People • Science • Regulation

PDA Letter

Volume LI • Issue 4 www.pda.org/pdaletter April 2015

Data Integrity Issues

Causes and Solutions 22

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Fundamentals of Cleaning and Disinfectant Programs for Aseptic Manufacturing Facilities

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Don't miss out on this unique and unparalleled opportunity to participate with the U.S. FDA and industry experts in face to face during the ***2015 PDA/FDA Joint Regulatory Conference!***

Attending this conference offers you an exclusive forum to hear from FDA speakers regarding the current efforts of the agency that may impact the development of global regulatory strategies. Industry professionals from some of today's leading pharmaceutical companies will present case studies on how they employ global strategies in their daily processes.

The opening session of the conference will feature a keynote speaker who was one of the first healthcare professionals deployed to deal with the Ebola crisis in West Africa. This speaker promises to offer insight into how the government deals with outbreaks and what activities need to transpire to quickly approve new medically necessary drug products to curtail potentially pandemic disease outbreaks.

Building from the opening plenary, subsequent plenary sessions will discuss the role of quality and regulatory systems in bringing new products to patients in an efficient and timely manner. The committee also plans to have the FDA speak on each of its Centers Initiatives in relation to the patient as well as having the traditional compliance update session.

You won't find this level of direct information exchange with FDA at any other conference!

Want to learn more? On October 1-2, PDA will host five courses designed to complement what you learned at the conference.

Learn about:

- Risk-Based Product Development Basics for Combination Products: Harmonizing Design Controls and Quality-by-Design in Product Development and Market Authorization Documents (October 1)
- Quality Metrics: Performance Indicators (October 1-2)
- Root Cause Investigation for CAPA (October 1-2)
- Process Validation and Verification: A Lifecycle Approach (October 1-2)
- CMC Regulatory Requirements in Drug Applications (October 2)

Visit pda.org/pdafda2015 for more information.

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Exhibition: September 28-29 | Post Conference Workshop: September 30-October 1 | Courses: October 1-2

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Cover Art Illustrated by Katja Yount

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Features

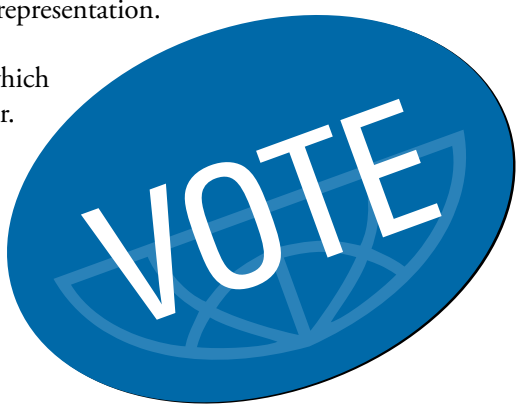
PDA Board of Directors Nominations Wanted

PDA members can nominate candidates for Officer positions on the Board of Directors for the 2017–2018 term and Directors for the 2017–2019 term.

"We do not want to miss outstanding members of our organization and strive for a diverse Board of Directors," says **Anders Vinther,** the current Nominating Committee Chair and Immediate Past Chair of PDA.

All PDA members are encouraged to nominate their peers within the Association for the Board of Directors election, although certain prerequisites are necessary. For example, only members in good standing can nominate and be nominated (that is, their membership is current).

The PDA Nominating Committee will consider all nominations and base their selection upon the following criteria: 1) status of membership; 2) level of activity within PDA; 3) volunteer history; and 4) diversity of representation.



"When you nominate a candidate, please be so kind as to include a brief explanation, which makes it easier for the selection committee to make their final choice," requests Vinther.

To nominate, send an email to: nominate@pda.org. Nominations for the 2015 Board of Directors elections will be accepted through May 15, 2015.

PDA Rolls out Points to Consider on Aseptic Processing

PDA's *Points to Consider for Aseptic Processing: Part I* was published on March 13, updating the original document published in 2003 just before release of the U.S. FDA's aseptic processing guidance. Part 1 of the new document is available at www.pda.org/bookstore for free member download until mid-April.

At a press conference at the *2015 PDA Annual Meeting,* President **Richard Johnson** and Chair **Hal Baseman,** ValSource, discussed the significance of this revised document. When the EU announced plans to revise Annex 1, PDA felt it was time to update the 2003 Points to Consider with a focus on the science behind manufacturing, such as environmental monitoring and cleanroom design. While the document will not be submitted directly as a commentary on the revised Annex 1, Baseman said that the Association hopes that the Annex 1 authors will look at the Points to Consider.

The Points to Consider provides a thought process for manufacturing based on science- and risk-based approaches, looking beyond the current state of the industry into the future as technology advances. Manufacturers can use this Points to Consider document to make more informed decisions.

PDA also discussed its new Manufacturing Science Program℠ at the press conference, which was held the first day of the *2015 PDA Annual Meeting* in Las Vegas. This new program aims to identify issues that need to be resolved in order to better promote manufacturing innovation and efficiency. Previous initiatives have focused more on quality and quality systems; this initiative aims to delve deeper into the science of manufacturing.

PDA wants to help manufacturers be "good stewards of their manufacturing operations," said PDA President Richard Johnson.

"PDA has been around for almost 70 years. We've been working on topics related to manufacturing for pretty much the whole time, but we're very much aware of the fact that, at the core, you want to manufacture the product. So, that's what our program is about…highlighting the things that we're doing [and] trying to identify gaps that we need to work on."

PDA recognizes that there is a perception within the industry that there have been little change, leading to frustration. In general, product is delivered in basically the same way today as 35 years ago.

PDA Volunteer Spotlight

Jayesh Patel

- Global Quality Manager
- *F. Hoffmann-La Roche AG*
- Member Since | 2008
- Current City | Little Falls, New Jersey
- Originally From | Gujarat, India

Joining PDA gave me the opportunity to interact with some of the most talented and experienced experts in the industry and learn from them

Jayesh likes to take plenty of photos when he visits the Alps

How has your career changed since you started?

I started my career in the automotive industry and worked there for 11+ years. Then ten years ago, I joined the pharmaceutical industry.

Why did you choose to join PDA?

As I was coming from a completely different industry, joining PDA was the right decision. It gave me the opportunity to interact with some of the most talented and experienced experts in the industry and learn from them.

Why did you decide to volunteer for PDA?

I started volunteering with PDA as the PCMO® task force member for Technical Report No. 54 on Quality Risk Management. This was invaluable and an opportunity to learn and contribute to an effort which led to the development of TR-54 with a diverse group of regulatory and industry colleagues.

Of your PDA volunteer experiences, which have you enjoyed the most?

While working on a PDA technical report team, I enjoyed the challenging task of working with large groups of team members coming from different companies, time zones and regions. We primarily worked remotely (mainly by teleconference) to accomplish the various tasks within each subteam. This gave me the opportunity to know some experienced professionals in the industry personally.

How many of your colleagues have you met by working on PDA technical report teams?

I met at least ten to 15 colleagues while working on two PDA technical report teams. That gave me the opportunity to share knowledge as well as network and learn from experts from various companies.

What is the most important statistical method used in production processes?

In my opinion, I would say process behavior charts (statistical process control).

Who do you admire most?

Originally from the State of Gujarat, India, I very much admire **Mahatma Gandhi** for his stance on nonviolence and equality.

INTERPHEX 2015

April 21-23 | Javits Center | New York City

FEATURING MORE TECHNICAL INFORMATION AND STATE-OF-THE-ART TECHNOLOGIES MOST IMPORTANT TO THE BIOPHARMACEUTICAL AND PHARMACEUTICAL MANUFACTURING INDUSTRY

Tuesday, April 21, 2015*	
9:00am – 5:00pm	INTERPHEX and BioProcess International Poster Hall Opens through Wednesday
9:00am – 5:00pm	INTERPHEX Live! with Pharmaceutical Processing
9:00am – 5:00pm	Rockwell Automation Center for Manufacturing Excellence #CP-3 and Fraser-AIS Printing Pavilion #4024
9:00am – 11:00am	PDA Learning Center@INTERPHEX: Continuous Manufacturing for an Aging Facility
11:15am – 12:00pm	Particles Causing End of Line Rejects and Drug Product Recalls: Overcoming Packaging Challenges and Need for Adequate Controls
11:15am – 12:00pm	PharmTech/BioPharm Presents: Real-World Serialization: How Good is Your Game Plan? Understanding Global Requirements and ROI
11:30am – 1:00pm	BioProcess Int'l Presents: Deciding on SU vs SS Bioprocessing Strategy: What Do CMOs Know That the Biopharma's Don't?
1:15pm – 2:00pm	The Road to the Biologic IND
1:15pm – 2:00pm	PharmTech/BioPharm Presents: Developments in Continuous Solid-Dosage Manufacturing
2:15pm – 3:00pm	Considerations for Sourcing of Film
2:15pm – 3:00pm	CRB Tech Tank: Impact of Delivery Systems on Mfg Strategies: A Look into Upcoming Aseptic Trends
2:15pm – 3:00pm	Powder Filling Considerations
2:15pm – 4:00pm	PharmTech/BioPharm Presents: Advances in Tableting
3:15pm – 4:00pm	CRB Tech Tank: Next Gen Biomanufacturing: Leveraging the Benefits of Continuous Closed Processing
3:15pm – 4:00pm	Advances in High Speed Rotor/Stator Mixing Technology in Emulsifying and API Milling Applications
3:15pm – 4:00pm	Granurex Conical Rotor Granulation and Coating Technologies
4:15pm – 5:00pm	CRB Tech Tank: Drug Supply Chain Security Act (DSCSA): Enterprise Disruption

Wednesday, April 22, 2015	
9:00am – 11:00am	PDA Learning Center@INTERPHEX: The Meaning of Aging and Modernization
9:00am – 5:00pm	INTERPHEX Live! with Pharmaceutical Processing
9:00am – 5:00pm	Rockwell Automation Center for Manufacturing Excellence #CP-3 and Fraser-AIS Printing Pavilion #4024
10:00am & 1:00pm	IPS Technology Tours: OSD, Aseptic, Biologics, Inspection & Packaging and Modular Construction
11:00am – 12:00pm	PharmTech/BioPharm Presents: The Contract Services Market: 2015 Update
11:15am – 12:00pm	Pushing Life Expectancy to 120 through New Technologies
11:15am – 12:00pm	Successful Implementation of a SU Process at the 2000L Bioreactor Scale
11:15am – 12:00pm	Stopper Insertion Solutions and IPC Modes for Filling Nested Syringes, Vials and Cartridges on Multi Use Filling Machines
11:30am – 1:00pm	BioProcess Int'l Presents: The Impact of Technology and Regulatory Changes on Fill–Finish Protocols Highlights
1:15pm – 2:00pm	CDMO Executive Perspectives
1:15pm – 2:00pm	Single-Use Bioprocess Container Film
1:15pm – 2:00pm	Why Innovative Drug Delivery Solutions Are Needed For Today's Patients
1:15pm – 4:00pm	PharmTech/BioPharm Presents: Succeeding in Cell Therapy Commercialization: What is Needed and How Do We Get There?
2:15pm – 3:00pm	Instrumented Tablet Presses
2:15pm – 3:00pm	Accelerating Freeze-Drying through a Controlled Aseptic Spray Freeze-Drying Process
2:15pm – 3:00pm	Quality Agreements Panel
3:15pm – 4:00pm	Quadro® H20 Comil® High Energy Conical Mill
3:15pm – 4:00pm	Contract Manufacturing Top 10 Trends in a Maturing Market
4:15pm – 5:00pm	Serialization's Early Adopters – Lessons Learned

Thursday, April 23, 2015	
9:00am – 11:00am	PDA Learning Center@INTERPHEX: The Meaning of Aging and Modernization
9:00am – 5:00pm	INTERPHEX Live! with Pharmaceutical Processing
9:00am – 5:00pm	Rockwell Automation Center for Manufacturing Excellence #CP-3 and Fraser-AIS Printing Pavilion #4024
1:15pm – 2:00pm	Research-Driven Marketing, Why Your Brand Matters

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chapter update

Implementation of SUS Discussed at Metro Chapter Event

Julie Barlasov, Perritt Laboratories

Bioprocess systems expert **Jerold Martin's** presentation on the benefits and challenges of implementing single-use systems (SUS) served as the highlight of the Jan. 14 PDA Metro Chapter's dinner meeting. Immediately following the dinner, he opened his presentation by describing the challenges of typical process designs. Manufacturers seek a better process that emphasizes quality, safety and efficiency. They want faster implementation, reduced time for discovery and development and increased speed to market. Manufacturers also want processes to be cheaper by decreasing facility, validation and production costs along with increased flexibility of the process. Yet, it is not easy to achieve the better-faster-cheaper approach in traditional manufacturing processes built from high-cost materials requiring extensive qualification. Some facilities are underutilized because of complex cleaning and sanitization procedures. As a result, more and more companies are looking into SUS.

Martin then pointed out the advantages of SUS: low installation cost, reduced cleaning cost, reduced maintenance cost, reduced/eliminated cleaning validation, minimized operator exposure and shortened development time for new facilities. The advantages of SUS, however, don't come without challenges. There are only a few facilities that can gamma irradiate this type and size of equipment. There is also very little guidance for manufacturing and implementation of these systems, outside of the July 2008 U.S. FDA guidance, *CGMP for Phase 1 Investigational Drugs* and *PDA Technical Report No. 66: Application of Single-Use Systems in Pharmaceutical Manufacturing*. It is also challenging to assure that system was implemented correctly.

Martin pointed to another resource that could help in implementing SUS: the Bio-Process System Alliance's Component Quality Test Matrices document, published in 2007 (currently under revision). This document helps manufacturers to perform a series of tests that can assure quality and robustness of the system. It also helps users to understand what to look for (e.g., film and containers, tubing, connectors and fittings: physical/chemical or biological functions, etc.) when purchasing/implementing a new system.

Section 3 of TR-66, "Points to Consider for Single-Use System Manufacturing Strategy," utilizes risk assessments, includ-

ing technical feasibility, business case, product risk, process risk, process control strategy, implementation strategy, and logistics control strategy. These assessments help determine if SUS can be used.

Martin continued by presenting information on physical risks and design improvements, leak/integrity testing, bioburden control and sterilization qualification, particulate risk qualification, as well as chemical and biological risk qualification. He noted that end users have to request validation reports for the gamma sterilization of process equipment. Each manufacturer should follow ANSI/AAMI/ISO 11137:2006 & AAMI TIR33:2005 (supplement) for proper selection of gamma radiation doses. They should provide end users with dose mapping reports, lot certifications and they should perform periodic dose audits. Each manufacturer should also have a list of materials to be avoided/excluded during production due to unsafe extractables/leachables. Unfortunately, the tests for leachables and extractables are not harmonized. Some manufacturers use unique tests which are not included in USP. He then explained that ASTM, ASME-BPE, PQRI/FDA, and USP are working to develop an acceptable harmonized standard for extractables/leachables testing.

Martin concluded his presentation by recommending use of Bio-Process System Alliance's Consensus Quality Agreement Template for Single-Use Biopharmaceutical Manufacturing Products to assure that all quality aspects between manufacturer and the end user of the system are covered.

During the Q&A following his talk, Martin discussed endotoxins from SUS, cytotoxins as a result of gamma radiation degradation, new e-beam technology as an alternative to gamma sterilization, and how changes in formulations can affect leachables and impact quality of the finished product.

Metro Chapter President **Leticia Quinones** concluded this dinner presentation by presenting a small token of appreciation to Martin. The Metro Chapter also thanks Overlook Industries for sponsoring the event.

PDA Who's Who

Jerold Martin, Sr. Vice President, Global Scientific Affairs, Pall Life Sciences

Leticia Quinones, PhD, Associate Director, Analytical and Bioanalytical Development, Bristol-Myers Squibb

PIC/S – PDA API (Q7) Training Course

Sessions

(l-r) Hassana Howe, PDA; Ronaldo Gomes, ANVISA; Lilian Cunha, ANVISA; Alessandro Magno Belisario, ANVISA; Wanda Neal, PDA

Stephan Rönninger, PhD, Amgen

Alicia Mozzachio, U.S. FDA

Personnel, Facilities, Equipment, Cleaning
Betsy Fritschel,Johnson & Johnson

Biotech API
Cormac Dalton, PhD, AbbVie

Closing Plenary
Ana Maria Pellim, PhD, AMPELLIM Consultoria e Serviços

(l-r) Richard Johnson, PDA; Ronaldo Gomes, ANVISA; Cormac Dalton, PhD, AbbVie; Wanda Neal, PDA; Stephan Rönninger, PhD, Amgen; Betsy Fritschel,Johnson & Johnson; Alicia Mozzachio, U.S. FDA; Manuel Ibarra, PhD, AEMPS

Closing Plenary Speakers
(l-r) Manuel Ibarra, PhD, AEMPS; Alicia Mozzachio, FDA; Angelo Henrique de Lira Machado, PhD, Brasília University; Ana Maria Pellim, PhD, AMPELLIM Consultoria e Serviços; Stephan Rönninger, PhD, Amgen; Jacqueline Condack Barcelos, ANVISA; Betsy Fritschel,Johnson & Johnson; Richard Johnson, PDA

Refreshment Break

Aseptic Instructors Teach Decontamination Cycles in Isolator

Rebecca Stauffer, PDA

PDA recently added an isolator to its Training and Research Institute (TRI) in Bethesda, Md., and it is now being used in a segment of the industry-leading "Aseptic Processing Training Program."

Students will now receive hands-on experience setting up for and running a decontamination cycle in an isolator as part of the second week of the aseptic training course, on top of receiving hands-on experience in TRI's Grade A filling suite.

Instructors **Martin Orlowski,** Biomonitoring Specialist, EMD Millipore, and **Peter Schofield,** Technical Sales Engineer, Walker Barrier Systems, took some time to discuss the portions of the course they teach as well as how changes in the industry impact the class. Both have extensive experience as TRI faculty. Orlowski began his involvement with TRI in 2007 while Schofield started teaching in 2010.

Anyone who's interested in attending the "Aseptic Processing Training Program" can learn more at www.pda.org/2015-aseptic-processing-training-program.

What portions of the aseptic processing course do you teach at PDA?

Schofield: For me, my portion is on the isolator technology…how isolators are constructed, materials of construction, how we integrate with other aseptic process equipment, features, etc., that you would see on a typical sterile application isolator.

Orlowski: My element focuses more on the sterilization of the isolators using hydrogen peroxide vapor technology. It talks about the integration with isolator systems and extends to discuss other applications, specifically the treatment of restricted access barrier systems (RABS).

You've both been in the industry for many years. What changes are you seeing right now?

Schofield: Well, I've been with my company now for over 15 years. We're starting to see an increase in sterile applications for isolators. I think the basic principle on the isolator has been the same for a while but there are features, particularly with the hydrogen peroxide decontamination and the integration of systems into isolators—that has certainly picked up the pace over the last few years.

Orlowski: I'd agree with Peter as far as the technology acceptance goes. From an experience standpoint and having worked at a hydrogen peroxide vapor decontamination company for over ten years, I think one of the main changes that we've seen has definitely been the optimization of the hydrogen peroxide vapor process. If you look at decontamination cycle times back from the early '90s, it was a very widely accepted technology that probably hadn't been optimized too well, but definitely over the last five or six years there have definitely been huge improvements by companies and consultants alike focusing on improving cycle times.

So how do you as instructors address these changes in the course?

Schofield: Well, we do change the course from year to year. We try and add in applicable slides and descriptions to reflect industry trends. For isolators, an example would be additions to the design to reduce the cycle times with introduction of heat and catalytic converters, which allow the system to aerate quicker. So, we added that into the course fabric and try to inform people on that basis.

Orlowski: We also receive very good feedback from the participants, so if you actually go back to the early years of the course, I taught the entire program. Being more of a specialist on the decontamination side of things, I looked at isolators at a very high level conceptually. After a while it was apparent that there was a demand to have an industry expert to be brought in and teach that segment of the course. And that's where Peter came in about four years ago, so we went from having a single instructor to splitting it off and keeping more up-to-date with what's going on.

(l-r) Peter Schofield and Martin Orlowski at PDA

Following donation of an isolator [to TRI], we're actually now including more of a hands-on component as well to have a look at what the validation process entails as well as giving students the chance to work with an isolator.

Can you explain more about this hands-on portion of the course?

Orlowski: Absolutely! I think it's quite tough for the participants and people attending this course to sit in the classroom for four or five hours before or after lunch, so we're planning on putting aside about 20 or 25 minutes where people actually get to see an isolator and the execution of a decontamination cycle. We'll cover some of the safety features like pressure tests, that Peter discusses, taking place, and they see the full physical barrier as well as how you go about implementing the development process.

Continued at bottom of page 20

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snapshot

Task Force *Corner*

Parenteral Packaging: Current and Best Practices for Glass Handling and Processing

Josh Eaton, PDA

A broken container cannot be filled. And certainly a cracked or damaged one cannot be used by a patient. When and how does damage to glass containers occur and how can it be prevented? A team of international PDA volunteers has undertaken an initiative to provide some answers and guidance on this topic through a technical report on current and best practices for glass handling and processing. **Roger Asselta,** Vice President of Technical Affairs, and **Bill Bogle,** President, both of Genesis Packaging Technologies, lead this team which includes members from various glass manufacturers as well as end users from pharmaceutical companies.

The report will begin with the science behind glass formation and then describe the various sources of stress encountered during pharmaceutical manufacturing which can contribute to damaged or broken containers. Current handling practices will be described as well as risk assessment methods and items to look for during those assessments.

Among other topics, the processing activities covered will include washing, filling, stoppering, terminal sterilization and final inspection and packaging. Throughout the report will be points of consideration for when pharmaceutical manufacturers optimize processing operations in order to minimize the stresses on the vials (e.g., line speed). In particular, this technical report will focus on the handling and processing of glass vials.

As the technical report nears completion, PDA will send out a call for volunteers to peer review the final product of the team's efforts. Further discussion and updates will be provided at the *2015 PDA Pharmaceutical Packaging Conference,* May 18–19. For more information, visit www.pda.org/2015-pda-pharmaceutical-packaging-conference.

PDA Journal *Top 10*

PDA Papers Remain Popular Draw for Readers

Below are the top ten articles from the *PDA Journal of Pharmaceutical Science and Technology* read during the month of February.

1. PDA Paper

Stan Bukofzer, et al., "Industry Perspective on the Medical Risk of Visible Particles in Injectable Drug Products" January/February 2015

2. Conference Proceeding – *Introduction I*

Arifa S. Khan and Dominick A. Vacante, "Introduction and Workshop Summary: Advanced Technologies for Virus Detection in the Evaluation of Biologicals—Applications and Challenges" November/December 2014

3. PDA Paper

Steve Mendivil, et al., "PARENTERAL DRUG ASSOCIATION POINTS TO CONSIDER: Pharmaceutical Quality Metrics Updated September 2014" September/October 2014

4. Conference Proceeding

David Roush, Kurt Brorson, and Rich Levy, "Proceedings of the 2013 Viral Clearance Symposium (Princeton, NJ)" January/February 2015

5. PQRI Special Section – *Research*

Dennis Jenke, et al., "Extractables Characterization for Five Materials of Construction Representative of Packaging Systems Used for Parenteral and Ophthalmic Drug Products" September/October 2013

6. PQRI Special Section – *Review*

Diane Paskiet, et al. "The Product Quality Research Institute (PQRI) Leachables and Extractables Working Group Initiatives for Parenteral and Ophthalmic Drug Product (PODP)" September/October 2013

7. Review

Dennis R. Jenke, Cheryl L. M. Stults, Diane M. Paskiet, Douglas J. Ball, and Lee M. Nagao, "Materials in Manufacturing and Packaging Systems as Sources of Elemental Impurities in Packaged Drug Products: A Literature Review" January/February 2015

8. Case Studies

Andrea Simonetti and Filippo Amari, "Non-Destructive Vacuum Decay Method for Pre-Filled Syringe Closure Integrity Testing Compared with Dye Ingress Testing and High-Voltage Leak Detection" January/February 2015

9. Research

Liliana Marghitoiu, et al., "Extractables Analysis of Single-Use Flexible Plastic Biocontainers" January/February 2015

10. Review

Stephen E. Langille, "Particulate Matter in Injectable Drug Products" May/June 2013

VHP Low Temp Terminal Sterilization of Drug Products

Juha Mattila, STERIS

The need for low temperature terminal surface sterilization of delivery devices manufactured with heat-sensitive materials and/or containing heat-sensitive products has continuously increased. As the number of applications grows, driven by the demand for these types of parenteral drug products in the pharmaceutical products market, vaporized hydrogen peroxide (VHP) has proven to be both very efficient for microbial control and as an application that is relatively easy to adapt to manufacturing facilities. This process refers to such products requiring production-sized units with batch volumes up to 10,000 liters of chamber size, and are now applicable for in-house processing along with this technology. The safe environmental properties of hydrogen peroxide, yields the nontoxic byproducts of water and oxygen.

This is a typical loading cart configuration with an array of specified products for sterilization

A typical VHP low temperature surface sterilization cycle is based on the principles of controlled environment, meaning control over pressure, temperature, relative humidity, hydrogen peroxide concentration and cycle time. The sterilization cycle is performed in deep or partial vacuum conditions in order to achieve a controlled environment and to ensure that complex device surfaces receive exposure to VHP within the typical plastic blister package using a Tyvek® or equivalent layer, allowing penetration of vapor in and out of the package. During VHP exposure, peroxide condensation is completely avoided.

The sterilization cycle consists of the following main phases: preconditioning of the load and chamber, injection and exposure, postconditioning to remove peroxide, and equalization to atmosphere. Typical cycle times vary between two and four hours depending on load configuration and on the amount and type of plastic materials used in the package. An environmental safety sensor is often required to verify <1 ppm residue after cycle completion.

The described sterilization application and equipment is subject to cGMP and GAMP requirements. Process control requirements often demand electronic data integrity, requiring compliance with 21 CFR part 11. Process validation is performed for each application, treating each as a novel sterilization process. Product feasibility testing and load cycle development provide an excellent basis for the validated cycle, and benefit the approval process. Chemical and biological indicators are used for cycle development, and biological indicators for validated cycle verification and production cycle quality control.

Typical products to be sterilized are single-packaged delivery devices with aseptically prefilled parenteral drugs such as biologicals, biosimilars or other sensitive products, e.g., with specific proteins that are sensitive to heat and radiation. Benefits of implementing a VHP surface sterilization process include: the validated 6-log reduction, sterility of delivery device surfaces and packaging that ensures safe patient injections. Other benefits of this process include automated and controlled batch process, increased production capacity, less manual labor and the possibility for lower manufacturing area classification for delivery device packaging.

This technology may also enable application of such drug products in a typical medical office rather than a more controlled environment. This is enabled by having proven sterile injection device surfaces.

About the Author

Juha Mattila is a Product Manager for STERIS Finn-Aqua WFI Water & Pure Steam, VHP Low Temperature Sterilizers and Effluent Decontamination systems based in Finland.

Can You Manufacture Like a Chipmaker? Yes, You Can

Hal Baseman, ValSource

As I was watching the Super Bowl last month, I pondered an intriguing philosophical question: how can the snack food industry coat each and every chip with a consistent flavoring, achieve such quality, and still sell it for a penny or so each? Perplexing. I suspect it has to do with some mysterious, innovative and continuous manufacturing processes.

Can we adopt the same thinking? Why not? Think about how nice it would be to set your drug product manufacturing line up and let it keep running on and on for days at a time. No worrying about line clearances, batch record integrity, breakdowns and setups. Just contamination-free, high-yield supply ensuring a continuous manufacturing of quality product.

Stop dreaming. It can be done. To do that, you really have to stop dreaming and start doing. It takes quite a bit of thought, planning, assessment, analysis, process understanding, innovative thinking and courage. Yes, you say, but other industries do not have to contend with postapproval change submissions, a requirement of most countries the product will be distributed in. New technology, such as continuous manufacturing, would surely need to meet all of those submission requirements before it could be implemented. True? Of course, but imagine there were ways to make it less burdensome than one might think.

Are you intrigued? If so, then you may want to attend a very special PDA workshop following the *2015 PDA/FDA Joint Regulatory Conference* Sept. 30 and Oct. 1.

In an effort to provide information and some very practical approaches to new technology, the workshop's planning committee has designed an interactive, practical, and quite unique workshop. PDA workshops always get great reviews and feedback, especially when they tackle new and challenging topics. And what could be more innovative and timely than using manufacturing science and technology to meet the quality and supply needs of our industry?

Why just listen, when you can be a part of the conversation? Why watch from the sidelines, when you can be a part of the game? Attend the workshop. Bring your desire for manufacturing improvement and thirst for knowledge. For more information, visit www.pda.org/2015-pda-manufacturing-science-workshop.

New Challenges Impact Combo Product Development

Doug Mead, Janssen Research and Development

All those involved with developing combination products face common challenges in applying the new cGMP rule, refining their quality systems under a "streamlined" approach, planning for their first U.S. FDA inspections, and establishing robust practices for testing these devices on the bench, in human factors studies, and in clinical trials. Design control practices and criticality analyses coming from the "device world" require new competencies and, in some cases, a change in R&D, quality, and management "culture." Industry is developing safe and effective drugs, but now must also ensure the usability of the devices that patients and health care provider will use and provide data that shows this.

As the industry and FDA evolves, so does the rest of the world, and regulators across the globe are grappling with how to regulate new combination products. Whole new combination product areas are opening up in the form of companion diagnostics—devices or tests associated with specific drugs—or drugs and devices that are distributed separately but are intended for use together as a combined therapy (the controversial cross-labeled combination product). When complaints or adverse events are reported with these products, industry needs to document and perform investigations appropriate for combined effects, and begin looking at how these reports will be made to global health authorities as regulations.

With the release of the FDA draft guidance on the Agency's combination product cGMP rule (21 CFR Part 4a), it is essential that those involved with these products gain the latest perspectives leading industry and FDA experts. Therefore, the program committee for the *2015 PDA Drug Delivery Combination Products Workshop* invites anyone with an interest in drug delivery combination products to attend this timely and important workshop on combination products in May. The invited experts for this advanced workshop will help all attendees come up to speed on this new FDA guidance. For information on the workshop, visit www.pda.org/drugdelivery2015. To learn more about the TRI Education course following this event, visit www.pda.org/technical-development-of-prefilled-syringes-autoinjectors-and-injection-pens.

Virus and TSE Safety Continues to Evolve After 18 Years

Hannelore Willkommen, PhD, RBS Consulting and Kurt Brorson, PhD, U.S. FDA

Virus and transmissible spongiform encephalopathy (TSE) safety are critical quality attributes and no product can be placed on the market that does not meet current requirements. These principles and requirements were developed 18 years ago ***(1)*** but questions still arise today. Why is virus removal by an established unit operation not as high as expected and as demonstrated before?

A good example is an anion exchange chromatography process. Normally, it shows very good virus removal, especially of retrovirus and parvovirus, if used in the flow-through mode. Critical process parameters (CPPs) are pH, conductivity, and load. Impurities like host cell protein and DNA, however, are also CPPs as well. Filtration is an important unit operation that is implemented whenever the product characteristics allow it. Virus retentive filters of the second generation are on the market. They are reliable tools to remove viruses of different type and property from the product stream. The major mechanism of virus removal is size exclusion; it is generally accepted today that a large virus like a retrovirus is reliably removed by a filter designed for removal of smaller viruses like parvovirus. But when looking at the filtration performance with small viruses, there are limitations, and the interactions between virus, product and filter membrane may influence virus retention.

These and other examples demonstrate that virus safety needs attention and continuous research. This is particularly the case because new challenges occur regularly, either by bioreactor contaminations, through the detection of new viruses in cell substrates, or by the observation of human viruses previously not observed in humans or in a specific region.

Renowned virus and TSE experts will be available to explore these and other questions at the June PDA *Virus & TSE Safety Forum* in Lisbon, Portugal. The Virus & TSE Safety Forum is the continuation of meetings which have taken place since 2001. For more information, please visit https://europe.pda.org/Virus2015. Summary reports of previous conferences have been published ***(2, 3)***.

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Aseptic Instructors Teach Decontamination Cycles in Isolator continued from page 14

What makes you excited about the future of this course?

Schofield: For us to be in front of these people…a lot of these students are coming in at the beginning of their career, and they are very inquisitive about our industry. They're going to be obviously coming across the equipment on a regular basis. So, I think the fact you're with these young people generates their involvement, our involvement and keeps you focused on it.

Orlowski: I think also with our being on the more commercial side of things—by being a vendor to the industry, it's quite interesting and exciting being here and getting feedback from the industry and people who actually use this equipment on a daily basis.

If a student has a couple of years in the industry already, what can he or she gain from the course?

Schofield: No matter how long you've been in the industry, it can refresh certainly, as I mentioned earlier, we do try and update the course on a yearly basis, so if there are things we are finding that are becoming trends in the industry, maybe their particular company may not know of these trends. It may trigger a few things that they can then go back to their organization and discuss further.

Orlowski: If they've been in the industry for a couple of years, they [students] have usually have a good appreciation of the overall picture as it were. But their involvement in particular segments might be limited. There are obviously other modules beyond just the isolator and the decontamination one which allows them to gain a lot of in-depth knowledge about various topics. For instance they may very well be aware that their sites have a VHP system and isolator but they may not be aware of what it entails to design it, validate it, and revalidate it.

Schofield: Even if you're not involved in day-to-day business with what we are discussing here, the knowledge of that certainly is going to help anybody that's working in the industry. Even though you may not be responsible for dealing with a particular isolator, knowing what's required in the design of it might affect what you do in your role. So, having a broad spectrum of knowledge across all of the teaching subjects that impact this industry can only be beneficial.

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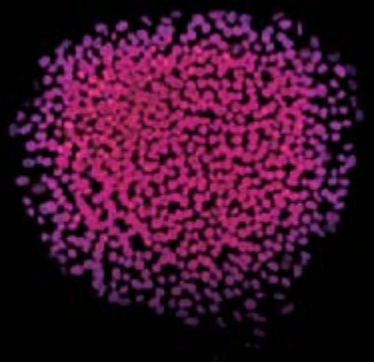

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Data Integrity Issues
Causes and Solutions

Elayne Best, Biogen Idec

The integrity of the data collected and recorded by pharmaceutical manufacturers is critical to ensuring that high quality and safe medicines are produced. What exactly is data integrity and why is it so important?

Data rising to the standard that is commonly referred to as having "integrity" generally include five key attributes ***(1):***

- Accuracy – no errors or editing without documented amendments
- Attributable – information lists who acquired the data or performed an action and when
- Available – for review and audit or inspection over the lifetime of the record
- Complete – all data are present and available
- Consistent – all elements of the record, such as the sequence of events, are dated or time stamped in expected sequence

Howard Sklamberg, Deputy Commissioner for Global Regulatory Operations and Policy, U.S. FDA, has said that the lack of data integrity is often "just fraud" ***(2).*** In today's complex supply chain, it is more critical than ever to ensure the integrity of the data documented for the testing and manufacture of medicinal products.

Data integrity is mandatory for the regulated healthcare industry, as processing and disposition decisions regarding product quality, safety, efficacy, purity, and compliance with the applicable regulatory requirements are made based on data that is recorded and reported. Drug, medical device manufacturers, service providers, health authorities, end users and administrators of the product (patients and healthcare professionals) rely on robust traceable data.

What happens when data integrity is breached? The worst case scenario is impact on patient safety and the loss of lives. Although not regulated by the FDA or subject to cGMPs, the recent New England Compounding Pharmacy incident in the United States can be used as an example of the consequences of fraudulent activity. Here, 64 patients died and over 750 were sickened from fungal meningitis as a result of sterility negligence and data integrity issues. In this case, a FDA official said pharmacy technicians were instructed to lie on cleaning logs, showing rooms as being properly cleaned when they had not been ***(3).***

Data integrity issues pose such a high risk and are not always easily detectable. As electronic data recording and management systems are implemented instead of paper systems, the detectability of data manipulation becomes more complex. Certain controls and requirements should be validated to mitigate any risk for data to be manipulated electronically. In addition, verification of audit trails in electronic management systems, training of operators and staff to promote cGMP awareness, along with the ramifications of breaching data integrity when recording results is critical.

The FDA and other health authority agencies have recently expanded efforts to target manufacturers and laboratories with potentially questionable data. A MHRA guidance provides a clear message, discussing the importance of the data integrity lifecycle and places an emphasis on senior management and supplier management programs. The guidance places the responsibility on senior management to ensure systems and procedures are implemented utilizing the principles in ICH Q9, Quality Risk Management to minimize the potential risk to data integrity. ***(4).***

Additionally, the guidance states that any "contract giver" outsourcing work should ensure that the supplier management program review potential risk of data integrity for their suppliers. Over the past two years, the FDA has issued over fourteen warning letters to API manufacturers in India for data integrity issues ***(5).***

It is compelling that the FDA issued such a large volume of warning letters in India for data integrity issues. With the MHRA guidance emphasizing the importance of evaluating data integrity risk for the contract giver's suppliers, we have to ask the question, why did supplier quality audits not detect this risk? As the industry continues to develop and identify data integrity risks, data integrity risk evaluation should be part of the routine developed for the established supplier management program, instead of performed solely in-house.

The observations in these warning letters are startling. Some citations describe fraudulent activities such as documenting microbial results on a Certificate of Analysis when there was no objective evidence to support that any testing was actually performed. Through interviews, employees confirmed that the testing was never performed, however, results were reported on the CoA as sterile ***(5).***

Adequately ensuring data integrity requires companies to create a company culture of ethics and compliance. This starts at the basic level, such as a company that follows the fundamentals of cGMPs, e.g., making all personnel aware that everyone is accountable for their own signature. Training programs must stress the serious ramifications of unethical behavior, and that documenting ➤

It is critical to ensure employees understand the accountability and traceability requirements for retention of raw data and the consequences of data manipulation

2015 PDA Upcoming Events

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APRIL EVENTS

15
Visual Inspection Interest Group Meeting
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europe.pda.org/IG-Visual2015

16-17
Introduction to Aseptic Processing Principles
Berlin, Germany
europe.pda.org/TCAseptic2015

20-23
Train the Trainer Week
Bethesda, MD
pda.org/trainer

27-29
GSA Schedule Contract GS-02F-113BA
Validation of Biotechnology-related Cleaning Processes
Bethesda, MD
pda.org/biotechclean

MAY EVENTS

4-7
GSA Schedule Contract GS-02F-113BA
Lyophilization Week
Bethesda, MD
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11-12
Recommended Practices for Manual Aseptic Processes
Bethesda, MD
pda.org/MAP

13
NEW COURSE
Risk Based Approach for Prevention and Management of Drug Shortages
Bethesda, MD
pda.org/prevention

14-15
Development, Manufacturing and Handling of Primary Packaging Containers, Drug Delivery Device Formats and Actual Market Trends
Bethesda, MD
pda.org/markettrends

18-19
2015 PDA Pharmaceutical Packaging Conference
Baltimore, MD
pda.org/packaging2015

18-22
2015 Aseptic Processing Training Program – Session 3, Week 1
(Week 2: June 15–19)
Bethesda, MD
pda.org/2015aseptic3

19
PDA Metro Chapter Day Symposium
Somerset, NJ
pda.org/metrochaptersymposium

20-21
2015 PDA Drug Delivery Combination Products Workshop
Baltimore, MD
pda.org/drugdelivery2015

20-21
2015 PDA Pharmaceutical Packaging Course Series
Baltimore, MD
pda.org/packagingcourses

22
Technical Development of Prefilled Syringes, Autoinjectors and Injection Pens
Baltimore, MD
pda.org/techdevelop

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JUNE EVENTS

2-3
Advanced Therapy Medicinal Products
Amsterdam, The Netherlands
europe.pda.org/ATMPs2015

4
Process Simulation Testing for Aseptically Filled Products
Bethesda, MD
pda.org/simulation

9-10
2015 PDA Aseptic Processing-Sterilization Conference
San Diego, CA
pda.org/aseptic2015

9-10
GSA Schedule Contract GS-02F-113BA
Fundamentals of Cleaning and Disinfectant Programs for Aseptic Manufacturing Facilities
Bethesda, MD
pda.org/cleaning

9-11
Virus & TSE Safety Forum
Lisboa, Portugal
europe.pda.org/Virus2015

11-12
2015 PDA Aseptic Processing-Sterilization Course Series
San Diego, CA
pda.org/sterilizationcourses

23-24
Quality & Regulations
Brussel, Belgium
europe.pda.org/QuaReg2015

23-24
2015 PDA Single Use Systems Workshop
Bethesda, MD
pda.org/sus2015

25-26
2015 PDA Single Use Systems Workshop Course Series
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results or activities which did not occur is a fraudulent activity. Data integrity issues are the return to the basics of cGMP documentation.

Critically, companies need to ensure that the culture and environment is built on trust and follows basic cGMP foundations, avoiding the often implied message: "Let's just get this done...it's okay to take shortcuts to meet deadlines." The culture should be one where individuals are responsible for ensuring product, patient safety and drug efficacy and purity, having the responsibility to escalate any potential fraudulent activity without fear of repercussion. If a lower level employee observes data falsification at any level in the organization, there should be a defined confidential escalation program. This concept is a fundamental element to any ethics and compliance program.

Above all, the company culture of a drug manufacturer should ensure ethics. Ethics is vital at all levels of the organization, but certainly of management. There are serious ramifications for an organization with data integrity issues including regulatory actions of seizure and injunction of operations, individual incarceration and debarment. The FDA can also place an organization under consent decree, perform a directed and limited inspection regarding data integrity issues, cite an organization with a warning letter and halt the submission of any new products, and recall and withdraw products from the market.

The most important reason we are in the drug industry is to help make patients' lives better. The consequences of data integrity lapses could be patient death, chronic illness or disability. Organizational impact could include a negative public and regulatory reputation resulting in devaluation of stock and market share loss. Once the trust of regulatory agencies and the public has been lost, it is not an easy thing to recover.

In a warning letter issued in 2014 ***(6),*** the FDA required the firm to "identify the specific managers in place who participated in, facilitated, encouraged, or failed to stop subordinates from falsifying data in CGMP records, and determine the extent of top and middle management's involvement in or awareness of data manipulation." Furthermore, in the same warning letter, the FDA stated: "That a senior manager was engaged in the falsification of documents is troubling and raises questions about validity of documents generated by your firm. Furthermore, your response to the FDA Form-483 is deficient in that it fails to address the root cause or the extent of the falsification of training documents" ***(6).*** The FDA then required the company to not only provide the deficient information but also how the company will change its systems to address these issues along with extensive information about employee cGMP training at the facility.

The message for data integrity is clear. It's not a new concept; it's about getting back to the roots of training all staff on the importance of data integrity in cGMP documentation and honesty. It is critical to ensure employees understand the accountability and traceability requirements for retention of raw data and the consequences of data manipulation. Training operators and analysts to document the performance of a task by recording what happened at the time it occurs, including information about the person who performed it along with clearly documenting and investigating deviations, is vital for patient safety and product efficacy. This is achievable by providing the training and creating a company culture that promotes and rewards ethical behavior as a core value from top to bottom of an organization.

[Editor's Note: The *2015 PDA/FDA Joint Regulatory Conference* will feature a plenary session on data integrity on Sept. 29. Visit www.pda.org/pdafda2015 for more information.**]**

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About the Author

An auditor for Biogen Idec with over 17 years of experience in the biopharmaceutical industry, **Elayne Best** audits the supply chain for clinical and commercial products including raw materials, components, contract manufacturing API, bulk drug substance, contract laboratories, parenteral and oral solid dosage drug product and distribution.

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- Steam Sterilizers: Getting it Right from the Beginning (July 21)
- Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Validation and Ongoing Control (July 22)
- Steam in Place (July 23)

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Incorporating Data Integrity into Your Quality Management System

Anthony C. Warchut, PAREXEL

ICH Q10, Pharmaceutical Quality Systems was recommended for adoption to the regulatory bodies of the European Union, Japan and the United States in 2008. EMA then formally approved it that same year. In 2009, the U.S. FDA adopted it as a guidance document. This begs the following question, if companies have adopted the principles of ICH Q10, why have the FDA and EMA been experiencing an increase in the number of data integrity issues found during recent inspections?

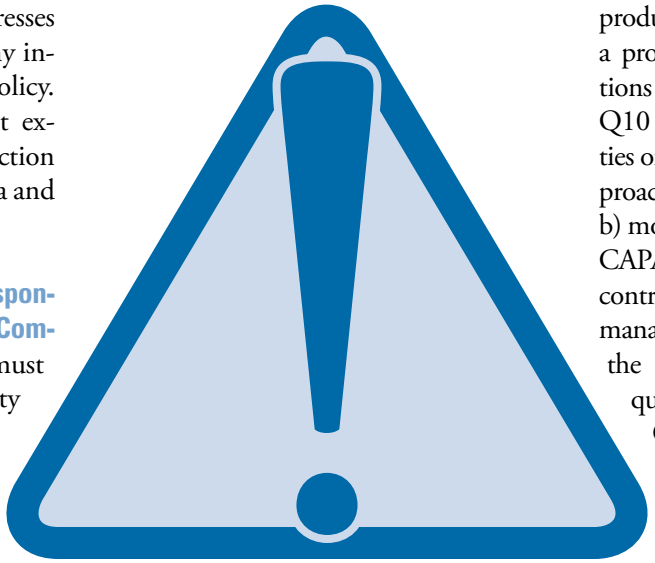
ICH Q10 does not specifically address data integrity issues. It, however, was conceived with the purpose of implementing a Quality Management System (QMS) based on GMP regulations, ISO concepts and to complement ICH Q8 and Q9. A viable QMS cannot be based upon anything except data and records that are attributable, legible, contemporaneous, original, accurate, complete and easily retrievable. Therefore, while Q10 does not specifically address data integrity, it is a concept critical to GMP compliance.

Below are the relevant parts of Q10 and how they pertain to data integrity.

ICH Q10, Part 1, Pharmaceutical Quality System, Section 1.8: Quality Manual: A company's quality manual should contain a corporate policy that addresses data integrity and how the company intends to follow its data integrity policy. There should be a clear statement expressing zero tolerance for any action that impacts the integrity of the data and records generated by the company.

ICH Q10, Part 2, Management Responsibility, Section 2.1, Management Commitment: Senior management must ensure that there is a data integrity policy for the company that defines data integrity and details how the company will handle data integrity issues if discovered. Companies should establish and support a culture of compliance that promotes bringing potential data integrity issues to the attention of management. Senior management must make clear to all employees that any verified reports of deliberate data falsification, unauthorized changes, destruction of data, or other conduct that compromises data integrity will be addressed vigorously and promptly via the company's HR policies and procedures, resulting in appropriate disciplinary action up to, and including, termination.

In order to promote a culture of compliance that encourages employees to bring compliance issues to the attention of management, "safe" systems for reporting potential data integrity issues—supported by company policies that assure reporters will not be retaliated against—should be established. The seven-point compliance policy of the U.S. Department of Health and Human Services Office of Inspector General's voluntary compliance program for pharmaceutical manufacturers ***(1)*** advocates this approach. Adoption of such an approach should be consistent with a company's general ethics; integrity standards need to be made known to each new employee during orientation and supplemented with annual refresher training. New employees need to understand that following the company's ethics and integrity standards are a condition of employment. This approach will allow employees to come forward with potential data integrity issues without fear of being immediately terminated.



ICH Q10, Part 2, Management Responsibility, Section 2.3, Quality Planning: Senior management needs to communicate this zero tolerance policy regarding data integrity through a training program that incorporates the company's data integrity policy and data integrity SOPs as part of the training curriculum for all employees. The establishment of new employee training that includes the company's ethics and integrity standards will also communicate to company employees that any actions compromising data integrity will not be tolerated. This training program should also inform all employees of the consequences for anyone who violates the corporate data integrity policy. Just like cGMP training, reinforcement of the data integrity policy should also be provided to all employees annually.

ICH Q10, Part 3, Continual Improvement of Process Performance and Product Quality, Section 3.1, Lifecycle Stage Goals iii) Manufacturing: The Quality Unit is largely responsible for the lifecycle approach to product quality. The goal of production and quality is to manufacture a product that meets all of its specifications on a regular basis. Section 3 of ICH Q10 describes the following responsibilities of the Quality Unit in the lifecycle approach: a) monitor process performance, b) monitor product quality, c) manage the CAPA process, and d) manage the change control systems. ICH Q10 states that management is responsible for reviewing the process performance and product quality. This model is based upon the Quality Unit metrics, which rely on accurate, complete and attributable records and data. ➤

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Of the recent data integrity findings by the FDA and EMA, the majority have been discovered in the Quality Control laboratory. The QC laboratory determines whether or not a product meets specification, and therefore, focusing on this lab should provide an indication of how a company maintains the integrity of generated results. Management of a QC laboratory should not only review the analyst laboratory notebooks or worksheets (which is the norm) but should also include a review of the metadata as part of the regular review process. It has been the EMA and FDA review of the metadata from High Performance Liquid Chromatography (HPLC) and Gas Chromatography (GC) analyses that has produced the majority of the evidence of data integrity issues in the laboratory. The review of the metadata has revealed the use of "trial" injections, orphan injections, injections not used in calculations, injections out of sequence or out of chronological order. These data integrity issues have been found in the metadata of HPLC and GC instruments that are interfaced with computers but not interfaced with a laboratory information management (LIM) system. At a minimum, laboratory management needs to periodically review the metadata that supports the laboratory notebook or worksheet. It is recommended that this be done for all suspected OOS results to ensure that there are no anomalies with the metadata whether the OOS is confirmed or not. The laboratory management review should also be extended to the audit trail for the analytical sequence of invalidated OOS results to verify that the data is accurate and complete. The Quality Assurance department should include the review of the audit trail of electronic batch product records (BPRs) records as part of the batch release process, just as it would review hard copy BPRs for any changes made to entries.

The laboratory should also have a written SOP on how HPLC and GC data can be integrated. It is recommended that the SOP concerning the integration of HPLC and GC data should state that the manual integration of data is only allowed with the prior approval of laboratory management. It is also recommended that the QC laboratory should track and trend all manual integrations in order to identify potential issues with a specific validated analytical method or with an individual analyst who may require additional training. A corrective action can then be initiated.

ICH Q10, Part 4, Continual Improvement of the Pharmaceutical QMS, Section 4 .1: Management Review of the QMS (Internal Audits): The company's self-assessment should include data integrity as one of its main focuses. Most internal audit programs do a good job of monitoring compliance with cGMPs, corporate policies and local procedures but not as many do a good job in assessing the integrity of the data and records that are generated. On Dec. 16, 2013, MHRA announced that pharmaceutical manufacturers and contract laboratories must ensure the effectiveness of their governance systems so that data integrity must be included in their self-inspection program ***(2).*** MHRA also stated the Agency would begin enforcement of assurance of data integrity starting in 2014 as part of their evaluation of company's compliance with the self-inspection, Chapter 9 of Eudralex, Volume 4. The MHRA didn't amend this chapter; they only provided their expectations that data integrity be included in a self-inspection program.

QC Labs and Continuous Improvement

In the laboratory operations, the internal audit program should be looking at the security of the data on standalone computers interfaced with instrumentation that is not interfaced with a LIM system and to a certain degree the data on computers that are only interfaced with instrumentation and a server. Some of the main points that internal audits of laboratory operations should verify include the following: a) that the system administrator is not responsible for the data being collected, and preferably is someone from an independent department, b) use of unique usernames and passwords, c) the rights and privileges of each user role is consistent with their role, d) verify that the audit trail feature is activated and cannot be turned off except by the systems administrator, e) review of audit trails from a sample of standalone computers to verify data has not been manipulated, and f) review the metadata for a sampling of the sequences from invalidated data, OOS, OOT and some passing results of product release and stability data. These exercises should be conducted in the in-process laboratory as well as finished product and stability testing laboratories, if applicable. A mature QMS will utilize the results of the internal audits as part of their continuous improvement program and institute corrective action plans.

Production Operations & Continuous Improvement

In production operations, the internal audits should be looking for the following: a) control of the issuance of batch product records, forms to records in-process testing and other production records on which data is recorded, b) contemporaneous recording of data, c) ensure that records are not prerecorded prior to performed operations, d) no use of "post-it" notes or other extraneous documentation, e) no discarded data, f) no spaces left blank for later recording operations that were not performed, g) out of sequence log book entries, and h) employees signing off on operations they did not perform or witness.

The results of these internal audits need to be distributed to senior management for review. Senior management should implement additional oversight or allocation of resources to address any issues that are found. Management cannot wait for a trend to develop and must act immediately to stop any actions impacting integrity of the data, determine the extent of the problem and address the situation transparently.

Continued at bottom of page 41

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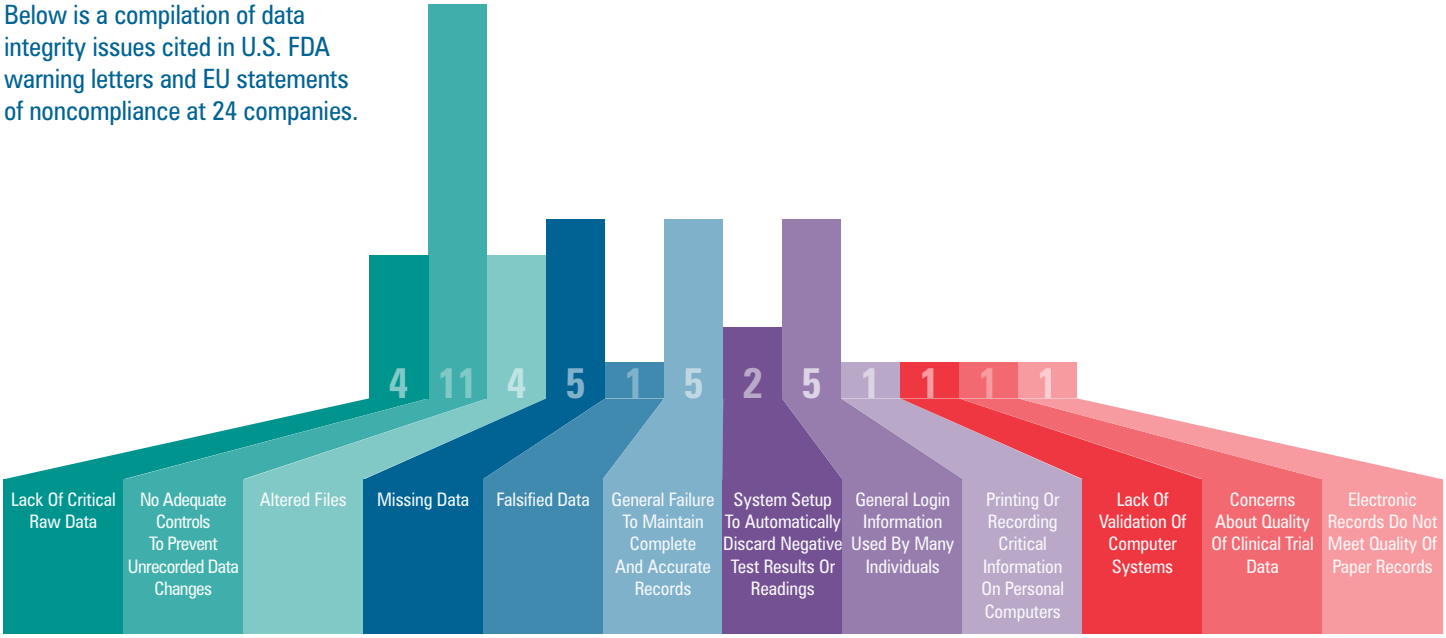
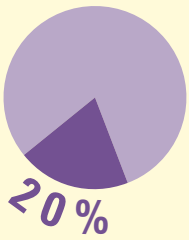
Data Integrity Citations in 2014

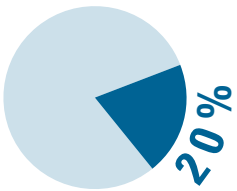
Below is a compilation of data integrity issues cited in U.S. FDA warning letters and EU statements of noncompliance at 24 companies.



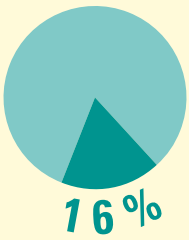
A Sampling of Common Data Integrity Citations



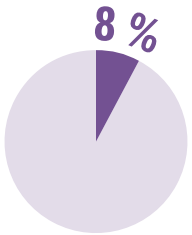
General Login Information Used By Many Individuals



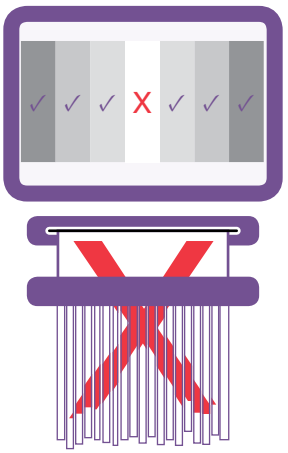
Missing Data



Altered Files



System Setup To Automatically Discard Negative Test Results Or Readings



Special thanks to **David Perkins** and **Cormac Dalton** of AbbVie for their assistance with this infographic.

Source

Lopez, O. "2013-15 Cases of Data Integrity Issues." Computer Systems Validation. www.computer-systems-validation.net/images/Data_Integrity_Deviations_Rev_03Jan15_.pdf

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book review

Author Casts a Spell on Quality Management

Robert Darius, GlaxoSmithKline

The Making of a Quality Manager
By Mort Levin
Trafford Publishing (July 6, 2006)

Once in a while, a small book can provide great insights, especially when crafted by a 48-year veteran of the medical device industry. I first noticed **Mort Levin's** *The Making of a Quality Manager,* a 100-page book, on Amazon many years ago. I purchased it and stored it at the bottom of my "to-be-read" book stack for several years. It was published by a small vanity publishing house so I did not think it would offer any great learning or insight. But the age-old adage about not judging a book by its cover proved to be very correct in this instance.

When I finally read this book, I instantly fell under Levin's spell. Through his humble book and very basic graphics, his spirit and mind were fully open on his thinking of all aspects of Quality. He shared stories of his mistakes and lessons learned in simple and tangible ways. To me, it felt like I was listening to the wisdom of a grandfather or a mentor who had worked through similar challenges in the industry. The guidance in his book helped me verify that what we were trying to achieve was possible—improving the Quality Mindset and driving positive change in a large company across many different sites.

Levin started his career as an engineering manager and was thrust into the role of quality manager in the early 1970s while working in the medical device industry. As an engineer, he was quite sensitive; he stated that "managing quality is much more than numbers. It is about people."

The goal of perfection in quality is approached asymptotically and never reached. Superiority can only be achieved with vision, commitment and passion from leaders at all levels within the organization.

"A quality manager is not able to help their company by staying in the quality department only. They must understand how the other departments function. They must understand the processes as well or even better, than most members of the company," Levin wrote.

I believe Quality has reached an ideal state when they can out think production and validation teams, knowing the process so well that multiple solutions or designs of experiments to prove a hypothesis emerge. Importantly, individuals working in Quality must work diligently to not give answers to their teams but instead steer team members to help reach the answers themselves.

The author urged readers to remember to pay attention. Dig. Learn the fundamentals. Analyze. Work to high standards. Remember that details are important. How many of us have the time, or make the time, to live by these points now that we drown in information on the internet and our mailboxes overflow with hundreds of emails each day? Implementing these points alone could avoid many challenges in the industry.

Levin offered the following ten points for Quality success:

- Acknowledge that everyone wants to do a good job. They just need the appropriate training, tools, the right environment and leaders.
- Auditing is not the best way of assuring safe and effective products. The system must be in control at all times.
- Reliability, reliability, reliability!
- A standard or regulation is not a substitute for a quality system.
- A quality manager should be as interested in profit as any other manager. Do your best to help make a real product, one that meets cost and profit objectives.
- Quality is too important to be left solely in the hands of the quality manager. Everyone has a part in providing the proper quality.
- Wander around the factory and the field. Listen, learn and communicate.
- Do not be quick to blame the worker. There is likely a manager or supervisor who might be the cause of the problem.
- Talking is not enough. Take action.
- Quality begins with emotional attachments (from Tom Peters' *Thriving on Chaos*).

Levin dedicated his book to all those who did the real work in improving Quality and to those who helped him become a quality manager. His book inspired me so much that I purchased copies to share with my team and other peers.

In his book, Levin wrote about the giants in his career, people who helped others by sharing their wisdom, knowledge and experiences—ultimately allowing others to climb on their shoulders and take advantage of what they have done, giving others a view of the future and how they should reach their goals. I would say that Levin is a giant and I appreciate being able to stand on his shoulders after reading and reflecting on his little book, *The Making of a Quality Manager.* Thank you, Mort Levin.

About the Reviewer

Robert Darius is Vice President of the Regional Quality Unit for GlaxoSmithKline Vaccine's four manufacturing sites located in Germany and North America.

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North America

U.S. FDA Commissioner Steps Down

At the end of March, U.S. FDA Commissioner **Margaret Hamburg,** MD, stepped down from her role. Acting Chief Scientist **Stephen Ostroff,** MD, has agreed to serve as Acting Commissioner until a replacement for Hamburg is named. She had served as FDA Commissioner since 2009.

Kathleen Uhl Now Permanent OGD Director

Earlier this year, the FDA announced that the current acting Director of the Office of Generic Drugs, **Kathleen Uhl,** MD, will be hired as the permanent director of OGD. Uhl had been serving as acting director following the departure of **Greg Geba**.

Uhl has been leading OGD at a time when it has been elevated to a "super-office" within the Agency under restructuring. OGD is currently working to develop efficient application processes and facilitate greater inspections of foreign generic drug facilities.

Proposed U.S. Legislation Seeks More Efficient FDA Reviews

Recently released draft legislation from the U.S. Congress' House Energy and Commerce Committee includes provisions focusing on expediting FDA regulatory review of new and existing drug and device products. This legislation, the 21st Century Cures Initiative, seeks to improve the efficiency of the development process for innovative medical products.

Key Regulatory Dates
Comments Due
May 20 and June 19 — FDA Provides More Info for Compounders

FDA Provides More Info for Compounders

In February, the FDA released five draft documents concerning drug compounding and repackaging in an effort to ensure relevant entities comply with key public health regulations. These documents follow the enactment of the Drug Quality and Security Act (DQSA) in November 2013.

One document details the regulatory impact of registering as an outsourcer.

Another document explains how FDA will respond to repackaging violations by entities falling under the DQSA. A third document describes conditions under which the Agency will not take action for certain regulatory violations that occur due to outsourcing facilities mixing, diluting and repackaging biologics. A fourth explains adverse reporting steps for recognized outsourcing facilities. And a fifth, a draft Memorandum of Understanding, outlines a state's responsibilities when signing the MOU to investigate complaints regarding compounded drug product.

Comments on all of these documents, except the MOU are due May 20. MOU comments are due June 19.

Europe

Britain's MHRA Releases Data Integrity Guidance

In Q1, Britain's MHRA released a guidance outlining the authority's expectations for data integrity within the industry. The document also lists MHRA's definitions for data integrity-related terms.

The guidance is intended complement existing EU GMP regulations.

Asia-Pacific

India Plans to Formalize Presubmission Meetings

India's Central Drugs Standard Control Organization (CDSCO) laid out plans to formalize presubmission meetings in a Jan. 28 notice. Presubmission meetings allow companies and regulators an opportunity to review potential submissions and ensure they conform to regulatory requirements. By formalizing these meetings, CDSCO is aligning itself with practices of other global regulators.

ATMPs Gain Regulatory Acceptance, But Challenges Remain

Dirk Groenewegen, Cells4Therapy, and Wilfried Dalemans, PhD, Tigenix

Advanced Therapy Medicinal Products (ATMPs) represent a promising class of new products for treating highly complex medical conditions. First generation products have obtained regulatory approval, and the field is rapidly moving towards even more complex second generation products. In fact, in December 2014 EMA approved the first stem cell ATMP in the European Union—Holocar, a treatment for limbal stem cell deficiencies due to burns to the eye. As in the case of other product types, this first approval means the pathway for approvals of additional products is now established.

Clearly, there is a need for discussing the many challenges involved in developing, testing, producing and the registration of ATMPs. This includes at the pharmacopoeial level. Recently, the European Pharmacopoeia published a draft chapter addressing the challenges of ensuring quality requirements for raw materials used in ATMP production. There had been little guidance in this area, although the proposed chapter is analogous to certain chapters in the U.S. Pharmacopeia.

As this example shows, while ATMPs have their challenges, regulators and others in industry recognize these challenges and seek harmonized approaches.

To tackle the challenges of ATMP manufacturing and to seek further global regulatory harmonization, PDA has established its *Advanced Therapy Medicinal Products* conference as a unique interactive discussion platform that offers plenty of opportunities for knowledge exchange between representatives of industry, academia and regulatory authorities, both from Europe and the USA.

This year, the co-chairs are especially proud to present speakers from several European regulatory agencies on this very hot topic of ATMPs, including the Finnish Medicines Agency, Britain's MHRA, the European Directorate for the Quality of Medicines, Dutch Health Care Inspectorate, Paul-Ehrlich-Institut, INFARMED, and more.

Prior to this two-day conference, PDA Europe offers a preconference workshop specifically dedicated to the *Manufacturing and Testing Challenges of ATMPs*. In this workshop, relevant issues like raw materials selection, GMP management and quality control will be discussed in depth.

This preconference workshop will be held in cooperation with the EU AGORA Project, the European ATMP GMP Open Access Research Alliance, see www.agora-gmp.org.

For more information about this conference, please visit https://europe.pda.org/ATMPs2015.

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FDA Lauded for Clear Guideline on Adipose Tissue Use

For the comments grid, visit www.pda.org/regulatorycomments

February 23, 2015

Division of Docket Management (HFA-305)
Food and Drug Administration

5630 Fishers Lane, Room 1061

Rockville, MD 20852

Reference: Human Cells, Tissues, and Cellular and Tissue-Based Products from Adipose Tissue: Regulatory Considerations; Draft Guidance for Industry

Docket No. FDA-2014-D-1856

The Parenteral Drug Association congratulates FDA for preparing a clear guideline with the content presented in a logical and helpful fashion. The document is largely well written and the content of guideline is necessary to provide clarification to manufacturers working with adipose tissue. PDA recommends adding a couple of additional clarifications which are noted in the attachment.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in gene and cell based therapies including members representing our Board of Directors, our Biotechnology Advisory Board and our Regulatory and Quality Advisory Board.

If there are any questions, please do not hesitate to contact me.

Sincerely,
Richard Johnson
President, PDA
cc: Denyse Baker, PDA

PDA Commenting Task Force

Michael VanDerWerf, Organogenesis (Chair)
Karen Ginsbury, PCI Consulting
Karen Walker, Novartis
Allen Burgenson, Lonza

Incorporating Data Integrity into Your Quality Management System continued from page 30

Conclusion

The industry needs to understand that data integrity is something that has to be dealt with in a holistic manner. It is the expectation of regulatory agencies that the records and data generated by a company are attributable, contemporaneous, complete, accurate, reliable and retrievable. Although ICH Q10 does not specifically address data integrity, this article has used it as a template to demonstrate how companies can incorporate data integrity into their QMS.

References

1. "OIG Compliance Program Guidance for Pharmaceutical Manufacturers." *Federal Register* 68 (May 5, 2003): 23731-23743 oig.hhs.gov/authorities/docs/03/050503FRCPGPharmac.pdf

2. "MHRA expectation regarding self inspection and data integrity," MHRA News and Hot Topics: December 16, 2013.

About the Author

Anthony Warchut, Vice President, Technical, PAREXEL, has over 29 years of experience as an investigator for the U.S. FDA and more than eight years as a consultant. He has prepared clients to achieve successful preapproval, GCP Sponsor/Monitor and FDA cGMP systems inspections.

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Data Integrity: Partnering for Success

C. Gregory Williams, Novartis

Data integrity breaches continue to challenge the pharmaceutical industry, but regulatory agencies and industry are partnering together to raise awareness and solve these issues.

Over the past two years, pharmaceutical manufacturers operating in India have received over twelve U.S. FDA warning letters alleging, in part, deficiencies related to data integrity. As a result of the continued struggles with data integrity in this market, the FDA partnered with the Drug Information Association to host a *Multicentre International Data Integrity Workshop*, a series of conferences aimed at increasing the knowledge of manufacturers to identify and resolve these issues.

In an effort to demonstrate a unified approach and to assist in promoting an open dialogue, the hosts worked with PDA, the Indian Drug Manufacturers' Association, the Organisation of Pharmaceutical Producers of India, and industry to present the two-day workshop at three cities across India during the first two weeks of November 2014. The target cities were Mumbai, Hyderabad, and Bangalore based upon their geographic locations and due to the number of manufacturers in those areas. The response was overwhelming as small and large companies signed up to attend.

The first session began with opening remarks by **Peter Baker,** Assistant Country Director, FDA India Office, to introduce the workshop and set the stage for the remaining discussions. Baker informed the audience of the top areas of concern for data integrity, which include quality control inspection and testing, batch records, equipment qualification and use, and training. He discussed the importance of documentation, but stressed that the data is much more important and added that industry should focus on their daily practices.

Carmelo Rosa, Division Director of Office of Compliance, Office of Manufacturing and Product Quality, CDER, FDA, provided a solid background on data integrity and made the case for change by highlighting the number of data integrity warning letters issued by FDA and stressing the importance of global corrective actions. He emphasized that this issue is not only found in India, but is an industry-wide issue. Rosa informed the group of FDA's emphasis on responses to issues identified in an inspection and their expectation of implementing systemic corrective and preventive actions.

As data integrity is not only an issue for the U.S. market, **Thomas Hecker,** PhD, GMP Inspector, EDQM provided the group with a European perspective based upon regulations, standards, and guidance documents. Hecker's presentation highlighted applicable sections of 21 CFR Part 11, EU GMP Annex 11, and ICH Q7 and how the three documents can work together to meet regulatory agency expectations.

While data integrity covers a broad topic in both electronic and paper form, **Robert Tollefsen,** National Expert Investigator, Drugs and Computers, Office of Regulatory Affairs, FDA, focused on validation, collection, and storage of electronic data in his presentation. He provided attendees with an overview of the requirements for a successful validation. In his second presentation, Tollefsen discussed the importance of management, culture and oversight in not only identifying and correcting data integrity breaches, but in prevention.

Industry presentations by Hospira, Johnson & Johnson, and Novartis provided the audiences an opportunity to hear from their peers. **Meera Khullar,** Vice President, Quality, Hospira, presented on the development of an operator and analyst training program. Her presentation went beyond data integrity into the elements of a successful and compliant training program.

Anil Sawant, Vice President, Enterprise Regulatory Compliance, Johnson & Johnson, presented on establishing a management culture that goes beyond the identification and correction steps and into the proactive process of prevention.

Novartis representatives **Mairead Goetz,** Head of Compliance, Group Compliance and Audit, presented in Mumbai, **Sudhir Goudar,** Regional Head APAC, Group Compliance and Audit, presented in Hyderabad, and **C. Gregory Williams,** Head of Audit, Group Compliance and Audit, presented in Bangalore, on the topic of internal audits and how companies can establish their programs to identify data integrity issues. The presentations highlighted how to establish an audit program.

Three interactive workshops were conducted covering establishment of an effective training program, establishing an effective audit program, and establishing a data integrity risk analysis process. The workshops required all the attendees to participate in small work groups and then report to the larger group about their findings.

The success of these workshops highlighted a strong collaboration between regulatory agencies and industry. Baker stated that, based upon that success, additional workshops will be planned in the future. Protecting against breaches of data integrity is not only a hot topic with the FDA today, but forms the basis by which industry protects our patients in providing safe and effective medicines across the globe.

About the Author

C. Gregory Williams is active in various industry groups, including PDA, AAMI, and Rx-360, and is currently the Head of Audit in the Group Compliance and Audit department of Novartis.

Martin VanTrieste, Amgen

Integrity of Data Reflects Integrity of Our Industry

We have all heard or even used the adage that "if it is not documented, it was not done." These few words truly describe one of the major products that all pharmaceutical manufacturers produce: data. But why is the data that these companies produce so important?

Well, healthcare providers and patients base their trust in the data used to produce these medicines. It is virtually impossible to look at a pill, capsule or other dosage form and determine if the medicine within the dosage is the right formulation, the right potency, or is pure and safe to use. There are many ways to build and maintain trust, but two key processes that we undergo in industry to establish trust are: 1) a thorough review by the quality organization of how a batch was produced prior to release of the medicine to the market, and 2) routine and rigorous cGMP inspections by regulators.

For these processes to be an effective means to protect patients, the data reviewed during product release and inspections must be complete, consistent and accurate.

Here is the definition I like to use when describing data integrity: *the degree to which a collection of data is complete, consistent and accurate, while maintaining and assuring the accuracy and consistency of data over its entire lifecycle.*

For global regulators, especially the U.S. FDA, this focus on data is not new. FDA's focus dramatically increased in the early 1990s following the generic drug scandal, in which the Agency found a number of generic companies had submitted false and misleading data in applications, including: innovator product quality control and bioequivalence data submitted in place of the generic version, substitution of stability tests results, failing tests results retested without justification or mention, and other more fraudulent activities such as bribing FDA officials.

As a result, FDA instituted some key compliance programs, including CP 7346.832 NDA/ANDA Pre-Approval Inspections, that outline for investigators a process to specifically check the accuracy of data submitted in regulatory filings and generated during GMP product manufacturing and testing. In addition, FDA outlined a new process for NDA/ANDA validity assessments. Also, the Generic Drug Enforcement Act authorizes FDA to debar and fine individuals and companies that misrepresent data in applications. FDA instituted the Application Integrity Policy as well, which created a process to stop company regulatory filing reviews when a pattern of material misrepresentation of data was found during inspections or data reviews.

These issues are not limited to generic companies. Most recently, regulators have uncovered numerous instances of fraud during preapproval and GMP inspections. This has mainly occurred in emerging market countries, but at the same time is not limited to these regions. As a result, FDA has increased their inspection staff and provided more specific training to investigators. Staff responsible for generating, processing or securing data must have a clear understanding of the framework over which the data integrity program lies. The strength of the program is closely tied to everyone's understanding of the responsibility they carry in assuring company data integrity.

PDA is also making an effort to tackle the issue of data integrity. Last November, PDA's India Chapter heard about a meeting in India hosted by the U.S. FDA and the Drug Information Association on the topic of data integrity. In recent years, the U.S. FDA has cited several well-known Indian manufacturers for lapses in data integrity. The India Chapter identified some potential speakers for this event, which proved to be highly successful. The chapter eventually hopes to hold its own data integrity-focused event.

Human nature is to be trusting, and as such, we first think about fraud when the issue of data integrity is discussed. There are many reasons other than fraud, however, that can cause data integrity issues, such as sloppy record keeping or incidents that cause the loss of data. Any reason that causes a data integrity issue can lead to significant regulatory action against a company, but more importantly healthcare providers and patients will lose confidence in the medicines produced by that company.

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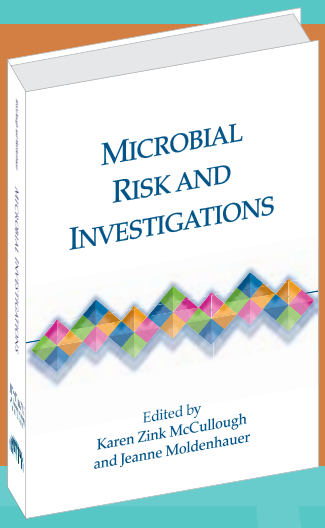

Microbial Risk and Investigations

EDITED BY: KAREN ZINK MCCULLOUGH AND JEANNE MOLDENHAUER

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The Barr Decision (Barr, 1993) forever changed how pharmaceutical companies look at data that is out-of-specification (OOS). Following issue of this legal decision, many companies and regulators worked to determine how this decision affects microbiological test results.

Microbial Investigations, written by authors with years of industry experience and edited by industry experts Jeanne Moldenhauer and Karen Zink McCullogh, provides a wealth of information on microbial investigations and dealing with aberrant data. Many of the chapters include case studies that can provide guidance for common situations that may occur at your facility.

Some of the many topics covered include:

- Types of Investigations
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Good Data is Good Science

No one is taught to manipulate data when learning how to conduct good scientific methods, yet data integrity is a huge problem. Maybe people are naturally dishonest, or maybe people are too eager to see their projects succeed, and in our industry, too afraid of the regulatory impact of bad news. But whatever the reason, pharmaceutical and biotech companies are not alone in dealing with data integrity issues.

A 2009 article in *Nature Neuroscience* (2009, 12:1205) highlights a number of high-profile cases of "data misconduct." In 2010, the president of the U.S. National Academy of Sciences wrote about the Academy's efforts to ensure data integrity, including a framework developed by its Committee on Science, Engineering, and Public Policy. The U.S. National Institutes of Health also has a policy and procedure on the topic (issued in 2012). The U.S. Geological Survey has an Office of Science Quality and Integrity as well.

Those are just a few examples of the shenanigans that take place in the research world. Whether it is the instinctual drive to get ahead, to promote oneself, to not be wrong, or perhaps the fear of failing, people struggle with the simplest basis of science: Truth. For sure, ethical challenges with deceit and lying exist in all fields. Just ask **Brian Williams** of "NBC Nightly News."

So, it is no wonder the problem exists in the pharmaceutical industry. There are many ways to get at solutions, but I suspect culture is a big part of it. We need honest actors in our business. We need people who are not afraid to deal with the truth, even if that truth means destroying a batch or shutting down a process to find the cause of deviations.

We face these issues in the world of science publishing. All over the globe, "science" journals are popping up with low standards of peer-review and open access models. This is wreaking havoc on the integrity of science publishing. Plagiarism, falsified results and just plain fake science is becoming endemic in these publications because the role of the gatekeepers, the peer reviewers, is diminished. Speed to press and quantity of content is the governing ethic now, unfortunately.

That's why I want to take this moment when the *PDA Letter* is full of articles on data integrity to remind readers and PDA members that PDA offers a highly ethical scientific journal: the *PDA Journal of Pharmaceutical Science and Technology*. Yes, the peer review introduces a sometime significant time delay in getting manuscripts published, but the benefits far outweigh that. When readers access the PDA Journal, they are assured they are receiving high-quality scientific and original work that has been vetted. Authors are assured of having their work rigorously evaluated. The 2014 Frederick D. Simon Award winners for best paper in the Journal were a team of authors from Genentech/Roche. Their paper, "Filing of High-Concentration Monoclonal Antibody Formulations into Pre-Filled Syringes: Filling Parameter Investigation and Optimization," was not only deemed the best scientific manuscript by the Journal editors, it remains in the top 50 most-read articles a year later. I want to congratulate the authors for their hard work and accomplishment: **Wendy Shieu, Sarah Torhan, Edwin Chan, Aaron Hubbard, Benson Ginkanga, Oliver Stauch** and **Yuh-Fun Maa.**

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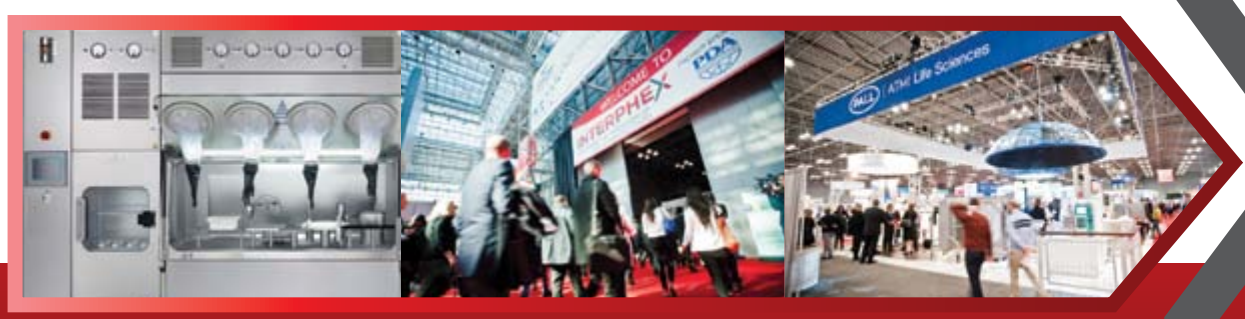

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