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PDA Letter

Volume LVI • Issue 5 www.pda.org/pdaletter September/October 2020

PDA SURVEY RESULTS

Current State of Biopreservation in Cell and Gene Therapy Products and Biopharmaceutical Commercialization

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PDA Survey Results

Current State of Biopreservation in Cell and Gene Therapy Products and Biopharmaceutical Commercialization

Brian J. Hawkins, Raluca Marcu, Pluristyx, Inc.

The first successful cryopreservation studies were performed in 1949 and, since then, numerous strategies have been proposed and adopted to facilitate the rapid restoration of cellular function following freezing. Unfortunately, despite decades of research and increasing emphasis in the clinic, harmonized cryopreservation standards for cell and gene therapies (Advanced Therapy Medicinal Products or ATMPs) do not exist, and cryopreservation protocols vary widely in practice both between, and even within, commercial and academic groups.

Cover Photo by dra_ schwartz, iStock.com

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Best Practice Guide for Using KPI's/Metrics

Bernhard Hinsch, Hinsch Consulting

The PDA Quality Systems Interest Group (QSIG) provides a forum for industry experts to discuss "hot" topics, which usually relate to rapidly evolving interpretations of current regulations. One such topic is the use of Key Performance Indicators (KPIs) and metrics.

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The House of Data Integrity Compliance

by Matthew Paquette, Charles River

Various industry influences have challenged how we—as scientists, manufacturing technicians or quality control professionals—approach the processes that protect the integrity of the data we collect during the manufacture and release of products that impact human and animal health globally.

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The Evolution of USP <800>: A Q&A with Cathy Zhao and Allison Radwick

The *PDA Letter* talked with **Cathy Zhao,** Director of Scientific Insights Lab, and **Allison Radwick,** Scientific Affairs Manager, from West Pharmaceutical Services about closed system transfer devices and the evolution of *USP <800> Hazardous Drugs—Handling in Healthcare Settings*. Below are their responses.

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2020 PDA Rapid Microbiological Methods Workshop
Oct. 22-23
pda.org/2020rapidmmicro

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Contact **David Hall**, Vice President, Sales, at **hall@pda.org** or +1 (240) 688-4405

pda.org/eu/2020VIForum

2020 PDA EUROPE

Visual Inspection Forum

NEW DATE AND VENUE!
The Event will take place at the Steigenberger Hotel Berlin, Los Angeles Platz

19-20 OCTOBER 2020
BERLIN, GERMANY
EXHIBITION: 19-20 OCTOBER
TRAINING: 21-22 OCTOBER

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Get Published *And* Noticed!

Walter Morris, Senior Director of Publishing

@Walt_PDA
www.linkedin.com/in/walter-morris-82191a4

Why would anyone want to publish an article in *PDA Letter* or their research in *PDA Journal of Pharmaceutical Science and Technology* (JPST)? After all, aren't these restricted access publications that no one but PDA members can read?

These are great questions, and ones we can do a better job answering. In fact, anyone can read both *PDA Letter* and JPST.

Let's start with *PDA Letter.* Ever since we began posting articles online over a decade ago at www.pda.org/pdaletter, we have included a selection of "open access" articles. Since the pandemic began, all articles have been open access, incidentally, but not before long, we will return to the blend of member-only and open-access content. Nevertheless, non-members always have the option of purchasing articles of interest or joining PDA if they want full access.

PDA Letter articles are highly visible. Our online readership is strong and growing stronger. From January through June, **over 60,000 pages at the Letter Portal were visited,** a 6% increase over the same period in 2019 and a 36% increase over the same period in 2018. For all of 2019, there were 110,000 page views for the Letter Portal.

We recently updated both the About and Submit pages to better assist readers. We are always seeking articles in the following PDA-critical topic areas:

- Aseptic Processing & Sterilization
- Biopharmaceuticals & Biotechnology
- Manufacturing Science
- Quality & Regulatory
- Supply Chain

PDA's fantastic community of sponsors and technology enablers can publish "Advertorials," which are sponsored articles for a fee. Limited opportunities for sponsored content are available, so be sure to contact Dave Hall, hall@pda.org for details.

How about JPST? Well, PDA members might not realize that tens-of-thousands of people have access to JPST every year through PDA membership, well over100 institutional subsciptions, and article sales. Every PDA member have access to the current volume and immediate past volume of the JPST. Institutional subscriptions provide access to all individuals using registered IP addresses. And anyone can purchase an article! In 2020, we are averaging 120 article sales per month.

All of this contributes to healthy readership of JPST. **Articles published in the last six JPST issues for which metrics are available (Jul-Aug 2019-May-June 2020) have been accessed, on average, 2,500 times.** These numbers only grow over time, as the JPST archive extends all the way back to 1980.

Since 2019, PDA has worked diligently to provide better author instructions and improve the submission process: https://journal.pda.org/content/author-resourcessubmit-paper, https://submitjournal.pda.org/.

So, as you can see, publishing with PDA's two member-benefit publications will help you achieve valuable visibility for your articles and scientific manuscripts.

My question to you is, what are you waiting for? Turn to PDA to get published *and* noticed!

We Want You! Volunteers Need for New PDA ATMP Advisory Board

Michael Blackton, Adaptimmune, LLC, and Stephan Krause, PhD, AstraZeneca Diagnostics, ATMP Advisory Board Co-Chairs

The last few years have shown us that cell and gene therapies, now called Advanced Therapy Medicinal Products (ATMP), are not just academic exercises in innovation but life-changing and viable candidates for regulatory approval. PDA has worked for several years to advance these therapies through the development lifecycle with an ongoing series of workshops and conferences, development of the ATMP Interest Group, publication of PDA *Technical Report No. 81: Cell-Based Therapy Control Strategy* and presentation of the annual PDA Europe Conference on Advanced Therapy Medicinal Products. Given the importance of these products to patients worldwide and the need for holistic collaboration across both industry and global regulatory authorities, PDA established the ATMP Advisory Board. The Advisory Board, which reports to the PDA Board of Directors, is tasked with driving the strategy for stewardship of emerging ATMP science, guidance and regulation.

The ATMP Advisory Board will help the industry navigate the complexities surrounding this relatively new class of biologics. Because the space is so new, the industry is experiencing a highly dynamic regulatory environment with new guidance and regulations developed at a rapid pace. This is significant in that the technologies used in ATMP manufacturing often outpace the regulatory framework required to guide organizations toward approval. The ATMP Advisory Board is focused on these topics and will help facilitate consistency across the industry through collaboration with volunteers and engagement with worldwide regulatory agencies.

The charter developed for the ATMP Advisory Board focuses on three priorities:

- Those technical aspects of ATMP that PDA believes are needed
- New members, particularly early career professionals, not just because the board is new, but because the ATMP space is new and requires new ways of thinking and approaching challenges
- Near-term concentration in the areas of product development, control strategy and microbiological methods

To pursue these goals, the ATMP Advisory Board is looking for volunteers to provide leadership through this complex milieu of science, technology and regulation. If you are interested in becoming a member of the ATMP Advisory Board, please click on this link to fill out the skills and experience survey so the advisory board can evaluate your qualifications. If you have an idea for a project that the ATMP Advisory Board and PDA should consider, please follow this link to fill out a project proposal form.

About the Authors

Michael Blackton is the Vice President, Quality Assurance and CMC, with responsibility for the quality assurance function supporting chemistry, manufacturing and controls (CMC) for Adaptimmune's clinical pipeline. Michael Blackton's career spans over 25 years in biotechnology, medical device and pharmaceuticals where he has held leadership positions in manufacturing, quality, operations, and engineering.

Stephan Krause, PhD, is the head of AstraZeneca Product Quality Leader Group. He is a frequent PDA volunteer and current member of PDA's Board of Directors.

2020 Election Promises to by Raucus Affair

So Vote Now for the 2021 PDA Board of Directors!

Just because the world is focused on the presidential election in the United States, it doesn't mean there aren't more important elections. In fact, it is that time of year for PDA members to vote for the 2021 PDA Board of Directors.

Six members are candidates for three open seats on the all-volunteer PDA 2021 Board of Directors. Unfortunately, you cannot mail in your ballots nor show up at your local school or community center to cast your ballot in person. But you can, and must, vote online! Please have your member i.d. and password to vote.

You can vote early or late, as long as you vote by **11:59 pm EST on November 15.** Unfortunately, for those of you so inclined, you cannot "vote often!"

For full bios and a link to your member ballot, go to https://www.pda.org/bodelection

The candidates are:

Bettine Boltres, PhD, West Pharmaceutical Services

Patrick Costello, Abbvie Inc

Mary Oates, PhD, Lachman Consultant Services, Inc.

Brigitte Reutter-Haerle, Vetter

Osamu Shirokizawa, Life Scientia Ltd.

David Spaulding, Consultant

SoCal Chapter Donates Masks to Aid Service Providers

Christy Wong, PDA Southern California Student Chapter President and Student, Keck Graduate Institute

The COVID-19 pandemic has disrupted every industry and affected all walks of life. Given the globalized and interconnected world that exists today, this pandemic has drastically challenged the norms of work and human interaction. That is not to say we humans lack resilience or are unable to help one another in our journeys to adapt and reconstruct. Instead, these times have highlighted our strength as a collective and our shared humanity in supporting each other.

In the Los Angeles and Orange County areas, a bevy of organizations are dedicated to continuing their crucial services to the elderly and those in need—the hungry, displaced youth and nursing mothers and their children. Despite the associated risks, volunteers and employees show up every day to support their surrounding communities. While they do so, donning masks and following government safety precautions, the dwindling supply of masks has been a fundamental issue that continues to threaten the operational capabilities of these essential services.

As a professional organization dedicated to improving lives through scientific exchange and other means, the members of the Parenteral Drug Association (PDA) Southern California (SoCal) Chapter felt they needed to contribute to the greater effort of service during this challenging time. On behalf of its chapter members, volunteers, sponsors and supporting companies, the PDA SoCal Chapter donated 1,000 masks to essential service providers located in the region. Led by **PDA SoCal Student Chapter President Masami Amakawa**, donations were made during the month of May to:

- Orange County Food Bank
- Los Angeles Youth Emerging Stronger
- Special Supplemental Nutrition Program for Women, Infants, and Children
- Anaheim Crest Nursing Center
- Home Instead Senior Care

While our small donation pales in comparison to the impact of the incredible services these organizations provide to the community, we are fortunate to have had this opportunity to "pay it forward." Looking ahead, we hope to continue playing our part in this collective effort to sustain and bolster both the morale and vitality of the Southern California region.

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PDA Honor Awards

The winners of the 2019 Honor Award were recognized online and at the PDA Annual Meeting earliers this year. PDA thanks all of the recipients for their contributions to the Association. The July/August print edition includes the other award winners.

Honorary Membership

This is PDA's most prestigious award, conferring lifetime membership benefits to the recipient, given in recognition of long service significant in nature to PDA and requires unanimous approval from the Board of Directors. For 2019, PDA confers this honor on **Hal Baseman** and **Yoshihito Hashimoto.**

A former Chair, Hal has been instrumental in developing and leading the PDA Education courses on aseptic processing. His volunteer service for PDA has ensured the Association remains a leader in the area of aseptic processing. He continues to support other efforts for PDA in this area.

Yoshihito served on the Board of Directors from 2003 to 2007. He has also served on program planning committees for PDA events in Asia. Additionally, he has participated on numerous regulatory commenting teams. His volunteer work has helped expand PDA's Yoshihito Hashimotopresence in the Asia Pacific region.

Edward Smith Packaging Science Award

In honor of long-time volunteer **Edward Smith,** who led PDA's packaging science activities, this award honors extraordinary contributions to packaging science. PDA honors **Derek I. Duncan,** PhD, Lighthouse Instruments, for his volunteer work in packaging activities, including task forces, technical reports and on program planning committees. **Ronald Forster,** PhD, Amgen is honored for his work on PDA's activities related to glass packaging.

◀ **Derek I. Duncan,** PhD, Lighthouse Instruments

Ronald Forster, PhD, Amgen

Gordon Personeus Award

Presented in the memory of past PDA President and longtime volunteer, **Gordon Personeus,** this award honors a PDA member, other than a Board member, for long-term contributions of special importance to PDA. For 2019, PDA recognizes **Cylia Chen-Ooi,** Amgen, and **Thomas Schoenknecht,** PhD, Lonza.

Cylia has been involved in PDA's quality metrics and quality culture initiatives. She is the co-leader of PDA Quality Metrics/Culture Task Force Team and has served on program planning committees for PDA's quality metrics conferences in addition to her involvement on commenting teams for U.S. FDA guidance documents.

Thomas, who unfortunately passed away earlier this year, was also a longtime volunteer for PDA. Most recently, he was conference chair for the *2019 The Universe of Pre-filled Syringes and Injection Devices* conference and exhibition. He was also a member of the Glass Task Force and served as the European leader of the Combination Products Interest Group ➤

PDA Parenteral Drug Association

www.pda.org/pdaletter http://journal.pda.org

Where do **leading experts** turn to communicate with the PDA community?

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STEPHAN ROENNINGER
ANDERS VINTHER
JAMES AGALLOCO
JAMES AKERS
JAMES COOPER
DENNIS JENKE
IRVING PFLUG
MARK JORNITZ
MICHAEL MILLER
KURT BRORSON

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pda.org/EU/2021UPS

2021 PDA EUROPE

The Universe of Pre-filled Syringes and Injection Devices

5-6 OCTOBER 2021
GOTHENBURG, SWEDEN
PRE-CONFERENCE WORKSHOPS: 4 OCTOBER
CONFERENCE & EXHIBITION: 5-6 OCTOBER
TRAINING: 7-8 OCTOBER

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Frederick Carleton Awards

Presented in tribute to lifetime contributor, past President, past Executive Director, and Honorary Member, **Frederick J. Carleton,** this award recognizes past or present Board members. PDA recognizes former board members **Ursula Busse,** PhD, Novartis, and **Dr. -Ing. Stephan K. Rönninger,** Amgen, for their contributions to PDA.

Ursula received the award in recognition of her service on the Board of Directors from 2012–2018. She has been a member of the Paradigm Change in Manufacturing Operations℠ Task Force and the PDA Post Approval Change: Innovation for Availability of Medicines Task Force. She has also participated as a member of the planning committee for several Annual Meetings.

In addition to serving on the Board of Directors, Stephan has volunteered for numerous task forces and committees. He has also served on the Regulatory Affairs and Quality Advisory Board. Stephan has also served as a leader on PDA's drug shortages initiatives as well as a resource for ICH guidelines.

Martin VanTrieste Pharmaceutical Science Award

Established in honor of long-time contributor and Chair, Martin VanTrieste, this award honors outstanding contributions to the advancement of pharmaceutical science. **Michael Sadowski,** Baxter Healthcare, received this recognition for his extensive volunteer work for PDA, including involvement in the Association's sterile manufacturing initiatives. He has also served on the PDA Board of Directors.

Michael S. Korczynski Award

In honor of Michael S. Korczynski, PhD, this award recognizes contributions made toward the development of PDA's international activities. **Andiyanto Sutandar,** PhD, HGP Asia, is recognized for his leadership in the Asia-Pacific region, including extensive volunteer work for the Singapore Chapter and in supporting events in the region. **Cristiana Campa,** GSK, is recognized for her work supporting PDA conferences in Europe; she served as co-chair of the inaugural BioManufacturing conference in September.

President's Award

This award recognizes a PDA staff member whose exemplary performance has contributed to PDA's success during the previous year. For 2019, PDA recognizes **Lindsey Navin**, Senior Manager of Marketing. Her work for numerous campaigns in support of PDA's events, education courses, publications and other activities contributed to the success of the Association.

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Joint Associations' Response Letter on EU Annex 1 Draft

Hal Baseman, Valsource, Inc and Annex 1 Response Team Co-Chair

On July 10, 2020, PDA, on behalf of a group of over 10 industry associations, submitted a letter **(see box below)** to the European Commission and the European Medicines Agency (EMA) to augment the submittal of industry comments which had been requested by EMA for consultation on the February 2020 draft revision to Annex 1.

While the associations submitted their individual sets of more detailed comments, this joint association letter noted where the associations had reached a consensus on several general aspects of the Annex 1 revision.

The letter presented below is significant, because it shows regulators that industry associations with varying membership and objectives can speak with one voice when needed to point out the importance of addressing common concerns.

The latest version of the Annex 1 is one of the most anticipated regulatory guidance documents issued in the past several years. It is expected that the revised Annex 1 will be used worldwide (i.e., not only in Europe) as it is the outcome of the effort of a joint EMA-PIC/S task force. It addresses questions and concerns related to both aseptic process and terminal sterilization of current sterile products and therapies. It will likely be seen and used to help guide companies and regulators to address: the challenges of manufacturing new ATMPs and other advanced therapies, the utilization of innovative technologies and approaches, and the needs for global distribution. It should be appropriate for approaches and innovative technologies that are just now being contemplated and ones that will be developed as we move into the future.

To meet its objectives, the Annex must be clearly written and understood by a wide span of companies manufacturing products in numerous countries throughout the world. It must be based on good scientific and risk management principles. It must allow for, and if possible, encourage, the pursuit and adoption of continuously improved processes and process control technologies and approaches. It should not be overly prescriptive and become a barrier to companies challenging existing approaches that may not fit modern manufacturing processes.

The associations signing this letter did so to emphasize the importance of the effort and the willingness of the industry to work with regulators to make this a more effective guidance, to better promote its accurate use, and to achieves the common objectives and benefits of all stakeholders, and specifically of the patients.

PDA also submitted its own comments to EMA (see page 18).

10 July 2020

Olivier Gross
Policy Officer
European Commission – DG SANTE
Unit B4 - Medicinal products – Quality, safety, innovation
Health and Food Safety Directorate General
101 rue Froissart
B-1049 Brussels/Belgium

Jane Moseley
Head of Office, Inspections
European Medicines Agency
Domenico Scarlattilaan 6
1083 HS Amsterdam/Netherlands

RE: Second Consultation of the Draft Annex 1 Revision

Dear Mr. Gross and Ms. Moseley,

This is a letter from the joint group of industry associations that is being sent separately from the submission of each association's individual comments.

On February 19, 2020, notice was sent by the European Commission to industry associations requesting a second targeted consultation of version 12 of the draft Annex 1 revision. In response, the undersigned industry associations will be submitting their comments, recommendations on changes, and the justification for changes to the Annex. Each association established and followed their own procedures for soliciting, considering, and submitting specific comments from their respective membership. Although, each association's set of comments represents a different segment of the industry and geographic area, the association representatives see value in communicating some important common points uncovered during the Annex 1 revision process.

1. ***The Annex should be flexible to support the use of appropriate alternative approaches.*** It is important that where alternative approaches are supported by appropriate rationale and risk assessment and meet the intent of the Annex, that these alternative approaches be considered as acceptable. Regulators should allow flexibility to implement alternative process control strategies that effectively support product supply and patient (human and animal) needs, while meeting *the underlying intent of the* Annex for uncompromised product quality and safety principles. The importance of emphasizing in the Annex that adequate alternative approaches based on quality risk

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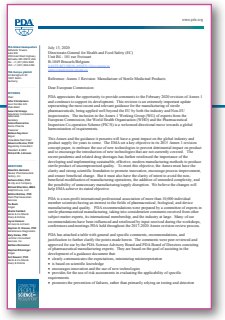
Annex 1 Comments



July 13, 2020

Directorate-General for Health and Food Safety (EC)
Unit B4 - 101 rue Froissart
B-1049 Brussels/Belgium
SANTE-REVISION-ANNEX-1@ec.europa.eu
sante-consult-b@ec.europa.eu

Reference: Annex 1 Revision: Manufacture of Sterile Medicinal Products

Dear European Commission:

PDA appreciates the opportunity to provide comments to the February 2020 revision of Annex 1 and continues to support its development. This revision is an extremely important update representing the most recent and relevant guidance for the manufacturing of sterile pharmaceuticals, being applied well beyond the EU by both the industry and Non-EU inspectorates. The inclusion in the Annex 1 Working Group (WG) of experts from the European Commission, the World Health Organisation (WHO) and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) is a welcomed directional move towards a global harmonization of requirements.

This Annex and the guidance it presents will have a great impact on the global industry and product supply for years to come. The EMA set a key objective in its 2015 Annex 1 revision concept paper, to embrace the use of new technologies to prevent detrimental impact on product and to encourage the introduction of new technologies that are not currently covered. The recent pandemic and related drug shortages has further reinforced the importance of the developing and implementing sustainable, effective, modern manufacturing methods to produce sterile product of uncompromised quality. To meet this objective, the Annex must have the clarity and strong scientific foundation to promote innovation, encourage process improvement, and ensure beneficial change. But it must also have the clarity of intent to avoid the nonbeneficial modification of manufacturing operations, the addition of unneeded complexity, and the possibility of unnecessary manufacturing/supply disruption. We believe the changes will help EMA achieve its stated objective.

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. PDA recommendations were prepared by a committee of experts in sterile pharmaceutical manufacturing, taking into consideration comments received from other subject matter experts, its international membership, and the industry at large. Many of our recommendations have been influenced and reinforced by input received during the workshops, conferences and meetings PDA held throughout the 2017-2020 Annex revision review process.

PDA has attached a table with general and specific comments, recommendations, and justification to further clarify the points made herein. The comments were peer reviewed and approved for use by the PDA Science Advisory Board and PDA Board of Directors consisting of pharmaceutical manufacturing experts. They are based on the goal of assisting in the development of a guidance document that:

- clearly communicates the expectations, minimizing misinterpretation
- is based on scientific knowledge
- encourages innovation and the use of new technologies
- provides for the use of risk assessments in evaluating the applicability of specific requirements
- promotes the prevention of failures, rather than primarily relying on testing and detection

The revision represents significant progress towards this goal. We see much improvement and acceptance of earlier comments. However, because of the complexity of the subject matter, the varying experience of companies, and the interpretation of ancillary inspectorates relying on the Annex, additional clarification is needed. In the absence of modification, there are concerns that some sections of the Annex will create confusion and uncertainty for both the industry and inspectors leading to a focus of resources away from areas where advancements have the greatest impact on both improving the manufacturing process and ensuring long term product supply.

As part of the commenting process, we identified and wish to point out some important concerns that should be further addressed, including (more details are in the comments form):

1. The use of prescriptive requirements and examples (perceived as prescriptive requirements), that may restrict or limit current and future innovative approaches.
2. Mixed messaging on the allowance of alternative approaches based on risk, by alternating a language supporting a risk based approach with very prescriptive requirements.
3. A focus on reactive process monitoring and product testing as a primary means of process control, that results in less emphasis on process design, training and failure prevention.

Complete PDA Regulatory Comments are available at https://tinyurl.com/yxjtvor6

Continued at bottom of page 39

A New Standard for Cold Storage and Lyophilization in the Fight Against COVID-19

Cold storage and lyophilization of vaccines and therapies for COVID-19 require a robust container. Glass vial failures due to damage and breakage are a source of product loss and result in higher process costs, delays due to product loss, potential safety risks, and possible drug shortages.

Compared to conventional borosilicate vials, Valor® vials significantly reduce damage and breakage during low temperature processing and storage and may lower manufacturing cost by reducing start-to-finish times and improving yields.

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2020 PDA Upcoming Events

VIRTUAL CONFERENCES AND EVENTS

The full Conference experience will be replicated to the extent possible with live virtual plenary sessions, live Q&A, chat lounges to facilitate networking, and Virtual Exhibit Halls!

OCTOBER

19-20 2020 PDA Europe Visual Inspection Forum
Sold out in-person, virtual attendance still available!
pda.org/EU/2020VIForum

19-20 PDA 595.1 Polymer Primary Packaging
pda.org/virtualedu

19-21 15th Annual PDA Global Conference on Pharmaceutical Microbiology
Virtual | *pda.org/2020micro*

20-21 PDA Europe Virtual Conference – Aseptic Animal Health
pda.org/EU/Animal2020

21-22 Mastering Automated Visual Inspection – Fall Edition
pda.org/EU/

21-22 An Introduction to Visual Inspection: A hands-on course – Fall Edition

22-23 2020 PDA Rapid Microbiological Methods Workshop
Virtual | *pda.org/2020rapidmicro*

26 PDA 709 Using a Risk-Based Approach to Successfully Qualify Your Machine
pda.org/sterilizationtraining

29-30 PDA 114.1 TR No. 67: Exclusion of Objectionable Microorganisms from Pharmaceutical and OTC Drug Products
pda.org/qctraining

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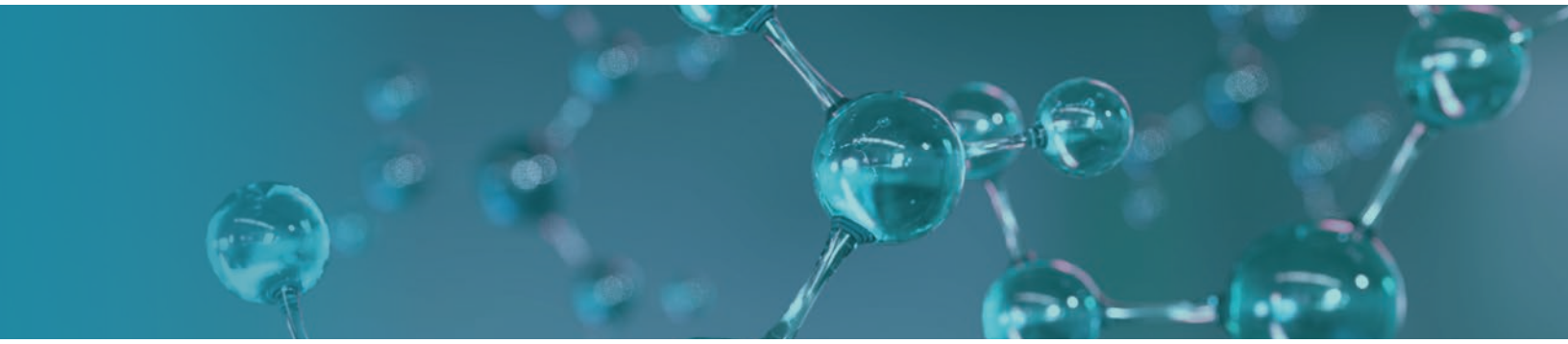

NOVEMBER

4-5 PDA 113.1 Establishing and Implementing an Effective GMP Auditing Program
pda.org/qatraining

4-5 PDA 569.1 Drug Delivery Device and Combination Product Risk Management and Safety Assurance Cases
pda.org/packagingtraining

4-6 PDA 468 Validation of Moist Heat Sterilization Processes
Bethesda, MD | *pda.org/sterilizationtraining*

9-12 Fundamentals of Aseptic Processing
Bethesda, MD | *pda.org/asepticttraining*

16-17 TR No. 13: Fundamentals of an Environmental Monitoring Program
Bethesda, MD | *pda.org/emtraining*

17 PDA 374.1 TR No. 22: Process Simulation for Aseptically Filled Products
pda.org/asepticttraining

DECEMBER

1-2 Analysis of Environmental Monitoring Data with Respect to cGMP and Data Integrity Guidelines
Bethesda, MD | *pda.org/emtraining*

1-3 Design, Operation, and Qualification of Pharmaceutical Water Systems
Bethesda, MD | *pda.org/facilitiestraining*

2 Environmental Monitoring Methods and Investigations – Looking for the Needle in the Haystack
Bethesda, MD | *pda.org/emtraining*

3-4 Foreign Particulate Examination, Isolation and Analysis
Bethesda, MD | *pda.org/vitraining*

8-9 PDA 615.1 Injectable Combination Product Integrated Development
pda.org/packagingtraining

PDA Requests Pause to USP's Biologics Nomenclature Proposal

31 July 2020

Jessica Simpson
Manager, Compendial Operations
United States Pharmacopeia
12601 Twinbrook Parkway
Rockville MD 20852

Re: General Notices revision proposed in Pharmacopeial Forum 46(2)

Dear Ms. Simpson:

PDA appreciates the opportunity to comment on the revision to the General Notices proposed in *Pharmacopeial Forum* [PF] 46(2), which would add a sentence regarding biologics nomenclature and official titles. We understand that USP published this proposal for a second time to gain updated comments and feedback on this difficult nomenclature topic.

As you know, biologics nomenclature is complex. USP's decisions, while focused on US regulatory policy, would impact products manufactured and marketed around the globe. Because nomenclature affects supply, USP's language in the *General Notices* may impact patient access to important medicines worldwide.

PDA encourages USP to pause use of the PF's formal notice and comment process to advance this issue and to provide clear messages about USP's overall goals and intentions. This would begin a conversation focused on finding answers. USP's conversation with stakeholders could thoroughly consider all the issues involved, including global harmonization.

PDA would be happy to serve as a facilitator for this conversation. Because PDA has not expressed any views on USP's proposed policy, we can help guide the conversation in a thoughtful and productive manner. As a neutral party seeking only continued patient access to high quality products, PDA can convene and guide a workshop or conference of originator and biosimilar manufacturers, regulators, and USP. PDA feels confident that such a conversation would reach a satisfactory result.

Finally, we support USP's continued focus, as expressed in the Briefing, "on developing performance standards, which are applicable to classes of biologics (e.g., monoclonal antibodies or cell therapies), as well as standards for raw materials," rather than monographs. As the Briefing notes, USP has received non-aligned feedback from key stakeholders regarding the development of monographs for biological products. Test methods for quality attributes, in contrast, provide meaningful value to patients and to manufacturers. PDA would be pleased to continue to engage with you in scientific dialogue on standards that would be most helpful and advance our common goals of promoting access to and protecting the quality of biological products.

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 have been prepared by PDA members with expertise in pharmaceutical, biopharmaceutical, and combination products manufacturing and compendial topics on behalf of PDA's Regulatory Affairs and Quality Advisory Board and Board of Directors.

If you have any questions, please do not hesitate to contact me via email at johnson@pda.org.

Sincerely,
Richard Johnson
President and CEO
cc: Glenn Wright, PDA; Ruth Miller, PDA

Complete PDA Regulatory Comments are available at https://tinyurl.com/yxjtvor6

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Best Practice Guide for Using KPI's/Metrics

Bernhard Hinsch, Hinsch Consulting

The PDA Quality Systems Interest Group (QSIG) provides a forum for industry experts to discuss "hot" topics, which usually relate to rapidly evolving interpretations of current regulations. One such topic is the use of Key Performance Indicators (KPIs) and metrics.

Because health authorities consider KPIs and metrics important indicators for judging the maturity of a company's quality system ***(1,2)***, the QSIG is frequently asked, "Which is the best practice for using KPIs and metrics within a quality system?" That this topic receives so much attention is not surprising, as KPIs and metrics are a good way of judging the state of maturity of selected elements of a quality system or of the entire system. What is surprising, however, is that there is currently little standardization in the industry for using KPIs and metrics.

This background is what triggered the work of a subgroup within QSIG that has been working on developing a *Best Practice Guide for Using KPIs and Metrics*. They recently presented on the status of their work in the monthly video meeting of QSIG.

The subgroup presented the following list of content to be covered in the *Best Practice Guide:*

- Purpose of KPIs/metrics
- Essential/desirable features of KPIs
- Areas of application
- Categorization
- Example definitions
- Visualization
- Points to Consider

The "Points to Consider" section will serve as a resource for various aspects of the use of KPIs and metrics that reflect the current thinking on best practices.

- Metrics influencing behavior
- KPIs/metrics categorization
- CMO integration into system of metrics, achieving alignment and understanding
- Compliance vs. quality metrics
- Data source where data come from
- Escalation of process to management
- FDA metrics (2017 approach vs. 2019 approach
- Hierarchy of metrics
- Leading vs. lagging
- Predictive vs. descriptive
- Normalization of data for long-term comparability
- Prioritization
- Purpose of metrics
- Quality culture, metrics as part of
- Targets, how to establish

One item in the "Points to Consider" section may be highlighted here specifically:

> **The presentation at the QSIG meeting raised great interest among the participants and stimulated a lively discussion**

Standardization of KPIs and metrics. This item is central to understanding the complexity of creating a *Best Practice Guide*. Whereas standardization of KPIs and metrics is a prerequisite for anyone who uses these tools within an organization for assessing the state of the pharmaceutical quality system and its subsystems, the attempt to standardize between different organizations has repeatedly proven to be a challenge. One reason for this is because good definitions of KPIs and metrics are usually quite specific to an organization, especially when it comes to such details as how to calculate the KPIs from the raw data or how to calculate the targets. Definitions may also vary by size of organization, because smaller organizations may need fewer complex hierarchies of metrics than larger organizations. Furthermore, good KPIs and metrics systems need to undergo continuous review and occasional controlled adjustment of definitions to the dynamic environment in which they are used, e.g., to changes in the competitive environment and coupled changes in business objectives, strategies and targets.

The presentation at the QSIG meeting raised great interest among the participants and stimulated a lively discussion, including suggestions for further work and the most appropriate format for publication of the *Best Practice Guide for Using KPIs and Metrics* within the available PDA formats.

If you are interested in participating in the activities of the subgroup, additional participants are welcome to assist in the creation of the final version of the *Best Practice Guide*.

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About the Author

Bernhard Hinsch, PhD, leads the subgroup KPIs/Metrics within PDA's QSIG. His professional experience includes senior management positions in Quality Systems functions in the pharmaceutical and medical device industry. Since 2013, he has worked as a consultant for quality system topics and process improvement in the healthcare industry.

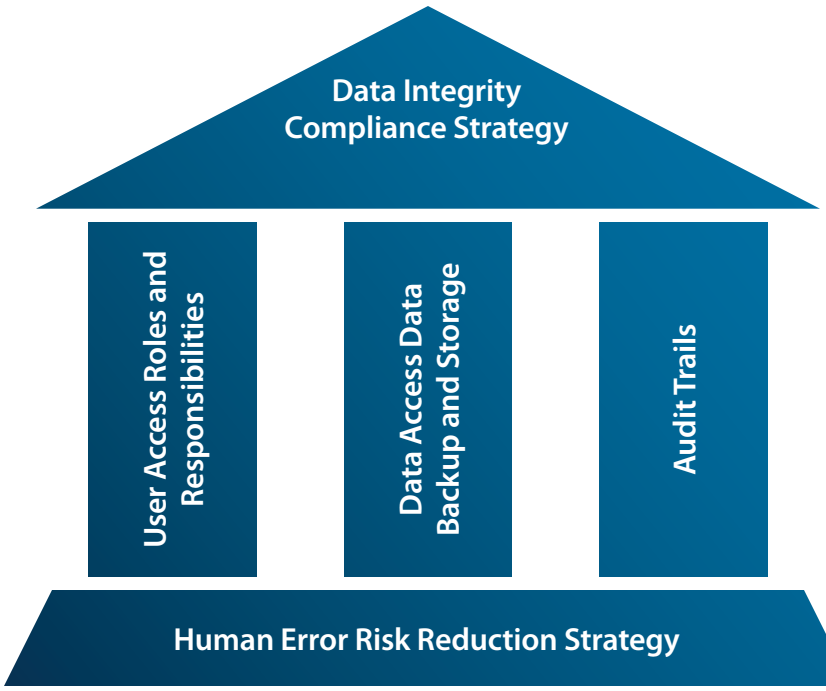
The House of Data Integrity Compliance

by Matthew Paquette, Charles River

Various industry influences have challenged how we—as scientists, manufacturing technicians or quality control professionals—approach the processes that protect the integrity of the data we collect during the manufacture and release of products that impact human and animal health globally.

Factors like the shift to more computer-interfaced processes in the laboratory and the manufacturing suite necessitated the shift from paper-based data collection systems to any combination of paper/electronic data collection systems. This shift affects all areas of the product lifecycle, from raw material to commercial product release and maintenance.

Visualization is often used to aid teams in creating a structured methodology for problem-solving or illustrating key targets for program success. With data integrity,



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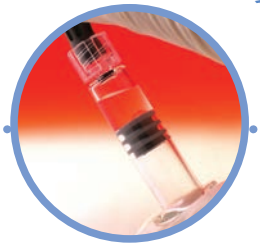

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The availability and cost-effectiveness of automated systems coupled with electronic data collection platforms have made the paper-to-electronic-data capture shift even more attractive for organizations looking for the right balance of efficiency and cost, while increasing product quality and confirming patient safety. The wide availability of data has also spurred initiatives like the adoption of LEAN and Six Sigma principals that focus on making data-driven and scientifically sound decisions about the processes that take place in the manufacturing space and laboratory. Collectively, these factors have impacted our interpretation of data integrity expectations and regulations so that a focus on patient safety is at the forefront of every debate, conversation or regulatory citation.

In December 2018, the U. S. FDA published an updated, comprehensive guidance for industry, in the form of a question and answer document, on current GMP and compliance with data integrity regulations in the laboratory and beyond ***(2)***. Regulatory authorities require the data we collect during the manufacture of drugs and medical devices to be reliable, relatable, representative and accurate. The challenge given to us as an industry is to define sound strategies that rely on representative data and to drive a quality culture that can recognize and mitigate the risk for data integrity lapses. The data we collect in the manufacturing and laboratory spaces is critical to confirming process control, product quality and, most importantly, patient safety. Therefore, it is a critical part of our jobs to ensure that this data is attributable, legible, contemporaneous, original, and accurate (ALCOA).

> **The foundation of the house is constructed of the strategies that enable an organization to reduce or completely mitigate the risk for human error**

the intent is to enable conditions that drive systematic control of the creation, storage conditions and access to records and data that lead to important decisions about product quality and patient safety. These key points can be organized into what is called the "house of data integrity compliance."

The foundation of the house is constructed of the strategies that enable an organization to reduce or completely mitigate the risk for human error that occurs in their processes. Each beam of the house represents the specific software and electronic strategy for compliance with data integrity regulations and guidances.

These collective factors provide the support structure for compliance—the roof of the house—and complete the house of data integrity compliance.

House Foundation: Human Error Risk Reduction

Human error risk reduction strategies provide an important tool for organizations to evaluate their data integrity compliance stance and provide avenues to improve product quality. Research from many industries shows that mitigating the risk for human error is not related to analysts lacking the knowledge, skill or ability to perform a task, but rather correcting the processes that allow for errors to occur in the first place ***(1)***. As an example, let us look at the assays and processes carried out in the typical microbiology laboratory. These processes tend to be based on methods that are antiquated in the face of current GMPs and involve a layer of subjectivity that forces the manufacturing or laboratory analyst to make a judgment call in order to generate data. Good examples of this are the gel-clot assay for endotoxin detection, gram-staining for microbial identification and counting colonies on a plate for the detection of bioburden in the manufacturing process.

Recent research in the airline manufacturing industry has gone a long way to categorize the different types of human error and common mitigation strategies; these same strategies can be used in the pharmaceutical industry. Processes that rely on subjective judgment calls to generate data tend to necessitate strategies to mitigate the risk for human error that fall into a category called "duplication." This strategy involves using a second analyst to make the same read for every sample after the first analyst; both reads are then checked for agreement with each other. Employing this strategy to ensure performance of a subjective process is the least-effective method in reducing human error-related failure modes.

On the other end of the spectrum is updating or changing the process in some way as to remove the subjectivity that allows for human error to occur at all. This strategy falls into a category called "error proofing," which typically involves automating part or all of the process and is the most effective strategy for eliminating the risk for human error in any process. A reduction in human error has the added benefit of making processes more efficient and more effective, leading to more impactful data generation. Representative data and increased process knowledge allow organizations to transform into more effective decision-makers in terms of product quality and data integrity compliance.

House Beams: Software and Electronic Data

The house beams constitute a strategy for continual improvement and validation of three key components of software and electronic data integrity compliance:

- User access and roles and responsibili-

ties of specific users
- Data access and data storage and backup
- Compliant, consistent and complete audit trails

Control of these processes is a key indicator of the risk to noncompliance with regulations that provides a health check of what methods and strategies an organization has in place to mitigate or eliminate that risk. Restricted user access protects against unauthorized access to the critical data that determines product quality. Defining the roles and responsibilities of each user ensures that a system of checks and balances is in place to further limit access to data based on pre-defined internal knowledge levels. Data backup provides organizations with a route of recovery in the case of an emergency or a disaster. These strategies also become critical during justification of decisions to all key stakeholders, including in audit situations. Last, but not least, accurate and complete audit trails allow an organization to catch anomalies in data generation and backup. An audit trail provides a roadmap of events that enable organizations to investigate root causes, recover, and close gaps that present a risk to the data they depend on to make manufacturing and quality decisions. Although not a complete overview of data integrity risk, these three components provide a structure for organizations to standardize their electronic data integrity compliance strategy.

Taken together, the key components that make up the house of data integrity compliance provide the building blocks of a successful compliance strategy. Reducing the risk for human error translates into the production of higher quality data in both manufacturing spaces and the laboratory, while also ensuring efficient and effective electronic and automated processes. A well-defined electronic data integrity strategy ensures that access to critical data is controlled, that data is protected, and that the organization is able to recover from an emergency or failure mode. A strong data integrity compliance strategy yields the highest product quality and ensures safe products and healthy patients.

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About the Author

Matthew Paquette is the Operational Excellence Manager for Charles River Microbial Solutions in Charleston, S.C. He holds a BS in Microbiology and an MBA in Six Sigma/Quality Management and uses that knowledge to drive to root causes of complex QC and manufacturing problems. His experience also includes leading cross-functional teams that investigate complex manufacturing and laboratory deviations, method development and validation and beta testing for complex laboratory instrumentation.

PDA Survey Results: Current State of Biopreservation in Cell and Gene Therapy Products and Biopharmaceutical Commercialization

Brian J. Hawkins, Raluca Marcu, Pluristyx, Inc.

The first successful cryopreservation studies were performed in 1949 ***(1)*** and, since then, numerous strategies have been proposed and adopted to facilitate the rapid restoration of cellular function following freezing. Unfortunately, despite decades of research and increasing emphasis in the clinic, harmonized cryopreservation standards for cell and gene therapies (Advanced Therapy Medicinal Products or ATMPs) do not exist, and cryopreservation protocols vary widely in practice both between, and even within, commercial and academic groups.

To address the state of cryopreservation protocols currently employed, PDA designed and distributed the survey *Cryopreservation Practices and Experiences* for members to share their experiences pertaining to biological handling practices, the results of which are summarized here.

The survey was divided into a general overview, sections on the generation and monitoring of cell banks, and questions related to troubleshooting and resolution.

Since 32% of the respondents' products combine cryopreservation with nonfrozen storage and shipment at refrigerated temperatures, the term "biopreservation" was adopted for the survey unless discretely specified.

Overall, biopreservation was primarily incorporated into product commercialization activities (38%), followed closely by clinical (31%) and research (24%) activities.

Storage temperature varied widely among respondents, which reflected the diversity of biological handling requirements, with liquid nitrogen (LN_2; -196 °C to -140 °C) being the most common (42%), followed by -80 °C (30%) and 2-8 °C (12%). In practice, only temperatures below the glass transition of water [T_g; ~-135 °C] ***(2)*** would completely arrest molecular motion and permit long-term storage of cells in banks ***(3).*** Storage temperatures above T_g would allow for gradual degradation and should only be employed for cellular products as a short-term storage solution.

Despite the importance of temperature maintenance, a plurality of respondents (50%) employ biopreservation only for the final cell product and not for the incoming biological source material (24%). Incoming cellular material that does not incorporate appropriate biopreservation controls can experience significant cell loss or a reduction in functionality, which may adversely affect downstream manufacturing and final product potency ***(4).***

Temperature excursions are most commonly recorded using data-loggers (52%) or monitored by a combination of data-loggers and real-time monitoring (30%). Most biopreserved material is transported in insulated thermal shippers containing dry (~-80 °C) or wet ice (72%).

In commercial and research practice, most cell banks were generated in a self-identified "low-density" (69%) cell concentration (<2 x 10^7 cells/mL density) in plastic cryovial format (67%). At least some form of "practice" banking was performed by a majority of groups during which cryopreservation protocols were optimized for a given cell type (57%). Container closure integrity protocols varied considerably among most groups but centered primarily on a dye-ingress as-

say. Similarly, the cryopreservation process varied in length from immediate freezing (LN_2 immersion) to slow cooling over 8 hours. And, while process pause steps were not typically validated as part of the workflow (65%), a large majority (73%) incorporated stability studies to ensure the cryopreservation process did not impact sample integrity.

Despite the availability of commercial biopreservation media, a number of respondents employ a combination of commercial media with a form of "home brew" formulated in-house (42%) or commercial media alone (39%) that is specifically optimized for each cell line (78%). When commercial media was chosen, it was primarily manufactured under good manufacturing practice (GMP) guidelines (86%). Commercial cryopreservation media was largely devoid of animal/human proteins (54%) and employed dimethyl sulfoxide (DMSO) as the primary cryoprotectant (85%). Controlled rate LN_2-based freezing devices were the most common method of sample freezing (43%), although generic protocols were primarily adopted (55%) without an optimized freezing rate that forces ice nucleation at a specified temperature (64%). For 76% of respondents, frozen samples are typically moved from the freezing device to vapor phase LN_2 with the aid of dry ice to maintain the temperature of <-80 °C during transit. Cryopreserved samples are primarily thawed using manual methods (76%) in some form of water bath. Cryopreservation media is largely removed from the sample via centrifugation or wash prior to patient delivery (52%), although many respondents reported that the cryopreservation media is validated for infusion as an excipient, i.e., without wash (48%). Determination of post-thaw viability and functionality was application-specific, but most groups considered cryopreservation success to be viability greater than 75% across multiple cell bank thaws (91%).

This survey provides valuable insight into the current state of biopreservation with regard to biopharmaceutical and cell therapy manufacturing. In summary, biopreservation practice varied widely among survey respondents, which reflects both the relative infancy of cell usage in clinical product development and the lack of cryopreservation standards by regulatory bodies and professional organizations. Nonetheless, several commonalities can be surmised from the PDA's cryopreservation survey.

In practice, biopreservation was largely adopted by commercial groups as part of the final product configuration for storage and transportation at frozen temperatures using LN_2-based infrastructure. Procedurally, cryopreservation was performed using an LN_2-based active freezer, and samples were thawed manually using a water bath.

Reflecting the need for appropriate quality assurance, a large majority of respondents sourced commercial cryopreservation media manufactured under GMP guidelines that was devoid of animal or human proteins and contained DMSO as the principle cryoprotectant. And finally, post-thaw viability was primarily determined by membrane integrity ➤

with a benchmark of >75% immediately post-thaw, but methods and functional measurements were specific to each group and application.

Despite these apparent commonalities, several potential deficiencies were revealed that may reduce the health and effectiveness of cells following storage. The primary cause of concern is that current practice primarily focuses only on the final product, as opposed to appropriate biopreservation controls being incorporated as a continuum throughout the product lifetime, including at the creation of the critical master and working cell banks. This is especially true of the incoming biological raw material, improper biopreservation of which could lead to excessive degradation and could impact all subsequent downstream steps in the product workflow.

Indeed, poor quality cellular starting material may propagate undesirable genetic traits that could negatively affect all aspects of downstream processing and compromise the final cellular product. Additional biopreservation protocols largely absent in current practice that may improve post-thaw cell health and function include, but are not limited to, cell-specific freezing/thawing rates, inclusion of a prebiopreservation incubation hold step, temperature of cryoprotectant addition and regulation of ice nucleation **(4).** Inadequate control over these variables may introduce undue sample variability and compromised post-thaw functionality. Indeed, more than half of the respondents (52%) experienced at least one incidence of poor post-thaw cellular function due to an unknown cause (69%), which emphasizes the importance of suitable biopreservation controls throughout the manufacturing process, from incoming raw material through final patient delivery.

PDA is taking a lead role in helping both commercial and clinical groups with their cryopreservation efforts. To better harmonize ATMP cryopreservation practices, the Association convened a working group comprising experts from academia, industry and governmental regulatory bodies to compile and draft current best practices into a single reference document.

Indeed, poor quality cellular starting material may propagate undesirable genetic traits that could negatively affect all aspects of downstream processing

The efforts of this PDA working group resulted in a document entitled, *Cryopreservation of Cells for Use in Cell Therapies, Gene Therapies, and Regenerative Medicine Manufacturing: An Introduction and Best Practices Approach on How to Prepare, Cryopreserve, and Recover Cells, Cell Lines, and Cell-Based Tissue Products*, that was submitted in July 2020 (tinyurl.com/y43876rh) for consideration as American National Standards Institute (ANSI) standard. In doing so, PDA continues its ongoing mission to advance pharmaceutical and biopharmaceutical manufacturing science and regulation so members can better serve patients and provide critical guidance to hasten the translation of promising ATMP products from the bench to the bedside.

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About the Authors

Brian J. Hawkins, PhD, Chief Technology Officer at Pluristyx, is an advanced tools and services provider whose mission is to overcome the challenges of manufacturing cell-based therapies for clinical use. He has over 15 years of combined experience in academic and industrial research focused on cell metabolism and cell biopreservation, and serves on numerous committees and working groups that aim to advance the development and manufacture of cell therapy and regenerative medicinal products. Hawkins received his PhD in molecular cell biology and biotechnology from the Virginia Polytechnic Institute and State University. Hawkins was team leader for the PDA Cryopreservation Standard Initiative; *BSR/PDA Standard 02-201x, Cryopreservation of Cells for Use in Cell Therapies and Regenerative Medicine Manufacturing* is currently available for public comment.

Raluca Marcu, PhD, is a Senior Scientist at Pluristyx, Inc., specializing in cell therapy and stem cell manufacturing. Previously, she was a Research Scientist at the University of Washinton Kidney Research Institute, and a Senior Research Fellow at San Raffaele Scientific Institute. Marcu received her PhD in medical nanotechnology from the University of Milan, European School of Molecular Medicine and Italian Institute of Technology.

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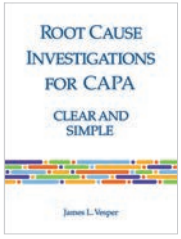

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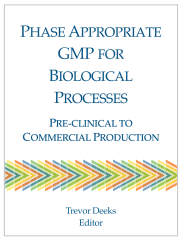

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The Evolution of USP <800>: A Q&A with Cathy Zhao and Allison Radwick

The *PDA Letter* talked with **Cathy Zhao,** Director of Scientific Insights Lab, and **Allison Radwick,** Scientific Affairs Manager, from West Pharmaceutical Services about closed system transfer devices and the evolution of *USP <800> Hazardous Drugs—Handling in Healthcare Settings*. Below are their responses.

PDA Letter: Can you tell us a little about the history of *USP <800> Hazardous Drugs—Handling in Healthcare Settings*?

In the early to mid-1970s, it was discovered that many chemotherapy drugs were indeed hazardous drugs. They could cause skin rashes, hair loss, infertility, miscarriage, birth defects and even leukemia and other forms of cancers. In 1981, after over 10 years of conformational research, the U.S. National Institute of Occupational Safety and Health (NIOSH) issued *Recommendations for Safe Handling of Injectable Antineoplastic Drug Products*, which recognized inhalation and direct skin contact as high-risk routes of exposure and recommended the use of Class II biosafety cabinets when compounding antineoplastic drugs. These recommendations from NIOSH were recognized as an official publication in 1983 and updated in 1999.

In 1985, the American Society of Health-System Pharmacists (ASHP) published a technical bulletin on handling cytotoxic drugs in hospitals. The bulletin was updated in 1990 and included the first use of the term "hazardous drug," instead of cytotoxic drugs or antineoplastic drugs.

In 1986, U.S. Occupational Safety and Health Administration (OSHA) released guidelines for cytotoxic (antineoplastic) drugs. It only made recommendations, with no mandatory standards. In 1995, OSHA released *Controlling Occupational Exposure to Hazardous Drugs*, which included the expanded definition of "hazardous." In 1999, OSHA amended its guidelines and recommendations by adding periodic testing, proper personal protective equipment, using ventilated cabinets, closed system transfer devices (CSTDs) and needleless devices, etc.

In 2004, NIOSH published its *NIOSH Alert: Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings*, which required the safe handling of hazardous drugs at all steps of the medication use cycle. The hazardous drug list was updated in 2010, 2012, 2014, 2016 and 2018, and the 2020 list is currently in draft form.

In 2008, *USP <797> Pharmaceutical Compounding – Sterile Preparations* was updated to include a specific section for hazardous drug (HD) preparation to resolve conflicts with the NIOSH Alert. However, its scope was limited to sterile preparations.

Until then, it was still a challenge to prevent exposure of healthcare workers to HD. There was a lack of clear evidence of HD effects until 2010, when the *Journal of Occupational and Environmental Medicine* published two studies:

- The first was a study of antineoplastic drug exposure to U.S. healthcare workers at three university-based health centers that showed continuing surface contamination in pharmacy and nursing areas despite HD handling guidelines.

- The second study reported that the exposure to HDs led to healthcare ➤

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workers sustaining damage to those chromosomes related to secondary cancers in treated patients.

In April of 2011, OSHA, NIOSH and The Joint Commission sent a jointly drafted letter discussing the safe handling of HDs.

Meanwhile, in 2010, an investigative reporter wrote a report entitled "Lifesaving Cancer Drug May Put Workers' Lives at Risk" that exposed the tribulations of Sue Crump, a Seattle-based pharmacist who died at age 55 of pancreatic cancer. This report had its desired effect, resulting in the Washington State legislature passing two HD rules in 2012: one setting requirements for handling HDs, the other establishing an HD workers' registry to track adverse experiences.

General HD compounding was part of the work plan in the 2010-2015 USP Council of Experts cycle. The purpose was to create a single guidance standard for the safe handling and compounding of HDs that would apply to sterile and nonsterile compounds on top of USP <795> and USP <797>. The result was USP <800>. Most of the USP <800> requirements had been recommended for more than 30 years, but USP <800> formalized those recommendations and best practices and established a *minimum* standard. In March 2014, USP posted a proposed *General Chapter <800> Hazardous Drug – Handling in Healthcare Settings* on its website and in the May-June issue of *Pharmacopeial Forum* to more fully cover the handling of HDs in both sterile and nonsterile compounds. Public comments closed on July 31, 2014, and a revision incorporating the comments was posted in December 2014. USP <800> was published on February 1, 2016. Its revision bulletin was published on May 31, 2019, and it became effective on December 1, 2019.

PDA Letter: What are the issues for closed system transfer devices (CSTDs)?
Early in the year, we published "**5 Challenges of Closed System Transfer Devices**" in the *PDA Letter* to address the issues for CSTDs:

1. Lack of standards, guidances or requirements for functionalities of CSTDs
2. Closed system design magnifying problems of current vial transfer devices, such as high forces and drug hold up volume
3. New challenges in vial transfer devices applications, such as stopper intrusion or device breakage
4. Performance differences as the result of design differences
5. No measurement method of CSTD efficacies covering all CSTD types, including product agnostic (hold-up volume and stopper coring/fragmentation and product specific), drug product compatibility and duration of drug product in contact with the CSTD

> **Pharmaceutical companies have been receiving an increasing number of complaints on the incompatibility of their drug product with transfer devices**

PDA Letter: PDA is sponsoring a Product Quality Research Institute (PQRI) working group. What is the group doing and who is involved?
Both the pharmaceutical market and regulatory agencies are driving the use of CSTDs in HD preparation and administration. Pharmaceutical companies have been receiving an increasing number of complaints on the incompatibility of their drug product with transfer devices. According to the U.S. Food and Drug Administration (FDA) MAUDE database, from July 1, 2018, to July 31, 2019, there were 535 complaints about the use of CSTDs; among these, 411 complaints were device-related problems and 71 complaints were related to container closure. It became clear when looking for guidance and standards that, while high standards in general were found, neither guidance nor standards specific to vial adapter design and application were available. Attaining effective safety standards is a challenge to the industry.

In 2018, Eli Lilly and West Pharmaceutical Services started to build a cross-company working group on the interconnectivity of vial container closure systems and transfer devices under PQRI to examine the interconnectivity of a vial and transfer device. PDA is sponsoring this project. The group's objectives are:

- Raise awareness within the key stakeholder communities of the necessity to evaluate the performance characteristics of transfer devices when used with vial presentations (e.g., penetration force, coring/fragmentation, interconnectibility).
- Establish a common understanding of user requirements, usability criteria and instructions for use pertaining to the connection between vial systems and vial transfer devices.
- Develop appropriate guidance for performance attributes of vial container closure system (CCS)/vial transfer device connections. These may be implemented through appropriate and recognized institutions (e.g., USP, Ph. Eur., ISO).
- Raise awareness of performance requirements of existing vial CCS/vial transfer device connections within the healthcare provider and patient communities to ensure positive outcomes, to reduce risk where possible and to alert users to potential hazards.
- Develop appropriate design guidance for manufacturing and evaluation of new vial CCS/vial transfer device connection components to mitigate performance risk as early in the design and development process as possible. These may be implemented through appropriate and recognized institutions (e.g., USP, Ph. Eur., ISO). Alternately, proposals for appropriate ➤

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language for inclusion in vial presentation or vial transfer devices instructions for use may be considered within the scope of the project.

At this time, the PQRI working group has members from 18 manufacturers, including nine pharmaceutical companies, six device manufacturers, and three vial component manufacturers. There are PQRI committee members from regulatory agencies such as the FDA, Health Canada and USP. PQRI continues to recruit end-users who are healthcare providers.

PDA Letter: How can CSTDs harm healthcare workers? Does USP <800> help?

CSTDs are designed and made to meet USP <800> requirements by containing HDs during drug compounding for both sterile and nonsterile uses. There are about a dozen CSTDs on the market right now. Due to the general nature of the requirements governing CSTDs, there are a variety of configurations and significant differences in their designs, performance and compatibilities with vials and drugs. Some CSTDs require a very high connection force when they are connected to the drug vials. These require a physical force that can cause repetitive motion injuries to healthcare workers, which may require surgery treatment, such as a carpal tunnel release. Some CSTDs push the vial stopper into the vials, causing splashes. This not only exposes the healthcare workers to the HD and may even waste the entire vial of the drug product but leads to drug loss and waste. Some CSTDs break more easily than others. Some CSTDs bring more particulates into the drug than others and even cause protein aggregation.

PDA Letter: Does the formulation of an elastomeric closure impact the attachment force?

Yes. The formulation of the elastomer closure also impacts the attachment force/connection force. A CSTD interacts with the vial stopper in two ways during the connection: The CSTD spike punctures the center of the stopper, and its wings compress the edge of the stopper. Elastomer properties, such as modulus and elasticity, will impact the attachment/connection force.

PDA Letter: What are some of the deliverables from the PQRI project? Is there a timeline?

Some deliverables from the PQRI project include:

- Raising awareness of gaps and challenges through publication on PQRI, PDA and other open-access sources and workshops
- Developing procedures and processes to evaluate the use of transfer devices with vials and bring the instructions-for-use and user requirements into the scope of vial transfer system evaluation and usage
- Defining and promoting best practices for system design, application and use, and developing standardized test methods to test vial transfer systems
- Defining best practices for the pharmaceutical industry and healthcare providers for system selection

The project group has developed a working plan with sub-teams working on each step with specific timelines. The plan covers four to five years of activities. In 2020, there are four major activities:

1. Identify and recruit key stakeholders: Continuously since 2018, and still ongoing, recruiting representatives of end-users.
2. Compile complaints filed to separate manufacturers (complaints cleansed of proprietary information) for trend analysis. Q1 – Q3 2020
3. Develop user requirements and usability criteria for vial CCS/vial transfer device connection based on healthcare provider and patient use. Use analysis techniques, such as failure mode and effects analysis, to evaluate and categorize risk. Translate established user requirements, usability requirements and risk into connection system requirements. Q4 2019 – Q1 2020
4. Draft a publication to post on the PQRI website and in open-access journals to raise awareness of the issues and proposed work. Organize a workshop. Q2 – Q4 2020

About the Experts

Cathy Zhao has worked in the medical device and pharmaceutical packaging industry for more than 18 years. She has been at West for 14 years and, prior to that, worked as a Principal Materials Scientist for almost five years at Becton, Dickinson and Company. She received a BS in polymer chemistry from the University of Science and Technology of China, and an MS and PhD in polymer chemistry from City University of New York. In the past four years, she has lead application research at West to solve problems and fill gaps in customer applications. The application in CSTDs is one of the areas where there are industry gaps and challenges.

Allison Radwick has been at West for a year and half with over 20 years of experience in pharmacy and the pharmaceutical industry. She received a BS in pharmacy with a minor in psychology from the University of the Sciences in Philadelphia, and a PhD in pharmaceutical sciences from the University of Connecticut. She has hands-on clinical and pharmaceutical science expertise in sterile and nonsterile pharmacy compounding with hospital, retail, home infusion, ambulatory care, academia, industry and clinical trials.

Both Cathy and Allison are part of the Strategy & Science Integration team at West Pharmaceutical Services. Together, and with other West colleagues, they look at the physical and performance differences in CSTDs that are currently available.

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Annex 1 Comments continued from page 18

4. The need for recognition of the impact and feasibility of certain Annex requirements and changes to existing manufacturing processes, facility, and operations, as compared the product quality benefit of those requirements and changes.
5. The need to clarify the intent of and harmonize language in Annex sections, to prevent misunderstandings due to the wide geographical scope of this guidance document
6. The lack of clear distinction between and the perceived grouping of technologies that requires different contamination control strategies, including RABS and isolators, terminal sterilization and aseptic processing, and ATMPs and conventional therapy manufacturing.

Many of the topics presented in the Annex are complex and reflect the need for further discussion and the evaluation of scientific evidence to reach an optimal state of control. Foremost among these is the practical means to achieve contamination free conditions for larger indirect product contact surfaces in isolators, QRM approaches for sterile filtration control and PUPSIT, and best uses and limitations of Aseptic Process Simulations. We encourage a continued dialog with this body, the industry, and other health authorities to further clarify and refine these and other topics in this important Annex.

PDA continues to be committed to assisting in the development of this importance guidance. Upon completion of the revision we remain commitment to assist the EMA (PIC/S and WHO) with any educational, training, or communication efforts required to ensure the correct interpretation and implementation of the principles, recommendations, and requirements presented in the Annex. If there are any questions or any further assistance we can provide, please do not hesitate to contact me.

Richard Johnson
President & CEO, PDA
CC: SANTE-Revision, EC, Jahanvi (Janie) Miller, PDA

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