to process control, variability, and performance of finished pharmaceuticals, McNally again referred to the requirements not being new. They are part of the regulation (not guidance) which goes back 40 years. In order to work with "previous acceptable process average and process variability estimates," it is necessary to know what "good" and "normal" look like. GMP should not just be about measuring problems, but measuring what's right. It's necessary to measure normal variability in order to recognize special variability.

Moving on to talk about some typical warning letters, McNally reminded companies that while it is commendable to be pursuing the more complex aspects of PV, they should not ignore the obvious "low-hanging fruit." Some common issues observed by investigators included: misunderstandings of AQL; failure to satisfy the long-standing expectation that implications of all changes must or should be assessed prospectively; conclusions drawn by the company on process capability not in line with submissions to the agency; lack of understanding of sampling plans; and failure to fix root causes.

McNally concluded by emphasizing that both industry and the agency need to build up their statistical knowledge. She then agreed to take questions from the delegates.

Q Are Annual Reports sufficient for Stage 3?

A It depends on how the system is set up. "At least annually" is required. It's necessary to ask why a particular frequency was chosen. If it's a new process or product or a major change, then one year is too long.

Q Is there an expectation that the clinical data defines the range of parameters going into Stage 2, or can statistical analysis be used to widen parameters?

A Yes, it is possible to use data to drive decision-making although this is not an absolute. With a new scale, it is entirely possible that change in variation will occur and a new range will be appropriate.

Concludes on page 4.

FDA's PV Guidance...

Continued from page 3.

Q If the process doesn't change on scale-up, is it okay to use some clinical data for later stages of PV?

A Yes.

Q Is there an expectation by FDA of a minimum confidence level?

A There is no number specified due to the wide variation in products, but if a lower than normal value is used, this needs to be justified.

Q Does PV cover cleaning validation?

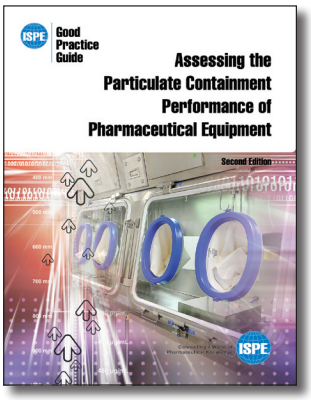
A It is not applicable to cleaning validation or anything else that has specific guidance already; however, it can be used if appropriate.

Booklet Labels Paper Available Online

A concept paper by the Investigational Products Community of Practice (IP COP) Booklet Label Task Team reflects on the results of a study site survey, draws conclusions from an assessment on comparison of Booklet Labels versus Single Panel Labels performed, discusses benefits of a Good Practice Guide, and defines the need for training on the proper use of booklet labels.

The paper is available to ISPE Members on the IP COP site, under the tab "Resources."

ISPE Revises Guide on Containment Performance



The ISPE Good Practice Guide: Assessing the Particulate Containment Performance of Pharmaceutical Equipment (Second Edition) is now available. The Guide provides technical guidance and consistent methodologies for evaluating the containment capability of systems and equipment in the pharmaceutical and biotechnology industries under defined conditions. The Guide was revised to address a broader selection of containment technologies and processing equipment than those covered in the first edition.

The Guide aims to define current good practices in this area, providing information to allow organizations to benchmark their practices and improve on them. Specifically, the Guide provides a methodology to derive data associated with handling of pharmaceutical ingredients that is useful in the assessment of potential risks, such as:

1. the potential exposure of the operator
2. the potential for uncontrolled release of pharmaceutical ingredients within the facility
3. the potential exposure of the outdoor environment

The Guide is available for purchase from ISPE at www.ispe.org/ISPE-Good-Practice-Guides/Assessing-Particulate-Containment-Performance.

PAT COP Concept Paper

The Data Management Task Team of the Process Analytical Technology Community of Practice (PAT COP) has published the Concept Paper, "Implementing Knowledge Management in Bioprocesses: A QbD Driven Approach Turning Data into Knowledge in Reference to the CMC A-Mab Case Study." The paper discusses information and knowledge management implementation in a QbD environment based on the CMC A-Mab Case Study. The aim of the paper is to analyze gaps in state-of-the-art QbD strategies for data and knowledge management, suggest solutions, and demonstrate potential benefits for improved quality and economy.

The paper is intended to emphasize that a sophisticated information management concept is a key requirement in enabling the establishment of knowledge management in QbD. Based on the CMC A-Mab Case Study (which should be read in conjunction with the Concept Paper and can be found at http://www.ispe.org/index.php/ci_id/33766/la_id/1.htm), an interdisciplinary team of representatives from the pharmaceutical industry, suppliers, academia, and consultants analyzed individual activities from the product discovery phase through process understanding to manufacturing. The data acquired in each individual activity were analyzed for gaps of current data management concepts, and concepts and methods which support the translation of data into information and knowledge. The results of their analysis demonstrated the urgent need to generate data in a structured format as early as possible to increase the business benefits from implementation of PAT and QbD projects.

The Concept Paper is available to ISPE Members at http://www.ispe.org/patcop/resources. To comment on the paper, visit the Community Discussions section of the PAT COP website at http://www.ispe.org/patcop.

ISPE Releases First-Ever Industry Resource for Comparator Processes

ISPE released in March 2012 the ISPE Good Practice Guide: Comparator Management. The pharmaceutical industry's first-ever resource for comparator processes, the Guide provides the industry with a complete picture of the steps to be followed to execute a clinical study that includes comparators. It also gives advice on how to make the right purchasing decisions in selecting/acquiring comparators and avoid costly delays in comparator trials.

Comparative effectiveness research is designed to inform healthcare decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options, according to the US Agency for Healthcare Research and Quality. The evidence is generated from research studies that compare drugs, medical devices, tests, surgeries, or ways to deliver healthcare.

"With the industry's increased focus on proving drug effectiveness when compared to other, similar pharmaceuticals, comparator management is becoming increasingly important," said Mark Ware, one of the Guide's authors. "There are so many factors to consider when sourcing or preparing a comparator product for use in a clinical trial, and a mistake in the process could cost companies literally millions of dollars. Clearly, the pharmaceutical industry has an urgent need for a document like this one, and ISPE was the perfect forum for pulling together the industry expertise needed to create it."

The ISPE Good Practice Guide: Comparator Management is a central reference source that establishes strategic and tactical considerations when sourcing and procuring comparators for use in a clinical trial. It aims to identify and develop industry good practices for: making sourcing decisions, technical considerations for blinding, and release of a comparator for use. One of the main benefits of the Guide is that it provides a unique overview of the management of a sponsor's comparator needs. These strategies can potentially save sponsoring companies and research teams significant time and money.

The Guide is available for purchase from ISPE at www.ispe.org/ISPE-Good-Practice-Guides/Comparator-Management.

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