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Zero-Particulates Goal Promotes Continuous Improvement

Subrata Chakraborty, GxPFONT Consulting Group

Irrespective of the differences in such pharmacopeial expressions as "essentially free," "practically free," and "free from readily detectable" particles, the growing expectation around the world is that injectable products should be free of visible particulates. We know why: The particulate matter in injectable products denotes a critical quality attribute impacting patient safety. The clinical implication of particulate matter depends on various factors—size, number, composition, potential for micro contamination, route of administration, intended patient population and clinical condition of patient—that make the risk assessment complex ***(1)***. And, according to data, particulate matter is the number one reason for sterile injectable drug products being recalled between 2015 and 2020 ***(2)***.

The irony is our current production systems are neither capable of producing particle-free injectable drug products nor proficient in detecting particulate rejections with 100 percent accuracy. The Probability of Detection (POD), which is dependent on multiple factors—container characteristics, inspection conditions, formulation characteristics and particle nature, still remains a strong point of contention in the industry defending our limitations.

Prevention is Better than Detection!

Particles can be contributed from practically everything that comes in and around any aseptic processing facility, from consumables used like wrapping papers, sterilizable bags, hand gloves, silicone tubing and gaskets, from such packaging materials as vials and rubber stoppers, and even from the equipment itself. Knowing what contributes particles is important to counteracting them. Our incapability to precisely detect and completely eliminate particulate rejects in a finished package, even with the latest tools and technologies, leaves us with no other option than controlling them at the source. But how do we do that?

Adopting a CI Program

Adopting an efficient continuous improvement program is key to moving toward a zero-defect goal (see **Figure 1**). This involves creating a continuous process of identification of particles, tracing them in the processing area, equipment and materials, and establishing a control strategy to prevent them from contaminating the product. The first step is to set up a good visual inspection program that leads to a primary level of identification and segregation of observable particle rejects based on their visible nature, for example, fiber-particles, light-dark, sinking-floating, black-brown-red, glass-crystal. This data is retained to develop a trend and set alert and action limits.

A secondary level of identification is performed by microscopic observation of visually segregated defects, which helps in estimating the gross composition of such particles, such as metallic, glass, rubber, fiber (natural-synthetic), and undissolved raw materials. This also helps in verifying the defect categories identified by the visual inspectors and in creating a library of defects for later training and qualification. Usually, skilled analysts perform this technique in house, as they can segregate the particles by category and keep track of ongoing production batches.

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July 2021

PDA Letter

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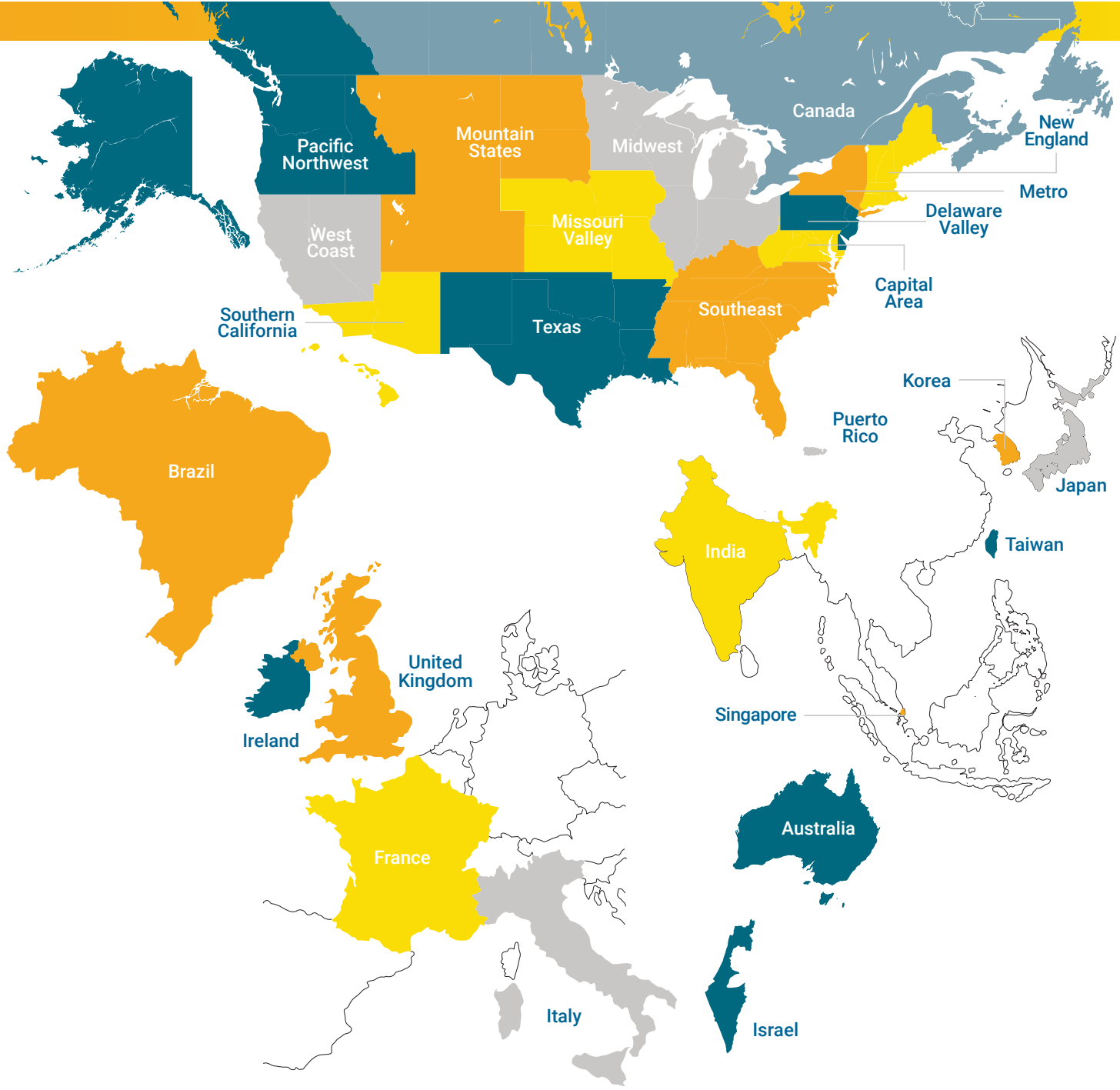

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Are you curious about the issues unique to your region?

Another layer of PDA leadership resides at the grassroots level in the Chapter organizations. Regional PDA Chapters provide local services to the membership, including translations of PDA publications, networking social events, student scholarship and annual regulatory and technical conferences. Each Chapter is managed by volunteer leaders.

Learn more about your local Chapter at *pda.org/Chapters*

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Who would have thought …

Marcel Ewals, PDA Asia Pacific Office

… that somehow we started the year expecting to slowly return to our new way of life in Asia, as travel bans and relatively tight quarantine rules seemed to overcome COVID-19. But the Delta variant was a game-changer, and we are pretty much back to where we started 18 months ago.

So now we begin talking about moving from pandemic to endemic. "Living with COVID," in a non-literal way, seems to be the new topic. How to do we open up our world again to a freedom-of-movement model without risking the health of the general population? While the politicians and their expert advisers work this out, we in the work force continue to wonder how we can prevent disruptions in our own environments.

Remote inspection has made giant advances in just the past few months, but it has not yet reached a level where it can take over as the norm. Visual inspection remains a key element of achieving our goals. But as we move towards Pharma 4.0, these developments will clearly continue to evolve. Learn more about this at the "2021 PDA Remote Audits and Inspection Workshop" on 13-14 Sept 2021. While most of you will probably be asleep at the time of the live session, you can catch up with the on-demand option that will be available.

The Asia-Pacific manufacturing infrastructure is not equal. From outdated factories, systems, and practices to state-of-the-art plants, we seem to have it all. What we are missing, though, is a knowledgeable base of inspection experts from the region who talk to each other and can aim to close the gaps. We need a refreshed movement to drive our quality standards up and ensure they remain workable and objective. In order to achieve this, we need volunteers for our committee who will participate in writing or reviewing reports and help create the keys the industry will need to evolve.

Now is very a good time to get active, enroll the younger generation and make a difference…a difference for the region! Please email AsiaPacific@pda.org for more information and let us know how you intend to become active in PDA.

PDA's Volunteer Board of Directors Includes 2 Members from Asia-Pacific

The 2021-2022 PDA Board of Directors is one of the most diverse ever. Besides the first all-female Executive Committee and the first Chair working in Europe, it includes two Directors who work in Asia-Pacific.

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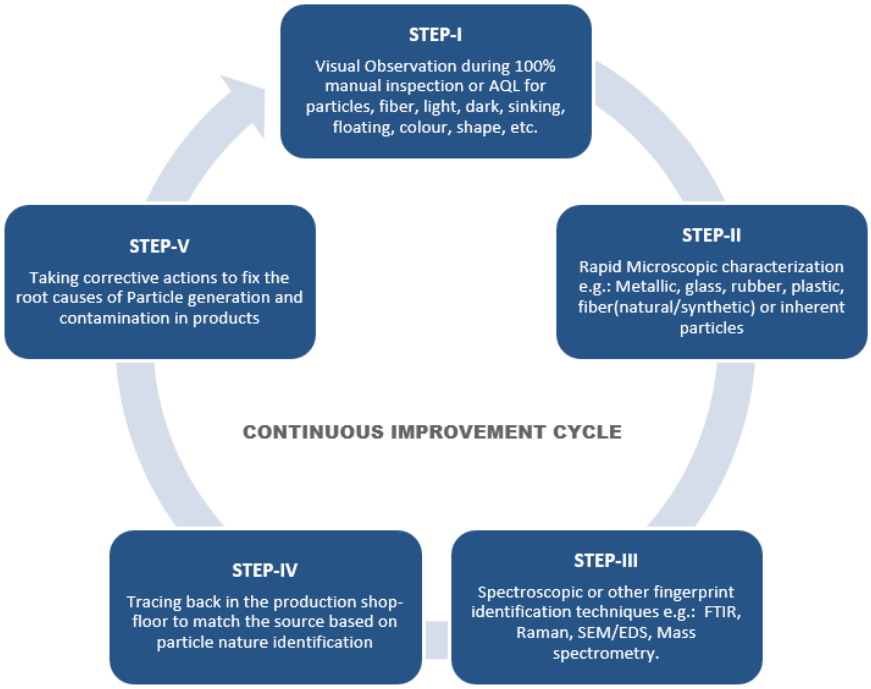

Figure 1 Continuous Improvement Cycle for Visible Particulate-Free Injectable Products

Next, further in-depth analysis of these representative particle samples can be conducted using spectroscopic or other fingerprinting techniques using such technologies as FTIR, Raman or SEM/EDS. This ultimate level of identification provides meaningful information about the nature of the particles. The findings from this level of identification are helpful for scouting the source of the particles in the production area and incoming materials.

Having identified the nature of the particles, the next step is to identify the source. This requires scanning through everything that comes into the vicinity of the aseptic processing area, adeptly collecting particle samples and running a similar characterization test.

The entire program can best be managed by a shop-floor cross-functional team using a predefined protocol that governs the complete process of sampling, testing, investigation, corrective and preventative actions and follow-up. A well-defined frequency of conducting such an exercise helps maintain continued control over potential particulate sources and improves on the process. Special attention should be paid if any atypical particles or unusual rejection trends are observed during inspection or the subsequent identification process.

Implementing Qualification Criteria

Implementing good testing and qualification criteria, with respect to the particle-shredding characteristic of each material, component and equipment part entering into the aseptic processing area, is the key to good particulate control in the products. This entails constant collaboration and benchmarking with the suppliers to build and maintain the quality of all input materials by setting mutually agreeable specifications. Choosing the right fit-for-purpose materials or components and assigning a usage life to each of them is an important part of this control strategy. A change in any of the materials, components, equipment or parts—however trivial it might look—must meet those qualification criteria to avoid later consequences.

A thorough understanding of the failure mode that results in particle generation and contamination in injectable products is like winning the half-battle toward the zero-particulate goal. Setting up a continuous improvement program and controlling variability by the qualification and standardization of all materials, components and equipment parts can help get one step closer to this challenging goal. Constant collaboration and open communication among sterile-product manufacturers, suppliers, and regulatory agencies is an essential element in this endeavor.

It is not a question of whether Zero Particles is a realistic goal, but it is desirable for patient safety and drives continuous process improvement!

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1. U.S. Pharmacopeial Convention. USP <1790> Visual Inspection of Injections. In *USP43–NF38*, p. 8587.
2. Shabushnig, J G. The Changing Visual Inspection Regulatory Environment. Presented at 2021 PDA Visual Inspection Forum, 14-15 April, 2021.

Other Reading

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About the Author

Subrata Chakraborty leads the GxPFONT Consulting Group as Principal Advisor and has over 24 years of experience in handling pharmaceutical manufacturing and quality operations in various capacities with expertise in aseptic technology. He also volunteers for the *PDA Letter* Editorial Committee for the Asia-Pacific region.

PDA Parenteral Drug Association

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My Journey to Japan — Sort Of

Marilyn L. Foster, PDA

Almost four years in the making, the final guidance document from the PDA Japan Chapter is well worth the wait. *Environmental Control and Maintenance in the Manufacturing of Non-Sterile Drug Products: Kansai Study Group (KSG) of the PDA Japan Chapter* was added to the PDA Bookstore on 24 June, the culmination of a journey that began in July 2017.

My first introduction to the topic came from former PDA VP for Scientific and Regulatory Affairs and current *PDA JPST* Editor **Richard Levy**, PhD, when he asked me to work with **Keisuke Inoue,** Takeda, and **Osamu Shirokizawa,** Lifescientia, to prepare an article for the Journal reviewing the 90-page document and its background. A series of back-and-forth emails ensued, as I stumbled through the linguistics involved in understanding the different meanings of technical terms and concepts in the Japanese English version of the article. One instance really caught me up short when I saw the diagram for the entrance and exit paths of the dressing and *undressing* rooms.

In the process, I learned that in many Japanese pharma manufacturing facilities, the technicians are provided with uniforms to wear, rather than coverings over their street clothes; hence, the separate dressing/undressing rooms for men and women. I discovered more about the development of the guidance document that formed the basis for the Journal article when I viewed the poster Inoue and Shirokizawa presented at the "12th Annual PDA Global Conference on Pharmaceutical Microbiology" in October 2017. Their exhibition was very enlightening and meeting the gentlemen from Japan in person was a real treat. Finally, the faces behind the emails!

The opportunity proved valuable to Inoue and Shirokizawa as well; in addition to attending the conference, they toured the then-new TRI training center. Shirokizawa wrote: "We received a lot of visitors to our poster throughout the sessions. We had insightful discussion with them.***[At TRI] We saw PDA has been providing a variety of training to learn about many key features of aseptic processing. We know how effective and important hands-on training is to any trainee."

The sojourn through the manuscript submission process, needless to say, was a lengthy one. We tapped into the PDA membership to find reviewers knowledgeable about the subject. The first round of reviewers commented that it was difficult to make a decision about a paper based on a document they couldn't see. While the full guidance document had been translated to English, the initial version needed additional editing to convert some of the terms to their American English equivalents. And I became a translator.

Over the years of sending sections of my "translations" for the JPDA team to accept, reject or amend, we began a respectful business friendship: Shirokizawa and Inoue became the more informal Osamu-san and Keisuke-san. We learned a little about one another's lives, cultures and perspectives. Osamu volunteered to work on the TR 29 revision team and experienced the global collaborative effort of developing technical reports. He was later voted to join the PDA Board of Directors.

Osamu served as the primary contact between the PDA Publishing Group and the KSG, who provided feedback on all of the translated sections. I was humbled by the experience of knowing so many top business leaders took the time to read my many, sometimes minute, comments and changes in their valuable document. They truly valued the opportunity to share all they had learned through the original survey they conducted of pharmaceutical manufacturers in Japan and the best practices they had developed as a result.

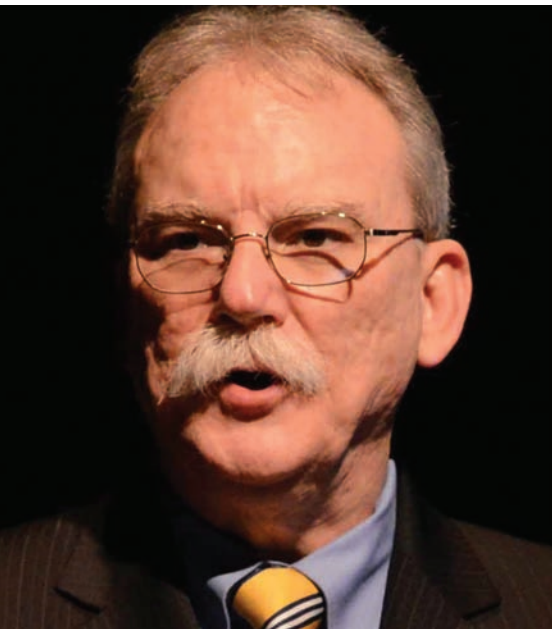
In October 2019, Osamu stopped over on a business trip to meet again with **Walter Morris,** PDA Sr. Director, Publishing &

Press Relations**,** and me at PDA's Bethesda office. We spent some time going over the plans and timelines for converting the chapters of the guidance document and checking on the progress of the Journal article. It was a great opportunity to juggle what we said and how they understood it and vice versa. (This was when I learned about the dressing rooms.)

The time between now and then comprised numerous rounds of editing, commenting, revising, proofreading, and correcting on both sides of the world and the strings of emails that bridged the globe. A global pandemic interrupted the process and slowed down everything it didn't stop immediately. And, at last, this production led to the final typesetting and publishing of, in my humble and completely unbiased opinion, both masterpieces.

To make a long story short, the final JPDA article, "Overview of 'The Study in Risk-based Manufacturing Environmental Control for Non-sterile Drug Products' by Osamu Shirokizawa, Keisuke Inoue and Tsutomu Kamikukita, was published as an Accepted Article on the *PDA JPST* website on 14 May 2021. And the English translation of the *Environmental Control and Maintenance in the Manufacturing of Non-Sterile Drug Products: Kansai Study Group (KSG) of the PDA Japan Chapter* was made available in the PDA Bookstore on 24 Jun 2021.

I hope sometime to visit our associates in Japan to see what else I can learn of their culture. In the meantime, pick up a copy of their guidance for yourself or your company. I am sure you will find some valuable and practical advice!



Richard Johnson, PDA President

PDA Mid-Year Update

Richard Johnson, PDA

Since early 2020, the entire world has been in the grips of a global pandemic. As of 4 June 2021, over 170 million cases of COVID-19 have been reported, with more than 3.7 million deaths. Each of us, directly or indirectly, has been impacted by this pandemic or its effects.

On a positive note, more than two billion doses of vaccine have been administered worldwide, largely through the efforts of our community, which has developed, manufactured and distributed vaccines with unprecedented speed. In some parts of the world, we are seeing a gradual return to "normalcy," but unfortunately, in other parts of the world, the pandemic is still raging, and vaccine administration has not yet reached desirable levels.

We understand some volunteers may be concerned how PDA is weathering the pandemic.

Since March of last year, our staff has been working mostly from home. We have had to shift many of our activities from in-person to virtual formats. This has been challenging and has affected our finances.

PDA is financially very sound, and through diligent management, PDA still has more than 12 months of reserves, despite the decrease in revenue through 2021.

We have had to react to the changing situations and, although we had hoped to begin face-to-face meetings in Q-2/3, for most of 2021, our conferences will be virtual.

Training, Membership and Publications revenue is starting to recover.

We have not laid off any employees due to the pandemic, but we have not filled some vacancies. We are gradually starting to fill some of these positions.

Our Board of Directors, Advisory Boards, Committees and Task Forces are all meeting virtually. Thank you to all the volunteers who continue to contribute!

These are challenging times for the whole world, including PDA. This year, PDA is celebrating its 75th anniversary. With your continued support and participation, PDA will continue to *Connect People, Science and Regulation*® for many years to come.