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PDA Letter

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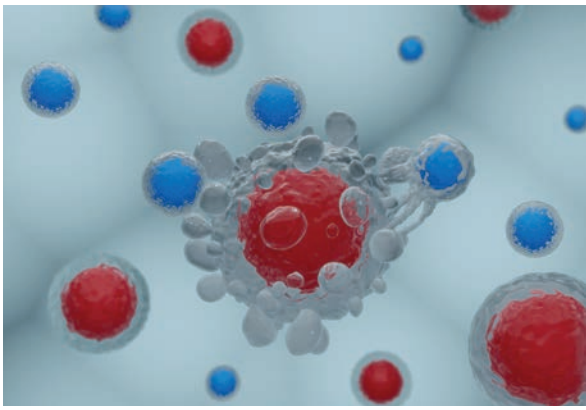

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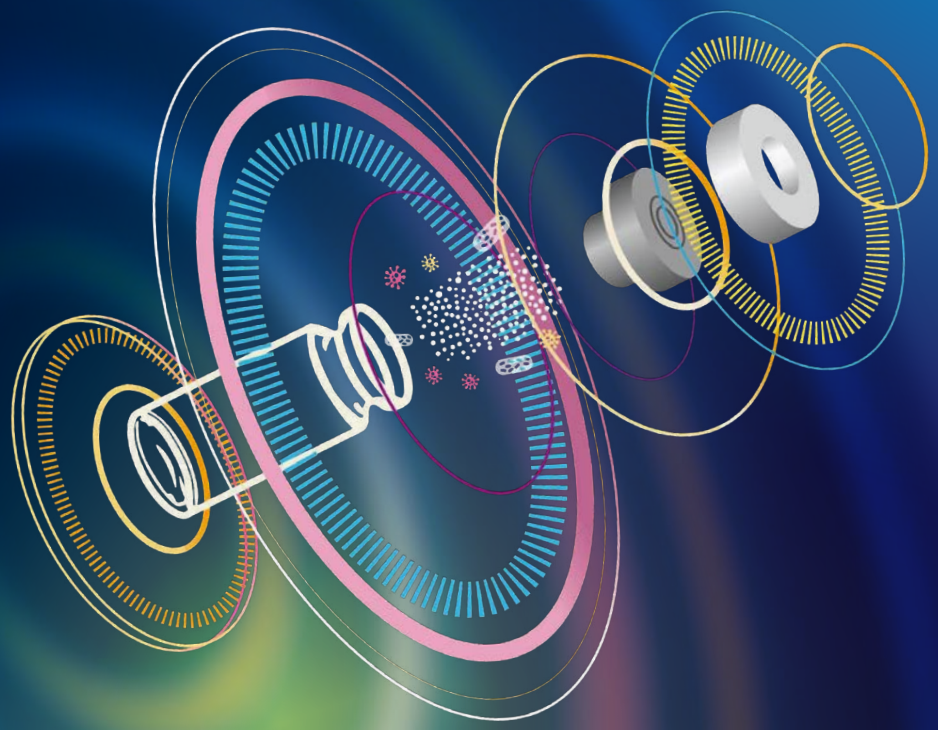

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Publishing by the Numbers: An End of an Era

Walter Morris, Senior Director of Publishing

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Electronic publishing provides readers, authors, and publishers many benefits. By now, the benefits to readers have been exhaustively discussed and analyzed: access anywhere, search, etc. But what are the benefits to authors and publishers?

Well, for authors, there is time to press. In traditional publishing, the time between initial submission to final publication can be over six months for a magazine and a year or more for a scientific journal. But for e-publications, the time is significantly reduced. Articles in the electronic *PDA Letter* can be processed and published in a matter of weeks. Feature-length articles take the longest, as they are distributed to the *PDA Letter* Editorial Committee for comment, but those that get green-lighted on the first pass can publish in four weeks.

The benefits of e-publishing to the publisher are many. Besides providing a better product to readers and making authors happier with faster publication times, e-publishing allows publishers to dig into the analytics to fully understand what readers want. This information also is used to help inform PDA's other activities, as the *PDA Letter* staff let's the other departments know what is hot and what is not. This data also is useful for our sponsors and advertisers.

Not only do the analytics help with editorial decisions, it assists in helping us choose the best papers published each year (papers-of-the-year have been recognized by JPST for several decades and by the *PDA Letter* since 2020). To be clear, the analytics are not the only factor in choosing these papers, but they are definitely one of the factors. There are many reasons why analytics alone are not the sole factor, such as length of time a paper is available during the year. The top five articles published this year by readership are:

- "Regulator Develops Remote Inspection Process Due to Pandemic," by Shestakoy (Russian Regulator) and Meyers (Amgen), published June 9
- "Visual Inspection Practices of Cleaned Equipment," Parts 1 and II, by El Azab (Steris) and Cousin (GSK), published April 14
- "Industry Must Move Away from Dye Ingress Testing," by O. Stauffer (PTI), published June 30.
- "Data Integrity: The New World of Virtual Audits and Investigations," by Henrici (THG) and Cahilly (Green Mtn. QA), published August 6
- "Virtual Audits in the Time of COVID for the Auditor and the Host," Gilbert (BDO), et al., published October 28

You can see from the titles that the pandemic is on the mind of our members. Much has already changed, and much more will change because of it. Because of it, PDA restricted the print editions of the *PDA Letter* to just its North American members. And in anticipation of continued work from home orders, limited attendance at PDA's conferences and events, and constrained resources in 2021, we are eliminating the print edition altogether next year. For 56 years, the Letter was sent by mail to all PDA members, a really impressive run!

So, yes, you are holding onto what might turn out to be the very last printed edition of the *PDA Letter* (there is a chance we resume printing in 2022 or at a time when the world returns to normal). I for one will have a copy framed. What you do with yours is up to you, but I hope you keep it.

The *PDA Letter* is thriving as an electronic publication, and we look forward to 56 and more years of publishing online!

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5th Annual Women in Life Science Panel Discussion

West Coast Chapter

"Do not be afraid to take on new tasks and seize every opportunity you can to learn and grow."

That was just one of the many profound pieces of advice five women leaders in the life sciences industry provided during the PDA West Coast Chapter's "5th Annual Women in Life Science Panel Discussion." While normally held in person, this year's event was held online on Aug. 20, 2020, due to the COVID-19 pandemic. Nonetheless, more than 500 individuals from across the nation signed onto Zoom to hear five accomplished women talk about their experiences working in the life sciences sector and ask them questions.

PDA West Coast Chapter President-elect **Liraz Oechsli** relayed a few messages from the event's sponsors, then welcomed the attendees. She introduced discussion moderator **Carolina Valoyes**, Executive Director of Quality/Site Quality Head, Boehringer Ingelheim Pharmaceuticals, Inc., Fremont, who introduced the five panelists:

- **Ghada Haddad,** PhD, Executive Director, Global cGMP Compliance and Auditing Organization, Merck & Co.
- **Lucy Cabral**, Senior Director, Global External Quality, Roche Genentech
- **Valerie Brown,** Vice President, Quality, Gilead Sciences, Inc.
- **Tara Callahan,** JD, Senior Director, Corporate Counsel Technical Operations, BioMarin Pharmaceutical Inc.
- **Diane Hagerty,** Senior Vice President – Quality, Compliance & Operational Excellence, Dermira, Inc.

Valoyes kicked off the discussion by asking each of the women to share an instance when they had to push themselves outside their comfort zone. While the panelists' responses varied, all concurred that it is important to take risks, embrace uncomfortableness and jump at the chance to lead a project.

The attendees could then ask the panelists questions of their own, which covered a broad range of personal and career topics. The more casual questions sought the women's thoughts and experiences with impostor syndrome and the expectations of their significant others supporting their career ambitions. Deeper questions involved the stereotypes that women face in business, how they can ensure the pay gap is minimized and how to support each other in the workplace.

In the life sciences sector, these are particularly pertinent questions given that women enter the industry in equal proportion to men but account for just 24% of C-suite positions and only 14% of board-level positions ***(1)*****.** While the panelists each had unique responses to this issue, all agreed that it is critical for women to not just expect to be given promotions due to their hard work, but rather to ask their superiors for the positions they seek. All five panelists also acknowledged that women need to have each other's back, best summarized by Haddad who stated, "A strong woman stands up for herself, but a stronger woman stands up for others."

Another speaking point that greatly interested attendees was the importance of mentorship; they asked what advice the panelists would give to both mentors and mentees. Cabral noted that it is imperative for mentors to serve as a guide to help focus a mentee's interests, while Callahan emphasized giving mentees space to work through their own issues rather than solving it for them. Brown added that a mentee needs to take ownership of the relationship with their mentor, laying out their goals and driving those conversations. In addition, she noted the significance of not just having a mentor but having a sponsor who can advocate on your behalf.

Valoyes concluded the discussion by asking each of the panelists what motivates them every day. Each responded by citing her company and her personal mission to provide the best care, the best medicines for all patients, especially amid this global pandemic.

The members of the PDA West Coast Chapter extend a special thanks to all the panelists, our moderator, and those who attended, as well as our sponsors, for making this event a success. They invited everyone to continue the conversation via social media, and they look forward to seeing you in person (hopefully) on August 19, 2021, for the 6th Annual Women in Life Science Panel Discussion!

Reference

1. The Massachusetts Biotechnology Council (MassBio) and Liftstream, LLC. 2017. "Opening the Path to a Diverse Future: Creating gender balance in Massachusetts life sciences sector." Cambridge, MA. https://www.massbio.org/wp-content/uploads/2020/03/MassBioLiftstream-Gender-Report-2017.pdf (Accessed Aug 26 2020)

Getting Closer to AI adoption in the Pharmaceutical Industry

Tony Manzano, bigfinite

How do you get a robust manufacturing process in pharma and biotech?

A theoretical answer would consider all the involved variables and constants that determine the system to establish the dynamic state equations that characterize the process. However, the laws of physics, chemistry and engineering force us to make approximations because the available data does not always explain the entire context. Taking real-time data of all the variables that must be taken into account to apply the theoretical model is an arduous, if not impossible task, because the multitude of information sources are usually not integrated or not available.

This scenario has drastically changed with the application of AI in industrial environments.

During the 2020 PDA Data Integrity Workshop we introduced the role of big data and AI under the biopharma manufacturing perspective, describing the differences between both terms and explaining good practices and real use cases with AI. A discussion of multiple AI algorithms brought light about how to improve the manufacturing process using good data, emphasizing one of the main takeaways from the workshop: quality data is the starting point for AI applications in Pharma and Biotech. Actually, AI algorithms only can provide realistic AI models when quality data is used to train the models and this topic was emphasized during the workshop. In the course of the AI workshop, several poll questions were popped up to the pharma audience. The answers of the attendees made a composition of the AI adoption in the pharmaceutical industry.

A total of 87 attendees participated in the session, of which 51% were representatives of pharmaceutical companies, 23% were consultants, 11% were regulators, 2% were manufacturers of equipment for the pharmaceutical industry, and the remaining 5% were from the PDA organization.

Participants were asked several questions regarding their use of data analytics approaches, and tools and data integrity management. The first set of questions was related to the general data analytics approaches that are being used in their organization. In total, 84% of respondents reported that they do not use chemometric methods to analyze their data problems. In a question about how often they use XY linear regression (bivariate) analysis, almost three-quarters of participants (74%) responded that they use such methods only rarely or sometimes, whereas 26% of participants use XY linear regression usually or very often. Similarly, when asked how often they use multivariate analysis (analysis of more than two variables at once), 14% of respondents reported very frequent use, whereas 38% of respondents use such methods usually and 48% only rarely.

More insight was obtained when participants were asked about obstacles and challenges in implementing data analytics in their process.

Almost 80% of respondents reported that the most time-consuming activity in the data analysis pipeline is data collection and data cleaning, while 20% reported the most time-consuming activity is result validation. In line with this result, 80% of the respondents indicated that they have not attempted to validate or in any way evaluate their in-use AI algorithms. This highlights that the most time-consuming tasks are generally related to data availability and data quality, rather than higher-level tasks such as choosing the most appropriate algorithms or putting AI model to production. Therefore, the still incipient deployment of AI in the pharmaceutical industry leads do not contemplate quality tasks in the governance of algorithms and models such as AI validation. Nevertheless, there are some initiatives already in place describing strategies to qualify AI algorithms based on Quality by Design principles ***(1)*** establishing the foundation for the usage of AI in GxP environments.

When new data-related problems must be tackled, 38% of the participants reported that the usual practices they apply to the data are applying standard operating procedures (SOPs) to manage the raw data and data transformations, 31% of the participants reported that they look for anomalies and random effects, and 15% of the participants reported they manage outliers in the data. Only 10% of the participants indicated that they keep data under the right governance procedure.

The participants were asked about their general opinion regarding the required quality around AI. Worryingly, two-thirds of the participants think that the Pharma, Biopharma, and medical devices industries are not ready to implement AI in their manufactur-

Continued at bottom of page 12

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ANNEX 1 Revision Task Force Update

Hal Baseman, ValSource, Inc., Gabriele Gori, GSK Vaccines, Jahanvi Miller, PDA

PDA continues to support efforts to improve the manufacture of sterile pharmaceuticals and the corresponding guidelines and regulations, being applied well beyond the EU by both the industry and inspectorates. Over the past five years, the PDA Annex 1 Revision Task Force, consisting of global subject matter experts, has updated PDA's aseptic processing documents and provided consensus-based comments to the EMA for the revision of Annex 1. Regarding the latter, the Task Force diligently developed recommendations taking into consideration input received during PDA workshops, conferences, and meetings held globally throughout the 2017-2020 Annex 1 revision and review process.

In July of 2020, PDA submitted 88 general and specific comments and recommendations prepared by the Task Force to the European Medicines Agency (EMA) as part of the Annex 1 targeted second. In addition, the PDA has worked on an Inter-Association effort across multiple global organizations to ensure that the common industry needs and thoughts on the revision are communicated to the EMA. As part of that effort, an Inter-Association letter presenting common views was sent to the EMA prior to the submission of specific comments.

It has been reported that the second Annex 1 consultation has resulted in approximately 2,000 comments collected by the European Commission, PIC/s and WHO. The Annex 1 Inspector Working Group (WG) is currently reviewing an addressing those comments. The EMA has not released an official timeline for the final publication of the revised Annex. It is speculated that once the revision is published, EMA will then communicate the planned implementation timelines.

The efforts made by the PDA and its Task Force are of importance considering the Annex 1 revision and the guidance it presents will have a great impact on the global pharmaceutical and biopharmaceutical 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 and to encourage the introduction of new technologies that are not currently addressed. The inclusion in the Annex 1 Working Group of experts from national and international (EMA, PIC/S, WHO) agencies across the world is a welcomed directional move towards a global harmonization of requirements.

PDA continues to be committed to assisting in the development of this importance guidance. Upon completion of the revision, PDA will remain committed to assist the EMA (PIC/S and WHO) with any educational, training, or communication efforts required to ensure a harmonized interpretation and implementation of the principles, recommendations, and requirements presented in the Annex. PDA and the Task Force are in a joint effort to support our members, the bio-pharmaceutical industry, health authorities, and the patients we all serve.

Getting Closer to AI adoption in the Pharmaceutical Industry continued from page 10

ing processes. Similarly, 59% of the respondents believe that pharma, biopharma, and medical devices are not ready for AI implementation in general across the regulated industry. Finally, participants were asked about which particular hurdle their organization has experienced in the implementation of AI. The most significant obstacles reported are the lack of resources (38%), regulation (23%), and validation (21%), followed by insufficient budget (10%) or data (8%).

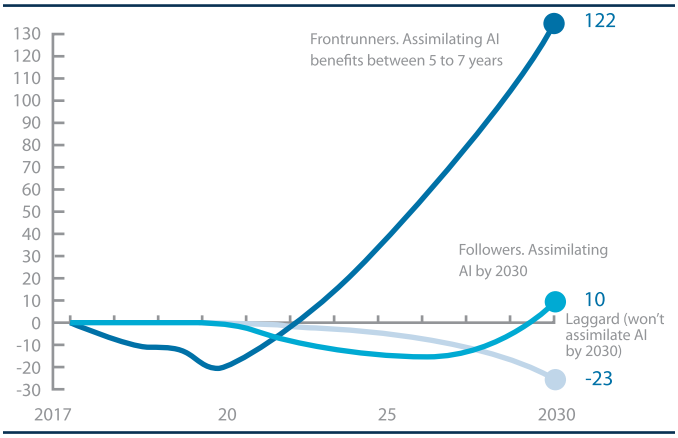

Figure 1 Forecasting about the expected benefits that frontrunners in AI adoption will get during the next years versus their followers. World Economic Forum and McKinsey

Overall, the poll question results indicate that there is a lot of work to be done to disseminate good data and AI implementation practices and encourage adoption of the technologies. Nevertheless, a McKinsey study suggests that there will be a significant disparity in benefit for manufacturers who are early adopters of AI verse those who hesitate on advancement and are thus left behind ***(2).*** As the graph below shows, leaders can expect a 122% increase in cash flow, compared to a 10% cumulative change seen by followers.

There is a promising horizon for the AI adoption in biopharma and at the same time, a good opportunity to improve some existing issues in regards of data integrity. On the first hand AI algorithms require good and quality data to generate valid AI models. On the other hand, the inherent complexity and continuous variability on biomanufacturing processes only can be driven by advanced systems based on expert algorithms which are able to reproduce the reality. This is an ideal combination of factors that is accelerating the AI adoption in the biopharmaceutical industry.

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1. Manzano, T.; Fernandez, C.; Ruiz, T.; Richard, H.; AI Algorithm Qualification; *PDA JPST;* **DOI:** 10.5731/pdajpst.2019.011338.
2. McKinsey Global Institute Analysis, "Lighthouse' manufacturers lead the way—can the rest of the world keep up?"; 2019.

Continued Process Verification: Reacting to Data Signals

Ajay Babu Pazhayattil, Industrial Pharmacist

With the availability of statistical analysis, modelling tools, and advancements in machine learning and artificial intelligence solutions, the utilization of a growing body of process knowledge gained through the lifecycle stages of process validation is an expectation in the bio/pharmaceutical industry.

The *U.S. FDA "Guidance for industry: Process Validation: General Principles and Practices* specifies process validation activities in three different stages: Stage 1- Process Design, Stage 2- Process Qualification, Stage 3- Continued Process Verification (CPV) **(see Figure 1).**

Process validation is no longer a singular finite activity. Stage 3, the Ongoing or Continued Process Verification stage is a formal plan to assure the process remains in its validated state during routine production and the process remains in a state of control. The stage presents various opportunities as well as challenges to the industry. Stage 3 may be best classified into Stage 3a and Stage 3b. The regulatory guidance documents do not delineate Stage 3a and Stage 3b, although the approach is as an industry practice. A robust Stage 3a assessment specifically for understanding and managing process variability provides the basis for a standardized ongoing Stage 3b plan. An effective CPV program would diminish the need for a scheduled/periodic revalidation.

State of Continued Process Verification

With the arrival of Stage 3 (CPV), the expectation is to apply the knowledge gained and to contemporaneously act on the data signals (variability or unexpected patterns in the data) for continuous improvement. This opportunity to analyze the process data more often than in the traditional annual product quality review (APQR) makes the CPV program critical in identifying drifts and proactively eliminating potential process failures.

The early trend detection advantage was one of the reasons for introducing the CPV stage in process validation guidances. The expectation is to apply the CPV insights for new process development and for similar products/processes as well. The CPV stage is expected to generate larger data sets of critical quality attribute (CQA), critical process parameter (CPP), key performance parameter (KPP), and critical material attribute (CMA) since it represents commercial manufacturing phase. Novel technol-

Figure 1 Process Validation Stages

ogy, data analytics and live data modelling solutions are now available for effective application in CPV programs.

A process validation lifecycle management system with easily accessible Stage 1, 2 and 3 data helps in knowledge management and use of the insights for continuous improvement. Harnessing CPV data is therefore an important business and regulatory need. Emphasis for using a Quality by Design (QbD) approach makes the CPV stage critical for legacy products which were commercialized without QbD ***(1).*** Such products may already have a substantial amount of process data for multivariate analysis to establish a design space.

PDA Technical Reports

The industry and regulatory technical guidance continue to evolve for CPV and for the lifecycle approach overall.

PDA technical reports provide sufficient insights on application of the statistical methods and approaches for the process validation lifecycle. For example, *PDA Technical Report No. 60: Process Validation: A Lifecycle Approach* aligns to the lifecycle process validation model with CPV, as outlined in the 2011 FDA process validation guidance and offers practical examples of process validation lifecycle. *PDA Technical Report No. 59: Utilization of Statistical Methods for Production Monitoring* present's relevant and easy-to-use statistical process control (SPC) methods that are applicable to detecting signals in the pharmaceutical/biopharmaceutical industry.

The Gap

Industry organizations like PDA and regulatory agencies have put considerable effort into developing industry friendly and applicable processes for CPV.

Application of standardized sampling plans (e.g., ASTM), SPC signal generation rules, and use of fit for purpose statistical method identified in the technical reports are some examples. They assist in development of the initial CPV program and analyzing the generated process data. However, as the industry matures into continuous improvement decision making, there is a need to apply standardized processes for managing CPV data signals.

To date there are no regulatory guidance on how industry should react to such signals. To fill this gap, the PDA Process Validation Interest Group (PVIG) created the subtopic "Responses to CPV Data Signal". The teams mandate was to work on rationalizing and standardizing the CPV signal decision making process. The need is imminent since the decisions made based on CPV data signals should not be delayed but also require a high level of statistical and scientific rigor. The decision making cannot be deferred as it impacts the sites operational continuity. The day-to-day CPV decisions once made should stand future regulatory scrutiny.

Another PVIG subtopic team has been exploring the use of CPV data for artificial intelligence applications. The initiative has the support of organizations like the PQRI. The CPV of the future task force is focused on identifying relevant signals which are critical to control ongoing biotech processes.

PVIG: Response to CPV Data Signals

The team, comprised of process validation experts from the biopharmaceutical and pharmaceutical segments, have developed decision-tree models based on brainstorming sessions.

The CPV signals representing CQA/Specification failures are addressed by the quality management system and investigated per standard operating procedures. Out-of-statistical-control (OOSC) and out-of-alert/control are some of limits used for CPV control, which are independent of out-of-specification (OOS) and deviation specification limits.

The scope of project in developing decision-tree model(s) for CPV signal is therefore limited to the data point signals that are out of CPV control limits. The team coined this type of signal as "yellow flags." Yellow flags represent the process variability and drifts. The FDA process validation guidance is very specific to state that trending should be performed in such a way that it should guard against overreaction to individual events. Thus, automatically categorizing the yellow flags as a quality failure investigation without additional review of the signal is not an ideal approach.

Problems Solved, Opportunity

An upfront approach on how to address the relevant variables and signals is important in avoiding under detection or overreaction. It needs to be noted that the signal can be for a quality attribute, material attribute, process parameter, and/or performance indicator with various degrees of severity.

Examples from biologics and small molecule manufacturing processes were reviewed for applicability. Wherever the term "process" is used in the decision tree, includes analytical methods and any other processes that can be a source of the variability. A CPV program with Stage 3a and Stage 3b delineation would need different approaches since there is not enough data generated in the earlier stages of commercialization (Stage 3a). A decision tree (see **Figure 2)** was developed for scenarios where there are statistically significant sample sizes.

When limited data is available a deep dive into the available data is warranted to understand what actions can be taken until additional data is generated. A risk-based categorization of signals received (KPP, CPP, CQA etc.) is also required, as all signals are not equally created, leading to requiring different action plans for the yellow flags.

The suggested action (which includes all possible next steps) were determined based on practical relevance and the statistical strength of the signal. For example, it is proposed to take path 1 when the observed drift is a result of an assignable event extrinsic to the process, characterised by an isolated event. This signal may or may not have been identified as a QMS deviation or incident.

Path 2 is suggested when it's a common cause variation where revision of your control limits may be justified based on current process data. Path 3 is identified for the special cause variations requiring investigation, determination of root cause and continuous improvement remediation and/or a control strategy update. The team's goal was to develop holistic decision tree examples that can be easily adopted and customized for a product by incorporating product/process specifics.

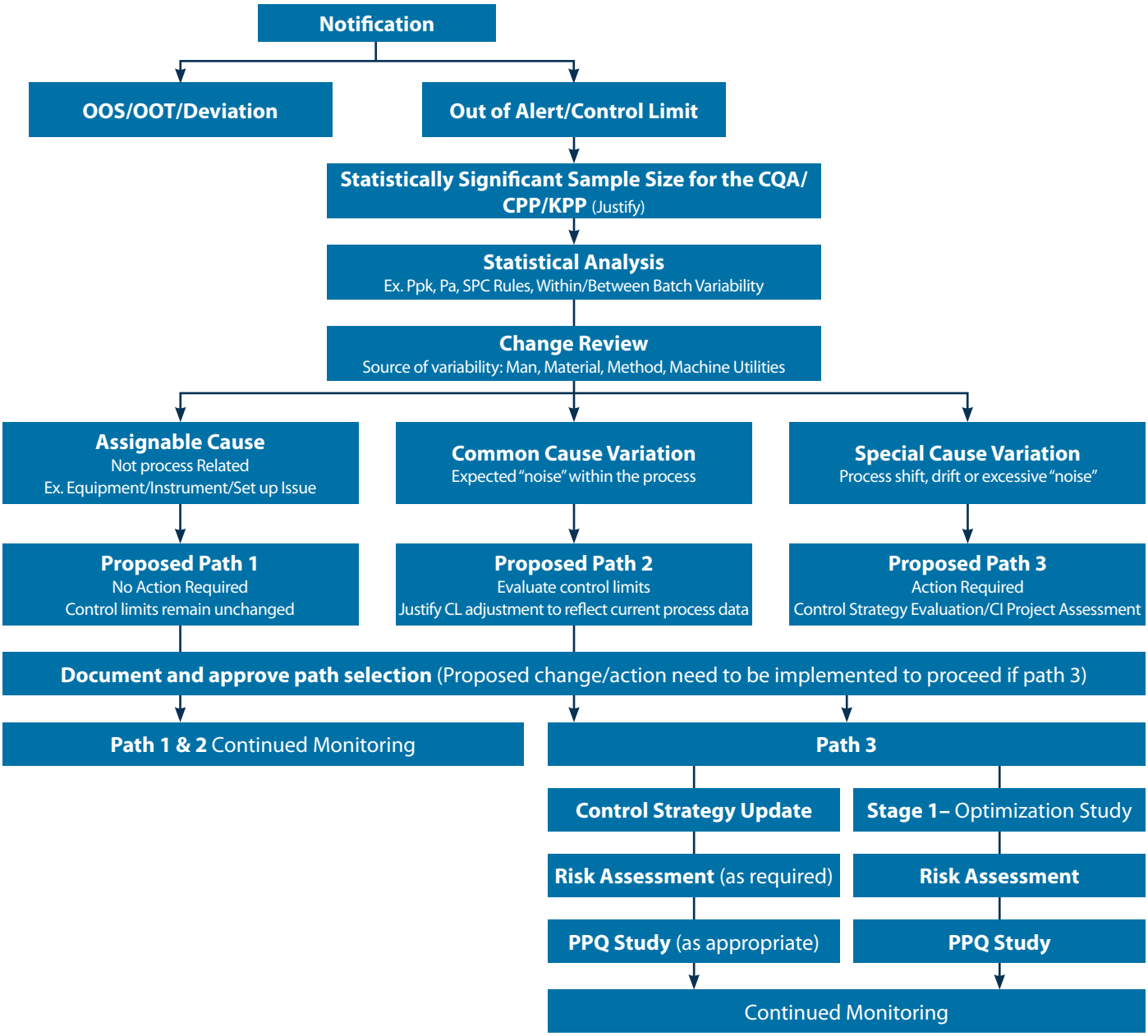

Figure 2 Proposed CPV Data Signal Decision Tree

Encouraging Feedback

The efforts of the CPV Subgroup on "Responses to CPV Data Signals" have resulted in developing decision tree flow charts for relevant scenarios. The test cases validated the applicability of the proposed decision trees. A structured decision-making process with grounded statistical rationales minimizes the potential for subjectivity and reduces regulatory compliance risks. The PDA PV subgroup that has developed the process flows invite interested PDA members and industry experts to review and apply the tools on your processes. The feedback and insights garnered will enable the team to further fine tune the tools.

To request more information and for the reaction to signal decision making flowcharts, Contact: apazha@kskmpharma.com

References

1. U.S. FDA (2009). Q8(R2) Pharmaceutical Development: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q8r2-pharmaceutical-development

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2020-21 PDA Upcoming Events

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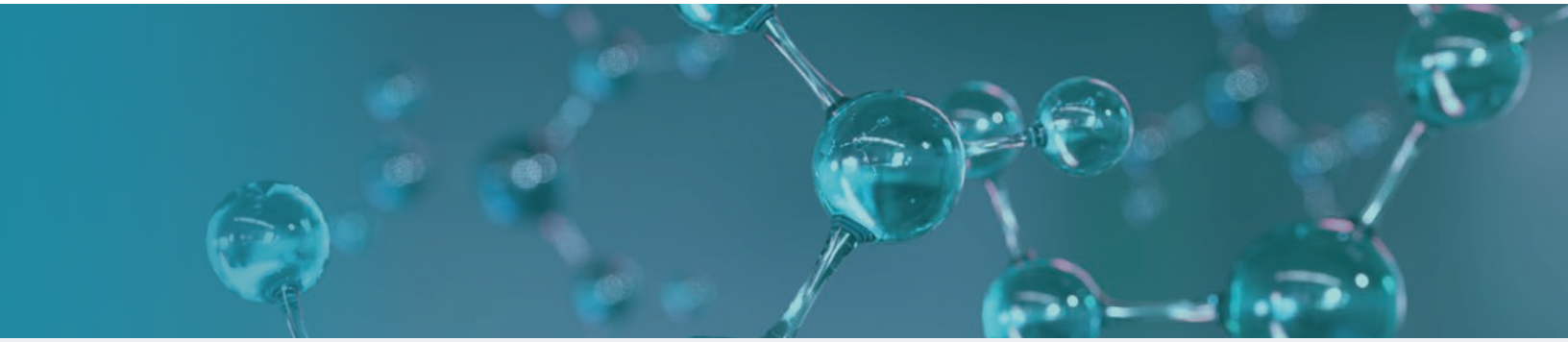


JANUARY 2021

11-12 PDA 143.1 Designing and Presenting GXP Training Programs to Meet FDA Requirements
pda.org/qatraining

MARCH 2021

23-25 PDA 468 Validation of Moist Heat Sterilization Processes
Sellersville, PA | *pda.org/sterilizationtraining*

APRIL 2021

12-13 PDA 617 Fundamentals of Life Sciences Cleanrooms and Controlled Environment Production
Bethesda, MD | *pda.org/aseptictraining*

14-15 2021 PDA Visual Inspection Forum
pda.org/2021visual

20-21 2021 PDA Robotics and Automation Conference
pda.org/EU/2021roboauto

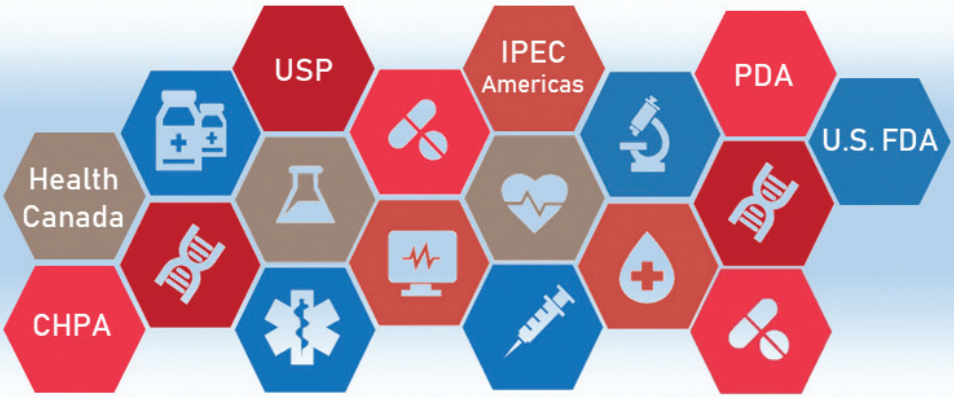
26 2021 PDA Pre-Filled Syringes Workshop
Basel, Switzerland and Online | *pda.org/EU/IG-PFS2021*

27-28 2021 PDA Parenteral Packaging Conference
Basel, Switzerland and Online | *pda.org/EU/2021ParPack*

29 2021 PDA Packaging Science Workshop
Basel, Switzerland and Online | *pda.org/EU/2021IG-PS*

The Product Quality Research Institute – Advancing Regulatory Science through Collaboration

Glenn Wright, PDA



For the past two decades, PDA has been a proud member of the Product Quality Research Institute (PQRI), a non-profit consortium of organizations working together to generate and share timely and impactful information that advances global drug product quality, manufacturing, and regulation.

It is important that all members of the PDA community are aware of PQRI is history and mission, its other sponsors, and how individuals can get involved.

PQRI's History and Mission

Established in 1999, PQRI originated from a collective effort between FDA's Office of Pharmaceutical Science (OPS) and several of the pharmaceutical industry's major trade associations. Their goal was to create a safe haven in which scientists from industry, academia, and regulatory agencies could collaborate to advance science in support of pharmaceutical and biopharmaceutical regulatory guidance.

Recognizing the important role that industry, standard-setting bodies, and regulatory agencies play in driving continuous improvement of pharmaceutical quality standards and methods, PQRI was designed to unite these stakeholders and leverage their combined knowledge, resources, and experience to address emerging regulatory science challenges.

The efforts that PQRI supports help to generate the scientific base needed for the adoption of new, innovative approaches to assuring product quality, safety, and efficacy. PQRI Working Groups have published over 50 research papers and cases studies, organized more than 25 workshops and conferences, and produced data leveraged by regulatory agencies to inform guidances and best practices.

Who are PQRI's members?

PQRI members are organizations that are invested in the advancement of pharmaceutical regulatory science and technology, which currently include the following.

- Parenteral Drug Association (PDA)
- United States Pharmacopeia (USP)
- Consumer Healthcare Products Association (CHPA)
- U.S. Food and Drug Administration (FDA)
- International Pharmaceutical Excipients Council of the Americas (IPEC-Americas)
- Health Canada (HC)

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This book explores what each transformational technology does, the potential use of the technology, and the practical aspects for its implementation, along with the changes to culture and structure necessitated by digital transformation.

The themes covered in this first volume are process-centric and include:

- Application of blockchain and track and trace technology for the distribution of medicines
- Mechanisms for automating the process and fostering the digital pharma company
- How real-time metrics and Process Analytical Technology can lead to a more efficient plant

The second volume will address the digitization of the laboratory and a survey of data handling issues.

Regulatory aspects and standards are addressed throughout each of the two volumes.

Digital transformation continues to take place at an accelerating pace. This book provides a clear understanding of what has been, what is, and what will be happening and why.

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Each member organization is represented on PQRI's Steering Committee and Technical Committees. The Steering Committee oversees strategic planning of all scientific activities. The following discipline-specific Technical Committees provide guidance, direction and oversight to PQRI working groups and projects.

- Product Quality Technical Committee (PQTC)
- Development Technical Committee (DTC)
- Biopharmaceutics Technical Committee (BTC)

TechnicalcCommittees members play an essential role in PQRI by liaising with their organization to identify projects that would benefit from the collaboration facilitated by PQRI and recruiting scientists to contribute to those efforts. In doing so, they work with some of the best and brightest in their field to help shape the future of the industry.

What does PQRI do?

Technical committees work in concert with the Steering Committee to establish working groups, which address timely regulatory science challenges through applied research and knowledge sharing and communicate their findings through technical reports, scientific papers, workshops, seminars, and webinars. Each working group is sponsored by at least one of the member organizations and overseen by the technical committees to whom their work is most relevant.

For example, the PQTC's mission is to leverage the regulatory, quality, and manufacturing expertise of its members to define science-based approaches that encourage innovation and continuous quality improvement in pharmaceutical manufacturing and flexibility in the associated regulatory processes.

The PQTC currently oversees the following projects:

Artificial Intelligence (A.I.) Application in Continued Verification of Process Project

Members of PDA's Process Validation Interest Group have partnered with scientists from the University of Barcelona and University of Maryland Baltimore County to establish a standard procedure for continued process verification in fermentation operations, applying A.I. as an analytical method for process control. PDA members can read more about this project in the April 7th PDA Letter Article.

> **"Technical Committees members play an essential role in PQRI by liaising with their organization to identify projects that would benefit from the collaboration facilitated by PQRI and recruiting scientists to contribute to those efforts"**

Elemental Impurities Working Group

This IPEC-Americas sponsored group recently completed a large multi-site study to assess analytical impurity methodologies and is planning their fourth workshop to share the study results and discuss industry experiences with the implementation of ICH Q3D. The workshop will take place virtually November 9-10, 2020 and will be preceded by a webinar and public survey. For more information see PQRI's Events Page.

Restricted Delivery Systems in Children OTC Liquid Medications Project

This CHPA sponsored project seeks to evaluate the prevalence and effectiveness of different restricted delivery systems used in a wide variety of branded and private label liquid infant and children OTC medicines commonly implicated in accidental exposures. System efficacy will be measured using a standard procedure developed by the group and accepted by ASTM International. Advisors include scientists from the U.S. Centers for Disesease Control and Georgia Center for poison control.

Topical Classification System Project

This effort is a joint collaboration between the PQTC and BTC to validate a Topical Drug Classification System (TCS) based on the scientific principles developed for semisolid topical products (SUPAC-SS) and in vitro release of the drug product.

Responses to Proposed Regulatory Guidance

Where guidance is issued for comment by regulatory authorities and the member organizations are aligned on their response, the PQTC submits written comments to the agency, such as with the FDA's draft guidance on cGMP Practice for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Food, Drug & Cosmetic Act.

How do I get involved?

PDA members that would like to learn more about the PQTC and opportunities to join should contact Glenn Wright, PQTC Chair and PDA's Vice President of Scientific and Regulatory Affairs, Wright@PDA.org.

For more information on PQRI's other Committees and projects, check out PQRI's website (www.PQRI.org) and contact the PQRI Secretariat, PQRISecretariat@pqri.org.

PDA Parenteral Drug Association

pda.org/calendar

SAVE THE DATE

for the 2021 Line-up of Conferences

Plan ahead for a year filled with best-in-class content and experiences from PDA. We'll be starting the year mostly online, delivering flexible, accessible, and engaging events. We are optimistically planning to come back together in person in the second half of the year, while continuing to offer a virtual component to these events for those who are still unable to travel. The best of both worlds!

2021 PDA Annual Meeting
15-17 MARCH
Presented Virtually
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2021 PDA Visual Inspection Forum
14-15 APRIL
Presented Virtually
pda.org/2021visual

2021 PDA Parenteral Packaging Conference
27-28 APRIL
Basel, Switzerland and Online
pda.org/eu/2021parpack

2021 PDA Pharmaceutical Microbiology Conference
4-6 OCT.
Washington, DC and Online
pda.org/2021micro

2021 PDA Universe of Pre-Filled Syringes and Injection Devices Conference
5-6 OCT.
Gothenburg, Sweden and Online
pda.org/eu/2021ups

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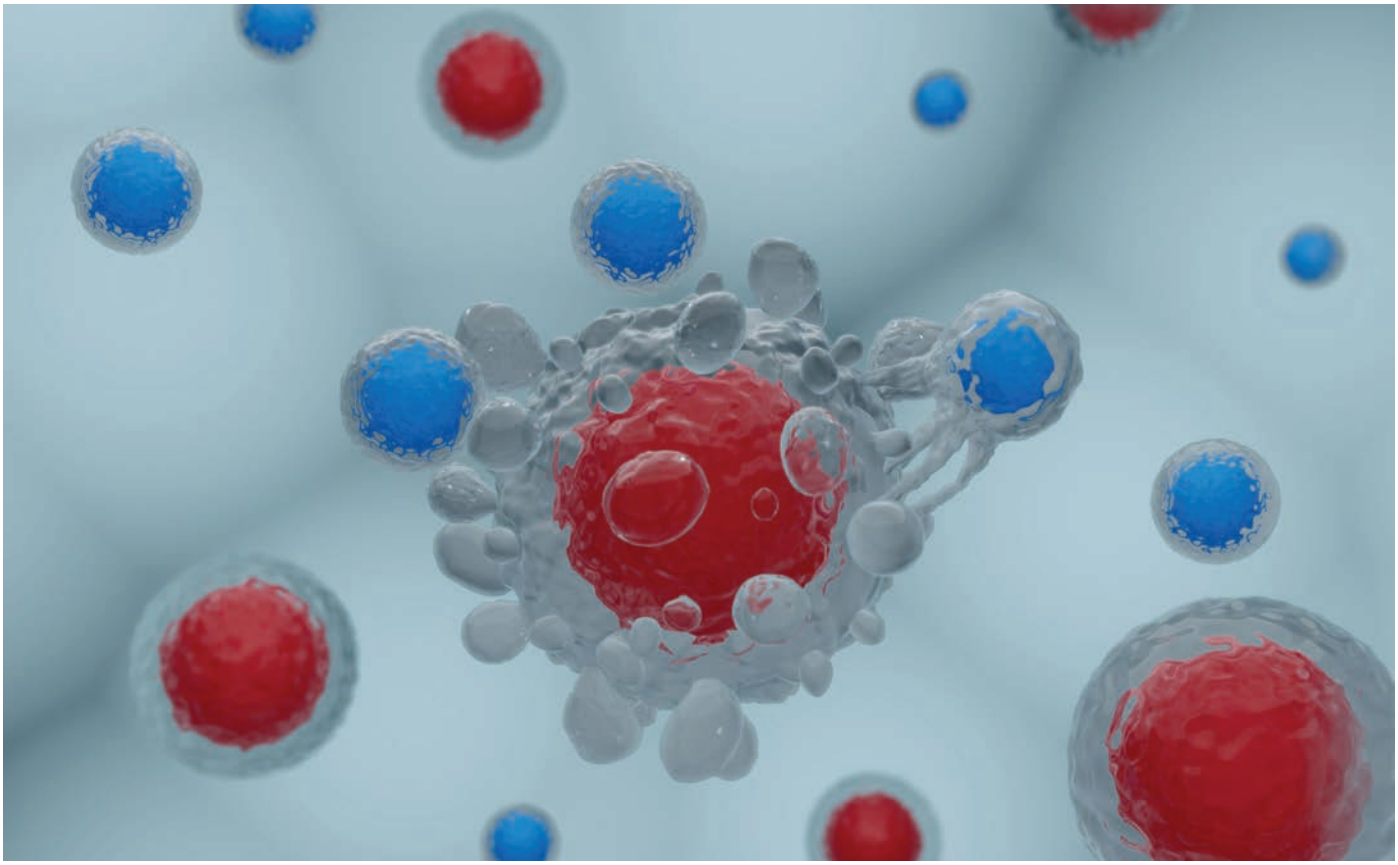
T-Cell Therapy Saves a Life

Marilyn L. Foster, PDA



Emily Whitehead was diagnosed with standard-risk pre-b acute lymphoblastic leukemia when she was only five years old. After two rounds of chemotherapy, an infection that almost cost her both legs and a full relapse, she became Patient 1 in a Phase 1 trial of T-cell therapy.

In the opening sessions of the *2020 Virtual PDA Annual Meeting* (Jul. 20 – 22), **Tom G. Whitehead** shared the moving story about how T-cell therapy saved his daughter's life, and **Elliot C. Norry**, MD, Chief Medical Officer of Adaptimmune, described how these life-saving therapies work.

In his presentation, "Delivering T-Cells to Patients: Challenges and Successes," Norry explained the Autologous Specific Peptide Enhanced Affinity Receptor (SPEAR) T-cell therapies his company develops for the treatment of cancer. T-cells, a group of white blood cells that help find and fight things foreign to the body like bacteria and viruses, attack and clear them using an inflammatory response. Adaptimmune has developed SPEAR T-cells that specifically recognize certain cancer cells as foreign and target them.

"Behind every bag of SPEAR T-cells manufactured," Norry stressed, "is an individual living with cancer." And the individual is usually a patient with an advanced form that has not responded to other treatments.

He illustrated the patient's journey from leukapheresis to infusion and the process of engineering the SPEAR T-cells. Adaptimmune ships the modified T-cells back to a patient's treatment center; the whole process usually takes 22-25 days. Before being infused with their SPEAR T-cells, the patient undergoes lymphodepleting chemotherapy to "make space" for the incoming cells and improve the efficacy of the treatment.

Several factors present a challenge to the process, Norry noted, starting with the fact that each product batch is unique to the patient.

The apheresis starting material and the cell dose range will vary depending on the patient's age, health and prior treatments, meaning no two products ever look the same. As such, a strict chain of custody must be maintained, location and temperature of the cells monitored at all times, and special measures taken to ensure that patients receive only their own cells.

Aligning patient scheduling with manufacturing capability creates a need for flexible capacity, requiring Adaptimmune to maintain control of the entire process. The growing success of the treatment in several different advanced cancers is why the company continues to pursue SPEAR T-cell studies, to improve the process and increase the availability of the treatment across a broader population. ➤

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Putting T-Cells to the Test

Whitehead enthusiastically supported T-cell therapies in his presentation, "Journey to Car-T Cell Therapy," where he detailed the steps his family took to save their daughter Emily.

Following Emily's diagnoses, Whitehead consulted with oncologists from Pennsylvania's Hershey Medical Center and Children's Hospital of Philadelphia (CHOP). They started Emily on outpatient chemotherapy at Hershey as it was "only a two-hour drive instead of four." Soon after, she awoke one night with severe pain in her legs; she had developed infection in both legs, necrotizing fasciitis. The ER doctor said they may have to amputate both legs to save her. Whitehead remarked, "We had started with hope. Now we were really scared." Fortunately, the infection was not in the muscle, but around it, so amputation wasn't necessary, and Emily went back to chemo.

The majority of children with ALL are cured after a two-year treatment with standard chemotherapy and, initially, that worked. But 16 months later, Emily "felt the cancer in [her] bones again." Despite the two rounds of chemo, a bone marrow test confirmed it. Because Emily went into full relapse, she was no longer considered a "standard risk" and a bone marrow transplant was not an option. All Hershey could offer was another round of more intense chemo.

Whitehead got a second opinion from **Susan Rheingold**, MD, at the CHOP Cancer Center, but received the same answer, so they continued treatment at Hershey, seeking a donor for an allogeneic stem cell transplant. One was found and the transplant was scheduled for February 2012, but before then, Emily relapsed again.

Her leukemia was so aggressive this time, doctors recommended Whitehead take Emily home for hospice care. Not giving up, Whitehead applied for an experimental clinical study of CAR T-cell therapy at CHOP. The study was underway, but the therapy had never been used on children. In the meantime, Emily underwent a new chemo they knew "wouldn't cure her but would give her some time."

> **"As the doctor explained the process to Emily, they would use her T-cells to "build an army that would fight the cancer," and took her T-cells "off to boot camp"**

It proved to be just enough, as soon the T-cell therapy clinical trial was approved, and in April 2012, Emily became Patient 1 in the Phase 1 pediatric trial.

As the doctor explained the process to Emily, they would use her T-cells to "build an army that would fight the cancer," and took her T-cells "off to boot camp." With no immune system, Emily remained in isolation for six weeks. When it was time to return her strengthened army of cells, they infused her in a stepped process—10% one day, 30% the next, 60% the last—to determine what was effective and to evaluate her reaction, especially since they had no existing protocol for dosing a child. Emily withstood the first two doses well, not even showing the flu-like symptoms the family had expected, but the final dose knocked her out.

After receiving the 60% dose, Emily experienced cytokine release syndrome, a "cytokine storm" that brought on a raging fever (106 °F at one point), chills, hallucinations, labored breathing and a sudden drop in blood pressure. She was put on a ventilator and induced into a coma to relieve the pain; the steroids they pumped into her to reduce pain and inflammation, instead swelled her body beyond recognition.

The doctors gave Emily a one in one-thousand chance of surviving the night, but Whitehead asked her to try to get through it, held her hand throughout the ordeal and told the doctors, "just don't give up on her." Emily kept fighting throughout her 14-day coma.

Whitehead said, one test revealed her interleukin-6 level was "higher than anyone alive," 1000 times above normal. By chance, **Carl H. June**, MD, who led the clinical team at the University of Pennsylvania, recognized the IL-6 protein as one involved in rheumatoid arthritis, a disease that afflicted his daughter. He determined that Emily be treated with tocilizumab, the drug his daughter takes, though it had never been used in cancer patients. The results were dramatic! Within hours, her fever was down, her breathing came easier and her blood pressure normalized. She woke a week later on her seventh birthday. Twenty-three days after that, she texted her family "no cancer cells, T cells worked!!" Eight years later, Emily is still cancer-free, thanks to the T-cell therapy that turned her life around.

In the Q&A that followed his presentation, Whitehead replied that Emily is now a typical 15-year-old girl who, while hanging out with her family in isolation during the pandemic, spends lots of time texting friends. As a strong supporter of T-cell therapy, Whitehead and his wife, Kari, started the Emily Whitehead Foundation to help other families navigate childhood cancer and advocate for pediatric cancer research so others can have the same positive outcome as Emily.

Asked about the future of cell therapies, Norry said, "Harnessing a patient's *own* immune system to help fight cancer makes sense. I don't know what the future looks like, but I hope it expands to help more patients even earlier in their course of therapy."

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Virtual Audits in the Time of Covid-19: For the Auditor and the Host

Anna Gilbert, BDO; Robert Greathead, Catalent Pharma Solutions; Michelle Bernards, Manager, Catalent Pharma Solutions

The many restrictive policies in place to control the spread of Covid-19 has limited the ability of pharmaceutical company personnel to travel to and conduct audits of contract development and manufacturing organizations (CDMOs). Due to these limitations, both auditors and audit hosts must adapt and move to what is called a "virtual" or "remote" audit.

One should not confuse paper audits with virtual audits, because they are not the same. Paper audits generally include a limited review of documentation, which may include a quality survey provided by the auditor and completed by the supplier and a subset of documents such as the quality manual and copies of certifications. Alternatively, some suppliers will provide their own prepared information in lieu of completing the auditor's survey. Paper audits are common for suppliers with many customers and help minimize the impact on their resources. A paper audit does not include a facility tour, the opportunity to interview subject matter experts (or "SMEs"), nor opening and closing meetings. Observations are not typically issued.

By contrast, a virtual (remote) audit is intended to mimic a site audit to the degree possible, based on the host's resources. The virtual audit has the cadence of a site audit, with opening and closing meetings, a tour, document review with the hosts and SMEs available for consultation and clarification. A formal audit report with observations is issued at the completion of the audit.

The following explores virtual (remote) audits, first from the auditor's perspective and then from the audit host's perspective, looking specifically at the preparation, planning and conduct of the audit. **Table 1** outlines differences between traditional and virtual audits.

Auditor's Perspective

Preparation

Agenda

The first step to prepare for a virtual audit is to create a detailed and organized agenda that will maximize the effectiveness of the audit. The agenda should clearly outline the objectives of the audit tour. What areas need to be included? Are there specific pieces of equipment to be evaluated? Are there specific items to view in the virtual tour? If clean rooms are involved, badge access and interlocking door lights, visual verification of cleanable materials of construction or coved flooring and nonporous ceilings need review. The more detailed the agenda is, the better able the host is to understand and prepare for the audit.

For document review, requesting the site's standard operating procedures (SOP) list and using this as a tool can aid in creating the agenda. As with a site audit, the agenda can be organized by area: Quality System, Facilities, Equipment, Manufacturing, Laboratory Controls, Materials, Packaging, Labeling and Distribution. Including the specific SOPs to review in the agenda and requesting them by area will enable the site to organize the documents. These documents should be uploaded to a cloud file share. Appropriate expectations should be set with the site that the documents in the agenda represent the minimum required, and that additional documents will be requested during the flow of the audit. In addition to the SOPs, any additional documents to be prepared for review, such as environmental monitoring trending reports, quality management review agendas, training records, pest control records, maintenance records and qualification/validation documents, should also be requested.

To set up the opening meeting, the first step is to agree on a date and time, just as with a site audit. The difference, however, is that regardless of all participants' locations, the audit will occur in the time zone of the site. This can be a simple offset of just a few hours if all participants are in the United States. It can be much more problematic if the participants span both coasts of the United States, Central Europe and Asia. Tuesday at 9:00 a.m. in Beijing is Tuesday 3:00 a.m. in Central Europe, Monday 9:00 p.m. on the East Coast of the U.S. and Monday 6:00 p.m. on the West Coast. As such, the agenda will need to be clear as to the opening meeting time for all associated time zones.

Planning Meetings

Meeting one or two times with the site prior to the audit may prove helpful.

The first meeting should occur at least one week prior to the audit and ensure expectations are well understood by all parties. This meeting is critical because it will allow for agreement on document-sharing and communication platforms, as well as discussion of the details of the virtual tour. Done right, this meeting will contribute to the success of the audit.

The second meeting—a "kick the tires" meeting—should occur a couple of days prior to the audit; this presents an opportunity to verify that the sharing site can be accessed, and the documents can be opened. This time can also be used to ensure that the online conferencing platform (e.g., Microsoft® Teams, GoToMeetings®, Cisco Webex®) works for all parties. The day of the audit is not the time to discover IT issues.

During the Audit

There is no single correct way to perform an audit tour; however, the tour format should be known ahead of time to avoid surprises. One key aspect to consider is that during a virtual tour, it is more difficult to fully understand personnel, material, equipment and waste flow. If this is clearly requested ahead of time, the audit host should be able to provide a strong overview by using facility drawings and detailed photos or a video tour.

Since the pandemic, the virtual audit tour has rapidly evolved, with a variety of approaches in use.

One approach is to use detailed still photographs with an SME to narrate and describe the images. If care is taken to show detail, such as equipment stickers with identification number, calibration date, calibration due date and preventative maintenance information, this approach can be effective. To date, this is one of the more common virtual audit formats used.

Another virtual audit tour method is to provide a live tour. This can be done with a smartphone or equivalent device mounted on a gimble with a Bluetooth® microphone used for the SMEs providing the tour. This option closely mimics the traditional audit. One downside is that many facilities have "dead zones" where the sound and images may be disrupted, which may make it difficult for the auditor to watch for long periods of time.

Prerecorded tours have also been used. Some hosts may have professionally recorded tours, complete with narration, subtitles and background music. Other prerecorded tours may be as simple as the host walking around the facility with a smartphone or equivalent device and narrating as they move through the facility. Yet another is prerecording 360° views, much like those on real-estate websites, with SME narration. Finally, some audit hosts are exploring such breaking technology as "smart glasses."

There are differences in approach for virtual audits when compared to traditional site audits, particularly when there are significant impacts due to multiple time zones. When time zones allow for it, an online conferencing platform can be opened for the working hours of the audit where the auditor(s) and host(s) can live chat, share documents and jump on a ➤

Table 1 Comparison of Traditional Site Audit vs. Virtual (or "Remote)" Audit

Audit Component	Traditional Site Audit	Virtual (or "Remote) Audit
Audit Agenda	Issued prior to audit, as per Quality Agreement; may be high-level or detailed	Issued prior to the audit, as per Quality Agreement; must be detailed to ensure documents are ready (must be uploaded to a shared document location)
Audit Planning Meeting	Recommended to align expectations	Critical to ensure all software and IT systems function and can be accessed, virtual tour format is discussed and understood, and expectations are aligned.
Audit Opening Meeting	Representatives from host site and, minimally, the auditor or audit team Introductions, audit scope and opening presentations are provided.	Representatives from host site and, minimally, the auditor or audit team Generally greater participation from auditor's and host's leadership teams due to lack of travel requirement Introductions, audit scope and opening presentations are provided.
Audit Tour	Typically begins after the opening meeting. Auditor and audit host, as well as site SMEs, physically walk through the facility. Audit "threads," such as requesting specific raw material lot files observed in warehouse or training files for personnel, are observed throughout the tour.	Typically begins after the opening meeting. If a live tour, the audit host, as well as site SMEs, physically walk through the facility with the auditor observing remotely. Audit "threads," such as requesting specific raw material lot files observed in warehouse or training files for personnel. are observed throughout the tour. Audit "threads" may be difficult in a still-photo tour format.
Audit Closing Meeting	Representatives from host site and, minimally, the auditor or audit team Observations are verbally communicated.	Representatives from host site and, minimally, the auditor or audit team Generally greater participation from auditor's and host's leadership teams due to lack of travel requirement Observations are verbally communicated.
Audit Report	Auditor issues report for host as per Quality Agreement requirements	Auditor issues report for host as per Quality Agreement requirements
Audit Responses	Host provides responses to audit observations as per Quality Agreement Requirements.	Host provides responses to audit observations as per Quality Agreement Requirements.

quick call. Live interactions with the host and the SMEs can provide a glimpse into the site's culture, attitude and depth of knowledge. The live format can also facilitate real-time requests for documentation, which provides a cadence similar to a site audit and can provide insight into the site's data integrity and data availability.

When time zones prohibit live interaction throughout the audit, email communication can serve as the primary method of communication. This is considered less effective and, if there are concerns about the host site, every effort should be made to have a live virtual audit.

Virtual opening and closing meetings tend to be quite similar to those of the traditional audit with the exception that there may be greater participation. The opening meeting includes introductions and an overview of the audit host's organization. Typically, all participants use live video for these meetings.

Discussing a follow-up visit when travel restrictions are lifted—not necessarily an audit, but a visit to allow a tour of the facility and interface with key staff—is recommended.

Audit Host's Perspective

Preparation

Site Preparation

Following confirmation of the scheduled audit, the site should begin preparations. Key personnel and SMEs will be required to support the audit, just like a traditional site audit, and early schedule coordination will ensure that personnel can devote their time to the auditor. Opening and closing meetings should be scheduled using a teleconferencing platform as soon as possible. During on-site audits, introductions to key personnel typically occur face-to-face in an office setting and business cards are shared. In the remote audit setting, developing a presentation introducing key personnel is beneficial; providing personnel names, titles and email addresses, will not only facilitate organized introductions with a set order, but will also provide personnel contact information for the auditors.

A planning meeting with the auditors is recommended to discuss the audit logistics. When requesting the planning meeting, providing relevant documents to assist the auditor with audit agenda preparation, such as a table of contents for the site SOPs, the Site Master File and the site organizational chart, is very helpful. Requesting the auditor share the agenda prior to the planning meeting will allow the host site to review the agenda content as well as provide an opportunity to discuss any points of clarification that might be necessary.

If the site has established a standard software platform for use during virtual audits, the environment should be prepared prior to the planning meeting. These preparations may include establishing a controlled environment with limited access, verifying IT access for the auditor's domain and ➤

providing guidance to the auditors for installation and use of the platform. When evaluating a platform to use for hosting, it is important to assess the security controls within the platform as well as the platform capabilities (e.g., file storage and access, instant messaging and teleconferencing). Using one platform to support all portions of the audit simplifies the logistics of the audit for both the host and the auditor.

Agenda

Upon receipt of the agenda, the host should review and prepare any clarifying questions.

In the document-sharing site, either the host or the auditor should establish a logical folder system to better organize the documents requested. An additional folder for deploying documents requested during the audit also provides an extra level of organization during document review. When populating the folders with the requested documents, it may be beneficial to rename the files. Often, sites will have a naming convention for documents that may be logical to site personnel but may be difficult for auditors to determine the contents of a given document without opening it. Using a "mirrored" document folder (e.g., an exact replica of the document-sharing platform) within the site network server can be beneficial for preparing the documents prior to the audit, as well as providing a repository for unloading and reloading the documents for each audit day. This mirrored folder can also serve as a record of the documents provided during the audit.

Planning Meeting

During the planning meeting, an overview of the platform to be used during the audit should be conducted. If access can be provided to the auditor prior to the planning meeting, verification of access can be performed during the meeting. At minimum, confirmation of access should be performed prior to the audit to ensure that any technical issues are resolved prior to the date of the audit.

On-site audits typically include a tour of relevant facility areas. In the virtual environment, if the capability exists, a virtual tour can be provided in lieu of the on-site tour. The auditor should be asked if there are any specific areas or items of interest (e.g., specific equipment) that are essential for viewing during the tour.

The virtual audit provides an opportunity that traditional audits do not. Typically, during the opening and closing meetings of on-site audits, only the auditor participates. When hosting the opening and closing meetings via teleconference, other members of the auditor's team can join the meetings without incurring any additional travel costs. This added benefit can be offered during the planning meeting with no additional strain on the host.

During the Audit

During the opening meeting, following personnel introductions, the virtual tour can be performed using the teleconference. This prevents the need for auditors, hosts and tour guides to switch to a secondary teleconference. Key personnel for each area of the tour can stay on the teleconference and walk through their respective areas, providing answers to any of the auditor's questions. While opening and closing meetings for the audit are hosted via teleconference, the document review portion of the audit does not necessarily require a continuous call. If the platform being utilized for the audit has the capability for instant messaging, this feature allows the auditor to ask a question and continue document review, while the host provides a response. Some platforms allow for replies to specific messages so that both the answer and question are grouped together. This is useful for both the auditor and host to keep track of which questions have been answered throughout the audit.

Some questions will require in-depth discussion and explanation from SMEs. For these types of questions, additional teleconferences can be set up to facilitate such discussions.

If the host and the auditor are unable to take part in the audit at the same time due to time zone differences, the instant messaging feature may still be a useful communication tool. While there will be delays in providing answers to the auditor, the auditor will have an easier time in evaluating the responses upon return to the audit.

Thoughts on the Future

Will remote audits have a place after the pandemic? The answer is "it depends." For high-risk audits, being on site for an audit is always preferred. However, for a low-risk, routine audit, a virtual audit may be a worthwhile option. For firms with minimal personnel or budget, eliminating the costs of travel and the subsequent loss of employee time may make performing a remote audit a desirable alternative.

Governing procedures and legal documents need to be evaluated. Quality agreements are legal contracts that, among other things, outline the communication and responsibilities of each party, including each party's responsibilities for audits. The language necessary to support virtual audits must be included in these contracts. Additionally, SOPs that govern supplier management should be updated to include the requirements and controls for virtual audits, and to allow for flexibility in conducting audits either on-site or using a virtual format.

The current situation has established that virtual audits can be a sustainable method of performing quality audits for both the auditor and host. Virtual audits are most likely here to stay.

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