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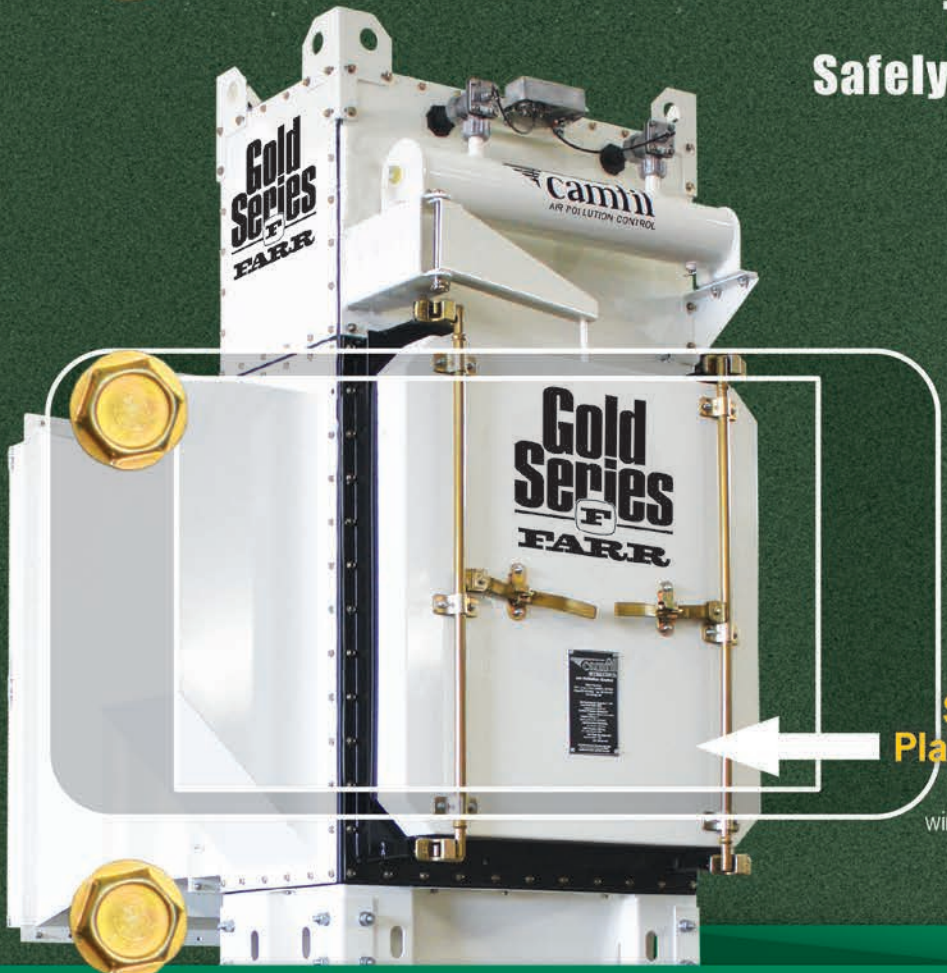


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Quality, how we define it, measure it and ensure its presence is at the heart of the conversation this month as *Pharmaceutical Engineering* looks at how risk management relates to the development of products and the facilities in which we manufacture them.

We look at quality metrics from the perspective of patient trust, page 9. Process capability can help ensure product quality, pages 35-43. You can implement Quality by Design across multiple regulatory applications, pages 44-53. HEPA filters bring home the clean in quality, pages 54-59. A compliance model for computer data integrity, pages 79-87.

PHARMACEUTICAL ENGINEERING®

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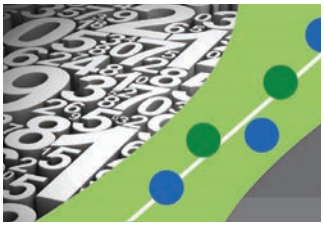

PV Statistician Forum
Use of Statistics in Support of the Lifecycle Approach to PV
14–15 April
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Silver Spring, MD

ISPE Quality Metrics Summit
Driving Quality Through Data and Knowledge
21–22 April
Sheraton Inner Harbor Hotel
Baltimore, MD

2015 ISPE/PQRI Quality Manufacturing Conference
1–3 June
Mayflower Renaissance
Washington, DC

Pharma Expo
28–30 September
Las Vegas Convention Center
Las Vegas, NV

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Process Validation Conference
6–7 October
Double Tree
Silver Spring, MD

ISPE Annual Meeting
8–11 November
Philadelphia Marriott Downtown
Philadelphia, PA

EUROPE

ISPE Europe Annual Conference
Driving Effectiveness in Pharmaceutical Operations with Integrated Quality
4–6 May
Frankfurt, Germany

ASIA

ISPE China Annual Spring Conference
Quality — The Cornerstone of Power Toward Pharmacy
20–21 April
Beijing, China

ISPE China Annual Fall Conference
October
Beijing, China

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ISPE Training Courses

18–21 May
St Louis, MO

- Pharmaceutical Water Generation (T04)
- Auditing (G07)
- Science and Risk-based C&Q (T40)
- Cleaning Validation (T17)
- GxP Process Control Systems: GAMP® 5 (T21)
- Facility Project Management (T26)*
- Storage Delivery and Qualification of Pharmaceutical Waters (T23)

4–6 May
Brussels, Belgium

- Verification of Facilities, Systems and Equipment Workshop (T48)
- Cleaning Validation (T17)
- Basic GAMP® 5, Annex 11 and Part 11 Update (T45)
- Facility Project Management (T26)*
- Practical Implementation of Process Validation (T46)
- Pharmaceutical Water Systems (T35)

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28–30 September
Barcelona, Spain

- Biopharmaceutical Manufacturing Facilities (T31)
- Science and Risk-based C&Q (T40)
- GxP Process Control Systems: GAMP® 5 (T21)
- HVAC (T14)
- Sterile Product Manufacturing (T12)
- Practical Application of Technology Transfer (T19)

19–23 October
Boston, MA

- Pharmaceutical Water Generation (T04)
- Biopharmaceutical Manufacturing Processes (T24)
- Cleaning Validation (T17) – Updated
- Verification of Facilities, Systems and Equipment Workshop (T48)
- Biopharmaceutical Manufacturing Facilities (T31)
- HVAC (T14)
- Practical Implementation of Process Validation (T46) – New
- Storage Delivery and Qualification of Pharmaceutical Waters (T23)

19–20 October
Raleigh, NC

- Process Validation in Biotechnology Manufacturing (T32)

14–16 September
Philadelphia, PA

- Basic GAMP® 5, Annex 11 and Part 11 Update (T45)

9–10 November
Philadelphia, PA

- Turning QbD into a Practical Reality (T43)
- Managing the Risk of Cross Contamination (T41)

7–10 December
Tampa, FL

- Q7A (T30)
- Cleaning Validation (T17) – Updated
- Oral Solid Dosage (T10) – Updated
- HVAC (T14)
- Facility Project Management (T26)*
- Quality Risk Management (T42)
- Sterile Product Manufacturing (T12)

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A VOICE OF OUR OWN

DRUG SHORTAGES AND THE QUALITY DEBATE

ISPE's Drug Shortage Prevention Initiative Enters Third Phase

By Carol Winfield, Director, Regulatory Operations and John Berridge, ISPE Strategy Advisor

With the publication of its groundbreaking Drug Shortage Prevention Plan (Plan), the ISPE's initiative is now entering its third phase – implementation. Unique for its data driven, systems approach, the Plan is ISPE's second key contribution since 2013 to ensure the quality and reliability of the drug supply.

The Plan represents a collective effort by pharmaceutical and biopharmaceutical industry experts. It has been reviewed by regulators from the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), and by national competent authorities including the Spanish Agency of Medicines and Medical Devices (AEMPS) and the Medicines and Healthcare Products Regulatory Agency (MHRA). In fact, the Plan is a roadmap designed to help the pharmaceutical industry avoid drug shortages and maintain a robust and reliable supply of medications to patients around the world.

The Plan is based on the 2013 Drug Shortages Survey, which examined the underlying technical, manufacturing, quality and compliance issues associated with a company's supply chain and provided a unique insight into the root causes of supply disruptions.

The key findings include:

- **Issues within the quality systems of manufacturing can lead to drug shortages.** Quality issues were cited as the single most important factor leading to drug shortages. Quality issues leading to drug shortages or near misses were present during technology transfer in a small but significant number of cases.
- **Companies that have successfully avoided shortages focus on strong quality systems, and the involvement of company leadership is notable in these cases.** Specific organizational goals to prevent shortages differentiated the companies who successfully avoided a shortage from those that did not.
- **Improved regulatory interaction can mitigate the likelihood of a shortage.** A significant number of respondents indicated that issues related to Health Authority inspections and approval processes also played an important role in shortages. Respondents from companies that avoided shortages also cited the importance of fostering communication links with the regulators.

Drawing on the survey, with valuable input from industry leaders and regulators in Europe and America, ISPE then developed a holistic, systems-based approach to address the survey findings. The Plan is globally applicable, addresses the end-to-end supply chain, and is aligned with regulatory expectations. It is organized around a framework of six dimensions, exploring them both individually and also how they interact with each other to impact shortages.

The six dimensions, pictured below, provide a structure for how companies, and regulators, may consider their plans for ensuring robust and resilient supply chains.

Given the common goal of ISPE with industry and regulating agencies to prevent drug shortages the Plan has been made freely available at http://www.ispe.org/drugshortagespreventionplan.pdf.

In this third phase, ISPE will continue to act as a global facilitator to proactively prevent drug shortages. We want industry to understand how to communicate with regulators and how to build greater capability in the areas critical to the development and management of resilient supply chains. Through its community of experts, ISPE will identify and build the tools needed by industry to implement the recommendations in the plan, including conference sessions, recommendation-specific tools, training courses, guidance documents, and other publications.

Drug shortages threaten the health and lives of people around the world. While both industry and regulators have already worked to alleviate drug shortages, a more robust initiative is required to truly address the root causes of drug shortages and to adopt a proactive approach to preventing them. ISPE is uniquely positioned to take on this issue, being able to draw on a large body of technical knowledge as well as long standing relationships with both industry and regulators, to develop innovative strategies for this initiative.

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GUEST EDITORIAL

METRICS THAT GIVE VOICE TO QUALITY

Joseph Famulare
Vice President, Global Quality Compliance and External Collaboration
Genentech/Roche, Pharma Technical Operations
Vice Chair, ISPE Board

When patients take their medicine, they trust it will be safe, effective and pure: that is the covenant that exists between patients, the pharmaceutical industry and regulatory bodies. What ISPE is doing through its Quality Metrics Pilot Program (QMPP) is collecting data to help the FDA make sure that covenant remains intact.

> ISPE is unique in having driven a data-based approach to effectively understand quality metrics.

On 9 July 2012, President Obama signed FDASIA into law, reauthorizing user fee programs for innovator drugs and medical devices and establishing two new user fee programs for generic drugs and biosimilar biological products. The law also gave FDA new authority to better protect the drug supply chain, which is critical in an increasingly global marketplace. In addition, FDASIA provided the Agency with new authorities to combat drug shortages and stimulate antibacterial drug development..., included provisions intended to encourage drug innovation, made a number of important changes to medical device regulation, and added a number of other important provisions.

When Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER), first introduced the concept of quality metrics in 2013, FDA was open in obtaining feedback how this best be done and provide the desired outcomes. ISPE, through its volunteers, has been responding and is now preparing to reveal the results and initial findings of a first wave of data collected across 44 sites and 18 companies. We are now ready to provide real-world experience with metrics definitions, data collection and reporting burden for the benefit of industry and regulators.

ISPE is in a unique position in that it uses data-driven approaches to understand and move forward on its strength of science technology, engineering, manufacturing and regulatory expertise of its membership.

The ISPE QMPP will bring in metrics—metrics that everyone in the pharmaceutical industry needs to come to understand—that can guage quality at a particular site and the products therein. The results of our collective effort will change how the pharmaceutical industry will be regulated going forward.

FDASIA really got this ball rolling, by making it possible for the FDA to gain information prior to inspections. FDA as a regulator serves as the patient's surrogate for quality. Properly applied and understood, quality metrics will enhance industry and FDA's understanding.

As an industry, the thinking needs to expand from meeting compliance to prioritizing quality. Quality metrics will help quality differentiation for patients and payers alike. If we succeed, and I believe we shall, the change will be transformational across our industry and within the FDA.

It is imperative to continually improve and innovate on the quality front in our manufacturing facilities.

But first, let's meet in Baltimore, MD from 21 to 22 April, along with industry and FDA colleagues at the Quality Metrics Summit. We'll discuss the QMPP findings and respond based on your input, your concerns and your ideas. And then we'll see how we want to tackle the second wave of QMPP.

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CONFERENCE ATTRACTS 250 ENTHUSIASTIC PARTICIPANTS FROM ACROSS INDUSTRY

The 24th Annual Aseptic Processing Technology Conference, themed "Cost Saving Solutions to Solve Quality Concerns," was held in Baltimore, Maryland on 23-24 February 2015.

The conference was divided into two tracks, "Aseptic Processing" and "Barrier Isolation and RABS". Attendees chose sessions and presentations from either track, yet came together for two breakfast sessions and two keynote addresses each day, as well as attending networking breaks and industry exhibits. Peter T. Bigelow, President, xCell Strategic Consulting and member of the ISPE Drug Shortage Taskforce at Monday's 7 a.m. breakfast session provided an overview of ISPE's efforts to prevent drug shortages and focused on aseptic techniques that would help in the effort. In Monday's keynote address, Thomas L. Bryant, Senior Director, Engineering, Sanofi Pasteur, proposed a practical approach for a typical pharma/bio-pharm manufacturing site to create a "road map", based on risk assessment, for re-investing in automation assets to avoid obsolescence.

Monday aseptic sessions included presentations on sterile filling systems and single use technologies while RABS sessions included a history of barrier isolation lessons learned and the design of next generation biologicals filling.

Tuesday's keynote address was offered by Thomas Warf, Director of the Division of Manufacturing, Facilities and Engineering in the Biomedical Advancement Authority Research and Development Authority (BARDA located in the Office of the Secretary for Preparedness and Response (ASPR) within the US Department of Health and Human Services (HHS). He discussed a program by which the US government was working with corporate partners to manufacture disaster and epidemic-related pharmaceutical products, including an Ebola vaccine, and get them into the marketplace. Tuesday's aseptic sessions included technology transfer of aseptic processes and launching a pilot plan. The barrier RABS sessions included presentations on customer expectations for contract manufacturers and a single-use clinical filling scale system.

The conference concluded with a panel discussion on aseptic and RABS issues and Q&A by FDA regulators. Following are highlights from the two-day event.

Practical Approaches for Process Control Automation and Building Automation System Lifecycle Management

23 February Keynote Speaker Thomas L. Bryant, Senior Director, Engineering, Sanofi Pasteur

Keynote speaker Thomas L. Bryant, Senior Director, Engineering, Sanofi Pasteur, proposed a practical approach for a typical

pharma/bio-pharm manufacturing site to create a "road map" based on risk assessment for re-investing in automation assets to avoid obsolescence.

"Do you have a good view of the probable obsolescence of your key site assets?" asked Bryant. "There are tools and practices that can be applied to anticipate failure and plan for replacement or life cycle management."

Obsolescence can result from many factors. Older versions of software that lose support, loss of internal contractor skills, system security evolution and lack of expansion capability are, among others, significant risks.

"The first step is admitting that you have a problem," suggested Bryant. "Often, manufacturing company leaders are not attuned to this issue, assuming it's covered by normal budgets. Technical leadership has to elevate the issue, and then the risk can be defined. You can get into a trap by deferring updates. Before you know it you are behind the curve."

He explained how Life Cycle Management can minimize disruption from obsolescence and presented the characteristics of a sustainable model, lifecycle maintenance, budgeting, upgrading validation approaches and execution approaches. He recommended performing initial risk assessment; confirming automation maintenance; using inventory automation-related systems (summary info, automation controllers, local displays, interfaces, IS Servers, workstations, software); performing "current state risk analysis" on all inventoried systems; prioritizing system upgrades; establishing technical standard; and creating multi-year re-investment plan based on risk analysis and upgrade prioritization.

He concluded by suggesting that life cycle management projects should not compete with other projects and that there should be a dedicated team with competent skills for life cycle maintenance.

Ramping Up for the Ebola Response: Implications and Challenges for Aseptic Processing

24 February Keynote Speaker Thomas Warf, Director of the Division of Manufacturing, Facilities and Engineering, BARDA

The Biomedical Advancement Authority Research and Development Authority (BARDA) created in 2007 and located in the Office of the Secretary for Preparedness and Response (ASPR) within the US Department of Health and Human Services (HHS), has a core mission to support development and availability of countermeasures for chemical, biological, radiologic and nuclear threats (CBRN), pandemic influenza and emerging diseases through advanced product development, stockpile acquisition and building, manufacturing infrastructure building, and product innovation, explained Thomas Warf, Director of the division of Manufacturing, facilities and engineering at BARDA.

"Our job is contracting to bring products into the marketplace," said Warf, adding that BARDA has fewer than 200 employees but a budget in the billions. "These are products that no one wants to buy, such as vaccines for anthrax or Ebola, vaccines that are not important until there is a disaster. The US government has made a sizeable investment."

When the Ebola crisis emerged last summer, said Warf, they had been focusing on MERS and a few other diseases, besides carrying out their normal, daily business and developing infrastructure for manufacturing vaccines.

He discussed at length BARDA's shift to Ebola as the crisis emerged in 2014. "We are dedicated to preparing for the unthinkable," explained Warf, who put in 25 years with Merck in a variety of positions pharmaceutical and biological manufacturing engineering services. "Being prepared to react to the unexpected is difficult."

He emphasized that "government is not a fast-moving organization," but that things are moving "faster than normal" when it comes to meeting BARDA's core objectives and goals and the nation's response to the Ebola outbreak.

Ensuring Supply: The Impact of Drug Shortages on the Pharmaceutical Industry

Peter T. Bigelow, President, xCell Strategic Consulting and Member of the ISPE Drug Shortage Taskforce

Peter T. Bigelow, President, xCell Strategic Consulting and member of the ISPE Drug Shortage Taskforce provided an overview of ISPE's efforts to prevent drug shortages and focused on aseptic techniques that would help in the effort.

"Historically, our patients and customers have relied on us to deliver quality medicines," said Bigelow. "We measure ourselves in terms of customer service, and drug shortages are an outcome of a lot of dynamics in our industry, including aseptic practices."

The shortage list of medically significant drugs increased during 2011, he told attendees. Shortages peaked and have been in a slight decline. Injectables have accounted for 75% of those drugs in short supply.

"ISPE is about solutions, and many of our discussions this week will touch on the drug shortage problem and, hopefully, help bring about some solutions," he explained. "ISPE has been focused on preventing drug shortages, first with the 2013 drug shortage survey, which laid out the causes of drug shortages, and subsequently with ISPE's Drug Shortage Prevention Plan (DSPP), released in October 2014."

He asked attendees for input on "where we should go to continue to work on this," and reviewed the information coming out of the 2013 drug shortage survey. He then discussed each of the six aspects of prevention subsequently built into the DSPP – Corporate Culture of Quality; Robust Quality System; Metrics; Business Continuity Planning, Communication with Authorities and Capability Building.

"ISPE's vision is to help the industry move beyond basic compliance to enhance supply chain resilience," he said. "Through its community of experts, ISPE will provide the education, guidance, and tools to enable manufacturing and compliance excellence through the product life cycle."

Retrofitting RABS to Existing Aseptic Filling Lines

Clive Brading, Injectables Quality Head, Global Manufacturing Quality Operations, Sanofi

Clive Brading provided practical examples of Sanofi's experience in retrofitting restricted access barrier systems (RABS) to existing sterile product filling lines. He offered some "dos and don'ts" for a successful transition to barrier systems and posited scenarios for when RABS was not the best solution.

"How can the industry adapt existing equipment to include effective barrier systems without going to full isolator technology," asked Brading. "No one would argue that taking steps to separate the operator, as a main potential source of microbiological contamination, from the exposed product, is an effective way to ensure a more robust process and product quality."

While he explained the most effective way of doing this is through complete isolation, Brading stated that the use of other barrier approaches can be equally effective, particularly as an alternative to conventional aseptic filling practices. Brading continued by saying there were a number of reasons for wanting to retrofit RABS: implementation is speedier and more cost effective.

Central to Sanofi's strategy, he explained to the audience, was ensuring an effective barrier was in place between the operator and the filling process. "Today Sanofi has more than 100 aseptic filling lines operating in conventional class A / B configuration, in locations around the world."

He concluded by cautioning his audience: "As with all projects, caution is needed. Carried out correctly, we do see this as a possibility to further improve the performance of conventional aseptic filling in a manner which is relatively rapid and cost effective."

FROM THE EAST TO THE WEST JAPAN AFFILIATE RETURNS TO THE US FOR ITS ANNUAL PLANT TOUR

by Shigeru Nakamura, CM Plus and Michael J. Lucey, JGC Corp.

The Japan Affiliate held its annual pharmaceutical plant tour in the United States from to 18 to 16 October, 2014, in conjunction with the 2014 ISPE Annual Meeting. Twenty professionals from across Japan participated, including ISPE Deputy Chairman Shigeru Nakamura and Adjunct Director Michael J. Lucey, who led an Organizing Committee made up of Affiliate Board Members. The team make-up was well-balanced, with eight members from pharmaceutical companies, ten from engineering/construction companies and two from equipment manufacturers.

Full and due recognition for this year's plant tour must be given to the San Francisco Bay Area Chapter with whom the Japan Affiliate has long enjoyed friendly relations. We express our sincere gratitude to the Chapter for their kind guidance and cooperation and to all at the plants who so graciously received us, extending the hand of friendship and offering hospitality. A special thank you to Boehringer Ingelheim for organizing an event in the courtyard of its Fremont facility for all of the visitors on the day of our visit, in the atmosphere of a German Oktoberfest.

As well as a poster display to promote the plant tour set up at the December Winter Meeting in Osaka, the Affiliate arranges a reunion each year for all participants from previous years. In fact, a joint reunion was held in March 2015 for the seven years spanning 2008 to 2014. This opportunity is without doubt founded on the great kindness of our numerous hosts in the US.

A summary of the 2014 plant visits follows.

Genentech

About 15,000 staff work at Genentech's extensive, rich green site of approximately 1,000,000 m^2. The B7 pilot plant visited manufactures pharmaceuticals for toxicological tests and animal experiments. It was notable that as a non-GMP facility free from regulatory requirements a high level of importance is placed on efficiency. Meanwhile, Genentech's corporate philosophy was felt through their well-planned approach to providing a comfortable campus-wide workplace. The company has provided exercise/training facilities, basketball courts and childcare centers, while

services such as car washing, haircutting, and nurseries are provided free of charge.

Novartis supported by Dome Construction

This campus is unique in executing technological research & development as well as the commercial manufacturing of pharmaceuticals. Novartis' focus is on the treatment of respiratory ailments. The plant was already in the commissioning stage, but the tour party was permitted a high level of accessibility and visibility. The tour members closely observed manufacturing equipment while maintaining an interactive relationship with their hosts, and subsequently enjoyed a wide-ranging Q&A session.

Boehringer Ingelheim

Boehringer Ingelheim's plant in Fremont functions as an important biotechnology hub for the company. The facilities are characterized by a unique design which allows visitors to uninterruptedly view the glassed-in manufacturing process from spacious passageways. The symmetrical layout of the facility enables simultaneous manufacturing of two kinds of products. The facilities are operated with great care given to cleanliness, as an impressive point for the visitors.

Agensys

Agensys in Santa Monica was first established as a bio-business venture in 1997 and bought by Astellas Pharma Inc. in 2007. The plant was commissioned in 2013, and comprises four buildings: Building A (cafeteria building), Building B (research building), Building C (administration building), and Building D (GMP manufacturing facilities). The main functions of the plant are R&D activities and investigational new drug manufacturing (to Phase II) for monoclonal antibodies and ADC (antibody drug conjugates) especially for use in cancer treatment. The facilities are designed with careful consideration given to the environment and have been awarded a silver certification of LEED (Leadership in Energy and Environmental Design).

ISPE COMMANDS BEST VIEWS IN BETHESDA

When ISPE President and CEO John Bournas took on his new role in September 2014, one of the first mandates he received from the Board was to find office space in the DC area. The regulatory issues facing the industry, as well as the ISPE's undertakings on drug shortages and quality metrics, meant that Agency proximity was a must. And Bournas took on the mandate in earnest, scoping out office space in both downtown Washington and nearby Bethesda, MD. Ultimately, Bethesda won out.

"With views to FDA and NIH, we are in the best spot to reach out to stakeholders and members alike," reflected Bournas. In fact, some 400 ISPE members reside in the Capitol area as well as dozens of pharmaceutical regulatory bodies.

He greeted Board members in the new office in January, just prior to their first meeting of the year, and told them just how excited he was to announce the opening of ISPE's Bethesda office. "This executive presence will provide the organization with a permanent base for ongoing dialogue with the regulators, as well as an environment where our Chapters, Affiliates and Members can hold meetings and discuss issues that impact our bio-pharmaceutical eco-system. I look forward to welcoming our members here and to continuing the conversation on pharmaceutical excellence."

Currently Bournas and executives Susan Krys and Shane Osborne (See below) have their permanent offices in Bethesda. More will follow suit as ISPE firms up its strategic plan for the next decade.

NEW EXECUTIVE LEADERS AT ISPE

ISPE President and CEO John Bournas recently welcomed two seasoned executives to his team: Susan Krys and Shane Osborne. "As the landscape in which we operate continues to evolve," explains Bournas, "we need to make sure the way in which we liaise with our stakeholders and how we re-align ISPE's internal resources to meet these opportunities also evolves. Thematic areas that were managed in separate departments have now come together to create a more unified and focused team-based approach.

"In this light, I have named Susan Krys as Vice President of Product Development, which will unite Continuing Education, Training, Sales and Event Management in one division. Membership and Marketing Communications will bring together ISPE's communication efforts – such as our digital presence, guidance documents and *Pharmaceutical Engineering*® magazine—with membership, component relations and communities of practice. This new division is under the leadership of Shane Osborne, our new Vice President, Marketing Communications and Membership."

Both Susan and Shane joined on 19 January.

Susan Krys
Vice President,
Product Development

"Continuing education and training are the lifeblood of ISPE. My goal is to take our offerings to a new level by ensuring that relevance and alignment with our members' needs, as well as innovative content, drive our programming."

Prior to joining ISPE, Susan was Vice President, Industry Events for the Food Marketing Institute (FMI), where she was responsible for re-annualizing and re-inventing the gathering of the food marketing industry. She oversaw all aspects of the FMI Connect meeting, including exhibit sales and management, marketing and public relations, logistics and educational programming. Her career includes eight years at the American College of Cardiology, where she oversaw all industry involvement in the ACC Annual Scientific Session including exposition sales, sponsorship sales and fulfillment, expo educational programming and venues, exhibit-related operations and logistical functions, and all expo processes and programs.

Susan also worked as the Director of Exhibit Sales and Exhibitor Marketing for the Telecommunications Industry Association for ten years, where she was responsible for a $32 million budget and a staff of twelve sales, marketing and operations professionals working on the largest telecommunications network event in the United States.

Shane R. Osborne
Vice President,
Marketing Communications
and Membership

"I will be focusing on increasing member satisfaction, exceeding membership and financial targets, and developing strategies that will meet member needs and expectations now and in the future."

Prior to working at ISPE, Shane successfully grew membership and non-dues revenue at the Association for the Advancement of Medical Instrumentation (AAMI), the National Center for Assisted Living (NCAL), and the American College of Cardiology (ACC). He has lead the creation of department-specific and organization-wide strategic plans, managed membership and marketing departments, led rebranding efforts, and developed new and restructured unsuccessful membership categories.

In addition to his membership and marketing experience, Shane has also identified and created new educational offerings based on member needs, organized "fly-in" events for members interested in lobbying Congress, and has provided a national perspective on issues important to members as a speaker at conferences around the country.

EDITORIAL

BUILDING CONFIDENCE IN QUALITY: THE FUTURE REGULATORY LANDSCAPE

by Roger Nosal, Chair, Pharmaceutical Engineering Committee

> For industry, confidence in quality is the underlying aspiration for the design, development and continual improvement of products.

A few years ago, while attending an ISPE meeting in San Francisco, CA, I had breakfast with Christine Moore, Deputy Director for Science, FDA, to discuss Quality by Design (QbD). Industry and regulatory leaders had reached an impasse. Several divergent perspectives had developed regarding the application and implementation of QbD. While its principles, adopted by several pharmaceutical companies, demonstrated improved product knowledge and process understanding, QbD applications were inconsistent and their regulatory merits, not fully realized. At one point that morning, as we discussed our respective concerns and aspirations for post-approval change management, Christine made a comment that resonated with me. She said "what we (regulators) want is confidence in the quality of a product as you (industry) manage it throughout its lifecycle".

Since then, as we have proceeded to improve the clarity of these and other quality concepts at various forums and meetings, *confidence in quality* has emerged as a unifying theme. But what does it mean to have confidence in quality?

> For patients, confidence in quality means they accept without reservation that every dose of medication they take is safe.

For regulators this may translate as confidence in the development of the product, its sustainability and in the reliability of the supply chain through the product's lifecycle. Some regulators express confidence in quality in terms of regulatory applications, where the regulatory commitments and data to support them demonstrate that risks have been appropriately and adequately mitigated. Other regulators describe *confidence in quality* as a function of change and knowledge management as reflected in the capability of a company to systematically and robustly accommodate and manage manufacturing and analytical changes and innovations within well-controlled quality standards.

Within the industry, confidence in quality is, fundamentally, the underlying aspiration for the design, development and continual improvement of products and a core principle of a company's Pharmaceutical Quality System. In QbD terms, confidence in quality is demonstrated by a product control strategy that consistently assures robust quality of a product.

As the pharmaceutical industry and regulatory authorities continue to engage on improving approaches to reduce uncertainty of risk, confidence in quality may serve as a qualitative driver for several initiatives including ICH Q12, risk-based regulatory review and quality metrics.

And most importantly, for patients, confidence in quality means they accept without reservation that every dose of medication they take is safe, efficacious and delivers its intended therapeutic performance.

The focus of this, and subsequent issues of *Pharmaceutical Engineering*, is on risk. Understanding risk and its implications for the patient is seminal to pharmaceutical development. Effective management of risk assures confidence in quality for the benefit of patients globally.

GLOBAL REGULATORY NEWS

ORGANIZATIONS

ASTM

ASTM International Updates Standard Defining PAT Terms[1]

E2363 – Standard Terminology Relating to Process Analytical Technology in the Pharmaceutical Industry has been revised to E2363-14. This document defines terms used in process analytical technology in the pharmaceutical industry. An increasing number of product designations and designations for chemical, physical, mechanical, analytical, and statistical tests and standards are coming into common usage in the literature, regulatory environment, and commerce associated with process analytical technology in the pharmaceutical industry. Section 2 lists those documents referenced in this terminology. The definitions are substantially identical to those published by the US Food and Drug Administration and other authoritative bodies, such as International Organization for Standardization, and national standards organizations.

ICH

ICH Q3D Guideline on Elemental Impurities Reaches Step 4 of the ICH Process[2]

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has developed a new guidance to provide a global policy for limiting metal impurities qualitatively and quantitatively in drug products and ingredients. The existing ICH Q3A Guideline classifies impurities as organic, inorganic, and residual solvents. The Q3A and Q3B Guidelines effectively address the requirements for organic impurities. An additional Guideline Q3C was developed to provide clarification of the requirements for residual solvents. The new Q3D Guideline would provide similar clarification of the requirements for metals, which are included in the ICH inorganic impurities classification. The ICH Q3D Guideline on Elemental Impurities reached Step 4 of the ICH Process in December 2013 and now enters the implementation period (Step 5).

PIC/S

Mexico Applies for PIC/S Membership[3]

On 18 December 2014, Mexico's Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS) applied for PIC/S membership. PIC/S is the abbreviation and logo used to describe both the Pharmaceutical Inspection Convention (PIC) and the Pharmaceutical Inspection Co-operation Scheme (PIC Scheme) operating together in parallel. The purpose of PIC/S is to facilitate the networking between participating authorities and the maintenance of mutual confidence, the exchange of information and experience in the field of GMP and related areas, and the mutual training of GMP inspectors.

AFRICA

New Partnership for Africa's Development

NEPAD Leads Discussions on a Critical Law to Regulate Quality and Safety of Medicines in Africa[4]

The New Partnership for Africa's Development (NEPAD) in collaboration with African Union Commission and Pan-African Parliament, have spearheaded the development of the African Union Model Law aimed at assisting African countries to enact or review their national laws and subsequently harmonize them with regional policies. The rationale behind the Model Law was inspired by the lack of comprehensive medicines legislation in many African countries. A NEPAD analysis revealed numerous gaps in legal frameworks. While some countries have legislation in line with the core elements recommended by the World Health Organization, others do not have medicines regulatory laws in place. This meeting has brought together experts from international organisations, funding partners as well as representatives from the pharmaceutical industry.

Accelerating Access to Quality Medical Products in Africa[5]

The New Partnership for Africa's Development Agency in collaboration with African Medicines Regulatory Harmonization Programme partners and the East African Community hosted a Donors Roundtable to discuss support for medicines registration harmonisation as a key aspect of improving medicines access in Africa at a time many sub-Saharan countries are struggling to streamline medicines registration processes and systems.

ASIA

China

China Regulator to Strengthen 'Grim' Food, Drug Safety Control[6]

Food and drug safety in China is «grim» and will get stronger oversight, the food and drug regulator said after a series of scares last year. China will increase «active» regulation to prevent food and drug safety scares, with more on-site inspections, random tests and unannounced visits, according to the regulator. Additionally, it said that the quality of personnel, legal structures, management methods and technological aspects were all currently insufficient.

CFDA Issues Good Manufacturing Practice for Medical Devices[7]

In order to strengthen the supervision and management of medical device manufacturing, standardize quality management, and further ensure the safety and effectiveness of medical devices, China Food and Drug Administration (CFDA) organized the revision of the *Good Manufacturing Practice for Medical Devices (interim)* in accordance with the newly revised *Regulations for the Supervision and Administration of Medical Devices and Administrative Measures for the Supervision of Medical Device Manufacturing*. The revised *Good Manufacturing Practice for Medical Devices* was adopted on 12 December 2014, pro-

mulgated on 29 December 2014 and will come into effect as of 1 March 2015.

The revised *Good Manufacturing Practice for Medical Devices* comprises 84 articles in 13 chapters, which requires medical device manufacturers to set up and improve the quality management system in accordance with this GMP, and specifies relevant requirements on organization and personnel, premises and facilities, equipment, document management, design and development, procurement, production management, quality control, sales and after-sales services, control of nonconforming products, adverse event monitoring, analysis and improvement and more.

CFDA Issues Good Supply Practice for Medical Devices[8]

To strengthen the quality management of medical device distribution, standardize medical device distribution behaviors, and guarantee the safety and effectiveness of medical devices, China Food and Drug Administration (CFDA) formulated the *Good Supply Practice for Medical Devices* in accordance with the newly revised *Regulations for the Supervision and Administration of Medical Devices* and the *Administrative Measures for the Supervision of Distribution of Medical Devices*. The *Good Supply Practice for Medical Devices* was promulgated on 12 December 2014, and came into effect from the date of promulgation.

Good Supply Practice for Medical Devices comprises 66 articles in nine chapters, which requires medical device distribution enterprises to set up and improve the quality management system in accordance with this document, and apply effective quality control measures in the purchase, acceptance, storage, sales, transportation, after-sales service of medical devices to guarantee the quality and safety of medical devices in distribution process.

CFDA Issues Guiding Opinions on Enhancing the Construction of Food and Drug Inspection and Testing System[9]

To further enhance the construction of the food and drug inspection and testing system, and better play the role of inspection and testing as technical support, China Food and Drug Administration (CFDA) formulated the *Guiding Opinions on Enhancing the Construction of Food and Drug Inspection and Testing System*. The *Guiding Opinions* was adopted at the minister's working meeting of CFDA on 18 December 2014 and was issued on 23 January 2015.

Japan

PMDA Publishes Summary of Discussion on the Assessment of the Current Status of Personalized Medicine Related to Development and Regulatory Review[10]

A joint subcommittee of three subcommittees within the Japanese Pharmaceuticals and Medical Devices Agency (PMDS) held discussions on (i) possible impacts of the emphasis on personalized medicine on the development and use of drugs, (ii) development of basic technologies for personalized medicine, particularly the development of companion diagnostics, and problems associated with their use, (iii) roles of biomarkers in evaluating the efficacy of drugs, and (iv) the possibility of using these biomarkers as endpoints of clinical trials. This document, found at http://www.pmda.go.jp/english/scienceboard/scienceboard/pdf/20140311/file01.pdf, summarizes these discussions.

AUSTRALIA/PACIFIC RIM

Australia

Therapeutic Goods Administration Releases Video to Help Industry Navigate Website[11]

TGA released an overview of the TGA website, focusing on the Industry section and how to navigate to guidance documents and where to go to submit applications online. The Industry area is the largest section of the site with over 1000 pages with access to more than 1400 unique documents. It is targeted at suppliers and manufacturers of therapeutic goods. The video can be found at https://www.tga.gov.au/navigating-tga-website.

EUROPE

European Union

EMA Recommends Record Number of Medicines for Rare Diseases for Approval in 2014[12]

In 2014, the European Medicines Agency (EMA) recommended the highest ever number of orphan designated medicines for marketing authorisation in a year. Out of the 82 medicines for human use recommended in 2014, 17 are intended for the treatment of a rare disease, providing therapies for patients who often have only few or no treatment options. During the past year, EMA provided more scientific support in the early stages of medicine development. Almost seven out of ten applicants received scientific advice from EMA's Committee for Medicinal Products for Human Use during the development phase of their medicine and this figure rises to four out of five when it comes to innovative medicines. This is a significant increase compared with 2013 when only half of applicants who had a positive opinion for their medicine had received scientific advice.

New International Standard to Improve Safety of Medicines[13]

The European Medicines Agency has published a guide to support the implementation of a new international standard for the safety monitoring of medicines in the European Union. The so-called ISO ICSR standard improves the reporting of suspected side effects of medicines in Individual Case Safety Reports. The use of the new international standard will take effect on 1 July 2016.

Europe to Boost International Cooperation on Generics[14]

The European Medicines Agency is ready to share its assessments of applications for generic medicines in real time with collaborating regulatory agencies outside the European Union. This initiative aims to facilitate the timely authorisation and availability of safe, effective and high quality generic medicines worldwide. The information-sharing initiative is part of the International Generic Drug Regulators Pilot. It started in July 2014 using the

European Union decentralised procedure as a model, and it is now extended to the centralised procedure. The first phase of the pilot project will involve the EU, Australia, Canada, Chinese Taipei and Switzerland.

All EU Pharmaceutical Legislation (Human and Veterinary) Available with an Integrated Search Engine[15]

The Eudralex V30, which provides access to human and veterinary pharmaceutical legislation, is similar to the EudraLex section of the European's Public Health web site, but it can be used off-line with the search engine. All the documents are in.pdf format and without protection. For a non-commercial use, Eudralex V29 may be duplicated, shared and the documents may be printed. It can be found at http://ec.europa.eu/health/documents/eudralex/cd/index_en.htm.

EMA Establishes Task Force to Implement New International Standards on Identification of Medicines[16]

The European Medicines Agency (EMA) is establishing a task force for the implementation of international standards for the identification of medicinal products (IDMP) for human use in the European Union. The Agency is inviting interested parties to express their interest in being part of the task force. The IDMP standards developed by International Organization for Standardization (ISO) establish data elements, formats and terminologies for the unique identification of medicines and the exchange of information on medicines, including pharmaceutical dose forms, routes of administration, packaging and active substances.

These standards are expected to simplify the exchange of information between regulatory authorities across the world and to support healthcare authorities in the development of electronic health records. They should also improve the safety monitoring of medicines by facilitating the assessment of data across classes of medicines and therapeutic areas.

EMA Explains its Redaction Rules[17]

The European Medicines Agency (EMA) has published a detailed response to the

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European Ombudsman's questions related to the redaction of certain elements of clinical study reports for the medicine Humira. It can be found at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/02/WC500182064.pdf. In a letter dated 27 October 2014, the Ombudsman requested EMA to explain why it had redacted certain information in response to an access to documents request that was received by the Agency in 2013. This particular access to documents request had led to a court case (T-44/13) against the Agency brought by the marketing authorisation holder of Humira, who sought to prevent the Agency from releasing the information under its access to documents policy. The case was ultimately withdrawn by the marketing authorisation holder after EMA agreed a limited number of redactions of the documents in line with the Agency's rules.

EMA Celebrates 20th Anniversary[18]

26 January 2015 marks the 20th anniversary of the establishment of the European Medicines Agency (EMA). Founded in 1995, the Agency has worked across the European Union and globally to protect public health by assessing medicines to rigorous scientific standards and by providing partners and stakeholders with independent, science-based information on medicines. 2015 also marks the 50th anniversary of the introduction of the first EU legislation on human medicines. On 26 January 1965 the Council Directive 65/65 on the approximation of the law relating to medicinal products was adopted.

Denmark

New Director at the Danish Health and Medicines Authority[19]

On 1 February 2015, Anne-Marie Vangsted, Acting Head of Division, took up the position as Director with responsibility for supervision at the Danish Health and Medicines Authority. The new position as director was created as part of our action plan aimed at modernising the supervisory function, in which Anne-Marie Vangsted has played a key role since we presented the plan on 15 September 2014.

United Kingdom

Cameron Urges Lighter Regulation to Speed New Drug Development [20]

U.K. Prime Minister David Cameron will push for lighter regulations on the pharmaceutical industry in order to speed the path of new medicines to the market. He wants drug companies to be able to move faster to develop treatments for Ebola and other diseases.

MHRA Launches New Website [21]

UK's Medicines and Healthcare Products Regulatory Agency (MHRA) website is now on GOV.UK. The new web address is www.gov.uk/mhra. As part of the move to GOV.UK content has been rewritten so it is easier and clearer to understand. Bookmarks and saved links to MHRA's old website will redirect to relevant content on GOV.UK, NHS Choices or to The National Archives, where a copy of the old website has been saved. The move to GOV.UK won't affect existing online services.

NORTH AMERICA

Canada

Health Canada increases transparency on health product and other regulatory information[22]

Health Canada is launching a number of new initiatives to improve the transparency and availability of health product and other regulatory information. These initiatives build on the progress already made with other Health Canada transparency measures achieved through its Regulatory Transparency and Openness Framework. Under the Framework, Health Canada is making more regulatory information available and easier to access than ever before, to aid Canadians in health and safety decisions for themselves and their families.

United States

FDA Publishes Guidance for Industry: DSCSA Implementation: Product Tracing Requirements - Compliance Policy [23]

The US Food and Drug Administration (FDA) posted guidance to inform industry that it does not intend to take action against manufacturers, wholesale distributors, or repackagers who do not, prior to 1 May 2015, provide or capture the product tracing information required by sections 582(b)(1), (c)(1), and (e)(1) of the FD&C Act. This action is to minimize possible disruptions in the distribution of prescription drugs in the United States. For more information, please visit the FDA "Are you ready for the Drug Supply Chain Security Act" web page, which contains an industry-focused checklist, links and descriptions for each of the DSCSA requirements which went in to effect on 1 January 2015.

FDA Publishes Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products: Draft Guidance for Industry and Food and Drug Administration Staff [24]

In this document, the FDA provides human cells, tissues, and cellular and tissue-based product (HCT/P) manufacturers, healthcare providers, and FDA staff, with recommendations for meeting the criterion under Title 21 of the CFR Part 1271, specifically the 21 CFR 1271.10(a)(1) criterion of minimal manipulation. The interpretation of the minimal manipulation criterion and definitions of related key terms has been of considerable interest to industry stakeholders since the criterion and definitions were first proposed during the Agency's rulemaking on HCT/Ps. This guidance, when finalized, will supersede the guidance entitled "Guidance for Industry and FDA Staff: Minimal Manipulation of Structural Tissue Jurisdictional Update" dated September 2006 .

FDA Launches Initiative to Cut Quality Control Lapses at Drugmakers[25]

The FDA launched an initiative aimed at reducing lapses in quality control at pharmaceutical manufacturing facilities. It is designed to establish consistent quality standards for all drugs, both brand name and generic. Under the new structure, drug companies can expect a more integrated review and greater communication with the agency. The FDA has established an Office of Pharmaceutical Quality that will be responsible for some 10,000 decisions a year and manage the process. Drugs currently being evaluated for approval will remain with their existing

WHY USE A DEFECT SAMPLE SET?

Pharmaceutical companies are challenged by the need to ensure the highest quality in parenteral products, therefore requiring manual, semi-automatic, or automatic inspection to detect and reject product with contaminants or defects. Alpha Tech USA joins them by offering services that facilitate complying with their commitment to quality.

Process and machinery both have to be validated to comply with FDA regulations and to ensure that they are performing as intended. A defect sample set serves as a standard to measure the efficiency of the inspection process, whether manual, semi-automatic, or automatic. The sample set can be used to perform routine challenges and to train inspectors for a manual inspection process.

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review team at the FDA. New applications will be filed with the new office beginning immediately. The FDA will propose a set of quality metrics for drugmakers. After a public comment period the agency will produce a final rule. A timeframe for these actions was not given.

MDSAP Pilot Reaches Milestone [26]

The FDA and regulatory agencies in Australia, Brazil, Canada, and Japan embarked in 2014 on a pilot called the Medical Device Single Audit Program (MDSAP). Its goal is to develop a process that allows a single audit, or inspection to ensure the medical device regulatory requirements for all five countries are satisfied, in an efficient yet thorough manner. On 1 January 2015 the MDSAP pilot reached a major milestone – manufacturers around the globe interested in marketing medical devices in Australia, Brazil, Canada, and the U.S. were invited to participate in the program. This summer, when Japan enters the MDSAP as a full member, the same invitation will be issued also to medical device manufacturers interested in marketing in Japan.

CDER Approves 41 Novel New Drugs in 2014 [27]

FDA approved 41 novel drugs this year, the most in nearly 20 years. Many of the 41 new drugs have the potential to add significant clinical value to the care of thousands of patients with serious or life-threatening diseases. They include eight new drugs for treating patients with various types of cancer, four new drugs to treat type-2 diabetes, four new antibiotics to treat serious infections, and two new products to treat patients with hepatitis C.

Update on Protecting the Public from Unsafe Compounded Drug Products [28]

In a blog post, FDA Commissioner Margaret Hamburg outlined the steps the agency has taken to address the safety of compounded drugs since the deadly outbreak of fungal meningitis in 2012 which was linked to unsafe compounding products. The FDA has conducted 175 inspections of compounding facilities in the last 2 years, using a risk based model. As a result, numerous firms have stopped making compounded drugs, and several recalls have been enacted. Some pharmacy licenses have been revoked, and warning letters issued. Working with the US Department of Justice, FDA has initiated investigations and enforcement actions against compounding facilities that violate federal law. The FDA has also taken steps to implement the compounding provisions of the Drug Quality and Security Act—legislation enacted by Congress last year in response to the fungal meningitis outbreak.

FDA Issues Current Good Manufacturing Practice Requirements for Combination Products - Draft Guidance for Industry and FDA Staff [29]

This guidance describes and explains the final rule on cGMP requirements for combination products (21 CFR part 4) that the FDA issued on 22 January 2013. Prior to issuance of the final rule, although cGMP regulations were in place to establish requirements for drugs, devices, biological products, and human cells, tissues, and cellular and tissue-based products, there were no regulations to clarify and explain the application of these cGMP requirements to combination products. The final rule was intended to provide such clarification and specify how compliance with applicable cGMP requirements may be demonstrated.

CDRH Priorities [30]

CDRH published a document describing its strategic priorities for 2014 - 2015. Top level priorities discussed in this document are: strengthen the clinical trial enterprise; strike the right balance between premarket and postmarket data collection; and provide excellent customer service.

FDA Seeks $4.9 Billion for Fiscal Year 2016 to Implement the FDA Food Safety Modernization Act and Improve the Quality and Safety of the Medical Products Americans Use [31]

The US Food and Drug Administration is requesting a budget of $4.9 billion to protect and promote the public health as part of the President's fiscal year (FY) 2016 budget–a nine percent increase over the enacted budget for FY 2015. The overall request includes $147.7 million in budget authority for initiatives tied to several key areas, including the implementation of the FDA Food Safety Modernization Act and the management of critical medical products issues.

FDA solicits comments on accelerated patient access to investigational drugs [32]

The FDA is introducing a much simpler draft form for comment that, when finalized, should accelerate patient access to investigational drugs. Additionally, to further assist the physician seeking access to an experimental therapy, the FDA has redesigned its website to make it easier to navigate and to explain the new proposed process in detail.

SOUTH AMERICA

Argentina

Argentina Begins First Stage of Implementation of National Traceability System [33]

On 15 February 2015, Argentina's National Administration of Drugs, Foods and Medical Devices (ANMAT) began the first stage of implementation of the National Traceability System for Medical Products, which includes the products listed in subparagraphs a) to e) of Article 1 ANMAT2303/2014. These products are the following: cardioverter / cardioverter; b) electrical stimulator for hearing in the cochlea; c) intraocular lenses; d) cardiac pacemakers; e) internal breast prosthesis. The National Traceability System Medical Products is mandatory for compliance with regulations involved in the distribution chain, dispensing and application of these products. It is a tool to validate the chain distribution and installation of the units and can detect anomalies that interfere with quality.

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THE FDA OBSERVATION RESPONSE: SEVEN COMMON MISTAKES

by Carol Brandt

Seven common mistakes are identified when responding to FDA inspection observations. This article presents examples of regulated-industry responses that may not meet the FDA requirements for a thorough response.

Your company had undergone a Food and Drug Association (FDA) inspection and now has a list of observations. You have decided to respond. Where should you start and what's expected? The response your company submits can mean the difference between successfully closing the observations file, or legal action by the FDA. There are at least seven (7) common mistakes that regulated companies make in responding to the FDA. Not onlwy does a thorough response confirm your commitment to correcting and preventing any problems, but it may also help identify other areas in need of improvement.

After an FDA inspection, any observations noted by the investigator(s) are provided to the regulated company in an FDA Form 483. The observations may not be all-inclusive due to the limitations of a general good manufacturing practices (GMP) audit. Most regulated companies will agree that it's wise to respond to the FDA and report any actions, taken or planned, to address each of the findings, accompanied by set target dates.

The FDA website (www.fda.gov) describes the reporting of observations as follows:

"An FDA Form 483 is issued to management at the conclusion of an inspection when an investigator(s) has observed any conditions that in their judgment may constitute violations of the Food Drug and Cosmetic (FD&C) Act and related Acts." [1]

Being on the receiving end of an FDA Form 483, can be an unnerving experience, because of te the legal implications of the observations and the potential consequences. These include a warning letter, civil financial penalty, import alert, seizure, injunction, and criminal prosecution. No one wants to lose their ability to do business.

The top of the 483 form states the following:

"This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an abjection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss this objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above." [2]

Although there is no regulation requiring a company to respond to a 483, it is recommended that a response be submitted within 15 business days from the last day of the inspection, or issuance of the 483. The FDA states that "Companies are encouraged to respond to the FDA Form 483 in writing with their corrective action plan and then implement that corrective action plan expeditiously." [1] A timely response is in a company's best interest.

Assuming that the company chooses to respond to the observations, the company has 15 days to prepare an acceptable response. Knowing when to get help is critical.

If the response is not adequate, follow-up action may be taken by the FDA. Most commonly, the FDA sends a warning letter. The company is notified in writing that "We have reviewed your response letter, dated xxx(date), and have determined your response to be inadequate."

Seven Common Mistakes

Many of the warning letters posted on the FDA website refer to inadequate responses that, for the most part, fall into one of the seven categories:

1. Taking a defensive tone
2. Failing to focus on the regulatory requirement
3. Failing to consider systemic implications of an observance
4. Failing to consider global implications
5. Failing to consider all of the products affected
6. Failing to establish the root cause of the problem, and take preventaive action according to Corrective Action, Preventative Action (CAPA) guidelines.
7. Failing to provide data and documentation

Taking a Defensive Tone

The purpose of the company's response should be to clarify information, document evidence of corrective actions already undertaken, provide sound scientific data, and provide time commitments for long-term corrective and preventative actions. It should be apparent from the tone of the letter that the company intends to cooperate with the FDA and comply fully with the regulations.

The FDA is protecting the health of the American public by ensuring the safety of regulated products. Taking a defensive tone is a mistake. If the decision is made to challenge the FDA, it's best to do so with the advice of a compliance attorney.

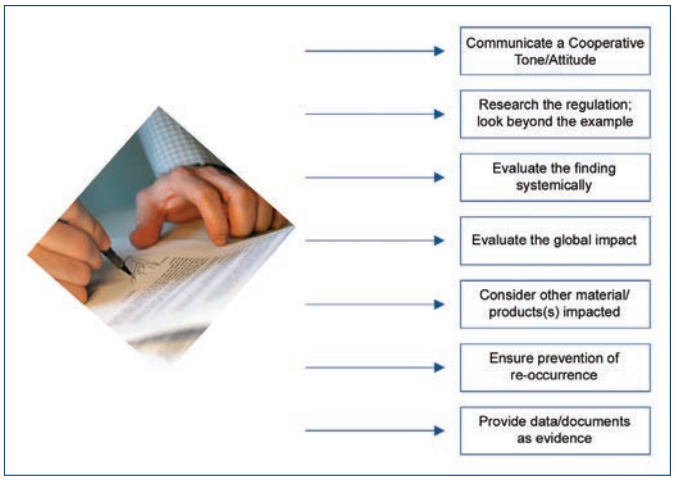

Figure 1. The FDA Response – Avoiding 7 Common Mistakes

The following are examples of responses to the FDA which, although they may have legal merit, don't present a cooperative attitude:

From a compounding pharmacy:

"We are also puzzled by the timing of the issuance of the warning letter. The five most recent warning letters issued by FDA's [redacted] District Office to non-pharmacy recipients were sent, on average, 114 days after the recipients' facilities had been inspected. The warning letter we received arrived 592 days after FDA's one-day inspection of our pharmacy. The eighteen-month delay, which is well over a year longer than the District's recent average, does not comply with FDA's internal procedures, which establish that decisions to issue warning letters are to be made in a timely fashion, because they are 'the agency's principal means of notifying regulated industry of violations and achieving prompt voluntary correction.' The warning letter also mentions the FDA's concerns about potentially serious health risks associated with the misuse by physicians and patients of compound topical anesthetic drug products. We assume that if the potential risk to the public health were, in fact, dire, the FDA would not have waited 18 months to issue the letter."

From a clinical investigator:

"We disagree. The patient [redacted] is not dead. He is alive and well. Patient [redacted] was last seen by an ACS physician for a 4-year follow-up visit on [redacted]. To paraphrase Mark Twain, the news of this patient's death has been greatly exaggerated."

Another example of a combative approach is the following excerpt from a response letter from a pharmaceutical company:

"Subsequently, the FDA dispatched two staff members from its Jacksonville office to review the measures we had taken in response to the consultant's recommendations. One of these people was an investigator and the other was a 'consumer safety officer' – neither of whom had ever visited our facility before. During the course of their inspection, they went outside several times to make telephone calls back to their office – presumably for guidance.... [redacted] has spent $75,000-$100,000 in an attempt to comply with federal regulations, even though only a minimal amount of business was at stake for the company."

One of the first rules in responding to a government agency with the power of the US federal court system behind them, is to be cooperative, admit mistakes and agree to correct what have been identified as non-compliant findings. Rebuttal with no intent of correction has one of two results: (1) prolonged disputes or (2) immediate legal action. Disputes may also result in legal action. It just isn't worth it to argue unless you have a strong legal compliance team behind you and the potential benefits are worth the risk.

Focusing on the Example Given, Not the Regulatory Requirement

The FDA investigators won't have the opportunity to complete a full audit of site practices, documentation and records. Assuming a routine GMP inspection, they will instead focus on areas of high compliance risk, and prior problem areas.

In this example in a warning letter from 2013, the FDA cited the following example:

"… two [redacted] API lots, lots [redacted], failed your company's action limit of [redacted] CFU/10mL with results of TNTC/10mL at the [redacted] step. However, your quality unit released them for further manufacturing without adequate scientific justification." [3]

Here, the FDA has provided an example of two active pharmaceutical ingredient (API) lots which were released by the Quality Unit (QU) without adequate justification. The regulations that apply are 21 CFR §211.22, Responsibilities of Quality Control Unit which indicates "there shall be a quality control unit that shall have the responsibility and authority to approve or reject all….drug products..(and).. if errors have occurred, that they have been fully investigated" and §211.160 Laboratory Controls, General Requirements saying *"…any deviation from the written specifications… shall be recorded and justified"*.

Some companies would respond only to the release of the lots mentioned, rather than address other lots potentially affected or other areas where the company is not compliant with the regulation. If the QU allowed release of these two API lots, has this occurred anywhere else? What assurance can the company make that the QU is meeting all of its responsibilities throughout the plant? Are they properly qualified and trained? For the laboratory controls regulation, what controls are in place to ensure an out-of-specification (OOS) result is flagged, investigated and resolved or reported? Are reporting methods in place to ensure the QU is made aware of the OOS prior to release of the API for further manufacture, or for any other materials or components the QU approves? And finally, what

controls will be implemented to ensure future occurrences are prevented? All are to be included in the response.

Another pharmaceutical warning letter included the following observation:

"You failed to investigate failing content uniformity test results for [redacted] Caplets, Lot [redacted]. This product was recalled during the inspection, after our investigators discussed the failing results with your company's representatives."

The same regulations as in the example above apply here, and the response needs to address not just the example noted, but all other failures during this time period (usually the two years prior to the incident) and ensure that investigations were properly performed. This should be performed according to written protocol, which should also be provided to the FDA.

Failing to Consider Systemic Implications of an Observance

Although the company should focus on the FDA observation, and not expand beyond its implications, if the observation could have systemic consequences, the company should advise the FDA that a full evaluation has been performed of other affected areas.

Too many companies think that revising standard operating procedure (SOPs) and training procedures that relate to a specific FDA observation will correct the problem, when, in fact, the problem may be systemic. It could indicate a failure of the quality system, extending much farther than the SOPs.

There is a balance required between providing information beyond the recorded observation, and fully evaluating other areas that could also have similar problems.

In one example a warning letter noted a "failure to record all quality activities at the time they are performed." The company responded and the FDA replied, *"Your response to this observation stated that a new SOP has been created to address this issue and that training on this SOP has occurred. Your response did not address the extent of this practice, the impact on the quality of the product and why your laboratory management failed to detect this practice. Your response also provided no actions to improve oversight by your quality unit (e.g., independence, authority, resources). The above practices observed during the inspection raise concerns regarding the reliability and accuracy of the data generated at your company, including any other inappropriate data-related practices permitted by your company when an inspection is not in progress. In response to this letter, provide a summary of your full assessment of all the raw data recorded on each of the batch production and QC laboratory analytical records for the APIs intended for the US market to ensure their reliability."*

The company should be considering all activities related to data collection, including all activities related to the batch records, line clearance, laboratory data sheets and notebooks, logbooks, etc..

An assessment of data collection for all of these types of data should be performed, according to protocol. Next, QU activities should be identified and documented in a procedure that will ensure appropriate oversight and control of data recording activities, going forward.

Another warning letter notes the following: *"…the investigator noticed that the scale used in production was not level, which can result in inaccurate measurements. The investigator asked how long the scale had not been level, and you indicated that you would investigate the matter and respond to the investigator."*

If this scale were out of calibration, it calls into question the entire calibration system. How long has it been out of calibration? What evidence exists that product quality was not affected? Has other equipment also been compromised? What systems are in place to ensure this cannot occur again? The response to the FDA needs to clearly delineate what the status is across all equipment, and summarize the potential impacts on product quality, following protocol.

> Companies should fully evaluate other areas for similar problems.

The FDA has recently reported a number of high profile data integrity issues, resulting in numerous 483s and warning letters. An example of a finding is the following: *"…our investigators noted that the SOP entitled, [redacted] Analysis and Documentation [redacted] effective date '20/11/2004' provides for 'discarding' of [redacted] data or for the data to be 'disregarded'. The SOP allows 'discarding' data due to 'variation in the [redacted] area, faulty [redacted] abnormal [redacted] or any other reason. The SOP has not been revised to clearly provide for maintaining complete data derived from all tests."*

This is an example of a culture of lack of a compliance that could extend into other areas outside of the laboratory. The discarding of data should never be allowed and the response to the FDA should indicate that all laboratory procedures have been reviewed to ensure it does not reoccur. This measure should be applied to electronic data as well. Computer systems should be reviewed to ensure data deletion is disabled. Other data sources should be evaluated as well, including deviation information, CAPAs, material and product release data, etc.. Follow-up monitoring should be implemented, which includes audit trail reviews of high-risk processes for all computer systems. The company should consider any other data which might have been discarded, such as calibrations, production readings, etc. What interim controls can be immediately implemented to ensure this isn't possible? Training to produce a new mindset must be performed.

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Failing to Consider Global Implications

Too often, companies with more than one manufacturing site don't consider implications of FDA observations beyond the site that was issued the 483. Procedures and processes might vary among sites but is the approach similar? Are the computer systems shared or software distributed between sites? Does the company have a method to immediately share and assess the impact of inspection observations across production and testing sites?

The following is an example of a warning letter addressing this very point:

"The Agency is concerned about [company's} responses to these matters. Among other things, although [company] was made aware of a major product defect/problem during FDA's … inspection at ... facility located in [location], ….you did not take appropriate actions to resolve the "trial" sample injection problem discussed above at the [location] facility or elsewhere within [company's] organization. Senior management is responsible for ensuring the quality, safety, and integrity of your company's products. Implementing adequate controls to prevent the manipulation of laboratory data, assuring timely investigation and resolution of product defects, and preventing distribution of defective products are all fundamental aspects of these responsibilities."

A global approach to managing operations with company-wide policies, standards and procedures is common practice. As mergers and acquisitions occur, global standardization is recommended to minimize site differences in compliance and to maximize efficiencies across computer systems. However, it also provides the opportunity for the same problematic systems to be used at multiple sites. For example, a company may choose to have a central information technology (IT) group, responsible for all computer software. A software package may be supported by the central site, with local databases and customized implementations running at each of the satellite sites. If an error occurs with the main software, the error might be shared with all of the sites. Any remediation that was performed at the site that found the error should also then be performed at all affected sites. If the error is identified in an FDA 483, the response should clearly state that the company recognizes the potential global impact and is acting appropriately to minimize the risk across all sites. Some pharmaceutical company s have a regulatory plan which specifies cross-site communication requirements and corrective action verifications in the event an FDA finding at any one site.

Failing to Consider All of the Products Affected

A primary responsibility of the QU is to ensure conformity with good manufacturing practices (GMPs), which includes ensuring the identity, safety and efficacy of every batch of product distributed. Investigation of a discrepancy or deviation needs to extend across all products and batches that might have been affected, to provide assurance that quality is maintained throughout.

The following is a warning letter example:

"Your company did not extend an investigation regarding blue plastic particles, originating from component drums that were found in a portion of Mag-Al Liquid (lot #OC47) to the first portion of the same batch that was already filled. Although your company identified a root cause and destroyed the portion of the lot located in the bulk tank, you released the part of the lot that had already been filled without proper justification. Your response does not indicate any additional actions to address the portion of the lot of MagAl Liquid (lot #OC47) that may contain the plastic particles and is currently on the market, or any other lots produced from the same co-blend."

The FDA's first concern is consumer protection. A review of all lots, material, blends, and all other products should always be performed in the investigation of an unplanned event to ensure no other product could have been affected.

Failing to Establish the Root Cause of the Problem, and Take Preventaive Action

The occurrence of an unplanned event or use of an uncontrolled procedure requires immediate correction, but also investigation into the cause to ensure it is prevented from happening again. This describes the corrective action/preventative action (CAPA) process. The response to an observation should always consider controls to prevent re-occurrence and the QU involvement in the prevention.

The following is an example of such a finding:

"In response to this letter, provide your evaluation of all laboratory equipment that may be affected by the lack of adequate controls to prevent data manipulation. In addition, address the root cause of your quality unit's failure to control and detect the manipulation or alteration of laboratory documents and describe actions to prevent recurrence. In response to this letter, provide your procedures to manage all computerized data and how the data will be used, retained and stored to ensure its integrity."

Failing to Provide Data and Documentation

One warning letter states, "We have reviewed your response letter, dated 9 October 2012, and have determined your response to be inadequate. Your letter states, "As part of the documentation is the establishment of the specifications of products. Our company has signed a contract with [redacted]. In order to send finished product samples for analysis. Our company has also decided to acquire the necessary laboratory equipments to monitor the manufacturing process." However, you have not provided documentation of any product specifications that you have established to ensure the quality of your dietary supplements and no timeline for when the specifications will be implemented."
In conjunction with providing scientific evidence and SOPs it is critical to provide reasonable timelines for taking action. Doing so, establishes a commitment to the FDA and timelines must then be met or revised deadlines provided along with reasons for those delays.

Conclusion

Avoiding these seven common mistakes in responding to 483 reports requires a thorough evaluation and response. If there are repeat observances, they should be given high priority and addressed in the written response and with immediate action, including preventative measures. Writing an acceptable response is not only beneficial in developing a "good faith" relationship with the FDA, but will also improve quality monitoring and compliance at your company.

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ABOUT THE AUTHOR

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USING PROCESS CAPABILITY TO ENSURE PHARMACEUTICAL PRODUCT QUALITY

by Lawrence X. Yu, Daniel Y. Peng, Robert Lionberger, Alex Viehmann, and Karthik Iyer

The concept of process capability was first introduced by the Western Electric Company in the Statistical Quality Control Handbook in 1956.[1] It is defined as "the natural or undisturbed performance (of a process) after extraneous influences are eliminated". Since then, various definitions and calculation formulas have been developed concerning the capability and performance of a process by national, regional, and international standardization organizations.[2-4] Among these guidelines, the definition in the American Society for Testing and Materials (ASTM) standard guide E2281 is considered by many as the standard.[2] The process capability index compares the variability of a process quality measure against product specifications or tolerances and assumes the process is in a state of statistical control. The process performance index is useful in situations when the process is not in a state of statistical control.

The process capability has been widely used by several industry segments, for example the automobile, electronic devices, and chemical industries, to determine how well a process produces a quality product.[5-8] There are also a few publications that discuss process capability in pharmaceutical industry.[9-16] Despite its usefulness, articles on process capability have not been widely discussed in the literature as a tool to ensure pharmaceutical product quality. In this paper, we will discuss the use of process capability as a tool to ensure drug product quality. We first give a brief overview of the definitions and calculation of process capability index and process performance index. Then, we discuss the differences between the process capability index and the process performance index. Further, we discuss the relationship between process capability and potential product batch failure rate. Finally, we describe the use of the process capability index in product development, process scale-up and qualification, and commercial production.

The Process Capability Index (Cp/Cpk)

Process capability is defined as the natural or inherent behavior of a stable process that is in a state of statistical control.[2] A state of statistical control (i.e. stable state) means that the process exhibits no detectable trends and hence the variation seen in the data is due to random causes and inherent to the process. Process capability is linked to the process variability. Therefore, a process must be evaluated for its state of control before evaluating process capability.

Process capability[2] (PC) is calculated as:

$$PC = 6\,\sigma_{ST}$$

where σ_{ST} is the inherent variability of a stable process. In practice, it is difficult to know the true value of inherent variability. Hence, variability within a subgroup (also referred to as short-term variability) is often used to estimate the true value of inherent variability, σ_{ST}. It is hoped that the observations within the subgroup are small enough not to include special causes of variability.

To compare a process with customer requirements (or specifications), it is common practice to think of capability in terms of the proportion of the process output that is within product specification limits. The metric of this proportion, **process capability index** (Cp) is the percentage of the process spread in relation to the specification limits. This index can be used to compare products and processes, drive process improvement, and identify the need of management action to reduce variation. The process capability index (Cp) is calculated by:

$$Cp = \frac{USL - LSL}{6\sigma_{ST}}$$

where USL = upper specification limit and LSL = lower specification limit.

The calculation of Cp does not consider the process mean. Therefore, in the situations where the process is not centered or where it is deliberately run off-center, Cp is not an appropriate index. Cp is also not an appropriate index if only the upper or lower specification limit is known. For these situations, the **minimum process capability index** (Cpk) is used. Cpk considers the process average against a unilateral or bilateral specification limit. It measures whether the process is capable of producing quality product by considering the specification limit and the current process mean as well as its variability. Assuming normal distribution, Cpk is the smaller of the upper process capability index (Cpku) and the lower process capability index (Cpkl). Mathematically,

$$\text{Cpk} = \min(\text{Cpku}, \text{Cpkl})$$

$$Cpku = \frac{USL - Mean}{3\sigma_{ST}}$$

$$Cpkl = \frac{Mean - LSL}{3\sigma_{ST}}$$

Cpk is always smaller than Cp unless the process mean is centered.

The Process Performance Index (Pp/Ppk)

Process performance is a statistical measure of the overall variability of a measured quality attribute of a process that may not have been demonstrated to be stable.[2] Comparison of process performance to specification limit results in process performance index (Pp). Similarly, the minimum of upper or lower process performance index (Ppk) offsets the weaknesses of Pp by introducing process mean into the calculation formula. When process mean is centered, Ppk is equal to Pp; otherwise, it is always less than Pp. Assuming a normal distribution, the calculation formula of the process performance index is:

$$P_p = \frac{USL - LSL}{6SD}$$

$$P_{pk} = \min(P_{pku}, P_{pkl})$$

$$P_{pku} = \frac{USL - Mean}{3SD}$$

$$P_{pkl} = \frac{Mean - LSL}{3SD}$$

where SD is the standard deviation of all observed samples (within subgroups and between subgroups) of a process which may not be demonstrated to be stable. SD is often referred to as the overall variability or long-term variability, and calculated by:

$$SD = \sqrt{\sum_{i=1}^{N} \frac{(X_i - \overline{X})^2}{N-1}}$$

Where, N is the total sample size, for k subgroups with a subgroup size of n, N is equal to k × n. X_i is the individual datum; and X-bar is the mean of the data set.

Difference between Cpk and Ppk

Because the calculation of Cp and Cpk only accounts for the within subgroup variability, it represents the potential (theoretical) capability, i.e. how well a given process would be able to perform under the ideal situation. The ideal situation is when all special causes have been eliminated and there are no detectable trends and the variation seen in the data is random and inherent to the process itself (process noise).[2] This is because special causes can increase within subgroup variability of the process or can cause the mean of between subgroups to shift, drift, or spike. If special causes exist in the system, overall variability is greater than within-subgroup-variability and therefore the calculated Cp or Cpk would overestimate the current process status.

The process performance index (Pp and Ppk) addresses how the process is actually performing relative to the specification limits, without the demonstration of the process being stable. In other words, Pp and Ppk can be used even when a process exhibits intermittent variation due to special causes. Pp and Ppk account for the overall variability in the system including within subgroup variability, between subgroup variability, analytical method variability, and any other variability. Therefore, in general, Ppk is less than Cpk. If the process is in a state of statistical control (stable), the estimates of Cpk and Ppk would be very close. Both Cpk and Ppk can be used to evaluate product quality with either unilateral or bilateral specification limits and centered or uncentered process means.

However, when the process has not been demonstrated as stable, only Ppk can be used to assess how the process is actually performing. Nonetheless, because Ppk does not require the process to reach a stable state as such, it cannot be used as an indicator to forecast if the process will produce a high quality product in the future. Ppk represents what the process has produced and Cpk represents what the process could produce.

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Interpretation of Cpk Value

In order to use Cpk values to estimate future batch failure rate, three prerequisites should be met for variable data: 1) sufficient number of the subgroups are included; 2) data are normally distributed or can be transformed into normal distribution. For non-normal distributions accurate results can be achieved with the reference interval calculation. This is also known as the percentile method, as detailed in ISO 21747[3]; 3) the process is in a state of statistical control which means that all special causes have been eliminated from the system and the variation observed in the data is only due to common cause (process noise) of the system (2).

Table A presents the non-conforming parts per million (ppm) corresponding to Cpk values for a process with unilateral specification or bilateral specification.[17] The non-conforming parts per million (ppm) were computed for different Cpk values using the Sigma value and the percentage area under the standard normal curve.[17] For example, a Cpk of 1.0 means there are 3 standard deviations from the process average to the nearest specification, and potentially there are 1350 ppm outside of this specification, assuming a normal distribution. If the quality characteristic under study has a unilateral specification, this is the total ppm. However, if the process has a bilateral specification, potentially, an additional 1350 ppm is outside of other specification and the potential total ppm is 2700 ppm if the process average is centered at the middle of the specification limits.

Based on the literature[17] and other international standards or guildlines[2-4] on process capability, when Cpk is below 1, the process is considered not capable. The higher the Cpk value, the better the process capability is. When Cpk is greater than 2, the process is considered excellent.[17]

Pharmaceutical drug products often involve more than one critical quality attribute (CQA) in the product specification. The overall defect level of the drug product is dependent on the joint probability of individual quality attributes conforming level. For example, three CQAs are identified for a drug product and their individual Cpks are 0.667, 1.0, and 1.333. To simplify the calculation, it is assumed that these three CQAs all have bilateral specification limits and the process means are centered at middle of the specification limits and all CQAs are independent to each other. The joint probability of conforming level of the drug product would be 95.45%* 99.73% *99.9936%, which is equal to 95.1862%. Therefore, the potential defect level (percentage of product with at least one defective CQA) of the drug product is 4.8138%, i.e. the potential non-conforming part per million is 48138 ppm.

As discussed in the previous section, when the process has not been demonstrated to be stable, only Ppk should be used to assess how the process has performed based on currently observed data. Ppk cannot be used as an indicator to forecast the future batch failure rate because it does not require the process to be in a state of statistical control. Even if a high Ppk value is obtained, it only indicates the current process performance rating is satisfactory, but the future status is still unknown because the process is not yet stable.

Using Cpk and Ppk to Ensure Drug Product Quality

In this section, we will discuss potential uses of Cpk or Ppk in ensuing drug product quality. We will explain their potential utility in product and process design and understanding, process scale-up and qualification, and commercial manufacturing. Figure 1 shows potential uses of Cpk and Ppk in product design, scale-up, and commercial manufacturing to ensure drug product quality.

1. Product Design

The goal of this phase of pharmaceutical development is to ensure the product is appropriately designed and the control of drug substance, excipient, container closure system, in-process material, and final product are appropriately established. Historically, the specification limit was often set based on manufacturing capability. This practice unintentionally allows manufacturers with poor manufacturing and process controls to have products with relatively wider specifications compared to good manufacturing and controls with tight specifications. This also could be one of the fundamental reasons why the pharmaceutical industry only

Table A. Cpk values and its corresponding non-conforming parts per million[17]

Cpk Value	Sigma Value	Area Under Normal Distribution Curve (% Conforming Level*)	Non-conforming parts per million (ppm)		Capability Rating
			Unilateral Specification	Bilateral Specification*	
0.333	1	68.27	158650	317300	Terrible
0.667	2	95.45	22750	45500	Poor
1.0	3	99.73	1350	2700	Marginally capable
1.333	4	99.9936	32	64	Capable
1.667	5	99.99994	0.3	0.6	Good
2.0	6	99.9999998	0.001	0.002	Excellent

* Process mean is centered at middle of the specification limits and has normal distribution

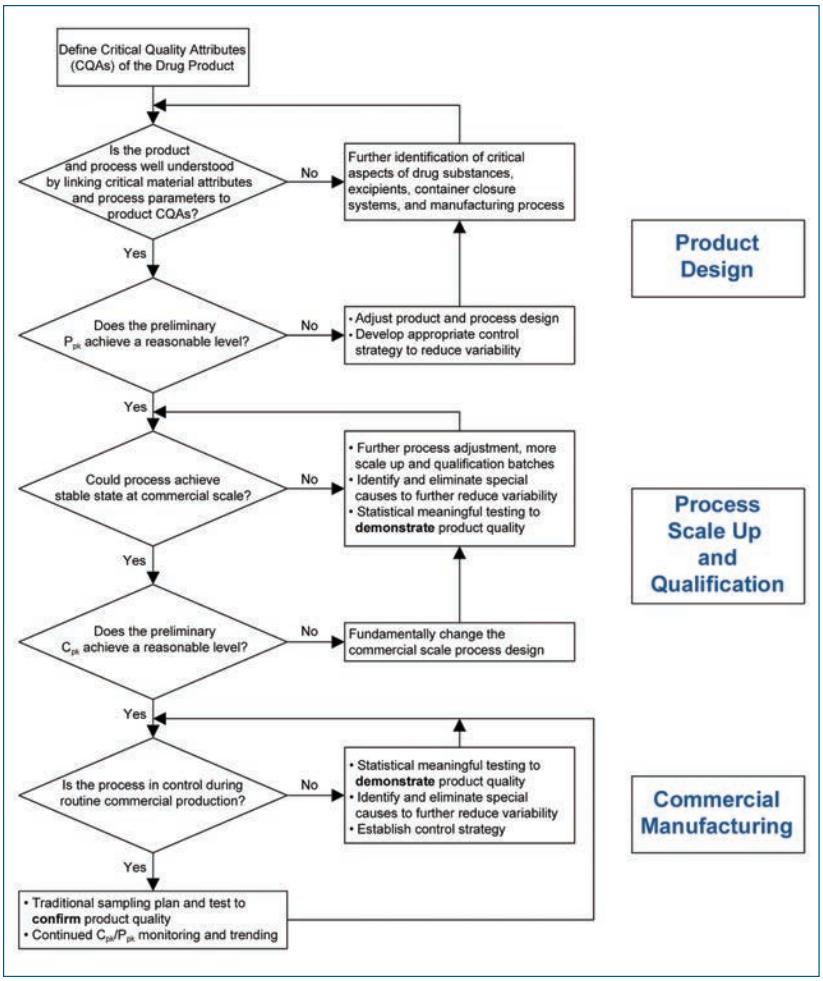

Figure 1. Potential uses of Cpk and Ppk in design, scale-up and commercial manufacturing

gets 2-3 sigma, since the specification is set based on process capability. Under the Quality by Design paradigm, one of the key objectives is to achieve meaningful product specifications that are based on clinical performance.[18] Once these targets are set, the subsequent development activities focus on how to achieve these targets. Therefore, those aspects of drug substances, excipients, container closure systems, and manufacturing processes that are critical to product quality need to be identified and control strategies are established and justified. During this development phase, a number of input material attributes and process parameters are deliberately varied across a range of values according to experimental design. Based on the impact of these parameters on the drug product intermediates and finished drug product critical quality attributes (CQAs), critical attribute of input materials and critical process parameters (CPPs) can be identified and an appropriate control strategy is then established.[18]

The variation in the process that results from this deliberate varying of these input variables is a type of special cause variation (i.e. variation that is due to assignable causes). In most of cases, the process is not in a statistical control state during early development phase; therefore, Cpk is not the appropriate index. If sufficient development batches are produced, preliminary Ppk and its confidence bound can be calculated. The data can be used to assess whether the designed product and process can approximately achieve the target quality attributes in the desired range. If not, fundamental changes to the product or process design may be necessary to improve the product to achieve the predefined target.

The concept is well illustrated in the ISPE PQLI® Guide: Part 2 – Product Realization using Quality by Design (QbD): Illustrative Example for a BCS low solubility mock compound (PaQLinol).[19] Dissolution as one of the CQAs discussed in this white paper is highlighted here as an example. The initially proposed dissolution acceptance criteria and the method for early formulation development is > 85% released at 30 min using USP paddle method (50 rpm) in 900 mL of pH 6.8 phosphate buffer with 0.5% polysorbate 80 at 37± 0.5°C.

However, the relatively rapid dissolution in this media resulted in little discrimination between formulation variants which were used in pilot bioequivalence studies in healthy volunteers (A: Standard formulation, B: over-compressed; C: over-lubricated; D: Active Pharmaceutical Ingredient (API) particle size (D_{90}) increased from 20 µm to 50 µm). Hence, a revised dissolution method using USP paddle method (50 rpm) in 900 mL of pH 6.5 phosphate buffer with 0.1% sodium lauryl sulphate (SLS) at 37± 0.5°C is developed and a clinical relevant acceptance criteria (Q= 80% in 20 min) has been established based on the pilot bioequivalence studies.

The revised dissolution method and acceptance criteria were used to evaluate the potential impact of changes in formulations and process variables on product dissolution. Based on the initial screening design of experiment (DOE) studies, a further response surface DOE (a reduced cubic design with center points giving 23 runs) is performed to determine the impact and interactions of four formulations and process variables (API particle size, magnesium stearate surface area, lubrication time and tablet crushing force) on product dissolution (% dissolved in 20 min). We used the raw data from this illustrative example and calculated the preliminary Ppk. The obtained Ppk value is 0.67 (with 95% confidence lower bound = 0.47, potential batch failure rate would be 2.2%), which did not meet the predefined goal (95% confidence lower bound >1). Hence, further fine-tuning the control strategy is necessary and the acceptable range for API particle size, magnesium stearate surface area, lubrication time and tablet crushing force were tighten from the studied ranges. In addition, for a given values of API particle size and magnesium stearate surface area of avai-

lable batches, the lubrication time and tablet crushing force will be varied based on the established multi-factorial relationship to achieve the predicted dissolution.

It is well known, however, these development studies are often conducted in the laboratory or on a pilot basis. Therefore, Ppk obtained from the lab or on a pilot scale cannot be extrapolated to production scale unless if one can demonstrate the process is scale-independent or a scale-up of the process can be predicted with a high certainty. As such, extra precautions need to be taken to interpret these indices obtained during the development stage. In addition, the effectiveness of the developed control strategy on a lab or pilot scale is to be verified on a commercial scale and monitored during routine commercial manufacture. Nevertheless, the enhanced understanding of the formulation and process creates a solid foundation on which to obtain high Cpk and Ppk for commercial manufacture.

2. Process Scale-Up and Qualification

Process scale-up and technology transfer in pharmaceutical industry involves, in general, moving a product from the research and development stage in which laboratory or pilot scale equipment is often used, into the production stage. Process qualification has two elements: (1) design of the facility and qualification of the equipment and utilities and (2) process performance qualification (PPQ). The PPQ combines the actual facility, utilities, qualified equipment, and the trained personnel with commercial manufacturing process, control procedures, and components to produce commercial batches. Process scale-up, technology transfer and process qualification often overlap or are combined for most pharmaceutical product development programs. The objective of this phase is to establish scientific evidence that the process is reproducible on a commercial scale and that the process will consistently deliver a product that meets the quality standards established in product design phase.

The knowledge gained during the product and process development on a laboratory or pilot scale build a solid foundation for a successful process scale-up and qualification. However, it is a well-known fact that often the process on a production scale cannot achieve the same quality of product as was envisioned in the development stages. It is important to identify the scale-dependent variables and make necessary adjustments to scale the process from laboratory scale to pilot scale and ultimately to commercial scale.

Various approaches can be employed to facilitate the process scale-up e.g. using mechanistic modelling, empirical modeling or semi-empirical (hybrid) modeling (dimensional analysis) based on the process geometric, kinematic and dynamic similarity. Nevertheless, these are simply models, approximations of reality. Some trials batches (e.g. engineering batches) can be manufactured on a commercial scale and the quality of the produced materials are comparable to products manufactured on a smaller scale during development stages. If significant differences are observed, the projected commercial scale process parameters are then adjusted. Even though these trial batches may not be released for distribution, the process becomes a solid foundation for a successful scale-up and qualification

The most desirable situation from the point of view of evaluating commercial manufacturing process capability is to have at least 25-30 commercial scale batches. This is probably more batches than would normally be produced during process scale-up and qualification. To address this issue, some alternative strategies can be considered:

1. Higher level of sampling and additional testing, for example having at least 100 observations, when the number of commercial batches is less than 25. Meanwhile, scientists should be aware that sampling at too high of a frequency can introduce correlations between successive subgroups.
2. If commercial scale batches can be well predicted based on the process model developed on a laboratory and pilot scale, then typical development batches can be included in the dataset.
3. If the testing plan used in the qualification stage is also used during earlier development stages, other representative batches, for example pivotal bioequivalence batches, registration stability batches, engineering or demonstration batches, may be combined with process qualification batches.

Once sufficient data points are collected, the trial process control limits of the control chart are calculated in a retrospective way to evaluate whether the commercial process has been in control over the period of time during which the data were collected. The objective of the process control limits is to identify, minimize, or eliminate special cause variability and to monitor future commercial process variability. Batches outside these initial trial control limits are investigated to identify special causes such as raw material variability, batch size change, equipment design and principle changes, commercial site facility and utilities changes. The control strategy is then adjusted or revised in an effort to eliminate or mitigate these identified special causes. Points outside the initial trial process control limits are excluded and new process control limits are calculated. The revised statistical process control limits are further evaluated for process stability with the newly collected data. This type of analysis may require several cycles, and eventually the process reaches stable state (i.e. in a state of statistical control).

As discussed in above section, a process can be very stable, however, and not meet customer needs (i.e. out of specification acceptance criteria which are established based on the product safety and efficacy (clinical performance) needs). Therefore, it is equally important to calculate Cpk and use it to assess if the commercial scale process can produce materials that meet the predefined acceptance criteria (for example the lower 95% confidence bound of Cpk > 1).

Figure 2 represents a theoretical example of a staged sampling approach when limited batches have been manufactured. The first three batches (A, B and C) represent a higher level of sampling within each batch than typical routine commercial production. The goal of the initial higher level of sampling is to demonstrate product quality throughout each batch, establish initial estimates of within and between batch variability, and use those estimates to generate an initial estimate of process performance. Then, sampling in subsequent batches (D, E and F) is adjusted (in this case, lowered) to a statistically representative level that was based upon the variability estimates established in the first three batches. The number of batches should be sufficient to provide sufficient statistical confidence of product quality both within a batch and between batches.

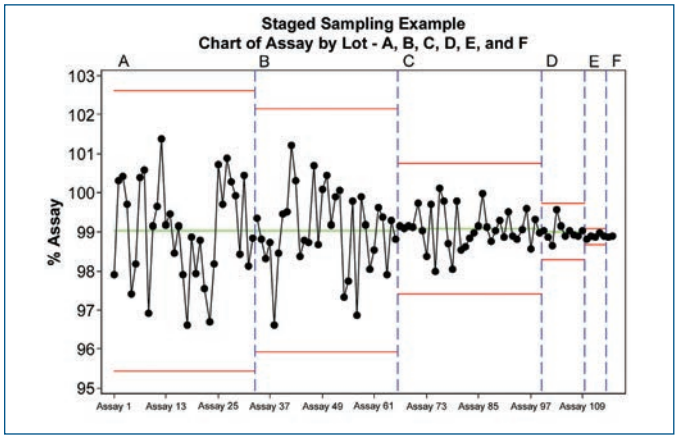

Figure 2. Theoretical example of a staged sampling approach when limited batches have been manufactured during the process performance qualification (PPQ) stage

Products manufactured during the process performance qualification stage, if applicable, can be released for distribution. Concurrent release is discussed in detail in the FDA guidance for Industry on Process Validation: General Principles and Practices.20 Before a stable state has been demonstrated, due to the uncertainty of the process variability of between batches, these batches will have a higher level of sampling, additional testing, and greater scrutiny

of process performance, that will continue through the process verification stage until commercial production is stable. The number of samples needs to be sufficient in order to provide sufficient statistical confidence of quality of each unit within a batch. The confidence level selected can be based on risk analysis as it relates to the particular attribute under examination.

3. Commercial Manufacturing

Once the process has achieved a stable state and a satisfactory Cpk is achieved, the process is ready to move into the routine commercial manufacture phase. As outlined in the FDA Guidance for Industry on Process Validation: General Principles and Practices:[20] the goal of the continued process verification is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture. Therefore, it is important to continually monitor the process for any sign of special cause variation and to detect shifts in the process that signal that future products may not meet specifications. Process capability and process performance index for all critical quality attributes for each batch are calculated and trended. If the statistical control state is maintained and no negative trend is observed for the process capability and process performance index, the extensive sampling employed during qualification stage can be reduced because the testing goal is to confirm the drug product quality.

It is hoped that most of the special causes of variability related to scale-up and commercial manufacturing have been systematically identified and removed during process scale-up and qualification. Appropriate detection, control, and or mitigation strategies, as well as appropriate alert and action limits will have been established. However, a process is likely to encounter additional sources of variation that were not previously detected or to which the process was not previously exposed. If any unplanned or undesired departures from the process are detected, a continual improvement strategy can be initiated to correct and prevent potential failures so that the process remains in control. Often, the special causes that occur in this stage normally result in small process shift, and Shewhart control charts are much less likely to be effective because they are not very sensitive to small to moderate size process shifts. Therefore, the cumulative sum or the exponentially weighted moving average control charts are often used. If an out of control event is observed, the statistically meaningful testing plan will be re-employed to determine if the batch can be released for distribution. The enhanced sampling testing plan will continue until the process become stable again.

Continual improvement is a set of activities that the applicant carries out in order to enhance the ability to meet requirements. Continual improvements typically consist of five phases:[21]

- Define the problem and the project goals,
- Measure key aspects of the current process and collect relevant data
- Analyze the data to investigate and verify cause-and-effect relationships. Determine what the relationships are, and attempt to ensure that all factors have been considered. Seek out root cause of any defect.
- Improve the current process based upon data analysis using techniques such as design of experiments to create a new, future state process. Set up pilot runs to establish process capability.
- Control the process to ensure that any deviations from target are corrected before they result in defects. Implement control systems such as statistical process control, production boards, visual workplaces, and continuously monitor the process.

Other quality metrics such as batch failure rate, right first time rate, out-of-specification investigation rate, number of recall batches, field alert reports (FARs) rate, consumer complaints and adverse events rate etc. can also be monitored and trended by using the attribute control charts. A Binomial process capability index or Poisson process capability index can be obtained on these counts and discrete data sets. This type of monitoring is a powerful tool to identify pharmaceutical quality system (PQS) problems for a particular product, a product class, a particular manufacture site, or a manufacturer's global quality issues.

Summary

Process capability is a useful tool to ensure drug product quality during product design, process scale-up and qualification, and routine commercial manufacturing. Because the calculation of Cp and Cpk only accounts for the within subgroup variability, it represents the potential (theoretical) capability, i.e. how well a given process would be able to perform under ideal conditions. Ideal conditions are when all special causes have been eliminated and the variation seen in the data is random and inherent to the process itself (process noise). When the process has not been demonstrated as stable, only Ppk should be used to assess how the process has performed based on currently observed data. Ppk cannot be used as an indicator to forecast the future batch failure rate because it does not require the process to be in a state of statistical control. Even if a high Ppk value is obtained, it only indicates the current process performance rating is satisfactory, but the future status is still unknown because the process is not yet stable.

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PHARMACEUTICAL INDUSTRY WHITE PAPER: IMPLEMENTATION AND APPLICATION OF QUALITY BY DESIGN

by Roger Nosal (Lead Author), Dan Bollinger, Andrew Chang, Xavier Castell, Graham Cook, Frank Diana, Jeff Ferguson, Georges France, Betsy Fritschel, John Groskoph, Nirdosh Jagota, Bob Kelly, John Lepo re, Rick Lit, Stephen Mason, Moheb Nasr, Ken Oh, Mark Rosolowsky, Tom Schultz, Steve Tyler, Jim Webb and Diane Zezza

Objective

This white paper describes the current status on implementation of quality by design (QbD) and recommends options to improve implementation and reconcile different perspectives regarding the application of QbD in regulatory submissions. While QbD concepts described in ICH Q8(R2) and Q11 are seemingly well accepted by the Federal Drug Administration (FDA) and the pharmaceutical industry, recent regulatory experience suggests that the implementation of QbD has created divergent perspectives and expectations.[1] In particular, there has been a lack of clarity and consistency in regulatory expectations regarding characterization and management of risks; delineation of regulatory commitments as a representation of a comprehensive control strategy in non-disclosure agreements (NDAs) and biologics license applications (BLAs); clear risk-based regulatory review and inspection activities; and post approval change management. These topics warrant clarification to maintain momentum and accelerate progress toward improving confidence in the assurance of quality of pharmaceutical products. In particular, this white paper underlines the conceptual context for ICH Q12 and the need to understand implications of QbD for post-approval change management.

Adoption of this guideline will promote innovation and continual improvement, and strengthen quality assurance and reliable supply of product, including proactive planning of supply chain adjustments. It will allow regulators (assessors and inspectors) to better understand, and have more confidence and trust in a firm's pharmaceutical quality system (PQS) for management of post-approval CMC changes.[2]

Background and Context

In several presentations promoting the FDA initiative, Pharmaceutical Quality for the 21st Century, Janet Woodcock challenged the pharmaceutical industry to develop: "A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight.[3]"

From an industry perspective, this was as much an opportunity and challenge for regulators as it was for pharmaceutical manufacturers. In fact, efficient, agile and flexible manufacturing cannot occur without adjustments and modifications to regulatory approaches. Toward that end, the FDA characterized a vision of a desired state, wherein:

- Product quality and performance are ensured through the design of effective and efficient manufacturing processes
- Product and process specifications are based on a mechanistic understanding of how formulation and process factors affect product quality and performance
- Continuous product and process improvement are facilitated
- Relevant regulatory policies and procedures are tailored to reflect the current level of scientific knowledge and associated risk
- Risk-based regulatory approaches recognize:
  - The level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance
  - The capability of process control str ategies to prevent or mitigate the risk of producing a poor quality product[4]

In accordance with this perspective, the emergence of ICH Q8(R2), Q9, Q10 and Q11 guidelines emphasized that a prospective science and risk-based, enhanced approach to product development and lifecycle management could increase the assurance of quality in the manufacture of pharmaceutical products beyond traditional, constrained manufacturing processes. Collectively, these guidelines reinforced the adoption of risk–based (Q9) and science–based mechanistic approaches (Q8(R2) and Q11) within a robust pharmaceutical quality system (PQS Q10). While many of the tools described in these ICH guidelines were not, by themselves, new, the implementation of the concepts within a more systematic, prospective and integrated framework introduced a fundamental paradigm shift in product development and manufacturing. In addition, they offered a pre-emptive opportunity for manufacturers to mitigate risks, simplify the manufacturing process commitments, and potentially reduce issues and costs in development and manufacturing.

The adoption, implementation and conveyance of QbD in regulatory submissions were not intended to change or increase the regulatory standards for product approval. The primary objective of embracing QbD was, and is, to increase the understanding of process, material and product variability and develop and implement a robust product control strategy, that improves the assurance of product quality through a product's lifecycle. By appropriately characterizing risks and understanding how those risks influence or impact quality attributes of the product, and by extension, the patient experience, a company can more effectively design, develop, and manage changes in manufacturing variables to meet pre-defined specification criteria and reliably assure product quality.

Understanding Process Variability

Initially, companies cautiously embraced QbD, attracted by the prospect that investing in product and process development would afford opportunities to achieve meaningful measures of regulatory flexibility.

"A greater understanding of the product and its manufacturing process can create a basis for more flexible regulatory approaches. The degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided in the registration application. It is the knowledge gained and submitted to the authorities, and not the volume of data collected, that forms the basis for science- and risk-based submissions and regulatory evaluations. Nevertheless, appropriate data demonstrating that this knowledge is based on sound scientific principles should be presented with each application." [5]

Companies adjusted their development strategies by adopting better documented and more comprehensive risk assessment processes and by improving prioritization of experiments designed to prospectively understand sources of manufacturing variability and their impact on critical quality attributes. By applying principles of quality risk management (QRM) during product design, process development, and technology transfer, several companies, particularly those that participated in the FDA's pilot program,[6] demonstrated increased assurance of product quality. This prospective investment reflects a paradigm shift from traditional development (an unchanged process giving an unchanged product, controlled by specifications linked to process capability) to an enhanced approach, wherein well-understood process variability is effectively managed within a control strategy that assures product quality.[7,8]

Aspects	Traditional	QbD
Pharmaceutical Development	Empirical, Focus on optimization	Systematic, Multivariate experiments, Focus on control strategy and robustness
Manufacturing Process	Fixed	Adjustable within design space, supported by robust quality systems
Process Control	Some in-process testing	PAT utilized, Process operations tracked and trended
Product Specification	Primary means of quality control, based on batch data	Part of the overall quality control strategy, based on desired product performance
Control Strategy	By testing and inspection	Risk-based control strategy, real-time release

Table A

Industry experience to date has demonstrated that implementation of QbD principles has also reduced the frequency of recalls, technical anomalies, manufacturing failures or deviations, etc.[9-12] Perhaps most significantly, understanding the sources of variability in the manufacture and control of a product has improved process capability, reduced manufacturing problems, and improved quality assurance and supply chain reliability.

The FDA recognized technical benefits of QbD for industry: enhanced product and process understanding and more comprehensive control strategy; increased manufacturing efficiency; higher level of assurance in product quality; reduced frequencies of out of specification (OOS) results, rejects, and recalls.[13] The FDA also acknowledged that flexible regulatory benefits could accompany QbD regulatory submissions:

- Risk-based regulatory decisions (review and inspection)
- Real-time quality control, leading to a reduction of end-product release testing
- Process improvement within an approved design space without further regulatory review
- Reduction of post-approval submissions[14]

While the technical merits of QbD are not a point of contention, the manner in which implementation of QbD has been translated into a regulatory submission and managed over the product lifecycle has been a source of divergent perspectives between industry and FDA.

Implementation of QbD in Regulatory Submissions

The ICH guidelines inadvertently introduced a conceptual challenge for the preparation, review, and prosecution of regulatory submissions, inspections and management of post approval changes. The vernacular that accompanied the QbD concepts: design space, control strategy, criticality, quality attributes, process parameters, etc., were described using relatively broad criteria. As a result, a variety of regulatory interpretations emerged. Translating technical and risk-based merits of increased process understanding into a regulatory submission raised many questions:

- What are the regulatory expectations for regulatory commitments?
- How do regulatory commitments reflect or represent a comprehensive and robust control strategy?
- How are regulatory commitments used to assess the regulatory impact of change management?
- What level of detail is appropriate in a regulatory process description relative to a master batch record?
- How is design space used as an important element of a comprehensive control strategy?
- Is there universal understanding that regulatory commitments, including design space, describe a product control strategy?

- How does application of the enhanced approach affect manufacturing process descriptions and post-approval change management?
- If a company effectively demonstrates process understanding, can regulatory commitments be limited to process descriptions containing those variables that are demonstrated to be critical to product quality with an appropriate justification?
- How are risk assessments conducted and used to establish (and manage changes within) design space?
- How is prior knowledge shared and used to justify risk assessment conclusions?
- Should a continuum for managing change within design space be defined – what is assessed, and how are changes justified?
- What constitutes appropriate design space verification on a commercial scale?
- What are the regulatory expectations for communication of changes within a design space?
- Does a design space have to be completely verified on a commercial scale to be approvable or does the control strategy adequately provide confidence in quality?
- How can a sponsor applying the science and risk-based approach to obtain better understanding but not claiming an enhanced approach (such as design space) avoid being penalized with punitive criteria during the regulatory review?
- How is residual risk defined and communicated?[15]
- How will QbD serve as the basis for exercising continued process verification (CPV)?
- Would a summary of risk assessments be sufficient to include in regulatory files?
- Do process parameters and material attributes have to be distinguished as critical or non-critical?
- Should design space be characterized as part of a comprehensive control strategy?
- How should a comprehensive product control strategy be described in a regulatory application?
- Should the CTD be modified to accommodate the articulation and description of a control strategy?
- What level of detail of the increased volume of data generated should be submitted for review vs. made available for inspection?
- How is a control strategy managed through the lifecycle to assure continuity of quality?[16]

These questions reflect some measure of misalignment between industry and FDA and suggest the need for enhanced and technically meaningful risk-based regulatory approaches, review and oversight. In fact, the FDA recognized the need for clarity as well. A summary of the outcomes from the FDA's QbD pilot program, while noting, "various flexible regulatory approaches were proposed,"[17] identified several remaining challenges :

- Level of detail in submissions demonstrating QbD application
- Industry's continued apprehension in sharing information, including failed experiments, with the FDA
- Expectations for a QbD-based submission while addressing traditional requirements
- Providing regulatory flexibility while assuring product quality
- Cultural changes needed in industry and by the FDA
- More resources needed initially for industry and the FDA[18]

Effectively and transparently conveying enhanced process understanding and product knowledge beyond what is traditionally provided in the regulatory submission has been a challenge. The translation of design space, control strategy, criticality, etc., into regulatory submissions has differed from company to company and from regulatory submission to submission. Cumulative regulatory experience suggests the divergence of expectations for enhanced regulatory submissions is largely associated with a pervasive and misaligned understanding and appreciation for managing risk and different expectations on how to appropriately satisfy and convey a comprehensive control strategy through a product's lifecycle. In addition, traditional regulatory criteria and review practices have limited a company's ability to effectively convey improved confidence in quality associated with enhanced understanding, leading to the following issues:

- A prescriptive and segmented CTD format that does not lend itself to effectively describing a comprehensive control strategy,
- A traditional regulatory review process that typically relies on empirical data as the basis for assessment and may not accommodate enhanced process data
- Traditional inspection criteria that are not, in all cases, integrated with review of an application,
- Enhanced regulatory approaches to expedite and facilitate post-approval changes rather than impede innovation and continual improvement,
- Punitive rather than incentive based requirements, and
- Inconsistent classification and unsatisfactory options for expediting post-approval changes.

For both regulators and industry, conveying a robust and comprehensive control strategy is indispensable to improving enhanced regulatory applications. The differences between industry and FDA are not simply related to increasing operational flexibility. They concern unequivocally establishing a product control strategy that provides confidence in quality throughout a product's lifecycle that will improve regulatory review and management of post approval changes. Ideally, for all parties, innovation and

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continual improvement could largely be managed within a company's pharmaceutical quality system without the need for extensive regulatory review and approval as long as the control strategy for the product remains comprehensive and robust through the product lifecycle. During the FDA pilot program, various proposals for a CMC post approval change management plan (PACMP) were tentatively entertained but never materialized. The PACMP was intended to foster continual improvement by providing clarity in defining regulatory commitments (control strategy) and simplifying the regulatory process for post-approval changes, i.e., substantial regulatory flexibility.[19]

Proposal for Regulatory Commitments and Change Management

Industry and the FDA should reconcile the different perspectives on regulatory commitments and lifecycle change management and develop a regulatory platform for effectively describing and conveying design space and control strategy in a regulatory submission. In addition, they will need to clarify regulatory expectations for change management, including suitable mechanisms for assessing and communicating post-approval changes and integrating inspections with regulatory submission reviews.

Regulatory Commitments

Regulatory Commitments describe how a company intends to manufacture and control a product. They include process descriptions, specifications and test methods for the drug product, drug substance, raw materials, excipients, packaging materials and components, and other specified commitments, i.e., stability, change management, and comparability protocols. In conjunction with a robust pharmaceutical quality system, regulatory commitments provide a comprehensive control strategy for the product through its lifecycle. In essence, regulatory commitments represent the company's license to operate by which decisions on post approval changes are made.

Regulatory commitments are distinguished from data, which is provided in an application to justify and substantiate that the regulatory commitments made assure appropriate quality. Regulatory commitments have essentially been used by industry for the last 25 years to assess whether a change in the manufacture, chemistry or control of a product requires a regulatory submission and determine the level of regulatory submission or notification. In most companies, all changes, major and minor, are assessed relative to their impact on product quality within a formal change management system in a company's PQS and in accordance with requisite cGMP standards. Those changes that have been demonstrated by scientific and risk-based assessment to have an impact on critical quality attributes of the product or those changes that will alter a regulatory commitment in an application generally require submission of a supplement, variation or notification.

Through regulatory queries (specific Information Request (IR) letters on product registrations) and at public forums the FDA has indicated that the regulations do not say the process description is the regulatory commitment.[20]

"A company's regulatory commitment is its assurance of product quality. It is not based on the process description, but rather the risk to product quality. Therefore a process description is not the commitment."

The FDA has expressed concern that a regulatory application that proposes a limited, or minimal process description focused solely on critical parameters is not sufficient to serve as a commitment of quality assurance. The disconnection between industry and FDA perspectives has been particularly evident from recent experience with enhanced regula-

tory submissions. Companies performing enhanced science and risk-based development have introduced criticality-focused information in process descriptions (for traditional as well as enhanced submissions) to reduce post-approval obligations to notify FDA of non-critical adjustments, deviations, optimizations and other minor changes. While many companies provide significant experimental detail in the development section of a non-disclosure agreement (NDA) or biologic license application (BLA), the process description has often contained limited detail, focused primarily on the most critical elements of the process. However, as enhanced knowledge is accrued that could allow an applicant to better focus the commitments made regarding process operation and control (i.e. to critical aspects), the FDA has found that this can lead to a minimal process description not in line with the code of federal regulations (CFR) obligations. Better means are needed to allow for the differentiation of commitments and their change management based on the true impact of process inputs and operations.[21] Under 21 CFR 314.50(d)(1)(ii)(c) companies are obligated to provide in the NDA:

"…the proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product or a comparably detailed description of the production process for a representative batch of the drug product."[22]

Within the industry, master batch records (MBR) are typically living documents that are revised routinely to accommodate operational learning and a contemporary understanding of the optimum process conditions and instructions for operators. Most revisions to an MBR do not warrant notification to a regulatory authority, as they do not impact the process description that serves as the regulatory commitment in the approved marketing authorization. The decision as to what constitutes notification to regulatory authorities is addressed within the change management system or may be managed in accordance with an approved change management protocol.

In some other regions, like Japan,[23] regulatory commitments are acknowledged by regulators as binding obligations that represent a product's control strategy. The application form in a Japanese NDA contains regulatory commitments, by which compliance via inspections and post-approval changes are assessed. Underlying all regulatory commitments is the company's adherence to its PQS/cGMP standards, within a change management process that integrates assessments of risk and impact to quality for all changes regardless of whether or not they change the criteria, limits or boundaries in a regulatory commitment.[24]

Change Management

Change management during a product lifecycle is the other fundamental element of a comprehensive control strategy. Regulators have expressed a need to understand how manufacturing changes are assessed, managed, and implemented as a product matures through its lifecycle. Transparency on how decisions will bemade regarding the implementation of a change within the context of the product and process understanding, with or without a regulatory submission, is critical to their assessment of regulatory submissions.[25] Industry acknowledges that post-approval changes of regulatory commitments warrant, at least, notification, and may require regulatory review prior to implementation. However, a unified definition of regulatory commitments and consistent expectations for post-approval change management is necessary to accommodate enhanced process understanding and facilitate and expedite innovation and continual improvement. The mechanism and rigor applied to substantiating changes to the manufacturing operations and control strategy (regulatory commitments in an application) should be commensurate with the technical complexity and the relative risk associated with those changes. A post approval change management protocol. (PACMP), comparability protocol or similar mechanism may serve as a useful and prospective option for agreeing on an appropriate level of regulatory oversight. In addition, consensus on a risk-based regulatory review of post-approval changes should reflect an integrated understanding of a company's change management approach within their respective PQS.

Change management is at the core of chemistry, manufacturing, and control (CMC) lifecycle management of a product and integrates assessments of risk and impact on approved product registrations for all changes regardless of whether or not these post-approval changes change the criteria, limits, or boundaries in a regulatory commitment. Interestingly, while GMP regulations, as described in 21 CFR 210 and 211, are entirely dependent on robust change management, there is no mention of change management or quality system in these GMP regulations. Nevertheless, change management is a key element of a PQS and an effective change management system is intended to promote a lifecycle approach to product quality.[26]

Conveying Confidence in Quality

Traditional development approaches typically rely on detailed process descriptions and specifications (and controls) largely established on the basis of limited manufacturing experience. This approach has historically provided sufficient confidence that quality is suitably controlled in an unchanged process and therefore meets appropriate statutory requirements for approval. This initial position operates in concert with traditional regulatory change management processes to assure lifecycle management of quality.

A company that adopts an enhanced approach, consistent with QbD principles, should not be held to a higher standard with greater regulatory expectations, particularly when increased understanding of manufacturing variability has been established. On the contrary, the application of science- and risk-based regulatory expectations should differentiate enhanced submissions from traditional submissions through more focused process descriptions and controls and more streamlined post-approval change management mechanisms (e.g. post-approval management plans or management of certain changes solely within the company PQS). Increased process understanding should engender higher confidence in quality.

Based on experience with several recent enhanced regulatory submissions, regulators have expressed concerns associated with a lack of understanding of change management. Uncertainty as to how a company manages changes within a quality system, compounded by an apparent lack of transparency to application reviewers and assessors, has reduced rather than increased confidence among regulators. Opportunities to improve the clarity of regulatory commitments and the management of post-approval changes through the lifecycle of a product have prompted the following Pharmaceutical Research and Manufacturers of America (PhRMA) recommendations:

1. Develop a Framework for Establishing Regulatory Commitments in a Submission

Regulatory commitments should be established in a regulatory application particularly for enhanced submissions. Defining regulatory commitments will facilitate regulatory inspections, assure appropriate regulatory oversight for post-approval changes, and ensure continuity of compliance to the approved regulatory application through a product's lifecycle. Appendices 1 and 2 delineate specific sections of the common technical document (CTD) that contain regulatory commitments. These CTD sections are differentiated from the CTD sections that contain information providing data, rationale, and relevant justification substantiating the content of the regulatory commitments. Supporting information includes the development and design history of the product and process, results from risk assessments, prior knowledge, material characterization, data from experiments, studies and validation exercises.

In addition to defining regulatory commitments, an appropriate level of distinction between critical and non-critical process parameters and material attributes will differentiate changes requiring regulatory review from low-risk changes that may be managed within a company's PQS. Non-critical process parameters and material attributes are relevant to the comprehensive control strategy and therefore are included for completeness in a regulatory commitment. However, the focus on continual improvement that warrants prior-approval is largely confined to critical variables. Regardless, any changes to the regulatory commitments may warrant some measure of notification to regulatory authorities commensurate with the associated risk of such a change. Comparability protocols may serve as an example of a proactive notification tool for change communication to the FDA.

2. Enhance Risk-based Approaches to Regulatory Oversight of Post-Approval Changes

Risk-based approaches and expanded post approval change management protocols (PACMP) should be available to provide the manufacturing operational flexibility needed for continual improvement, while maintaining appropriate regulatory oversight of post-approval changes. All changes to a manufacturing process are routinely assessed for their impact on product quality, regardless of whether they are critical or non-critical, or whether the change impacts an approved regulatory commitment. For some changes, the impact may be clearly demonstrated as critical, warranting prior approval by, or notification to, regulatory authorities. Alternatively such changes could be managed in accordance with an approved change management protocol. For other changes, the impact may be clearly demonstrated as not critical, and should be managed within a robust change management system without need for prior notification to regulatory authorities. For changes where the impact might be uncertain, risk assessments, supported by scientific evaluation to demonstrate impact or improve understanding of variability, can support the approval of submissions with an appropriate level of manufacturing operational flexibility.

3. Foster Enhanced Collaboration Between Offices Within the FDA to Streamline Post-Approval Changes

Direct engagement between industry and the Office of Pharmaceutical Quality's (OPQ) of the FDA is necessary to ensure the alignment of data requirements, application content, regulatory commitments, and opportunities for operational flexibility. For this engagement to be effective, the new OPQ should improve collaboration between inspectors/investigators and CMC reviewers and assessors. Roles and responsibilities should be clearly defined for the FDA inspectors and CMC reviewers. Where possible, both assessors and inspectors should be aligned, if not present, at a pre-approval inspection (PAI). Once the license application is initially approved, industry believes that the CMC reviewer must endorse any recommendation by the inspector for changing specifications and acceptance criteria, as reflected in the NDA or BLA, and that post-approval inspections should focus on cGMPs and the effectiveness of the PQS.[26]

Appendix 1: Drug Substance CTD Sections Containing Regulatory Commitments

CTD Section	Regulatory Commitment	Rationale	Examples of Change Management
S.2.1	Drug manufacturer	Must be GMP compliant	Change to alternate GMP compliant manufacturer requires prospective communication to regulatory agency or use of a comparability protocol or PACMP.
S.2.2	Description of manufacturing process and process controls	▸ A summary of manufacturing operating conditions to demonstrate quality of drug substance. ▸ Sufficient detail to allow assessor to understand risks to quality. ▸ Focus on critical material attributes (CMA) of raw materials and process parameters. ▸ Validated prior to commercial launch.	▸ Changes within an approved design space are managed without prospective communication to regulatory agency. Change management should be managed within the MAH's quality system as part of cGMP. ▸ Changes CPPs require prior approval or management via a post approval comparability protocol. ▸ Changes outside stated ranges but non-critical process parameters (NCPPs) do not require prior approval provided adherence to the current approved control strategy. Changes may be managed within the MAH quality system and subject to communication to regulators under some regular reporting mechanism (e.g. annual reporting).
S.2.3	Controls of materials used in drug Manufacture - Including starting material specifications	▸ Ensures control of CMAs and assures suitable quality and reliable supply. ▸ Support quality assurance provided by drug substance specification (tests may be performed in process).	▸ Changes to specification requirements for starting materials (except tightening) require prior regulatory approval (or use of a post approval comparability protocol, e.g., PACMP). ▸ Changes to supplier of starting material managed according to regional regulatory expectations. A PACMP may manage change in supply management (SM) supplier. Changes to non-critical aspects of input material specification w/no impact to the quality of the drug substance can be managed w/in the company PQS and may warrant notification in an annual report. ▸ Changes to CMAs of the drug substance require prior regulatory approval or use of a PACMP, which warrants notification in an annual report unless the impact of the change is understood and managed by downstream controls which warrants notification in annual report. ▸ Changes to non-critical CMA specifications no affect to quality of the drug substance can be managed within the PQS and may warrant notification in an annual report.
S.2.4	Critical controls during manufacturing, etc.	▸ Ensures control of process material/ intermediate CMAs. ▸ Support quality assurance provided by drug substance specification.	▸ Changes to specification requirements (presumed to be critical) for in-process materials/intermediates (except tightening) would require prior regulatory approval or use of a PACMP). ▸ Tightening of specification criteria would require notification.
S.4.1	Specification for drug	▸ Ensures drug CQAs meet appropriate quality requirements and are linked to CQAs of drug product. ▸ Tests may be conducted in-process (but attributes reside in design specifications). ▸ Support to quality assurance provided by the drug product specification.	▸ Changes to specification requirements for drug substance, with the exception of tightening a specification limit, would require prior regulatory approval (or use of post approval comparability protocol, e.g., PACMP). Any change in specification should remain capable of assuring the quality, safety and efficacy of the drug substance across its use period/retest. ▸ Tightening of specification criteria would require notification.
S.4.2	Analytical procedures	Provides information on analytical tests. Sufficient detail to allow assessor to understand the critical aspects of the procedure.	Changes to analytical procedures that impact upon the validated capability of the method to assure the quality of the test item would require prior regulatory approval (or use of a post approval comparability protocol, e.g., PACMP) unless the change is inside an established and approved design space for the method in which case, it warrants notification in an annual report.
S.4.3	Analytical validation reports	Provides information that analytical tests are fit for purpose and can assure quality as required.	Changes to analytical methods may require validation in accordance with a relevant validation protocol.
S.6	Container closure information	Provides information on packaging materials used for drug substance storage, shipment, and supply. Support for drug being of appropriate quality throughout use period.	Changes to aspects of packaging potentially critical to the quality of the drug substance require prior regulatory approval (or use of post approval comparability protocol, e.g., PACMP) unless the change has been shown to be within a packaging design space in which case it warrants notification in an annual report.
S.7.1	Retest period and storage conditions	States the storage conditions that the drug will be stored under and how long the drug can be used without retesting under these conditions.	▸ Changes to retest period or storage conditions require prior regulatory approval. ▸ A post-approval comparability protocol, e.g., PACMP and quality system may be approved to manage changes to the retest timeline, in line with expected stability data.
S.7.2	Post-approval stability protocol / annual test commitments	States how commercial lots will be evaluated in terms of stability to ensure quality is assessed.	

Appendix 2: Drug Product CTD Sections Containing Regulatory Commitments

CTD Section	Regulatory Commitment	Rationale	Examples of Change Management
P.1	Qualitative and quantitative composition of the product formulation	States the active substance content and the excipient content for the product (and manufacturing process).	▸ Changes to the active substance content are not expected. ▸ Changes to critical excipient content or function or to a critical material attribute of a raw material requires prior regulatory approval (or use of a post approval comparability protocol, e.g., PACMP) unless within an established design space. ▸ Changes to non-critical excipient function or quantity can be managed under company quality system, provided quality and stability is assured. Subject to routine reporting (e.g. annual report). ▸ Changes to non-critical excipient function require prior regulatory approval (or use of a post-approval comparability protocol, e.g., PACMP).
P.3.1	Manufacturer(s)	Must be GMP compliant	Change to another GMP compliant manufacturer – needs proactive communication to regulatory agency (or post -pproval comparability protocol, e.g., PACMP).
P.3.3	Description of manufacturing process and process controls	▸ A summary of manufacturing operating conditions for drug product. ▸ Sufficient detail to allow assessor to understand risks to quality. ▸ Focus on critical material attributes and process parameters. Validated prior to commercial supply.	▸ Changes within an approved design space are managed without prior approval and managed within the company's PQS as part of cGMP. ▸ Changes outside the stated ranges of critical parameters require prior approval (or management via a post approval comparability protocol, e.g., PACMP). ▸ Changes outside the stated ranges for filed but non-critical process parameters do not require prior approval, provided the current approved controls were met. Such changes are managed within the company's quality system and subject to routine reporting (e.g. annual report).
P.3.4	Critical controls during manufacture	Ensures control of critical quality attributes of in-process materials and intermediates.	Changes to critical controls during manufacture require prior regulatory approval (or use of a post-approval comparability protocol, e.g., PACMP) except for tightening. Tightening of specification criteria require notification.
P.4	Controls for excipients	▸ Ensures control of critical quality attributes of excipients (may be pharmacopeial) and assures suitable quality and consistency of supply. ▸ Supportive of quality assurance provided by drug product specification.	▸ Changes to excipient specifications that are critical to the quality of the drug product require prior approval (or use of a post approval comparability protocol, e.g., PACMP) except tightening. Tightening of specification criteria would require notification. ▸ Changes to non-critical excipient specifications (do not affect the quality of the drug product) can be managed within the company quality system under cGMP and subject to routine reporting (e.g. annual report).
P.5.1	Specification for drug product	▸ Ensures critical quality attributes of drug product meet appropriate quality requirements. Linked to drug product CQAs and meet quality target product profile (QTPP) of the product. ▸ Tests may be conducted in process (but attributes would be shown on drug product (DP) specification).	Changes to specification requirements for drug product require prior regulatory approval (or use of a post-approval comparability protocol, e.g., PACMP). Any change in specification should remain capable of assuring the quality, safety, and efficacy of the drug product across its shelf-life under approved storage conditions and container closure and packaging.
P.5.2	Analytical procedures	Provides information on analytical tests. Sufficient detail to allow assessor to understand the critical aspects of the procedure.	Changes to analytical procedures that impact the validated capability of the method to assure the quality of the test item would require prior regulatory approval (or use of a post-approval comparability protocol, e.g., PACMP) unless the change is inside an established and approved design space for the method.
P.5.3	Analytical validation reports	Provides information that analytical tests are fit for purpose and can operate to assure quality as required.	Changes to analytical methods require validation.
P.7.	Container closure information	▸ Provides information on packaging materials used for drug product storage, shipment and supply. ▸ Demonstrates drug product is of appropriate quality across its shelf-life.	Changes to aspects of packaging potentially critical to the quality of the drug product require prior regulatory approval (or use of a – potentially general – PACMP) unless the change has been shown to be within a packaging design space.
P.8.1	Shelf-life and storage condition for drug product	States the storage conditions that the drug product will be stored under and how long the drug product may be stored and used (in-use stability).	▸ Changes to shelf-life period or storage conditions require prior regulatory approval. ▸ A post-approval comparability protocol, e.g., PACMP or quality system may be capable of being approved to manage changes to shelf-life in line with expected additional stability data.
P.8.2	Post-approval stability protocol and commitment	States how commercial lots will be evaluated in terms of stability to ensure ongoing quality is assessed.	

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20. Ibid.
21. FDA references several recent regulatory submissions where process descriptions do not provide adequate detail. FDA has expressed concern that a regulatory application that proposes a "limited" or minimal process description focused on critical parameters is not sufficient to serve as a commitment of quality assurance.
22. Code of Federal Regulations. See Appendix 1.
23. Japanese Pharmaceutical Application Law. Increased globalization of pharmaceutical development and manufacture, and increased complexity of supply chains has produced divergent regulatory expectations. Although each ICH region has implemented approaches to support and facilitate CMC changes, the current global regulatory framework is not ideal or consistent among regions. Consequently, the overall framework does not facilitate a streamlined, strategic and globally harmonized approach to managing change. Implementation of global CMC changes can be difficult, slow, and resource-intensive for both the industry and regulatory agencies. This unintentionally inhibits continual improvement and innovation. Streamlined post-approval change management was envisaged as one of the key benefits from QbD. However this perceived benefit is not currently being fully realised, either for industry or the agency.
24. The principle that submissions can contain supportive information is recognized in Section 4 of *Points to Consider* prepared by the ICH Quality Implementation Working Group. "The type of information, as suggested in this document, is considered supportive and is intended to facilitate assessment and inspection without increasing the regulatory requirement." This distinction is the fundamental basis by which industry determines expectations for post approval change management, including the appropriate level of detail in the regulatory submission, if any, for post approval changes.
25. FDA has commented several times on the need to understand how industry manages change through the lifecycle specifically during interactions between FDA and PhRMA on 28 August 2012, 22 February 2013 and in several ISPE, PDA and AAPS conferences from 2011 – 2014.
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HEPA FILTERS, UNSUNG HEROES, USHERED IN 'BRAVE NEW WORLD' OF CLEAN

by Randolph Fillmore

HEPA filters, developed in the 1950s and 1960s for use in the early US aerospace program, enabled current practices in cleanroom technology and pharmaceutical manufacturing.

Since their development in the late 1950s, HEPA filters have had many important manufacturing applications, from microelectronics to aerospace, from everyday home appliance use to airliners. In its unsung role as a particle-removing action super hero for manufacturing processes, perhaps no HEPA filter application has been more important to human health than its application in pharmaceutical engineering, where a manufacturing environment free of airborne contaminants is crucial.

HEPA filters, typically made of fiberglass, can remove airborne particles of 0.3 µm and larger with a 99.97 percent efficiency or greater, as originally required by the Atomic Energy Commission and now required by the Department of Energy. HEPA filters are also required for use in aseptic processing facilities in the US by the US Food and Drug Administration, and required around the globe by international pharmaceutical manufacturing regulators.

Sturdy work horses since the late 1950s, HEPA filters are comprised of a filter frame (historically made of many materials, including plywood, aluminum, and stainless steel); filter media (fibrous materials); separators (cardboard or aluminum pleats, or later, molded elements); bond material (which act as a glue to attach the media to the frame); and a gasket or gel fluid seal to ensure air goes through, not around the filter.

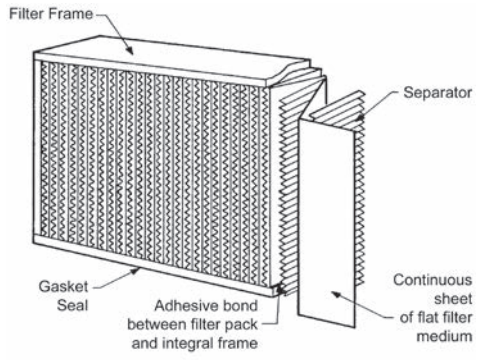

Figure 1. HEPA filter construction

Particles are removed from the air stream by HEPA filter fibers through a combination of three mechanisms: impaction, interception, and diffusion.

"Impaction is a collision, pure and simple," explains David Brande, lead consultant with Cleanroom Project Management Inc., "The particle goes straight ahead and collides with the fiber, unlike the airstream which separates and rejoins after hitting the fiber."

Inertial separation occurs, explains Brande, when particles are unable to follow the stream lines as they move around a fiber, separate, and contact the fiber; that is a process that most of us associate with all types of filtration. Inertial effects are greater for larger particles and at higher flow rates.

Interception is most effective method for removing larger particles simply because of the geometries involved, says Brande.

"Interception is explained by the effect a larger body has on a much smaller entity, when all particles bond to the filter fibers by what is called Van der Waals forces, more easily understood on a much larger scale, as the attraction of the moon to the earth," he explains.

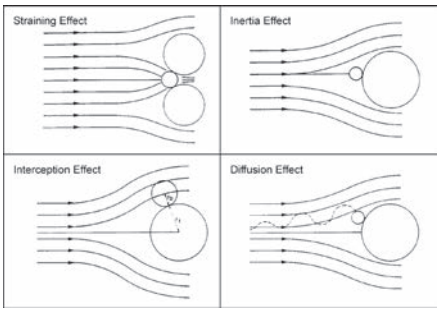

Figure 2. Filter effects

According to Brande, diffusion occurs on particles less than 1.0 µm due to the intrinsic natural random bombardment of these small particles (Brownian movement) by gas molecules of the airstream. It is a significant collection mechanism for small particles. As particles move around a fiber, the randomness of their motion brings them into accidental contact with the fiber and they are collected when that occurs. Diffusion effectively decreases as the particle size increases.

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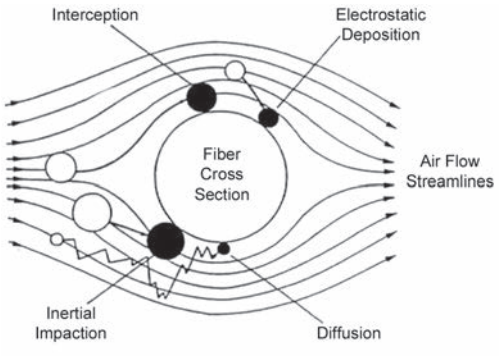

Figure 3. van der Waal's force

Capturing Gas Masks, Circa 1942

"You could say that the age of high efficiency air filtration began in 1942 when the British sent us some captured German gas masks," says George Cadwell, retired Vice President of Flanders Filters and currently a consultant to Flanders Filters. "The gas masks were sent to the US Army's Chemical Warfare Service Laboratories at Edgewood Arsenal, Edgewood, Maryland. After careful analysis, scientists there discovered that the masks used filter paper made from fine asbestos dispersed into esparto grass. They found that the Germans were way ahead of us in high efficiency filtration."

According to Cadwell, the US scientists found that the German-made masks had unusually high particle retention characteristics, good resistance to airflow and dust storage, as well as resistance to plugging from oil-type smoke screens, a deficiency in the resin-wool filters then being used by the British forces.

According to David Crosby, Vice President of Filter Testing at Air Techniques, International, Draeger Werke had patented this gas mask media in 1933. The US Army had carried out no gas mask development after World War I and, consequently, was "way behind." But, in 1942, the US government wanted gas masks as efficient as the German gas masks, and they wanted them yesterday.

"Wendell Anderson was working for the US Navy in the 1940s and he got the job of developing a comparable filter paper," says Cadwell. "The army and the US Naval Research Laboratory worked together with a paper manufacturer to reproduce the German version and to manufacture paper media in large quantities. Andy had to develop and source the fibers for the filter paper, then test it."

According to Crosby, Anderson worked with a domestic media manufacturer, Hollingsworth & Vose, to simulate the paper found in the German gas masks. Thus began the US military's classified effort to develop high efficiency filter paper, which involved experimenting with a variety of materials, including cellulose, cotton, wood pulp, esparto grass, and asbestos.

HEPA Filter Genesis

The use of membranes as a filter medium goes back to the 1880s when rudimentary filters were used in an attempt to protect industrial workers. The earliest filters used cellulose materials that were gelled and dried and used mainly to filter liquids because they were unstable when dry.

"After WWII, most of the Manhattan Project personnel morphed into the Atomic Energy Commission," says Crosby. "Humphrey Gilbert, a safety engineer involved with HVAC systems at Oak Ridge, was not happy with the larger army space filters. So, in 1948, the AEC gave a contract to A.D. Little Company. to develop a more efficient, lower resistance filter for nuclear and military HVAC systems. Part of this contract was to also locate a manufacturer."

It was Walter Smith who came up with the idea of using a corrugated cardboard separator to replace the solid cardboard separators in the Army Space Filter, say Cadwell and Crosby. This innovation reduced the air flow resistance tremendously and led to the beginnings of the current HEPA filter.

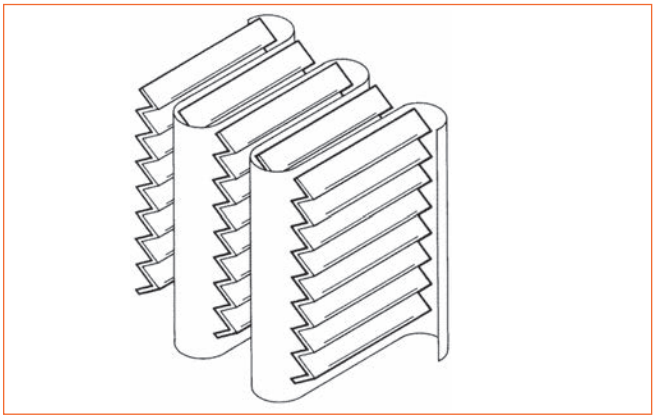

Figure 4. Pleats

"[Smith] was friends with the owner of Carrier and talked the company into manufacturing these filters when all the bugs were worked out," recalls Crosby. "They named the company Cambridge after the Massachusetts location of A.D. Little. Sam Allen of Flanders Filters also was interested and got on the band wagon."

These filters (not yet known as HEPA filters) were being developed for the production of nuclear materials and for protection against chemical warfare, not only for individual protection, but also for protecting those working in buildings, such as operational headquarters. For this purpose, the US Army had developed a mechanical blower and air purifier known as a collective protector, designed to remove chemical, biological, and radiological particulates.

"This was all top secret and the technology wasn't released to the public until late 1957," recalls Crosby. "This was due to the advent of many nuclear power plants coming on line which required these filters, plus Sputnik that launched us into the aerospace industry. Soon to follow were white rooms and pharmaceuticals, along with numerous industries that required particle-free air for manufacturing."

Early HEPA Filter Development Time Line 1940s – 1960s

1940s

1942 – Wendell Anderson works with a domestic media manufacturer to simulate the paper found in captured German gas masks. Classified military development of high efficiency filter paper begins using cellulose, cotton, wood pulp, esparto grass, and asbestos.

1945 – US military needed filtration of room areas for people and used gas mask media for a pleated filter for larger air flow; it became known as collective protection.

1948 – Arthur D. Little. Inc. is contracted to develop a better Space Filter. Walter Smith comes up with corrugated cardboard separator idea, used cardboard spacers between pleats, which offered high resistance.

1940s Nobel Laureate Irving Langmuir studies particle retention, discovers principles of interception and diffusion, and recommends testing minimal particle size of 0.3 µm to determine efficiency; a penetrometer is developed to test the new high efficiency gas mask paper media.

1950s

1950s – Initial instillation of HEPA filters at Oak Ridge National Laboratories' graphite reactor leads to the conclusion that HEPA's needed to be field tested. In situ testing is born and the Q107 Penetrometer is the tool.

1950 – First air cleaning seminar held at Harvard; 1950's radioactive containment at Oak Ridge, Hanford, Rocky Flats, Idaho Falls.

1956 – Military develops apparatus to test filter unit and related products

1960s

1961 – Humphrey Gilbert, formerly a Manhattan Project safety engineer working at Oakridge, presents his High Efficiency Particulate Air Filter Units, Inspection, Handling, Installation manual to the Atomic Energy Commission. Coins term HEPA filter.

1961-62 – Willis Whitfield develops clean room, concept of laminar flow at Sandia.

1960s – HEPA filter early applications – nuclear, U.S. Navy, rockets, guided missiles for Cold War; manufacturing film, Kodak, and Du Pont; new aerospace and semiconductor industries

Capturing Particles, Circa 1960s

The optimum particle removing efficiency of the best absolute filters during the late 1950s and early 1960s was 99.95% for 0.3 um particles. Their efficiency was later increased to 99.97% for the same size particles and became the regulatory benchmark for efficient filtration – as it remains today – even as the earliest high efficiency particulate air filters were just being developed in the early to mid-1960s.

The acronym HEPA was coined by filter pioneer Gilbert in the early 1960s when he was working at the Atomic Energy Commission's Oak Ridge (Tennessee) facility. According to Cadwell, Gilbert also called the HEPA a heapa filter because for him it was "a heap of a filter".

> ▸ *"…dust particles. Where are the rascals generated? Where do they go?"*
> Willis Whitfield, 1961 ◂

The 'Thinking Man's' Filter?

Because of its 99.97% efficiency at removing 0.3 µm particles, the HEPA filter became the filter of choice for the early aerospace and semiconductor industries. A bigger testing step forward came when HEPA filters could be tested and validated through the development of portable light scattering photometers and a process for the in-place testing of HEPA filters. According to Crosby, the initial instillation of HEPA filters at Oak Ridge National Laboratories graphite reactor lead to the conclusion that HEPA filters needed to be field tested.

The portable, light scattering photometer was the brainchild of David Sinclair and was improved by Sam Steinberg, who in the 1940s was working at Edgewood, but left in the early 1960s to start Air Techniques Inc. to build penetrometers and calibrate penetrometer meters.

"By the 1970s, scan testing of HEPA filters using the photometers was safe and effective and provided a nondestructive method for validating the performance and integrity of HEPA filters," says Milholland. "An artificially generated aerosol challenge was used to locate HEPA filter defects.

"Sam Steinberg was a pivotal figure because he worked in both particle containment and unidirectional flow," says Cadwell.

When he presented a paper at the 1965 meeting of the American Association for Containment Control (AACC), Steinberg not only raised interest in raising the bar from 99.97% to 99.99% efficiency, but also raised interest in HEPA filter testing in place and on site for leaks. But interest was not raised right away. Cadwell recalls that after Steinberg's presentation some said: "Who cares?

We already have 99.97!" But Cadwell also recalls that among those who did care were engineers working for Western Electric and Texas Instruments.

Willis Whitfield – "Dr. Clean" Time Magazine, April 1962

In 1961 Willis Whitfield and colleagues Claude March and Gordon King, working at the Sandia Laboratory, discovered that the air emerging from newly developed HEPA filters did so at a uniform and predictable speed and that the flow could carry away particles in its path. That phenomenon has become known as laminar flow. The term laminar flow is, however, a misnomer that has been widely adopted. The term unidirectional flow is more technically correct.

Unidirectional flow became the foundation for clean rooms, also developed by Whitfield, in which manufacturing processes – uncontaminated by dust and other particles – were required.

Whitfield and colleagues had been charged with solving a manufacturing problem for Sandia nuclear weapons components that needed to be free of microscopic dust particles. The use of unidirectional flow in clean rooms lowered dust counts to near zero, as compared to dust counts of one million particles per cubic foot in the best clean rooms of the time without the innovation.

"Whitfield is credited with patents on both clean rooms and clean benches," says David Brande. "The Atomic Energy Commission later released those patents for public use."

"The industry would not recognize the full impact of Sam's recommendations until 1966," recalls Cadwell. "The 99.99% efficiency was worked out in AACC sub-committee meetings."

Testing HEPA filters

Pharmaceutical clean rooms require extensive, in situ HEPA filter integrity validation. Filter integrity measurements include tests for leakage in the media or in the sealant, frame or gasket. Typically, testing is at six-month periods for GMP grade A aseptic processes. The most common testing tools are the aerosol photometer and the discrete particle counter.

HEPA to ULPA and Beyond

While the HEPA filter is still "a heap of a filter," the ultra-low penetration air filter, the ULPA, made its entrance some time ago. The advantages of ULPA versus HEPA have been debated. A HEPA air filter removes 99.97% of particles that have a size of 0.3 µm. An ULPA filter can remove from the air at least 99.999% of dust, pollen, mold, bacteria, and any airborne particles with a size of 100 nanometers (0.1 µm).

"There was some resistance to the advent and promotion of the ULPA filter," notes Cadwell. "Some claimed that ULPA was snake oil, or done with smoke and mirrors, even sleight of hand."

However, in a new century, new products are changing both HEPA and ULPA.

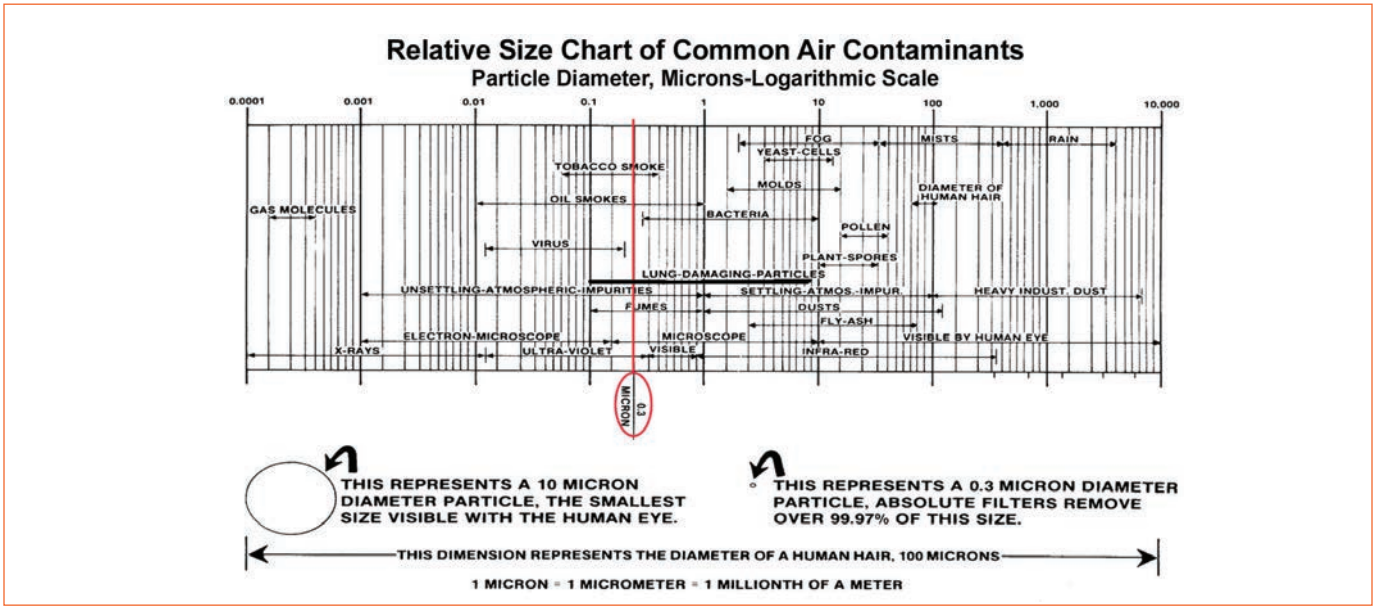

Figure 5. Containment sizes

For example, EPTFE filters were first developed by W. L. Gore Company in 1994. It was a Gore-Tex filter – expensive, but with a very high resistance to airflow. Teflon is the DuPont trade name for ePTFE and, according to Milholland, American Air Filter International has made the practicable use of ePTFE by reducing cost, reducing the resistance to airflow, and refining the media to a point where oil-based challenge aerosols are acceptable for integrity testing.

For Milholland, AAF International's ePTFE membrane media constructed of nano-scale fibers represents the filter of the future. It has a high resistance to damage and approximately half the resistance to airflow. The AAF ePTFE media, he says, is being used widely for filters in use in Europe and Asia.

Also, based on a patented membrane media of evenly distributed nano-scale fibers with high resistance to damage, NELIOR filtration technology is providing added value benefits to both HEPA and ULPA filters. NELIOR media, says Milholland. It is also being used extensively for filters in use in Europe and Asia.

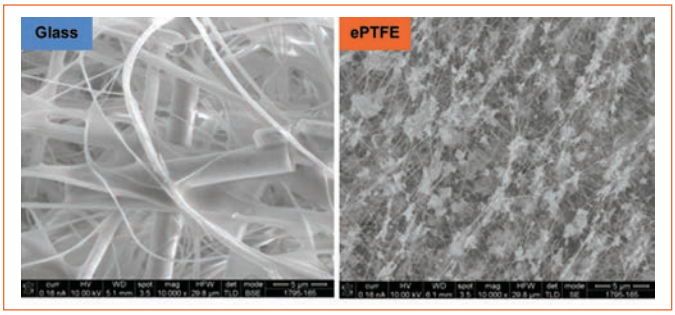

Figure 6. Glass and ePTFE HEPA filter media

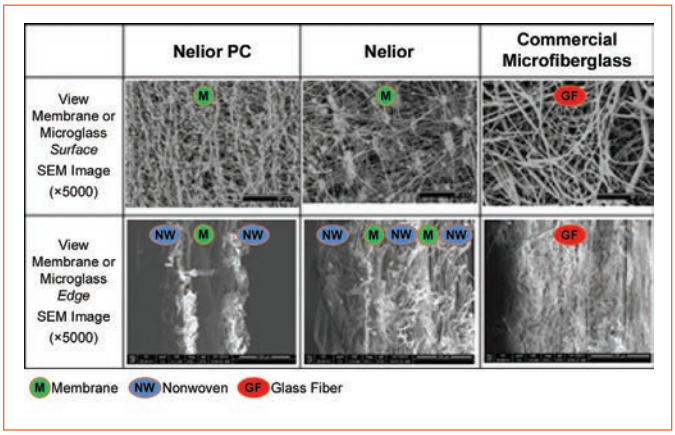

Figure 7. What is NELIOR and NELIOR PC?

The next decade promises developments in new filter materials and the development of rigorous test methods to suit the new materials. Also, improved monitoring systems and processes for continuous monitoring are being developed. What other changes are in store for this unsung hero of the industry?

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TESTS ON ROUGING AND EXPERIENCES DEALING WITH ROUGING IN PHARMACEUTICAL PRODUCTION (PART 1 OF 3)

by Thomas Blitz, Ernst Felber, Robert Haas, Birgit Lorsbach, Andreas Marjoram, Roland Merkofer, Tobias Mueller, Nathalie Schuleit, Marc Vernier and Thomas Wellauer

Part 1 of this article discusses the current body of knowledge on the subject of rouging. It is based on insights from tests and operating experiences of companies that manufacture pharmaceutical medicinal products.

Stainless austenitic steels represent a primary structural material in pharmaceutical production. Despite the use of this high-grade material, however, extensive changes of surface color can often be observed after some time.

The equipment primarily affected by these changes includes, in particular, purified water systems with hot storage and distribution, clean steam systems, and also production equipment that is regularly sanitized or sterilized.

In order to investigate and appraise the influence of these surface changes, which are known as rouging, the companies Ateco Tobler AG, Bayer AG, DSM, Intertek, Merck KGaA, Novartis, and Roche have collaborated since 2007 in the Arbeitsgruppe Rouging (Rouging Working Group).

The objective of this working group is to collect available knowledge about this corrosion phenomenon and to make it accessible to the working group members. Furthermore, test concepts were developed in order to expand the existing knowledge, so that the problem of rouging can be dealt with responsibly in pharmaceutical production.

The basis for the development of test concepts is a compilation of the risks potentially associated with rouging. For this purpose, worst-case conditions were defined for individual tests, in order to cover even unfavorable production conditions with the conducted tests.

The insights gained in the working group are presented in this article. In this way it is hoped that personnel responsible for production will be able to understand the risks associated with rouging and to appraise its impact on pharmaceutical production.

Comments on Existing Literature

A large volume of literature focuses, for example, on the passive layer of stainless steels. Numerous articles have also been written on the subject of rouging and rouging mechanisms. A literature search aimed specifically at information about the key words rouging, discoloration and passivation was conducted in the following databases: ISI Web of Science, Google Scholar and RWTH Aachen University Library. The literature search yielded the following information:

Chemical composition: Analyses of rouging wipe samples have shown that they consist predominantly of iron oxide with a low proportion of chromium oxide and very little nickel oxide. Iron oxides in the form of Fe_2O_3 and Fe_3O_4 have been mentioned as possible iron compounds, as have iron hydroxides (FeO(OH) and $Fe(OH)_3$) and iron carbonate $FeCO_3$.[1]

Various theories about the mechanism of rouging exist and will be briefly explained below:

- Ion pull theory: This assumes an active-to-passive transition of the material condition, resulting from precipitation of iron hydroxide on the surface due to the low solubility of iron in the system.[2]
- Pseudo passivity theory: The corrosion rate in the passive condition is elevated because of the high exposure temperatures.[3]
- Iron contamination of the surface: The surface of the austenitic stainless steel may be contaminated in the course of manufacture by iron from tools made of low-alloy or unalloyed steel. The ingress of iron particles from other components, such as pumps, is also placed in this category.[1,4-5]
- Ion contamination in the water precipitates on the surface: Because of the presence of oxygen and/or carbon dioxide, insoluble iron particles are formed from iron ions present in the solution.

  The influence of halide ions is also mentioned, although these contaminants are not relevant for the high-purity water used in pharmaceutical production.[1,6-7]
- Microcorrosion by impurities: Local galvanic elements are formed on the surface because of impurities.[4,8-9]

The following influencing variables with different effects will be discussed:

- The presence of CO_2 causes the pH to shift into the weakly acid range, thus favoring the development of rouging.
- The influence of oxygen has not yet been conclusively clarified, although by virtue of its redox potential it could favor both the development of rouging and the repassivation of the material.
- The presence of a nitrogen atmosphere favors the occurrence of rouging.[10]
- The occurrence of rouging is favored by higher temperatures. The explanation is that dissociation of the water molecules increases with rising temperature, thus shifting the pH from the neutral to the weakly acid range.

Furthermore, the gas solubility decreases and at the same time there is an increase of the reaction of CO_2, for example, with water. As a result, the free corrosion potential shifts to lower values with rising temperature.[11]

Judging from experience, the occurrence of rouging depends on the system type, operating conditions, and material used, usually after an operating time of between one month and two years. Investigations have shown that materials have different sensitivities to rouging. The resistance seems to increase in order from AISI 304 (1.4301) < AISI 316 (1.4401) < AISI 309 (1.4828), although this cannot always be unambiguously verified.[10] The occurrence of rouging cannot be ruled out, even for high-alloy CrNiMo alloys.

At one time, it was suspected that the delta ferrite content in the material would have a strong influence on rouge formation, but more recent investigations have not provided any confirmation for this.[12]

The surface condition in turn has a distinct influence on the development and extent of rouging. Ground samples exhibit much greater susceptibility to rouging than electropolished samples, for example.[10]

Particles that may be formed during rouging have been separated by filters in WFI circuits. Their sizes were between 0.01 and 1 µm. Material removal rates of < 0.001 to < 0.0001 mm/a (millimeters per year) have been measured on aged corrosion specimens exhibiting visible rouging.[12]

The data available in the literature provide the first hints about the phenomenon and development of rouging. Because the investigation results available to date are only few and far between, supplementary investigations have been carried out by the Rouging Working Group. Further motivation for these investigations was, in particular, the lack of results pertaining to consequences for the practice of pharmaceutical production.

The conduct of these investigations and the results obtained from them are described in Part 2 Section 2.

Materials Engineering

Bases

The corrosion-resistant steel alloys 1.4404 and 1.4435 are primarily used in pharmaceutical production. The main alloying elements in material 1.4404 are chromium, nickel and molybdenum. Material 1.4435 is somewhat higher-alloyed than material 1.4404 and therefore is also somewhat more corrosion-resistant. The AISI does not distinguish between these two materials and lumps them together under the designation 316L. Material 1.4571 (AISI 316Ti), which at one time was used frequently, corresponds substantially to material 1.4404 as far as corrosion resistance is concerned. Because of its higher carbon content, however, titanium was added as an alloying element in order to bind carbides. Currently, material 1.4571 is used only infrequently in new systems.

If even higher corrosion resistance is required, the higher-alloyed material 1.4539 (AISI 904L) or a nickel-base alloy such as 2.4602 may be used.

VPHP Decontamination of Surfaces Contaminated by Chemicals and Biochemicals

Libor Pánek (BLOCK®),
Jiří Kovařík (ICT Prague), Petr Kačer (ICT Prague)

This article presents possibilities of the decomposition of API by VPHP.

In recent years, PHP has been implemented to severalnew areas of application, including the biological decontamination of clean rooms, laboratories, production machinery,anddifferent types of process equipment. Prominent benefits of VPHP include its bactericidal effects and its superior reach into spatiallyobstructed surfaces and areas. Due to VPHP technology having been recognized to possess a significant sporicidal capability, it is especially suitable for the decontamination from UV-resistant microorganisms and chemicals. Besides the general spatial decontamination, VPHP offers a uniquely efficient solution for the decontamination of equipment and its parts, where UV-radiation is prevented from its access, but susceptible to air and liquid pollution, as well as spills, often involving high concentrations of pathogenic organisms. While liquid disinfectants are of a limited value for reaching inaccessible areas, vapor-phase germicides offer obvious penetration advantages. Formaldehyde and ethylene oxide, the vapors commonly used for centrifuge decontamination, require extended exposure times to achieve sterilization and are toxic or carcinogenic.

Conversely, VPHP provides rapid inactivation rates even at low temperatures and decomposes to water vapor and oxygen. VPHP thus offers an effective and safe alternative to currently used disinfectants. Last but not least, VPHP can be predicted as a unique useful tool to decontaminate facilities where electrophoreses are practiced. Here it is able to decompose the frequently used highly toxic chemicals as ethidium bromide and acrylamide used to label nucleic acids and prepare polyacrylamide gel, respectively.

Potential harmful effect of VPHP oxidizing potential towards various construction materials used in the above mentioned facilities have been either displaced by evidence or have not been proven.

Although a concentrated VPHP atmosphere, a strong oxidizing agent is ideallysuitable for the degradation of chemical contaminants, only very few scientific articles in this area have so far been published. This is because VPHP research has solely been focused on bio-decontamination.

We have studied the potential of VPHP for the degradation of active pharmaceutical substances, following a thorough screening of the wide variety of registered active pharmaceutical ingredients and their chemical and physical properties,on selected groups: analgesics, antibiotics, an antiepileptic, antifungal and antirheumatic drug, a steroid hormone, immunosuppressants, ergot alkaloids and anti-cancer drugs.

Although diverse in structure, they bear substantial common features (i.e. functional groups). Conspicuously, many of the pharmaceutical substances were resistant to the treatment by VPHP and remained intact after 12 hours of exposure. However, some of the compounds were highly sensitive to VPHP and underwent significant chemical changes. The sensitive substances were sulfonamides, amoxicillin, ergot alkaloids (except for bromocriptine) and anti-cancer drugs imatinib, methotrexate and platinum cytostatics.

It can be deduced from the data that substances sensitive to VPHP are those containing in their structures a tertiary nitrogen atom.However its type is pivotal: amine group undergoes degradation under VPHP exposure, whereas the amide group remains intact. It is obvious that the overall molecular constitution plays a very important role, which was demonstrated by the example of the ergot alkaloids (ergines and ergopeptines).

Ergines are formed either by an ergolene or dihydroergolene structure, while ergopeptines contain an additional peptide moiety bound via an amidic group. Although these substances are similar in their structure, the VPHP degradation proceeded in a different manner. Ergines (i.e. nicergoline, lisuride and pergolide) underwent a complete degradation with a mixture of lower aliphatic hydrocarbons detected as degradation products.

However, in ergopeptines, only the ergolene or dihydroergolene moiety degraded and the peptide structure remained intact. The structure of bromocriptine did not change at all.

Hydrogen peroxide vapour generator made by BLOCK®

These observations unambiguously confirmed that the presence of an aliphatic tertiary nitrogen atom in the structure facilitates its degradation by VPHP. It is also known that the tertiary nitrogen atom and H2O2form an N-oxide that can undergo a low-temperature-Cope elimination, leading to a corresponding

alkene and N hydroxylamine. In ergopeptines, N-oxide moiety remains intact as it contains only amide nitrogen. The resistance of bromocriptine to VPHP can be attributed to the presence of bromine in its structure, as it is well known that halogens deactivate some structures due to their negative inductive effect. It can be concluded that VPHP is highly effective for the degradation of ergot alkaloids, except for the aforementioned bromocriptine.

Nevertheless, the degradation path of other structures containing tertiary aliphatic nitrogen, were rather surprising. Imanitib, containing 1-methylpiperazine bearing two tertiary aliphatic nitrogen atoms, reacted to corresponding di-N-oxides. Loss of imatinib biological activity due to such a small structural change is yet to be revealed. The degradation products of morphinane compounds, such as buprenorphine and butorphanol, have also been unexpected. Even though a facile degradation was expected due to the presence of a tertiary amine nitrogen atom, the experiments confirmed forming N-oxide species as well as other products.Methotrexate underwent a complete degradation, yielding to a complex mixture of degradation products. NMR spectra indicated a presence of several components of certain common features. Obviously, the glutamic part of the molecule was not affected by VPHP.

Therefore, we deduced that structural changes took part in the pyridine moiety, where oxidation and/or condensation reactions were the most plausible. Hence, we believe that this substance lost its biological activity by the action of VPHP. In the case of successful degradation of amoxicillin, the sulfur atom was oxidized to higher oxidation products (sulfoxide→sulfone).

It can be concluded that the decontamination of pharmaceutical substances by VPHP is possible and useful for various compounds.

However, the method is not universally effective and requires a verification test of applicability for every compound. Such validation is a common practice and requirement applied to all currently used decontamination methods, therefore it should not be considered as a disadvantage of the presented method. The VPHP-susceptible molecular fragment was identified; an aliphatic tertiary amino group is easily oxidized by VPHP to a corresponding N-oxide becoming a starting point for further degradation processes, as shown in the case of ergot alkaloids.

Nevertheless, this assumption did not apply to all substances and the difference in their sensitivity to VPHP had to be ascribed to their overall molecular constitution. It can be anticipated that the compounds, which were degraded in the VPHP atmosphere, have most likely, either completely or partially (to N-oxide), altered their biological activity. In-vitro tests of biological activity will confirm this assumption and provide a definite proof of VPHP suitability for the decontamination of tested chemicals.

(Libor PANEK, senior product manager, panek@blocktechnical.ch)

The elements chromium and molybdenum are mainly responsible for the good corrosion resistance of stainless steels. The nickel content ensures that an austenitic microstructure can be preserved at room temperature despite the high chromium and molybdenum contents. Chromium is responsible for the development of the chromium-rich passivating layer, which actually is protective, on the material surface. Depending on the literature reference, a chromium content of at least 10.5 to 12% is necessary for development of a completely closed passive layer.[13]

The molybdenum is used to increase the resistance to pitting corrosion, which is of great importance in chloride-containing media. Nitrogen incorporated in low concentrations in the alloy also increases the corrosion resistance and besides this stabilizes the austenitic microcrystalline structure.

Pitting Resistance Equivalent Number (PREN) is calculated from the different contents of chromium, molybdenum and nitrogen of the alloys in accordance with the following formula:

PREN = % Cr + 3.3% Mo + 16% N.

PREN represents a measure of the corrosion resistance, to the effect that the larger the number, the more resistant the respective material is in aqueous chloride-containing media.[14]

Delta Ferrite Content

Delta ferrite (δ-ferrite) is a secondary type of ferrite which can be formed in austenitic stainless steels when re-exposed to high temperatures, e.g. welding, forging or casting.

It is now no longer considered necessary to comply with the δ-ferrite content of 0.2% for sheets and 0.5% for pipes as originally defined for material 1.4435 in Basel Norm 2.15

Investigations have shown that contents up to 3% have no significant effect on corrosion resistance (see also Section 3).[3, 4] According to DIN 11864 / 11866, it is nevertheless possible, with delta ferrite classes 1 (≤ 3.0%), 2 (≤ 1.0%) to 3 (≤ 0.5%), to specify the ferrite content (in the as-delivered condition).

Passive Layer

When stainless steels are in stable equilibrium with the environmental conditions, a thin, closed protective layer rich in chromium oxide (consisting of chromium(III) oxide and of iron(III) and chromium(III) oxyhydroxides with a layer thickness of 1 to 5 nm) is formed on the surface of corrosion-resistant steel alloys under the influence of atmospheric oxygen.

The oxide layer is formed on the surface in a short time in the presence of atmospheric oxygen, but it is fully developed only after approximately 4 weeks. Moisture promotes the development of the oxide layer. For example, formation of the passive layer can be significantly accelerated by a treatment with oxidizing acids, such as nitric acid.

Table A. Composition of the stainless steels used primarily in pharmaceutical production

Material	Chemical Composition (%)						PREN
	Cr	Ni	Mo	C	N	Further Components	
1.4571 (316Ti)	16.5 - 18.5	10.5 - 13.5	2.0 - 2.5	< 0.08	–	%Ti = 5*%C; max. 0.70% Ti	25
1.4404 (316L)	16.5 - 18.5	10.0 - 13.0	2.0 - 2.5	< 0.03	< 0.11		28
1.4435 (316L)	17.0 - 19.0	12.5 - 15.0	2.5 - 3.0	< 0.03	< 0.11		30
1.4539 (904L)	19.0 - 21.0	24.0 - 26.0	4.0 - 5.0	< 0.02	< 0.15	Cu 1.2 - 2.0%	39

Cr = chromium, Ni = nickel, Mo = molybdenum, C = carbon, N = nitrogen, Ti = titanium, Cu = copper

Table B. Composition of further materials used in the tests of rouge formation

Material	Chemical Composition (%)							PREN
	Fe	Cr	Ni	Mo	C	N	Further Components	
1.4591 (Alloy 33)	Remainder	31.0 - 35.0	30.0 - 33.0	0.5 - 2.0	< 0.015	0.35 - 0.60	Cu 0.3 - 2.0	51
2.4602 (Alloy 22)	2.0 - 6.0	20.0 - 22.5	remainder	12.5 - 14.5	< 0.01	not specified	Co < 2.5 W 2.5 - 3.5	70
2.4600 (Alloy B3)	1.0 - 6.0	0.5 - 3.0	>65	26.0 - 32.0	< 0.01	not specified	Co < 3.0 W < 3.0	109

Cr = chromium, Ni = nickel, Mo = molybdenum, C = carbon, N = nitrogen, Ti = titanium, Cu = copper, Co = cobalt, Fe = iron

This passive layer usually protects the material from corrosion in neutral aqueous media. Nevertheless, this layer undergoes dynamic formation and decomposition processes, depending on the environmental conditions.[16]

Surface Condition

The surface quality of stainless steel alloys has a considerable influence on corrosion resistance. In principle, surfaces with low roughness and an associated smaller area exposed to attack have greater resistance to corrosive attack.

For surfaces contacted by product, a surface roughness of $R_a \leq 0.8$ µm has been established in pharmaceutical production areas. As a rule, these surfaces are subjected to mechanical grinding followed by electropolishing.

This electropolishing not only reduces the surface roughness but also improves the chromium-iron ratio, which also has a positive influence on the corrosion resistance.

In principle, proper pretreatment is required for electropolishing. Any residues or oil, grease or grinding fluid from the mechanical machining as well as tempering colors must be completely removed, since otherwise they would prevent flawless electropolishing.

If only mechanical polishing is performed, grinding must be performed with sufficient skill that no surface stresses are introduced into the material which could reduce resistance.

As a rule, the specified surface quality is determined by measuring the surface roughness (arithmetic average height R_a). Mechanically polished surfaces have lower corrosion resistance than electropolished surfaces even if the R_a values are identical.

Another problem is that the limit values of R_a are not based on scientific evidence and the topography scanned during the measurement is recorded with some degree of imprecision.

In principle, rouge formation can be delayed by better surface quality but ultimately cannot be prevented.

Rouge Formation

When aqueous media with low oxygen concentration are used (such as purified water (PW), highly purified water (HPW), water for injection (WFI), clean steam, sodium hydroxide solutions), especially at elevated temperatures, the dynamic process of formation and decomposition of the passive layer is disturbed. Surface regions low in chromium are formed and are then able to develop reddish discolorations or coatings, which are known as rouge.

Process conditions such as high temperatures, nitrogen blanketing, and high flow velocities favor rouge formation. Depending on the above-mentioned influencing factors, rouging may develop over a period of approximately 1 to 12 months.[1]

The formation of rouge as a function of the prevailing process conditions takes place with corrosion rates of $\leq 3.4*10^{-3}$ mm/a (WFI 85°C) and $5.2*10^{-4}$ mm/a (WFI 25°C).[17] For the purposes of further discussion, the higher value of $3.4*10^{-3}$ mm/a will be assumed as the worst case scenario.

Rouge consists mainly of various oxides and hydroxides of iron in its different oxidation states (limonite FeO(OH), hematite Fe_2O_3, magnetite Fe_3O_4). Depending on the respective composition of the base metal, however, compounds (oxides or hydroxides) of other alloying elements such as chromium or nickel can be detected in rouge coatings.[18]

To date, the exact origin of rouging has not been conclusively clarified scientifically. The literature contains many different theses about the mechanism of rouging. For the most part, however, it is unanimously agreed that rouging constitutes an inversion of the passive layer, in which the Cr oxide matrix is converted to an Fe oxide matrix with greater micro-roughness. Because of the environmental conditions existing in purified water and clean steam systems with hot storage (high temperature, water with low ion and oxygen content, relatively low pH), the surface repassivation that usually takes place continuously is greatly inhibited or even completely suppressed. One possible explanation is that the medium with low ion concentration leaches metal ions from the alloy, and so the passive layer is converted by the altered interactions into a layer that for the most part contains iron oxides. Another explanation is that the lattice structure rich in chromium oxides (passive layer) is converted by a thermodynamic process to a lattice structure rich in iron oxides, to some extent with incorporation of the other alloying elements.

Rouging Classification

At present, no unambiguous and generally applicable definition yet exists for rouging. It may be categorized on the basis of several viewpoints: Besides categorization according to corrosion products, other classifications are possible, such as differentiation specific to the media.

For classification of rouge coatings in the present document, the rouging definition found in J.C. Tverberg and T. Tube[1] and also published in the ASME BPE Guideline of 2009 as well as in the ISPE Baseline® Guide: Water and Steam Systems (Second Edition) will be used as seen in Table C.

Derouging

Derouging is defined as mechanical, chemical or electrochemical removal of rouge. Acid or pH-neutral chemicals may be used for the chemical derouging discussed in this article.

Mixtures of sulfuric, phosphoric and citric acid are predominantly used as acids for this purpose. Derouging solutions of neutral pH contain reducing and complexing agents as the active components (see also Part 3 Section 2.1).

The action of an acid derouging solution is based on its etching effect, while that of the pH-neutral solution depends on reduction and complexing of the iron oxides contained in the rouge coatings.

The rouge residues dissolved or bound by the chemicals are flushed out together with the cleaning solution.

As a rule, derouging is followed by re-passivation of the material surface. The introduction of chemicals into a system that was not designed and constructed for operations with chemicals may well conceal process-related risks. A thorough appraisal of the dangers is necessary before derouging is performed.

Regulatory Requirements and Guidelines

At present, the subject of rouging is not directly mentioned in any regulatory requirement. Nevertheless, some regulations contain references to the subjects of stainless steels and ability to clean equipment used for production, as seen in Table D,. A definition of the concept of clean cannot be read in any of the cited regulations. What is required is that a risk to the product due to contamination with foreign matter originating from unsuitable or inadequately cleaned production systems must be prevented.

Furthermore, the EMEA "Guideline on the specification limits for residues of metal catalysts or metal reagents" lists requirements for permissible heavy-metal contents in active substance solutions as seen in Table E.

Guidelines in which the subject of rouging is directly mentioned are listed in Table F. In contrast to the regulatory requirements, these do not represent handling instructions.

Risk Overview

In order to qualify the risks associated with rouging correctly from cGMP viewpoints,[19] it is recommended that a risk analysis be undertaken and appropriate actions be derived from that if applicable.

Examples of the risks relevant to pharmaceutical production are summarized in Table G, together with the respective influencing variables.

Since a risk appraisal was not possible on the basis of the available literature, the risks and influencing factors listed in Table G were addressed by means of tests. These tests together with the respective results are presented.

The risk of interactions of rouge (particles) with intermediate or final products is not included in these tests. Because of the very great product diversity and of the associated interaction and reaction mechanisms, the aspects listed in Table G should be considered on the basis of product-specific stability tests and/or literature searches.

Tests adressing the risks and influencing factors according to Table G will be described in Part 2 of this article.

Table C. Rouging classification according to J.C. Tverberg,[1] ASME BPE 2009 and ISPE Baseline® Guide: Water and Steam Systems (Second Edition)

Rouge class	Description
0	No visually perceptible rouge
I	Consists of very diverse oxides (such as FeO) or hydroxides ($Fe(OH)_2$) and exists as particles. The particulate rouge layer is predominantly orange, orange-red to brown. Can be removed only partly by wiping.
II	Consists mainly of hematite (Fe_2O_3) and exists both in particulate and surface-bound form. The color spectrum of the rouge layer ranges from orange-red through blue and lilac to gray. Can be removed only partly by wiping. As a rule, chemicals must be used for removal.
III	Consists mainly of magnetite (Fe_3O_4) and exists in surface-bound form. After gold / blue coloration at first, an extremely stable, black oxide layer is formed. This may be removed only by an etching technique, which damages the underlying surface. This is particularly serious for electropolished surfaces.

Table D. Overview of the regulations that impose requirements on cleanness or cleanability

Regulation / Guideline	Origin	Section
AMWHV	Germany	§ 5(4)
EU GMP Guide to Good Manufacturing Practice, Part I, Chapter 3, Premises and Equipment	EU	3.39
EU GMP Annex 1 of the EU Guide to Good Manufacturing Practice	EU	5.11
FDA PART 211 Current good manufacturing practice for finished pharmaceuticals	USA	§ 211.65
FDA PART 211 Current good manufacturing practice for finished pharmaceuticals	USA	§ 211.67
WHO Guideline Water for Pharmaceutical Use	Global	5.1

Table E. Class exposure and concentration limits for individual metal catalysts and metal reagents

Classification	Oral Exposure		Parental Exposure		Inhalation Exposure*
	PDE [µg/day]	Concentration [ppm]	PDE [µg/day]	Concentration [ppm]	PDE [ng/day]
Class 1A **Pt, Pd** **Class 1B** **Ir, Rh, Ru, Os** **Class 1C** **Mo, Ni, Cr, V** Metals of significant safety concern	100 100** 250	10 10** 25	10 10** 25	1 1** 2.5	Pt: 70* Ni: 100 Cr (VI): 10
Class 2 **Cu, Mn** Metals of significant safety concern	2500	250	250	25	
Class 3 **Fe, Zn** Metals with minimal safety concern	13000	1300	1300	130	

* see section 4.4 and the respective monographs, Pt as hexachloric acid
** Subclass limit: the total amount of listed metals should not exceed the indicated limit

Table F. Guidelines in which rouging is mentioned

Guideline	Section
ISPE Baseline® Guide: Volume 4 - Water and Steam Systems (Second Edition 2011)	11.3.13 11.9.6.2
ASME BPE 2012	SF10 Appendix D

Table G. Risks associated with rouging

Risk	Influencing factor
Rouge ingress into the final product	▸ Relative proximity of the rouged surfaces in the process relative to filling of the active substance solution ▸ Ratio of potentially rouge-forming surfaces relative to filled product volume ▸ Particle size or statistical distribution of the particle sizes of dissolved rouge particles (retention capacity on 0.2 µm sterile filter) ▸ Presence of rouging-promoting media (CO_2, N_2) or absence of oxygen ▸ Release of particles from rouged surfaces as a function of the rouge classification ▸ Distribution of the (dissolved and particulate) elements (Fe, Ni, Cr) contained in rouge for toxicological risk assessment. ▸ Heavy-metal ingress due to WFI in drug formulation
Influence of rouge coatings on efficiency of cleaning of the process equipment	▸ Cleaning efficiency is dependent on the existing layer thickness or porosity of the rouge layer
Interactions of rouge (particles) with intermediate or final products	▸ Potential catalytic action of particles rich in heavy-metal oxides ▸ Formation of covalent bonds between heavy-metal oxides and active-substance molecules ▸ Hydrophobic / hydrophilic interactions between heavy-metal oxides and active-substance molecules
Derouging	▸ Effect on the functionality of system components ▸ Corrosion of system components ▸ Risk to the product due to derouging chemicals ▸ Production interruptions due to unscheduled derouging actions

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CORROSION OF AISI 316L IN ULTRAHIGH-PURITY WATER: SURFACE ANALYSES AND METAL RELEASE

by Elena Bernardi, Maria Chiara Bignozzi, Cristina Chiavari, Nicola Gandolfi, Carla Martini, Alice Mattei and Salvatore Silvio Sessa

The article presents a study on the corrosion behavior of AISI 316L in pharmaceutical environments over a three-week period. Results showed higher iron release and corrosion current density in distilled water.

Equipment for pharmaceutical industries is usually made of austenitic stainless steel (AISI 316L), which is widely used for its high corrosion resistance.[1,2,5] However, in certain service conditions, in ultraclean water and steam systems, the degradation of stainless steel may lead to the formation of a thin red surface film, sometimes changing to a thick black oxide layer, which can spall and generate particles downstream.[2] This phenomenon is known as rouge.[1-15] Rouging is often observed in pharmaceutical industry facilities where stainless steel is in contact with high purity water, for example water for injection (WFI), at about 70°C or 80°C. Among the different types of stainless steel, AISI 316L seems to be the more susceptible to rouging. Superficial observations reveal that rouge can differ in color and chemical composition; Tverberg[7,15] proposes a classification into three classes. Class I appears as an orange or magenta film, mostly formed by ferrous oxide (FeO), weakly adhering to the surface, and easily removed (by wiping or ultrasonic cleaning). It is also referred to as migratory rouge, because particles tend to deposit away from the source. Class II typically occurs in the presence of chlorides; in this case, scales, formed mostly of hematite (Fe_2O_3), can be removed mechanically (by grinding or polishing) or chemically. Class III is formed of magnetite (Fe_3O_4), which give a blue or black coloring. This type of rouge cannot be removed by simple cleaning, but instead must be removed chemically or by grinding.

According to Gonzalez[5], the propagation of rouge depends on four factors: (1) construction material, such as alloy components, sulfur content, microstructure quality, etc; (2) system dynamics, i.e., how the system was constructed; (3) environment-process service conditions such as corrosive fluids, temperature, and pressure gradients; (4) maintenance and repairs, which can damage stainless steel surfaces.

There are different techniques to verify the presence of rouge: visual examination, which is obviously limited to accessible areas of the system; analytical methods or product contact surface analysis (e.g., Auger electron spectroscopy (AES)), or invasive methods which describe the state of the equipment surface. In addition, process fluid analysis can provide information about the quality of the media in terms of ions or particles present in the water at sampling time. All these techniques are suitable for characterizing rouge, but they cannot help in making decisions about the necessity of rouge removal. Generally, rouge removal is conducted following the user's subjective decision. An innovative solution is the use of a rouge monitor,[14] which measures rouge rates and metal loss over a specific time period. Despite wide discussion and research on the subject, the phenomenon is still not fully understood. Specifically, there are different theories about the origins of rouge,[2] including localized corrosion in weak areas of the passive layer, poor welding, or surface contamination. Finally, there is an urgent need to better comprehend the likelihood of this phenomenon leading to a contamination of fluid products and in particular, of pharmaceutical products, and the possible danger of contamination for humans.[3,5]

Within this context, a research project was set up in collaboration with an international company, a leader in manufacturing equipment for the processing and production of pharmaceutical solid-dose processing equipment, with the purpose of evaluating the influence of different parameters, such as the environment (municipal supplied drinking water, demineralised water, and water for injection) and the type of welding (gas tungsten arc welding (GTAW), welded with or without filler material), on rouging. To this aim, AISI 316L coupons underwent exposure tests in the three types of water at 70°C for three weeks.

During and after the exposure tests, changes to the stainless steel surfaces were recorded. In particular, the morphology and composition of the corrosion products were studied by variable pressure scanning electron microscope (VP-SEM) integrated with energy dispersive X-ray spectroscopy (EDS) microprobe and μ-Raman probe. In order to assess the release of the main alloying element (Fe) in the different types of water, the ageing solutions were collected at the end of the test and the amount of dissolved iron was analyzed. Finally, polarization curves in the three types of water, at 70°C were recorded, in order to assess corrosion.

Experiment

Materials

Sainless steel coupons for exposure tests were obtained by cold rolling (2 mm thick plates) and hot rolling (5 mm thick plates). The material compositions are reported in Table A. Each coupon measured 50 × 50 mm. Only cold rolled coupons were used for electrochemical tests. In order to examine the influence of welding, both non-welded and welded coupons were tested. In particular, the GTAW welding technique, with and without filler material, was used, with AISI 316L as filler material. Welding joints were produced in the middle of each sample.

After rolling operations, materials were cut, welded, electropolished, passivated and electropolished again, following the same procedure normally used in the production of pharmaceutical equipment.

Metallographic analyses were performed to check the microstructure of the samples before the exposure tests. The Beraha II reagent was used as color etching solution.[16] Grain size was determined by the intercept method, as described in ASTM E122.[17] Secondary dendrite arm spacing (SDAS) was reported as the average of 50 calculations.

Table A. Composition of the materials under investigation

	%C	%Cr	%Mn	%Mo	%N	%Ni	%P	%S	%Si	%Cu
Cold rolled (2 mm)	0.022	16.61	1.25	2.04	0.038	10.08	0.031	0.002	0.43	n.d.
Hot rolled (5 mm)	0.019	16.75	0.90	2.01	2.04	10.24	0.028	0.001	0.37	0.33

Environment

The water environments that were evaluated were: municipal supplied drinking water (MSDW), demineralized water, and water for injection (WFI). Demineralized water was produced by using MSDW as a feed: MSDW was filtered and dechlorinated through an active carbon block filter and demineralized by reverse osmosis. Water for injection, produced by distillation and packaged in glass containers, was supplied by Eurospital spa.

In order to characterize the three types of water used during experimental tests, conductivity and main ion concentration were determined as seen in Table B. Specifically, anions were analyzed by ion chromatography, using Dionex ICS-1000 chromatograph equipped with Ion Pac AG14A guard column and Ion Pac AS14A inorganic anion-exchange column. Iron concentration was determined by atomic absorption spectroscopy with electrothermal atomization, using a Perkin-Elmer Analyst 400 spectrometer. As expected, MSDW showed the highest ion concentration and conductivity. For demineralized water and WFI, chloride, sulphate, nitrate, and iron concentrations were lower than the quantification limit. In all cases, conductivity was one order of magnitude lower for demineralized water than WFI.

Corrosion Testing

Exposure Tests

During exposure tests, two coupons were 80% submerged in 300 mL of water (MSDW, demineralized water and WFI) for 3 weeks at 70°C. For exposure, a hole was produced at the top of each coupon, near the welding joint. Then two equal coupons were attached to a glass stick, and put in a beaker and 80% submerged. A PTFE cap was used to cover the beaker. In order to maintain the a constant water level for the duration of the exposure time, water was added manually. Coupons with different welding and rolling conditions were tested separately in order to evaluate Fe release as a function of the various variables. During the exposure period, coupons were visually inspected for any changes. At the end of the exposure time, exposed coupons were observed by VP-SEM integrated with EDS microprobe and μ-Raman probe. In order to determine weight losses, samples were pickled following the standard procedure ASTM G1-03 for iron and steel, using nitric acid solution (10% vol.).[18] At the end of the test, a sample of each solution was collected and analyzed for quantity of dissolved Fe. To obtain water samples for Fe release determination, each solution was filtered at the end of the exposure period and acidified at pH < 2 with Suprapur nitric acid (65%), to stabilize metal ions in solution. The analysis of Fe released in the exposure solution was performed by atomic absorption spectroscopy with electrothermal atomization.

Table B. Conductivity and ions concentration in the different water environments

	MSDW	Demineralized water	WFI
Conductivity (μS/cm)	820	12	2
Chlorides (ppm)	38	<5	<5
Nitrates (ppm)	7	<5	<5
Sulphates (ppm)	162	<5	<5
Iron (ppb)	4.7	<2	<2

Electrochemical Tests

To study corrosion in different samples, electrochemical tests were carried out using a closed three-electrode jacket cell connected to a thermostat, set at 70°C. The cell was connected to an AMEL 7050 potentiostat. Tests were performed in the same environments used for exposure tests: MSDW, demineralized water and WFI. Free open circuit potential (E_{OCP}) vs. time and anodic polarization curves were recorded. The polarization curves were measured at 1 mV/s from E_{OCP} to 1.5V vs E_{OCP}. Each polarization curve was performed twice.

Results

Materials

Metallographic analyses revealed that the base metal microstructure consisted of equiaxed recrystallized grains, with annealing twins, as seen in Figure 1. Metallographic observations revealed the absence of carbides. For welded materials, the grain size in heat affected zone (HAZ) and base metal was comparable, as seen in Table C.

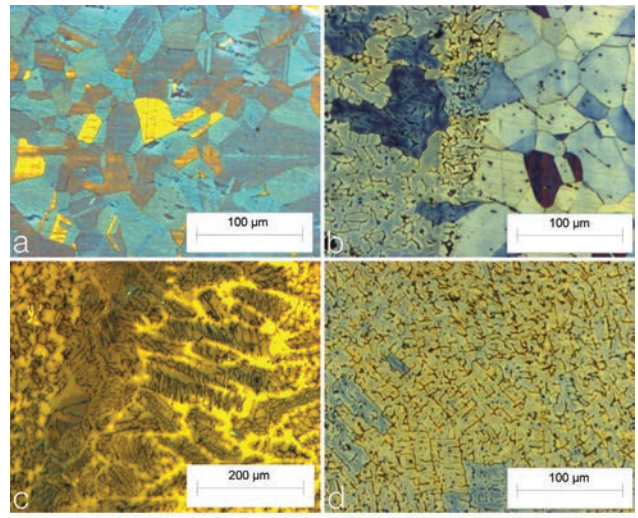


Figure 1. Micrographs (20x): base metal in non-welded, cold rolled coupon (a); dendrites and HAZ in coupon welded with filler material (b), dendrites in cold rolled coupon welded without filler material (c); dendrites in hot rolled, welded with filler material (d)

Exposure Tests

After 5 days of exposure, corrosion products became visible only on coupons immersed in WFI, as seen in Figure 2a; no changes were observed in the remaining exposure period. These products were largely iron hydroxides, as confirmed by Raman spectroscopy, as seen in Figure 2b.

Coupons in MSDW were completely covered by a thin white layer, mainly consisting of calcite and mixed sulfates (Figure 3). For coupons submerged in MSDW and demineralized water, VP-SEM/EDS observations revealed the absence of corrosion sites and the presence of superficial products related to the elements present in the exposure environment (e.g., $CaCO_3$).

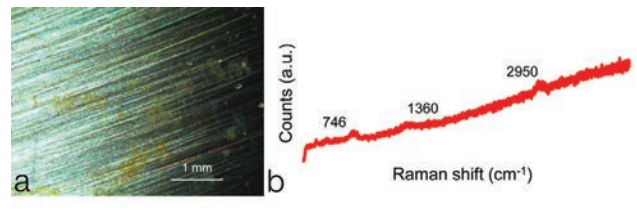
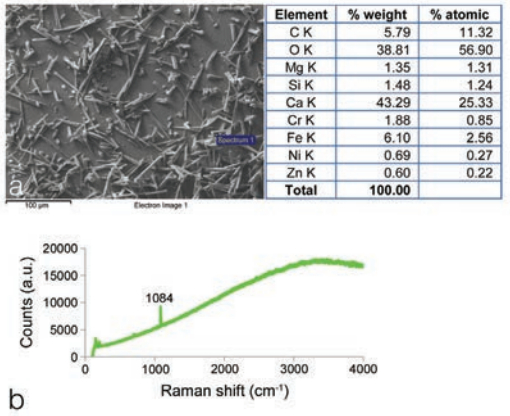


Figure 2. Rouge on coupon tested in WFI: micrograph at 12.5x (a), Raman spectrum (b) of superficial products after 5 days of exposure



Element	% weight	% atomic
C K	5.79	11.32
O K	38.81	56.90
Mg K	1.35	1.31
Si K	1.48	1.24
Ca K	43.29	25.33
Cr K	1.88	0.85
Fe K	6.10	2.56
Ni K	0.69	0.27
Zn K	0.60	0.22
Total	100.00	

Figure 3. Coupon tested in MSDW: SEM-EDS results, image and elemental composition (a), Raman spectrum: calcite (b)

At the end of exposure, the ageing solutions were analyzed to measure Fe release while the aged samples were pickled to determine mass loss and corrosion rate, expressed as loss of thickness per year (µm/y) (Table D). Generally, coupons tested in MSDW showed no weight loss and Fe was not released in solution in significant amounts; in demineralized water Fe release was higher than in WFI, as seen in Figure 4. In general, no difference was observed between hot rolled and cold rolled materials.

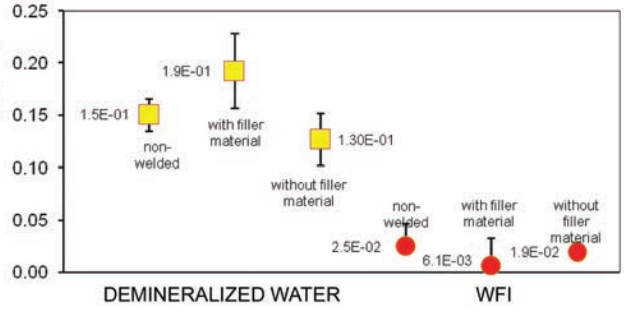


Figure 4. Iron release for cold rolled coupons after 3 weeks of exposure in demineralized water and WFI

Electrochemical Tests

Of the three types of samples (non-welded, GTAW welded with filler material, GTAW welded without filler material), the demineralized water slightly enhanced the anodic current density, specifically for the non-welded sample. This is consistent with the metal release measurements, where the dissolved Fe, compared to WFI, was higher for all samples (Figure 5), indicating higher corrosion activity in this environment. Demineralized water had higher conductivity compared to WFI (Table B), so was a more efficient electrolyte for electrochemical reaction. With regard to the environment (Figure 6), in MSDW and demineralized water no differences were detected related to the type of welding, while in WFI welded samples were slightly more corroded than the non-welded sample. This is in agreement with corrosion rate values (Table D): in a WFI environment welded samples showed higher weight loss than the non-welded sample. In every case, anodic current density was very low and inferior to 10^{-3} A/cm^2.

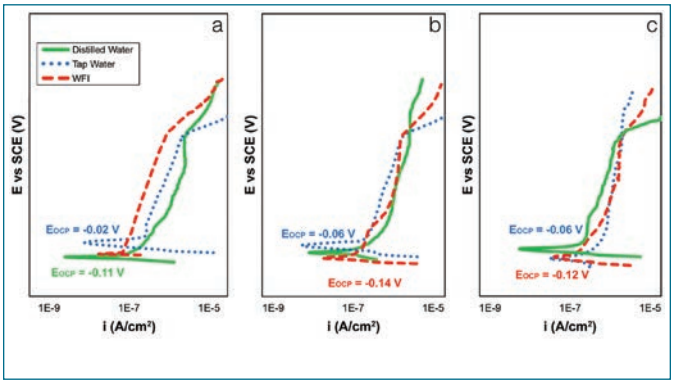


Figure 5. Anodic polarization curves in demineralized water, MSDW, and WFI for non-welded coupons (a), welded with filler material (b) and welded without filler material (c)

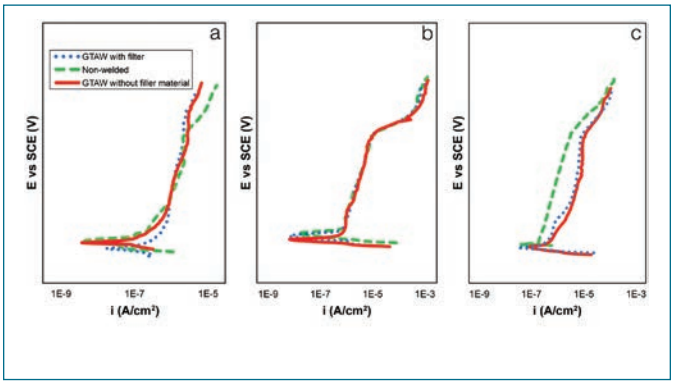


Figure 6. Comparison of anodic polarization curves in the three tested environment: demineralized water (a), MSDW (b), WFI (c)

Table C. Grain size and SDAS

Coupon		Grain size (µm)		SDAS (µm)
		Base metal	HAZ	
Cold rolled	Non-welded	29	–	–
	GTAW with filler material	24	36	7
	GTAW without filler material	33	35	2-8
Hot rolled	Non-welded	30	–	–
	GTAW with filler material	23	26	6
	GTAW without filler material	21	25	5

Table D. Corrosion rate after pickling

Coupon			Corrosion rate (µm/y)
DEMINERALIZED WATER	Cold rolled	Non-welded	13.52
		GTAW with filler material	0.72
		GTAW without filler material	6.31
	Hot rolled	Non-welded	10.28
		GTAW with filler material	6.94
		GTAW without filler material	3.42
WFI	Cold rolled	Non-welded	2.14
		GTAW with filler material	3.89
		GTAW without filler material	8.93
	Hot rolled	Non-welded	9.02
		GTAW with filler material	7.98
		GTAW without filler material	10.36

Conclusion

The purpose of this research was to examine the influence of parameters such as environment (municipal supplied drinking water, demineralized water and WFI) and type of welding on *the* rouge phenomenon in AISI 316L stainless steel (GTAW-welded with or without filler material). Among coupons that underwent exposure tests in the three types of water at 70°C for 3 weeks, rouge appeared only on coupons exposed to WFI after five days of exposure where deposits attached strongly to the stainless steel surface. These products were stable, and were removed from the surface only after pickling. This is in contrast with previous observations reported in the literature in which rouge is described as deposits along the water line. As expected, rouge was identified as iron-rich compounds. In contrast, no corrosion products were observed in MSDW or demineralized water. Voluminous deposits of calcite and products formed by environmental elements were observed on coupons immersed in municipal supplied drinking water. Fe release was higher in demineralized water, where no corrosion products were present on the surface, than in WFI, where rouge was present as superficial deposits. In municipal supplied drinking water no weight loss and no remarkable Fe release were detected, due to the less aggressive environment. No differences were observed between different rolling and welding procedures.

Regarding different welding conditions, only in WFI did the welded samples show a slightly higher corrosion rate in comparison to the non-welded sample.

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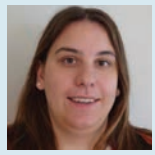

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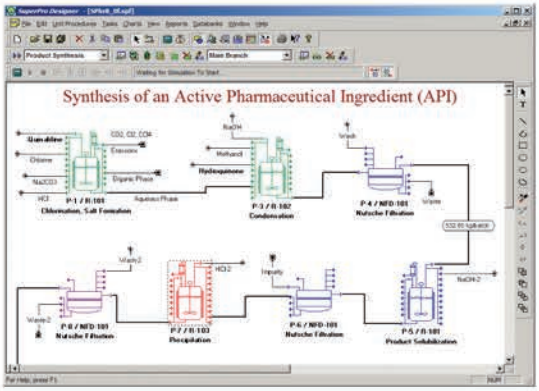

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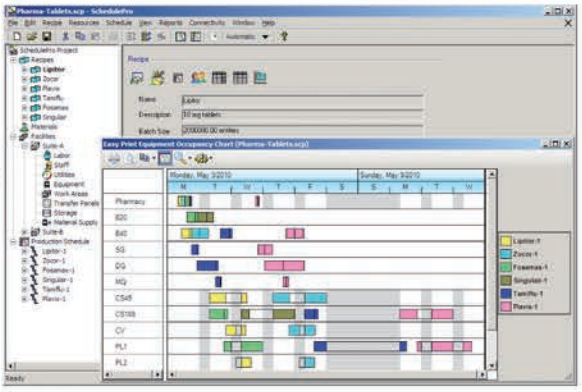

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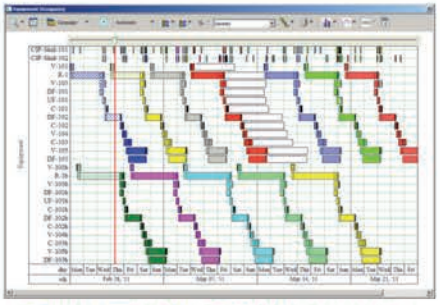

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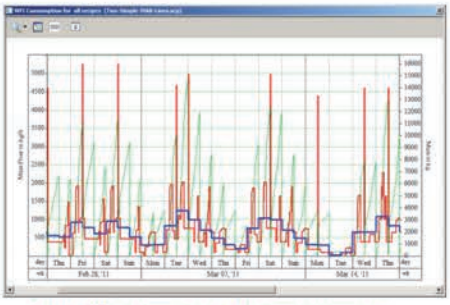

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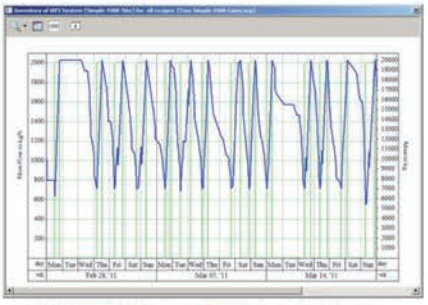

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A COMPUTER DATA INTEGRITY COMPLIANCE MODEL

by Orlando López

This article presents a model[1,2] that describes the required Annex 11 data integrity provisions applicable to new computer system implementations. and that can be used to assess computer systems in operation.

Introduction to EMA Annex 11

The European Medicines Agency (EMA) good manufacturing practices (GMPs) requirements for computer systems are contained in Annex 11.[3] Annex 11 provides EMA healthcare industries with a consistent criteria for effective implementation, control, and use of computer systems in GMP-regulated activities.[4] Medicines imported into EU need to take this abbex into account as an applicable requirement.

Non-EU countries are adopting the requirements of Annex 11. As an example, the Canadian GMPs requirements for medicinal products for humans[5] references the PIC/S Annex 11[6] as Canada's guideline for computer systems performing GMP-regulated activities. In addition, since May 2013, Annex 11 is applicable to active pharmaceutical ingredients (APIs) in Canada.

Another example of a non-EU organization embracing the content of the Annex 11 is the China Food & Drug Administration (CFDA). The 2014 draft GMP Annex 2, covering computer systems, incorporates the majority of the Annex 11 clauses.

Other non-EU countries using Annex 11 include: Argentina, Australia,Brunei, Cambodia, Indonesia, Japan, Korea, Laos, Malaysia, Myanmar, the Philippines, Singapore, South Korea, Thailand, the US, Vietnam, and many more.

The use of Annex 11 can be extended to other regulated applications. For example, the EU good clinical practice (GCP) inspectors agreed to use the published PIC/S Guidance on "*Good Practices for Computerised Systems in Regulated "GXP" Environments*" (PI 011-3) as the reference for inspection of GCP Computer Systems. This guidance is an internal document written to help inspectors with the interpretation of Annex 11.

Annex 11 may be applicable for software used in the production of a device (e.g., programmable logic controllers in manufacturing equipment) and software used in implementation of the device's quality control system (e.g., software that records and maintains the device history record), except for medical device software.

Since Annex 11 can be correlated with the principal regulations and guidelines,[7] it can be used as a computer system compliance model for computer systems performing regulated activities. A computer system must ensure that the methods for record keeping and retention allow at least the same degree of confidence as that provided by paper-based systems.

Annex 11 as a Computer Data Integrity Compliance Model

Annex 11 is organized into five areas: Principles, General, Project Phase, Operational Phase, and Glossary including 17 sub-chapters.

Sub-chapter 11-4.1 specifically refers to the need for ensuring that a computer system has been developed using a model which incorporates a system life cycle and associated risk management. Record keeping os one area where computer systems can incur risks. The computer system must ensure that the methods of record keeping afford, at the very least, the same degree of confidence as that provided with paper systems.

The provisions on data integrity in Annex 11 can be used as a compliance model for record keeping. These provisions can be used as rules for building computer systems which protect the integrity of the data they produce.

The basic EMA requirement on data integrity comes from EU Council Directives 2003/94/EC and 91/412/EEC.

"The electronically stored data shall be protected, by methods such as duplication or back-up and transfer on to another storage system, against loss or damage of data, and audit trails shall be maintained."

Basic assessments of data integrity controls need to start early in the system life cycle and be based on a risk assessment (Annex 11-1). These basic assessments must be translated into more specific requirements and established in requirements documents. The implementation of applicable controls needs to be traceable throughout the computer system life cycle (Annex 11-4.4). This process can be referred to as data integrity management, as seen in Figure 1.

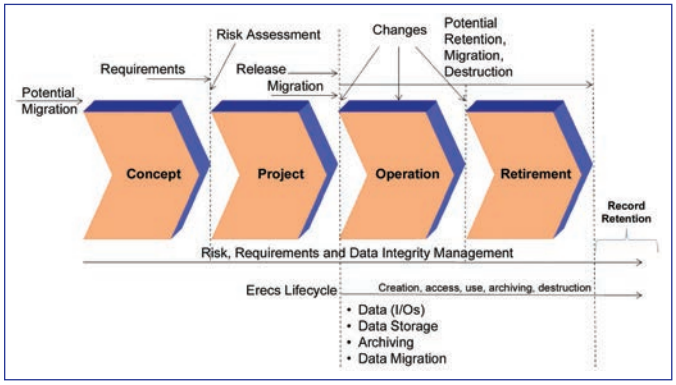

Figure 1

Consistent with the definition of data integrity in NIST SP 800-33, the data integrity-related chapters in Annex 11 govern the correct and secure entry of data (both manually entered and automatical-

ly captured data) and the subsequent data processing, storage and archiving, as applicable. These controls decrease the risk of an incorrect decision based on inaccurate results. The identity of authorized individuals carrying out work needs to be added to the records, including data and time stamps.

Supporting Processes Applicable to Data Integrity Controls

The following controls maintain the data integrity as part of the life cycle of the system:

Risk Management (Annex 11-1)
The basis for all these processes enabling the computer data integrity is the initial risk assessment as part of the risk management (Annex 11-1). An integration of system life-cycle (SLC) and risk management must be done in order to effectively implement and maintain data integrity controls. Based on the intended use and the risks associated with the computer system, the implementation and maintenance of a computer system should determine the approach, the combination of techniques to be used, and the effort to be applied.

Personnel (Annex 11-2)
Annex 11-12 requires that only authorized users be able to access a computer. Annex 11-2 requires that the level of access to a computer system be based on the users' assigned tasks.

Requirements Document (Annex 11-4.4)
This specification requires both structural and functional analysis (Annex 11-4.1 and Annex 11-4.7). This analysis describes what functionality is required and the data integrity controls (11-1) that need to be implemented, depending on the intended use of the computer system.

The requirements specifications must include "data flows and interfaces with other systems or processes, …and security measures". (Annex 4.3) The specifics of these requirements are to be found in the design-related specification.

Based on requirements and functionality, it is selected the appropriate data integrity controls pertinent to the application and the infrastructure supporting the application (Annex 11-4.4 and Annex 11 – 2nd Principle).

The requirements document determines the quality of the system to be implemented and is the guideline for all implementation and maintenance activities.

Security (Annex 11-12)
A means of ensuring records protection must be established for all computer systems. Strong computer security is the principal way of protecting the integrity of electronic records.

The system owner is the person responsible providing the records protection suitable controls over the application and network components. These record protection controls ensure that only authorized personnel can make changes to any component of the computer system and assures the security of the records residing in the system.

Security must be instituted at several levels (Annex 11-2). Procedural controls must govern the physical access to computer systems (physical security). Physical protection must also extend to devices used to store programs, such as tapes, disks and magnetic strip cards. Access to these devices should be controlled.

The access to individual computer system platforms is controlled by network specific security procedures (network security). Finally, application level security and associated authority checks control the access to the computer system applications (applications security).

A defined procedure at network and application levels should be established for the issuance, cancellation, and alteration of authorization to enter and amend records, including the modification of user passwords.

Periodic (or continuous) reviews must be performed after the initial validation (Annex 11-11). Electronic records should be verified stored, backed-up, and archived as part of periodic reviews of accessibility, readability and accuracy. In addition,

backup output should be verified in order to ensure te accuracy of audit traildata. As applicable, the periodic review must verify the accuracy and reliability of record transfers (WHO 3.2).

Where a record is deleted prior to meeting the planned retention date, an audit trail of the deletion should be kept until the end of the approved retention period (Annex 11-7.1).

Any instances where unauthorized persons attempt to access the computer system or data storage devices should be recorded.

It is critical their be a segregation of duties for people conducting data entry, reviews and system administration. Data must only be entered or amended by persons authorized to do so. Reviewers and system administrator must not have access to enter or amend data. If the application software security module does not allow the implementation of configurable segregation of duties, procedures need to be created to establish these controls.

In summary, the security controls in place include restricting access by non-authorized persons to computer equipment and data storage area.

The EMA principles relating to data quality, including security, are established in Article 6 of Directive 95/46/EC.

Incident Management (Annex 11-13)
Incorrect documentation, data errors, improper operation, and interface errors in computer system components, can affect the operation of a computer system. These events are also known as non-conformances.

Effective monitoring of the operation of a computer system involves users or operators trained in the proper operational procedure. This facilitates their ability to recognize unexpected responses and outputs, react to the incident properly, and fully document such incidents to aid in the evaluation and debugging process.

Correctly managing a situation using corrective and preventive actions (CAPA) guidelines, requires that the initial assessment of the incident include an analysis of the root cause of the situation.[8]

Business Continuity (Annex 11-16)
Business continuity ensures continuity in the event of a system breakdown. Business continuity refers to the measure of preparedness that is required to ensure business operations in case of system failure or problem. The procedural controls needed to restore the system must be adequately documented and tested regularly. All relevant personnel should be made aware of their existence and trained to use them. A copy of the procedures should be maintained off-site.

At the lowest level, the business continuity applies to the accidental deletion of a single file, in which case a procedure should be in place for restoring the most recently backed-up copy. At the other extreme, is a catastrophic event such as a complete destruction of the hardware, software and data files.

Suppliers and Service Providers (Annex 11-3)
Service providers include all parties who provide any services irrespective of whether they are employed by an independent (external) company, to the same company, or an internal service unit.

One of the services conducted by a regulated user is the procurement of application software used in GMP-regulated activities. Such software includes non-configured products, configured products and custom applications.

The use of vendor-supplied software presents some additional difficulties in acquiring objective evidence of the software's quality. The use of software in production, quality assurance, or as a component requires a level of knowledge sufficient to provide confidence in its accurate, consistent and reliable behavior when employed by a specific user. In the case of vendor-supplied software, the user must generate some of this documentation, while other documentation is generated by the software developer. This is the basic concept contained in the ASTM E2500-12.9

The documentation provided by the supplier must be reviewed by the regulated user to check if the regulated user's requirements are fulfilled (Annex 11-3.3).

The regulated user remains responsible for the quality of the computer systems performing GMP activities and their production processes and the integrity of the data.

The acquisition of quality software systems from outside sources necessitates a predefined, structured procurement process. The validity of potential suppliers should be evaluated appropriately (11-4.5) and the evaluation documented. There must be formal agreements with third parties, suppliers and service providers, including a clear statement of the responsibilities of that outside agency (Annex 11-3.1).

Similar requirements are applicable to cloud environments delivered by the cloud service provider to the regulated user. The performance of the provider must be monitored and reviewed periodically. Any needed improvements need to be identified and the implementation monitored.

Categories of Data Integrity Controls

The required data integrity controls can be categorized in three (3) spaces: data storage; data during processing and data while in transit (as seen in Figure 2). The data integrity controls applicable to data storage include:

Data Migration (Annex 11-4.8)
Data migration is the process of transferring data between storage types, formats, or computer systems. It is a key consideration for any system implementation, upgrade, or consolidation. Data migration is usually performed programmatically to achieve an automated migration, freeing up human resources from tedious tasks. Data migration occurs for a variety of reasons, including: server or storage equipment replacements or upgrades; website consolidation; server maintenance; and data center relocation.[10]

If data is transferred to another data format or system, the verification of the data migration should include corroboration that data are not altered in value, meaning, structure, context, and links (e.g., audit trails) or meaning during this migration process. Guidelines regarding the accessibility and readability of the data (Annex 11-7.1) are also applicable to the migration of data.

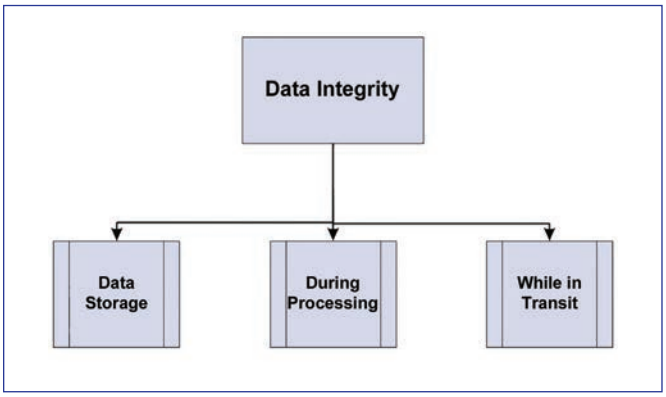

Figure 2

Data Storage (Annex 11-7)
Data storage refers to any device that records (stores) or retrieves (reads) information (data) from any medium, including the medium itself.

Design specifications or similar documents must describe the file structure(s) in which the data is stored, the capacity of the storage, and how security is implemented. The file structure and security should be tested during the implementation.

After the data is in the storage device, data integrity must be ensured. Logical and physical protections must be adequate to the criticality of the computer system (Annex 11-12.2). Logical and physical protections comprise the protection of data storage devices from unauthorized parties (Annex 11-7.1 and 12.1) as well as any environmental factors influencing the data storage device (Annex 11-7.1).

As an element of data integrity, there must be a record of any data change , including the previous entry, who made the change, and when the change was made12 (Annex 11-9).

To reduce the risk of losing the data and guarantee data availibility to tusers, periodic back-ups must be performed (Annex 11-7.2). The back-up must be stored separate from the primary storage location, and at a frequency based on an analysis of risk to GMP data and the capacity of the storage device.

The efficacy of the back-up and restore processes must be verified (Annex 11-7.2) as part of the qualification process. In addition, the capacity level of the storage must be monitored.

After completing the specified record retention requirements, the records can be archived (Annex 11-17).

Archiving (Annex 11-17)
Data archiving is the process of moving records that are no longer actively used to a separate records storage device for long-term retention, often disabling it from any further changes. In the context of electronic records, no longer actively records in which the retention period had not been finalized are archived.

Periodically, archived records needs to be verified for accessibility, readability and integrity. If changes are implemented to the computer infrastructure and/or application, then it is necessary to ensure and test the ability to retrieve data. Archiving is also impacted by Annex 11-4.8, 10, 11 and 12. The data integrity controls applicable to data processing include:

Built-in Checks (Annex 11-5)
Computer systems exchanging data electronically with other systems should include, if technically feasible, appropriate built-in checks for the correct computer inputs and outputs (I/Os). The correct I/Os ensures the secure exchange of data between systems and, furthermore, correct inputs on the processing of data. These built-in checks maximize the mitigation associated with I/Os errors. As the system automatically compares data on input with predefined limits, as an example, the user should be warned of potential errors when the data is entered manually or as an input from other computer system. For security purposes, the validity of the source of data input may be determined (Part 11.10(h), Device Checks).

An alternative control to the built-in checks when critical data are being entered manually, the check can be done by a second person (Annex 11-6 and ICH Q7 5.45). Refer to Accuracy Checks elsewhere.

There should be no difference between manual input by the user and input from another system. In the same way, processing operations performed by the system should be checked by the system itself.

Computer I/Os should be verified periodically to ensure correct inputs and outputs communication between computer interfaces.

Printouts (Annex 11-8)
Even with the increased use of computer systems in GMP-regulated activities, it is very common to see regulated users rely on

printouts as a hardcopy to be attached to the batch record and/or rely on printouts to perform regulated activities.

The same concepts delineated below are applicable to displayed reports. The displayed reports are often used for real-time decision making.

If these printouts are used as quality controls, then the design, qualification and controls of these printouts are critical. The reports need to be validated as per applicable procedural control.

In cases of internal audits (e.g., self-inspections (Eudralex Volume 4, Chapter 9)) or external audits (e.g., inspections by regulatory agencies or competent authority), it must be possible to obtain printed reports of electronically stored data that were not specified nor validated during the implementation of the normal required reports.

In this particular case, in order to generate reliable printouts, a report generator can be utilized to take data from a source such as a database or a spreadsheet, and use it to produce a document. If the printout is created by a report generator, then a verification of the printout must be performed before providing the printout to the auditor.

In any case, the printout functionality must provide the capability to print audit trails (Annex 11-8.2 and Annex 11-9). In addition, Annex 11-8.1 recommends that the printout be clear. "Clear printed" means printouts that apart from the values themselves, the units and the respective context can also be seen in the printout.[12] Units and the respective context are also known as metadata.

Printouts must be verified before hardware and/or software is exchanged. As part of the validation/qualification of the software/hardware, regression testing can be used to check that the data concerned can also be printed in the new configuration.

Audit Trails (Annex 11-9)13

As part of ensuring data integrity, it is imperative to keep track of all changes made to information in the electronic records that document activities related to GMP-relevant records.

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The use of audit trails or or other appropriate security measures helps to confirm that only authorized additions, deletions, or alterations of GMP-relevant electronic records have occurred and allow a means to reconstruct significant details about manufacturing activities and data collection. This is necessary to verify the quality of the data and the data integrity. Computer generated, time-stamped audit trails or other security measures can also capture information related to the creation, modification, or deletion of GMP-relevant electronic records and may be useful to ensure compliance with the appropriate regulation.

The need for audit trails should be determined based on a justified and documented risk assessment that takes into consideration circumstances surrounding system use, the likelihood that information might be compromised, and any system vulnerabilities. Should it be decided that audit trails or other appropriate security measures are needed to ensure electronic record integrity, personnel who create, modify, or delete electronic records should not be able to modify the documents or security measures used to track electronic record changes. Computer generated, time-stamped electronic audit trails are the preferred method of tracking changes to electronic source documentation.

Audit trails or other security methods used to capture electronic record activities:

- must contain any GMP-relevant electronic records are subject to all requirements regarding data integrity
- should describe when, by whom, and the reason changes were made to the electronic record. Original information should not be hidden though the use of audit trails or other security measures used to capture electronic record activities;
- must be available and, if necessary, be translated to an understandable form (Annex 11-8);
- must be regularly reviewed (Annex 11-11).

Security (Annex 11-12)
Refer to security elsewhere above.

Electronic Signature (11-14)[14]
Annex 11 sees the formalization of electronic signatures in EMA GMPs. Many computer systems have implemented electronic signatures based on the US FDA 21 CFR Part 11, but the European regulation does not appear as stringent as the US regulation. The requirements for electronic signatures are that they have the same impact as handwritten signatures within the company, be permanently linked to the respective record, and include the time and date that a signature was applied. There is not the stated bureaucracy and formality of 21 CFR 11 to send letters the US FDA, have no repudiation of an electronic signature requirements or the different types of signatures. However, many of the same requirements are implicit as the European legislation simply states that electronic signatures have the same impact as handwritten signatures and hence all of the non-repudiation requirements apply nonetheless.

Archiving (Annex 11-17)
Refer to archiving elsewhere above.

Operational Checks
The objective of operational checks is to enforce the sequencing of steps and events as applicable to the process managed by the computer system. The application-dependent algorithms, sequencing of operations, instructions to the operator, critical embedded requirements, and safety-related precautions to be followed within the computer system are encompassed in the computer program(s) that drive the computer system. These application-dependent and predicate rule requirements are defined in the requirements document, implemented as part of the project phase and executed during the operational phase.

The above controls applicable to data processing are implemented, as appropriate, during the project phase and each control is evaluated during periodic reviews (Annex 11-11). Consistent with GAMP5, the project phase in the EMA Annex 11 consists of computer systems development activities, including associated verifications and testing.

The data integrity controls applicable to data while in transit include checks for correct and secure entry of both manually entered and automatically captured data.

Principle #2 - IT Infrastructure Should be Qualified
Computer hardware infrastructure is considered as equipment.[16] All GMP controls associated with equipment are applicable to the computer infrastructure, including the location of the hardware, maintenance, calibration of hardware and the qualification. Qualification[17] of the hardware includes:

- installation
- evaluation of the system
- performance
- change control, maintenance and calibration, security, contingency planning, standard operating procedures (SOPs), training, performance monitoring and periodic re-evaluation.

The computer infrastructure must be brought into conformity with the regulated company's established standards through a planned verification process building upon acknowledged IT practices. Once in conformity, this state must be maintained by established processes and quality assurance controls, the effectiveness of which must be periodically verified.[18]

Data (Annex 11-5)
Refer to build-in checks elsewhere above.

Accuracy Checks (Annex 11-6)
Annex 11-6 is applicable to critical data entered manually into the computer system. The intent of Annex 11-6 is to confirm that critical data entered manually by an authorized person was, in fact, entered accurately and that there is an independent verification record to show this.

The independent verification of the manually entered data can be performed by a second authorized person or a computer system. In the context of the computer system check, verification is one that is programmed in to the background of the data entry and configured to ensure the accuracy of the data input. This could be specific checks on data format, ranges or values.

Summary

Annex 11 provides provisions that can be used to build computer systems with computer-managed data integrity.

To simplify the discussion, the data integrity provisions can be categorized into three (3) areas: data storage, data processing and data in transit.

As in the management of risks and requirements, data integrity management must be assured through the computer system life cycle and beyond.

The project phase starts with any potential migration issues and the creation of data integrity requirements. Based on these requirements, an assessment of the risk associated with the data is performed and possible mitigations are established and implemented as part of the project. Issues including data I/Os (Annex 11-5), data storage (Annex 11-7), and data migration (11-4.8) are addressed

During the operational phase the key supporting provisions are changes to the baseline (Annex 11-10) and data archiving (Annex 11-17). The effectiveness of the implemented data integrity provisions must then be evaluated periodically (Annex 11-11).

Glossary

Critical Data
Data with high risk to product quality or patient safety (ISPE GAMP COP Annex 11 – Interpretation, July/August 2011).

Data Integrity
The state when data has not been altered in an unauthorized manner. Data integrity covers data in storage, during processing, and while in transit (NIST SP 800-33).

Directive
A legal act of the European Union, which requires member states to achieve a particular result without dictating the means of achieving that result. It can be distinguished from regulations which are self-executing and do not require any implementing measures. Directives normally leave member states with a certain amount of leeway as to the exact rules to be adopted. Directives can be adopted by means of a variety of legislative procedures depending on their subject matter.

Non-conformance
A departure from minimum requirements specified in a contract, specification, drawing, or other approved product description or service.

Regulatory Expectation
"The electronically stored data shall be protected, by methods such as duplication or back-up and transfer on to another storage system, against loss or damage of data, and audit trails shall be maintained." (Chapter II, Article 9(2), the Commission Directive 2003/94/EC)

"All data defined as critical data and associated metadata should be printable." Aide Memoire (Ref. #: 07121202) of the German ZLG (Central Authority of the Laender for Health Protection).

System Owner
The person responsible for the availability and maintenance of a computerized system and for the security of the data residing on that system (EU Annex 11).

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A RISK-BASED APPROACH TO AUDIT TRAILS

by Randy Perez, Chris Reid and Sion Wyn

This article addresses the topic of audit trail review, by exploring pragmatic approaches to meeting requirements, while balancing efforts with benefits in terms of safeguarding patient safety, product quality, and regulated data integrity.

This article describes a risk-based approach to audit trails and audit trail review for GxP (Good-x-Practice) regulated systems. It places audit trails in the wider context of information security, and suggests a practical role for audit trails and audit trail review within that wider framework.

This article first outlines the current regulatory requirements for audit trails, as defined in EU Annex 11[1] and US FDA 21 CFR Part 11[2] and associated guidance documents, and then describes an overall risk-based strategy for meeting these requirements. Next, this article addresses the topic of audit trail review, exploring pragmatic approaches to meeting requirements, while balancing efforts with benefits in terms of safeguarding patient safety, product quality, and regulated data integrity.

Audit trails, if they are properly specified, implemented, and controlled, can be very useful in supporting in-process reviews of critical electronic records and as investigative tools. Indiscriminate review of all audit trail information is an expensive activity with very low probability of benefit. On the other hand, examining audit trails for a specific set of records as part of an in-process review, where data integrity has been determined to be uncertain, can be a powerful tool to help determine the trustworthiness of the records in question.

Regulatory Background

To understand the detailed requirements around audit trails, it is helpful to closely examine written regulatory requirements.

US FDA regulation 21 CFR Part 11,[2] in Section 11.10 (e), requires:

Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.

This requirement specifically covers operator actions that create, modify, or delete regulated electronic records, but not all activities performed by users, and not all system actions.

In the Part 11 Scope and Application Guidance,[3] FDA clarifies their expectations and interpretation:

We recommend that you base your decision on whether to apply audit trails, or other appropriate measures, on the need to comply with predicate rule requirements, a justified and documented risk assessment, and a determination of the potential effect on product quality and safety and record integrity.

We suggest that you apply appropriate controls based on such an assessment. Audit trails can be particularly appropriate when users are expected to create, modify, or delete regulated records during normal operation.

The guidance clarifies that when applying time stamps (such as in audit trails), they should be implemented with a clear understanding of the time zone reference used. In such instances, system documentation should explain time zone references as well as zone acronyms or other naming conventions.

The guidance also notes that audit trails may be just one among various physical, logical, or procedural security measures in place to ensure the reliability of records, within the context of a wider information security management framework.

EU GMP Annex 11, as revised in 2011,[1] includes the following clause:

9. Audit Trails
Consideration should be given, based on a risk assessment, to building into the system the creation of a record of all GMP-relevant changes and deletions (a system generated "audit trail"). For change or deletion of GMP-relevant data the reason should be documented. Audit trails need to be available and convertible to a generally intelligible form and regularly reviewed.

Again, the focus is clearly on rdata changes or deletions relevant to Good Manufacturing Practices (GMP). The phrase “regularly reviewed” has caused much discussion, and it is one objective of this paper to propose a practical approach to meeting this requirement.

Various other technical and system logs may be used, especially in the absence of true audit trails. These, however, are not intended to be audit trails in the sense that Part 11 and Annex 11 require, and declaring them as such may incur regulatory risk.

GAMP Good Practice Guide

The *GAMP Good Practice Guide: A Risk-Based Approach to Compliant Electronic Records and Signatures*[6] provides general guidance on the application and use of audit trails. An audit trail is typically used to provide two functions: attribution of action or change, and traceability of changes.

In a wider context, audit trails may also be used as to deter,and detect unauthorized record creation, modification, or deletion.

It should not be possible to modify audit trails themselves. For enhanced usability, systems should be configured to allow for the search, sorting and filtering of audit trail data. However, not all software applications support these features.

Requirements for identifying who performed an action, and when, are traditionally met in paper-based systems by initialling (or signing) and dating the relevant record, even though there may be no associated GxP requirement for a signature. In these cases the signature is intended to identify the person performing the action rather than function as an authorisation.

In an electronic system, an audit trail is one suitable way of meeting requirements for identification where there is no regulated requirement for a signature. The accuracy and reliability of the audit trail should be verified during validation.

Some GxP regulations require traceability of creation, modification, or deletion of regulated records.

In a traditional paper-based system, such a requirement would typically be implemented as follows: if a user recognizes that a certain data entry is incorrect, they strike out the inaccurate data in a way that it is still legible and add the correct value with their initials, the date, and in some cases the reason for the addition.

In an electronic system, an audit trail is designed to provide this traceability. Again, the accuracy and reliability of the audit trail should be verified during validation.

GAMP Community of Practice Interpretation

The following represents the consensus held within the Good Automated Manufacturing Practice (GAMP) Community of Practice (COP) regarding audit trails.

An audit trail should be applied when users create, modify, or delete GxP regulated records during normal operation. The audit trail should record the value of GxP relevant records at creation, as well as modifications and deletions, and the reason for such modifications or deletions.

With the exception of entering a reason for a change, audit trails should be secure and automated.. It should never be possible for the system user to modify audit trail.

An electronic audit trail is particularly useful and relevant for high impact GxP records. Other forms of audit trail, e.g. change control records, may be an appropriate audit trail method for lower impact records.

Audit trail information should include the identity of the person performing the action, and the time and date when the action was performed. In the case of a change or deletion, the detail of the change or deletion, a record of the original entry, and the reason for any change or deletion should be recorded,

The need for, the type of, and the extent of audit trails should be based on a documented and justified risk assessment. Specific GxP (predicate) requirements requiring audit trails may also apply. Alternative approaches may be used for low risk records.

Logical and possibly procedural controls should be established for the management of audit trails, including limitations to the ability to deactivate or modify audit trails.

Such procedures should cover the following: Initial verification of audit trail functionality, an established procedure for the management, monitoring, and periodic verification of audit trail configuration and system use. To support audit trail objectives, suitable security controls should be in place for high risk records, and appropriate segregation of duties should be enforced ..There should also be a way of ensuring that any change to audit trail configuration or settings is documented and justified, and that changes are not possibly by persons with normal user privileges), and it should not be possible to deactivate the system.

The approach to audit trail review should also be based on a documented and justified risk assessment. Audit trail review should focus on ensuring that audit trails are enabled and effective. If an audit trail is deemed necessary but the system is incapable of audit trails, then other measures, such as a logbook, should be implemented.

Audit trails should be regarded as only one element in a wider framework of controls, processes, and procedures aimed at an acceptable level of record and data integrity. Audit trails should be regarded primarily as a tool to be used for investigation, as and when required, and as a tool for data integrity review as part of an established business process, rather than for continuous routine review.

A Pragmatic Approach to Audit Trail Review

The objective of reviewing audit trails is to identify potential issues that may result in loss of data integrity. Such issues may include erroneous data entry, operations conducted by unauthorized persons, data not entered contemporaneously, or falsification of data. It is unlikely that a review of audit trail records alone would identify such problems. Validated electroniccontrols minimize the risk of such operations. For example, segregation of duties and role-based security are validated and periodically reviewed to ensure that only authorized persons can enter and transact data. Further, validated data entry verification ensures that results can only be entered within permitted data ranges and alerts are automatically generated when data is outside defined quality limits.

There are a number of different forms of paper audit trails.

1. Audit trail of process operations
2. Document histories
3. Hand amended data on written records, typically to address a mistake in the recording of original results

In the case of (1), audit trail of process operations are also typically embedded within the electronic record, and as such, this form of audit trail is reviewed during the approval process of the electronic record.

For (2), document histories provide an opportunity for reviewers to determine the specific changes made to a document during the review and approval cycle. Electronic audit trails may provide similar opportunity for reviewers of electronic documents. It is likely that such documents contain a history embedded in the document itself, as with the paper counterpart. An audit trail is typically not intended to be the equivalent of a document change history log.

Electronic audit trails as defined by current global regulations are largely biased towards (3). The primary objective of the review of hand amended records is to ensure that the amendment is legible, traceable and that the revised data is within a permitted range. As discussed earlier, in the electronic world other controls such as data range verification and role based security provide a proactive means to minimize the risk to data integrity. In such cases, validation and security management processes are far more effective than reviewing the audit trail.

It may be argued that internal audit should address the management of electronic records in the same way that it would paper records. However, an internal audit would not require all records to reviewed, or even a statistically valid sample.

The true value of electronic audit trails is in the support of a specific investigation, where a potential problem or fraudulent act has been identified, and the audit trail is used to confirm or disprove the problem. Even in this scenario, the audit trail would be only one element of an investigation. Periodic review of audit trails has limited scope for identifying such issues. For example, audit trails will not detect small deviations from expected values. Much more in-depth analysis is required to determine that a recorded value does not match the data in the Laboratory Information Management System (LIMS).

Current electronic audit trail solutions vary in the degree of effort required to access and interpret them. Some common challenges with audit trail solutions include:

- Audit trails may require specialist tools that are not readily available to system users
- System logs may need to be adapted from technical data into business information
- Audit trails may be very extensive so that identifying specific information is difficult
- Audit trails may contain much irrelevant information

As many audit trail systems are commercial products, not all details of the available audit trail are under the control of the regulated company using the system.

Many solutions may be technically "compliant" in terms of the information that is recorded, but limited thought may have been given to the actual business use of the audit trail information, making it a difficult and costly exercise to support in-process or periodic review of audit trail information, especially when considering the likely value of such reviews.

Avoiding Impractical Approaches

Resource requirements make it impractical to perform statistically meaningful reviews of audit trail content. Pharmaceutical companies use statistical sampling methods to evaluate the quality of finished products, an approach globally accepted by regulators. A logical approach to evaluating the integrity of a large number of records is to apply Acceptable Quality Levels (AQL) as described in ANSI/ASQC Z1.4-1993.8

Consider a database with between five hundred thousand and a million records, which would be a reasonable number for a Quality Control (QC) Laboratory Information Management System (LIMS) in operation for three years. Using a single sampling approach and a general inspection level of II (the standard level), an annual review of audit trails would require the examination of 1250 records. If the target is to have 99% accuracy, up to 21 of the reviewed records could have unacceptable changes to the records. If the target is 99.9% accuracy, only three deviations would be permitted.

While the technique is fairly easy to apply, the real issue is how to determine if changes recorded in an audit trail are acceptable or not. Every change made to a record would require a formal investigation. It would not be adequate to simply look at the reason for change, because anyone committing an unapproved change would likely enter a reasonable reason for the change. Formal quality investigations are resource intensive activities. If we assume that approximately 10% of records will have modifications that require review, and that a single investigation requires about 2 person-days of effort, then a statistically meaningful review of a single LIMS would require about 250 person-days, or about 1.1 person-years.

Regulated companies have hundreds of systems with GxP data. This would mean that regulated companies could need to significantly increase the number of people whose sole function would be to review audit trail data. This would be an extremely unproductive use of resources for the large majority of firms. It would certainly raise the cost of producing pharmaceuticals, a cost ultimately borne by the public.

What the above analysis clearly indicates is that retrospective review of the content of audit trails is not possibile. However, in cases where review for content has a meaningful value it should be built into the business process. In other words, as part of the final approval of a record of this nature, changes that have been made to the record should be evaluated. Retrospective review of audit trails should only be necessary in support of investigations related to possible data integrity questions.

Conclusions

Audit trails, can be very useful investigative tools. Reviewing audit trails simply because they exist is an expensive activity with very low probability of benefit. On the other hand, examining audit trails for a specific set of records as part of an investigation where data integrity is uncertain, or as a component in data integrity review as part of an established business process, can be a powerful tool to help determine the trustworthiness of the records in question. Company resources that would be required for routine review of all audit trails would be far better employed in other aspects of Quality Management.All audit trails are not equal, and the review of audit trails should be based upon:

- a thorough understanding of the business process supported by the computer system
- the risk to patient safety, product quality and GxP record integrity

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