# VALIDATION 4.0:
## Case Studies for Oral Solid Dose Manufacturing

By Brad Swarbrick and David Margetts

Three case studies on Validation 4.0 demonstrate how quality by design (QbD) principles, when applied with digitization, can verify processes in scale-up and technology transfer, and why blend and content uniformity matter for tablet integrity.

This article provides background on Validation 4.0 and presents case studies on applying Validation 4.0 in oral solid dose (OSD) manufacture. The ISPE Validation 4.0 Special Interest Group (SIG), part of ISPE's Pharma 4.0™ initiative, has written on the issue of Validation 4.0 previously in this magazine, first in "The History & Future of Validation" to provide history and overview of validation in the pharmaceutical industry and a definition of continued process verification and continuous process verification [1]. The group also published "Laying the Foundation for Validation 4.0" [2], discussing how the topic of validation has been "a central obstacle to adopting new concepts for quality," and has indirectly slowed the uptake of the very technologies that are required to bring pharmaceutical manufacturing into Industry 4.0.

## HISTORY OF QUALITY BY DESIGN

OSD manufacture is a multifaceted operation consisting of raw materials and unit operations that transform the raw materials into finished product. Traditional approaches to process development and validation involve the manufacture of validation batches to show that the combined unit operations and raw materials produce intermediates and finished products that meet a predefined set of efficacy and performance characteristics.

Major issues in the traditional approach to validation are the lack of information on representative sampling; the difficulty of real-time monitoring and control; and the snapshot, rather than continuous manner, in which validation is performed.

In 2011, the US FDA released an updated process validation guidance document [3] and included the concept of "continued process verification" with routine monitoring of process parameters and trending of data to have a process that is capable of consistently delivering quality product. They referred to ASTM E2500-07 [4], which states that quality by design (QbD) concepts should be applied to ensure that critical aspects are designed into systems during the specification and design process. In this article, there is no distinction between the terms "continued process verification" and "continuous process verification" with regard to US and EU definitions.

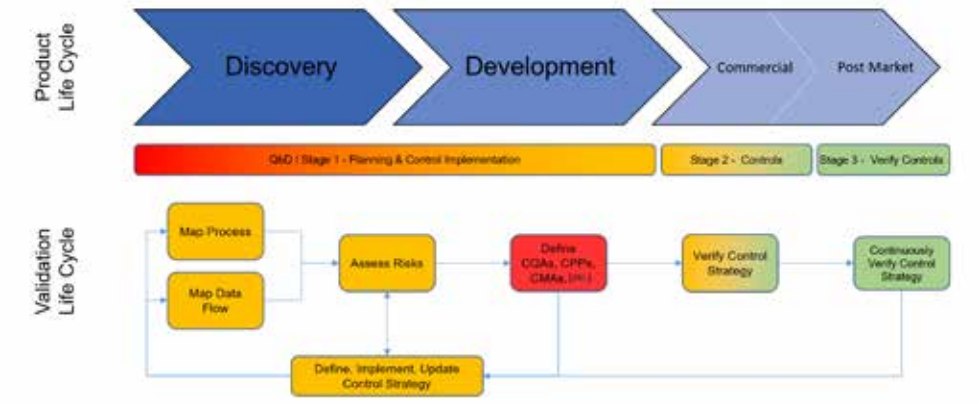
### Industry 4.0 as an Enabler of QbD

To verify the consistency of every batch in a sufficiently timely and accurate fashion, and to cope with inherent variabilities, some level of digitization is required. Information technology is not mandatory for QbD; however, the case studies show the capabilities of modern data systems for effective process understanding and control. Those that are increasingly available and accessible can improve product quality and efficiency and produce better medicines at lower manufacturing cost.

Industry 4.0, as a global manufacturing revolution, relies on collecting and using data in electronic formats to understand and improve process and product performance beyond legacy paper and manual methods [5]. QbD has a similar philosophy and encourages manufacturers to start their validation efforts at product conception so that control strategies are built into the process, by design. This also ensures that when the process is moved, or scaled up to commercial manufacturing, the entire quality strategy is in place. Increasingly, the pharmaceutical industry is looking to digitalization as an enabler of QbD using data from all available sources. The following case studies and the capabilities described in this article are simply not practical without modern measurement sensors and data analysis tools.

In 2004, the US FDA published its process analytical technology (PAT) framework guidance to promote the use of innovative technologies for the collection of timely quality data that ensure the quality of product throughout the entire manufacturing process, from raw material dispensing to packaging [6]. Together a combined QbD/PAT approach provides a solid platform for continuous verification and digitalization, particularly when linked to digital solutions and ways of working such as manufacturing execution systems (MES), supervisory control and data acquisition (SCADA) systems, and industrial databases that allow fast

Figure 1: Stage 3 of the Validation 4.0 model focuses on continuous verification as a targeted result of QbD.




retrieval of data over multiple batches, months, raw materials, and lots. This knowledge management within systems can be used to optimize manufacturing and allow some flexibility within design constraints.

It has been 20 years since the FDA released "Pharmaceutical CGMPs for the 21st Century—A Risk-Based Approach: Final Report" [7], and during that time, improvements in computing, data warehousing, sensor technology, and control systems now provide OSD manufacturers with the digital tools to address the validation requirements associated with continuous verification/validation and to move to Industry 4.0/Pharma 4.0™ and Validation 4.0 with confidence.

## Validation 4.0 Is QbD-Centric

This article is focused on Stage 3 of the Validation 4.0 model (as shown in Figure 1). Verifying controls is done continuously with a frequency dependent on the ability to measure and identify risks from a process and systems perspective. One of the goals of Validation 4.0 is that Stage 2 ultimately absolves by moving directly to a state of continuous verification.

Traditional OSD manufacturing consists of a series of disjointed unit operations that transform raw materials and intermediates into finished products. Such processes are batch processes and transform large, bulk powders via the unit operations. OSD manufacture typically has a number of processes to deal with different raw material properties such as direct compression, roller compaction, and high shear granulation.

No matter which approach is taken, there is a common variable that is commonly overlooked in all three processes: raw materials. Raw materials are typically assessed using pharmacopeia monographs that focus on identification and purity aspects alone. The samples assessed are typically nonrepresentative and do not provide any information on how the materials will perform in the process.

QbD allows a manufacturer to build flexibility into manufacturing processes, rather than keeping the process fixed. If the process is fixed, inherent raw material variability cannot be accommodated by the process. This leads to substandard intermediates that, more often than not, result in issues in compression. Through improved sampling techniques and measurements from the initial stages of manufacturing, better understanding of the raw material variability allows the development of conformity or classification models. And technologies such as near-infrared (NIR) spectroscopy and powder characterization are used to understand the "process-ability" of materials.

In the QbD and Validation 4.0 world, digitalization tools and systems can use this information to adjust the process. Thus, QbD needs to assess all sources of variability, including inputs from outside the manufacturing floor, because variability from suppliers' products can impact regulated customer's processes. The ability to adjust a process is not unlimited and must be bound by certain rules that ensure quality. In QbD terminology, the boundaries around the process are known as the design space. By definition, the design space is established by design, i.e., through timely measurements that are linked to quality, or that are defined as critical quality attributes. The QbD approach has also introduced a new vocabulary associated with modern manufacture. Some of the important terms include the following:

- Quality target product profile (QTPP): Efficacy and performance characteristics that ensure the safety of the end user. Essentially, this defines the target product.
- Critical quality attributes (CQAs): Attributes of the product that ensure it is fit for its intended use when assessed against the QTPP. Essentially, these define the attributes that need to be met to meet the target product.
- Critical process parameters (CPPs): Controllable aspects of the manufacturing process that ensure the CQAs meet their defined targets. Essentially, these define what needs to be controlled so that the attributes will be met.
- Critical material attributes (CMAs): Attributes of the input materials that should be within appropriate limits or distribution to ensure the desired quality of the product.

Based on the previous points, validation becomes product- and



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QbD allows a manufacturer to build flexibility into manufacturing processes, rather than keeping the process fixed.

process-centric through measurement data to maintain manufacturing within the design space, the resulting allowable limits of all the critical attributes and parameters that result in product that meets the QTPP requirements (also known as the desired state).

When a formulation is robust and the raw material characteristics are understood, the process can be adjusted within the design space, resulting in the highest-quality finished product. To fully achieve this and to incorporate it into an industrial production line, digitalization tools and appropriate sensor technology are required.

## AN INTRODUCTION TO CONTINUOUS VERIFICATION

A recent trend in pharmaceutical manufacturing is to move to continuous manufacturing (CM) systems. A CM system is a connected series of unit operations that converts small amounts of raw materials and intermediates at a time in small-scale equipment with much higher control and better sampling opportunities. The small amounts of materials processed at a time are called sub- or micro-batches. The combination of many sub-batches makes up a final batch, which is packed off while the next major batch starts and continues until the process is stopped.

In continuous manufacture, there is reduced opportunity to take physical samples from the process and assess them offline. When samples are removed, traceability becomes a problem, so timely information is required through highly digitized processing equipment and sensor technologies. In a CM system, every sub-batch is monitored and assessed for quality, thus providing a process chronology traceable back to unit doses in some cases. Such systems are not possible without QbD principles, PAT, and digitalization. In these types of systems, a real-time release strategy can be built into the process by design, allowing for materials to pass continuously through all unit operations to packaging and release without laboratory testing.

The principles of CM can also be applied to batch manufacturing operations if due consideration is given to better understanding of raw materials and correct process sampling strategies, based on large N sampling plans. To make large N sampling effective from an economical sense, the nondestructive, inline analysis of CQAs by PAT is required. In many cases, these PAT sensors will be NIR sensors and the data and models have to be taught by generating many spectra of the desired material. So there is a longer development phase when using PAT as a tradeoff to an improved process understanding and higher efficiency commercial production phase.

### QbD and Continuous Verification

The basis for implementing QbD is described through the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidance documents Q8, Q9, and Q10 [8]; how they relate to ASTM [4]; and the US FDA's guidance and GMP priciples [3, 6, 7].

ICH Q8 establishes what is relevant for product development based on QbD principles and defines the concept of design space [9]. The establishment of design space results from consideration of the risks to quality (ICH Q9), and the methodology used in these case studies starts with design of experiments and multivariate data analysis (MVDA) approaches to build predictive models based on available digital information from process equipment and process sensors. The iterative nature between Q8 and Q9 allows risk mitigation and the knowledge obtained is managed by the pharmaceutical quality system (PQS) of ICH Q10 [10].

Extending the concept of the PQS in Validation 4.0 is knowledge management as a repository, where digitized information collected from real-time measurements is used in conjunction with process models. These models were developed during the early-stage development learning/design phases, which ensure the process is operating within the design space and thus producing product in its desired state.

Data systems for QbD aspects of Validation 4.0 include:

- Electronic process definition and control (i.e., integrated manufacturing execution system / electronic batch records for manual operations with underlying industrial internet of things [IIoT], supervisory control and data acquisition systems, or distributed control systems for running automated equipment)
- Industrial databases that collect real-time data, alarms, and events (i.e., data historian)
- PAT knowledge management systems (a useful explanation of PAT systems is provided in *Multivariate Analysis in the Pharmaceutical Industry* [11]).

These systems operate synchronously and are used to detect and correct issues before they become problems and deviations. This is in contrast to the traditional manufacturing process, where correction is usually impossible and rework/quarantine and scrap is usually the result.

Process controls and digitized process equipment, combined with process sensors, assess the health of both the process and the product, as it exists in the process without unnecessary physical sampling. It is important to note that such systems are not about bringing the laboratory to the process, but rather about using the information to detect slight changes in materials and provide flexibility in the process operation. If only quantitative testing is the goal, this is quality by testing (QbT) and defeats the purpose of implementing technology to manage real-time control and assurance of QbD. Quantitative assessments of potency are to be considered side benefits of the QbD approach, not the major driver.

Figure 2 shows how digitized recipe systems, once integrated to process sensors and data that represents the process signature,

allow a complete and continuous assessment of the entire batch, effectively making every batch a validation batch.

## CASE STUDIES FROM OSD MANUFACTURE

The case studies outlined in this article are from oral solid dosage-type production; however, the principles are applicable generally and the objective of this article is to encourage similar approaches and applications across the Pharma and Biopharma industry. The following case studies are from different types of OSD manufacture and are representative for both batch and CM systems. A typical OSD process starts with raw materials, dispensing of raw materials, milling/sieving, blending, compression, coating, and packaging. The operations of granulation (wet or dry) differ with the raw material and are a particle engineering step used to provide the granule properties conducive to uniform blending. Powder blending is one of the least understood of scientific processes and is influenced by many aspects of materials, including their size, shape, density, electrostatic nature, and moisture content. Without a complete understanding of raw material characteristics, process improvement and optimization are very difficult.

Many organizations globally are starting to adopt PAT systems for a number of unit operations, particularly focusing on blend uniformity. When these companies monitor blend uniformity using technologies such as NIR spectroscopy, they are often disappointed with the results obtained. When a process is measured at the microscopic level, the flaws associated with traditional validation approaches are revealed. This may sound surprising and, in many cases, a manufacturer will argue that their product has been manufactured without variability issues for years. A quick review of batch documents, however, tends to reveal a long list of process deviations and reworks, simply because current validation strategies are short term, rather than long term and performance focused.

### Case Study 1

The first case study shows why the blending stage is typically the wrong place to start with PAT for process improvement, because operations have already transformed raw materials into intermediates before blending is performed.

Some raw material suppliers provide active pharmaceutical ingredients (API) that are pre-granulated so that the secondary manufacturer can produce tablets using direct compression batch manufacturing process. During the validation stage of the process, a traditional three-batch approach was used, whereas typically the raw material supplier sends exhibition batches of their material and the manufacturer typically assigns the company's best operators and analytical staff to perform the validation. In this scenario, the validation is already biased.

Problems start to arise soon after process validation is approved, and in one situation, the quality control (QC) laboratory allowed the material to pass based on pharmacopeia identification and purity testing. Process operators noted that the new raw

Figure 2: The relationship between digitized systems enabling Validation 4.0 continuous verification.

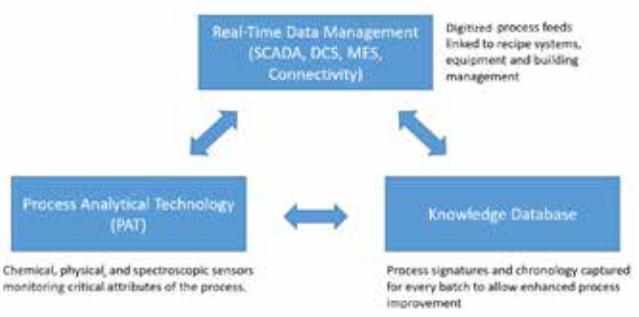
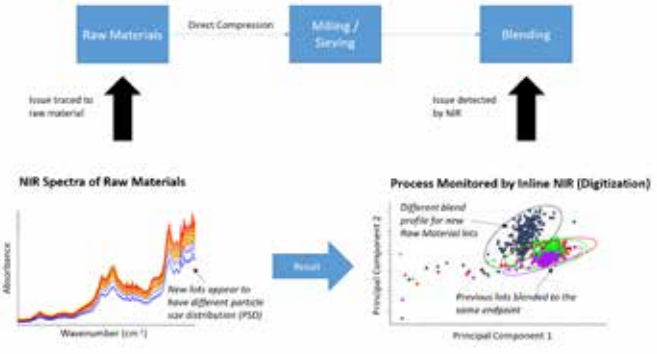



Figure 3: Process investigation to establish the root cause of a major issue in blend uniformity and compression.



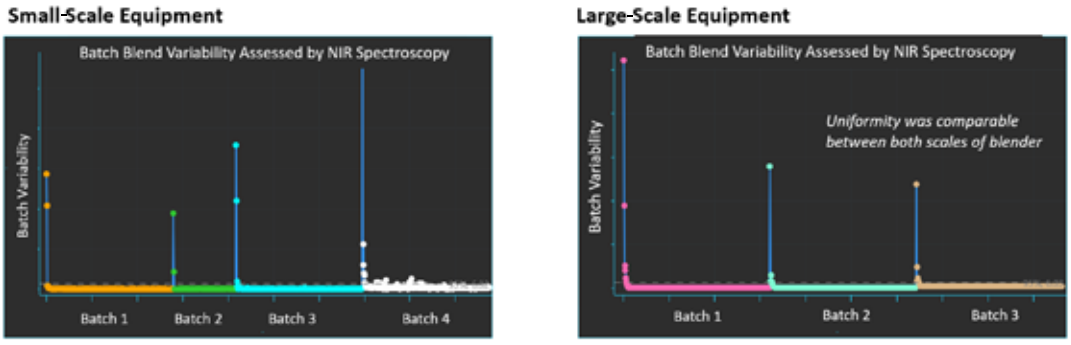

material lots were free-flowing at the top of the bags, but as they started to empty the bottom, heavier screening was required. The company decided to invest in NIR spectroscopy to evaluate the process and to cope with the expected high throughputs of the new product introduction.

The first observation was that the NIR detected a distinct difference in the original raw material lots and the new lots, even though they passed pharmacopeia testing. Figure 3 summarizes the findings of an extensive process investigation.

Using a combined NIR spectroscopic/chemometrics approach, deviations from the expected process signature were observed. When these issues were traced back to the raw materials, it was found that the particle size distribution (PSD) of the new lots was inconsistent. NIR spectroscopy is capable of detecting median particle size changes and this inconsistency resulted in more fines, based on lots that were not blended properly that had uniformity and compression issues.

As stated previously, granulation is the process of engineering particles to tight PSDs so that they are matched to the other material, allowing uniformity in blending. This is not homogeneity because a homogeneous material is perfectly mixed and is an impossible state in reality. Better terminology is heterogeneity minimization, which is more appropriate for pharmaceutical

Figure 4: Process scale-up between two commercial-scale blenders using a QbD/PAT approach.




blending operations. This example highlights the need to understand the raw material as the first stage of OSD manufacturing process validation and shows how technology can measure changes in raw materials and the characteristics of intermediates. Technologies such as NIR spectroscopy, inline particle sizers, and other sensors working in combination can be used to develop process models that assess data in real time and allow feed-forward process control.

## Case Study 2

A second case study focuses on the scale-up of a blending process from one commercial manufacturing batch size to a large batch size. The intermediate bulk container (IBC) geometry is similar between the two blenders, with one offset at 15 degrees and the other at 30 degrees off axis. Because the smaller scale process is considered validated, it can serve as a baseline when comparing the results to the larger blender.

Inline NIR spectroscopy was used for the evaluation and the results are summarized in Figure 4. The blend is a high-dose API formulation and can be monitored for uniformity using inline NIR spectroscopy. A spectrum is collected after each rotation of the blender and as the heterogeneity minimizes, spectra collected will begin to look consistent with each other. Statistical methods can then be applied to the data, resulting in the blend curves shown in the figure. In all cases, the endpoint was established rapidly compared to the endpoint established by traditional validation approaches.

The results in Figure 4 highlight the principles of Validation 4.0 continuous verification and why digitalization is such an important enabling tool for QbD. However, this does not negate the need for the application of suitable processing engineering mechanisms. In the preceding example, blend uniformity can be established without physically sampling the powder bed, whereas the traditional validation approach used sample thieves to extract nonrepresentative specimens from spatial locations. Not only is it impossible to representatively sample a three-dimensional lot, but the sampling errors induced by using a sampling thief contained 10 to 50 times the errors in the analytical instrumentation used to determine potency. We found that the traditional validation approach required 10 to 20 times longer blending of the product, which can induce demixing and reduction in particle size of softer materials.

This is one of the main reasons the US FDA has questioned USP <905> (Uniformity of Dosage Units) [13] as a method for establishing blend and content uniformity. The shearing and electrostatic forces induced by physical sampling devices can destroy blend uniformity and provide false information on true blend endpoints. The NIR spectra provide digital information in real time of the state of powder mixing and the process can be stopped when the desired state has been reached. This is an outcome of the philosophy of PAT that must be translated to Validation 4.0, i.e., processes are ready when they are ready. Fixed-time processing is not in alignment with QbD or Validation 4.0 and technology must be used to continuously verify when the desired state has been achieved.

In one example, a manufacturer wanted to validate the NIR method against physical aliquots extracted from the blender using a spatial sampling plan. After extraction of the aliquots, the blender was restarted and the NIR spectrometer indicated that the entire uniformity of the blend was lost. Uniformity was reestablished after 60 further rotations and the original blended state was not reached. Again, digitalization and no physical sampling were able to establish the correct endpoint of the process and using PAT, a continuous verification strategy was established.

## Case Study 3

In tablet compression, each tablet produced is a 100% statistically representative sample. The sample delivery of powder to the feed frame of a compression machine resembles the most accurate sampling device currently available: A spinning riffler. A rotary compression machine can be visualized as a compacting spinning riffler and therefore analysis of single tablets is a true representation of blend and content uniformity.

Because blending does not stop until compression, an opportunity exists for manufacturers to monitor uniformity in real time at the feed frame of a tablet press. In this case study, a NIR spectrometer is located on the spider wheel and is used to ensure representative sampling, and the NIR spectrometer can measure

Figure 5: Control chart of a tablet compression run monitored by NIR spectroscopy.




content uniformity in real time and report the data in control charts. When only random variations around a target value are observed, this can be used to establish that the blend has retained its integrity during transfer and that the content uniformity is confirmed.

The 100% measurement of individual tablets is practically not possible; however, due to the representative nature of the sample in the feed frame, pseudo 100% verification of blend and content uniformity is established. This is an example of the true nature of the scientific, risk-based approach outlined in "Pharmaceutical CGMPs for the 21st Century—A Risk-Based Approach: Final Report" [7].

The European Medicines Agency has published a "Use of Near Infrared Spectroscopy (NIRS) by the Pharmaceutical Industry and the Data Requirements for New Submissions and Variations" [12], which allows PAT applications to produce trend data for quantitative

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analyses. In this example, the NIR results represent uniformity of blend, then by measuring at the feed frame, content uniformity can be established through consistency in control charting.

The first step of monitoring at the feed frame uses digitalization to establish uniformity. The second step is a traditional approach where tablets are collected at uniform time periods over the compression run and assayed using the reference laboratory method. Because the samples obtained are representative, the first validation batch can be comparative and subsequent validation and continuous verification batches can all be monitored by inline PAT methods. Figure 5 shows the results obtained from two IBC bins run on a compression machine and assessed by inline PAT. The Y-axis can be a predicted value using a validated chemometrics model or a specific and selective wavelength that corresponds to changes in API or other important components. As is typical, during changeover of IBC blenders and tablet press startup, deviations can be observed in the control charts. Such tablets can be rejected off the line until uniformity is established and then tablets can be collected for coating or packaging.

## CONCLUSION

The world is rapidly becoming fully digitized, and concepts like the IIoT and Industry 4.0 have led to innovations in rapid data storage and use. Validation 4.0 must leverage these concepts and fit them into established QbD and PAT initiatives currently being adopted by the pharmaceutical industry and related industries.

New PAT instrumentation with smaller footprints and higher sensitivity are constantly being developed; when used correctly, they can allow manufacturers to become innovative and reduce or eliminate the need for physical sampling and offline analysis. This allows industries to apply the principles of Validation 4.0 to control and assure the quality in real time for every batch with an applied knowledge and data-driven intelligence from historical trends. Thus, Validation 4.0 is maintaining a chronological history through data of the entire manufacturing process and when deviations are detected, these finding can be analyzed by methods, either statistical or chemometrics, to establish the root causes of the issues and develop control strategies to minimize the occurrence of such events in the future.

The key takeaway is that the principles of Validation 4.0 are proactive, not reactive. Under the old paradigm, traditional approaches were biased and based on selecting batches with the best raw material, operators, and analysts as a baseline to pass product for release. In Validation 4.0 and a truly QbD system, the use of data models, PAT, and feed-forward/feedback control establishes a process chronology and digital signature for comparison to past and future batches. Therefore, digitization and QbD allows for true validation of every batch.

Please reach out to the Validation 4.0 SIG with your questions and to share your views, thoughts, case studies, and concepts on new methods that will better assure quality in pharmaceutical and biotechnology manufacturing. The Validation 4.0 community welcomes your input.

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# NOVEL DRY DECONTAMINATION METHOD USING

## Gaseous Chlorine Dioxide

By Mark A. Czarneski

Chlorine dioxide has been shown effective in decontaminating various types of chambers and volumes such as rooms, isolators, processing tanks, and entire facilities, but its use to decontaminate compressed gas piping systems has not been documented. This article discusses using dry gaseous chlorine dioxide ($ClO_2$) to decontaminate an oxygen ($O_2$) feed piping system in a pharmaceutical research laboratory and shows that a dry gas can be used to remediate a contaminated piping system.

Bacillus species are Gram-positive, endospore-forming, rod-shaped bacteria found in soil, air, dust, and debris that are quite common in the natural environment. Endospore-forming microorganisms have been found to make up between 5% and 10% of the microflora in a standard cleanroom [1]. Most of these bacteria are considered nonpathogenic and are commonly found in the dust and air of occupied buildings, including cleanrooms. They can enter cleanrooms through poorly filtered air, on clothing, and on incoming materials. Only one endospore is formed per cell and these spores are resistant to heat, cold, radiation, desiccation, and disinfectants, making it difficult to eliminate them from medical and pharmaceutical materials. Because of this, they are a frequent cause of cleanroom contamination.

One option to remove such contamination is to flush the system with a liquid sterilant such as hydrogen peroxide or liquid chlorine dioxide. Both are known to be effective at killing organisms and to kill bacillus spores. Using a liquid sterilant is considered unfavorable because it will introduce moisture into the system; this moisture might linger in the system in dead legs and low areas of piping and can potentially harbor future contaminations. To avoid this, gaseous chlorine dioxide was chosen as the agent because it is a dry gas and can be applied as a dry gas.

### CHLORINE DIOXIDE

Chlorine dioxide has been shown to be effective at eliminating viruses [2], fungi [3], bacteria [4, 5], and spores [6, 7]. It has demonstrated inactivation of various toxins and chemicals such as beta lactam [8], anthrax toxins [9], endotoxins [10], pinworm eggs [11, 12], and bed bugs [13]. Chlorine dioxide has demonstrated bacillus spore log reductions in various applications such as rooms [14, 15], suites of rooms [16], isolators [17, 18], tanks [19], electron microscopes [20], ambulances [21], biological safety cabinets [22], and whole buildings and facilities [23–25]. With all these applications, the question still remains: Can it be used to decontaminate piping systems with multiple drops and/or dead legs?

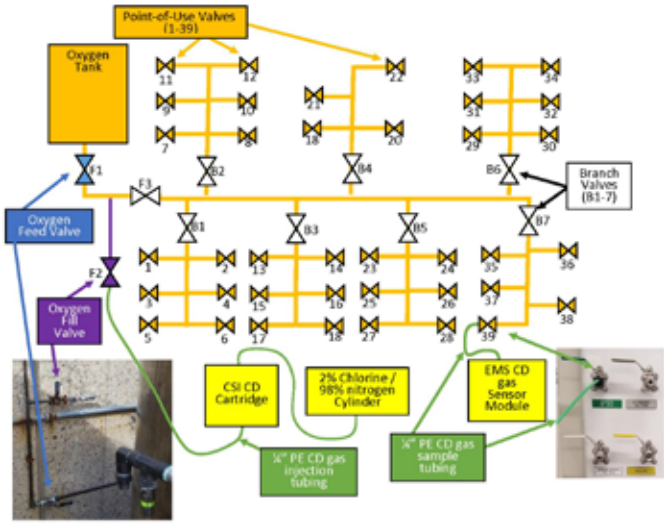
Chlorine dioxide can be generated by various methods and chemical equations. It is not a stable molecule that can be created, bottled, and shipped, so it is typically generated at the point of use. Most chlorine dioxide is generated in solution using acids, sodium chlorite, and water. When it is generated in solution, acidic byproducts that can be aggressive to materials are created. It can also be generated as a dry gas with no byproducts, which allows many materials to be treated with chlorine dioxide with few to no issues.

### CHLORINE DIOXIDE GAS EFFECTS

Chlorine dioxide gas has varying effects on materials. In a study [26], several materials were exposed to two cycles of chlorine dioxide gas under vacuum pressure, with 75% relative humidity (RH) and a dosage of 3,350 parts per million (ppm)-hours. The final dosage after two runs was 6,700 ppm-hours. There was no effect on 18-8 or 316 stainless, black oxide, or zinc-plated steel; Buna-N, SBR Black, EPDM, or Viton rubber; PFA, PLGA, PVA, PGA, or liquid crystal polymers; aluminum or zirconium oxide; ETFE or FEP plastic; or vinyl or oil-resistant vinyl (black). There was no effect on aluminum, brass, cellulose ester, copper, epichlorohydrin, gold, Hypalon, magnesium, neoprene, nickel, Nitinol, nylon 6/6, polyglycolides, polyacetals, polylactides, polyester, polyimides, polyketones, polyurethane, Santoprene, silica, or silicone.

There were color changes to butyl, cellulose, cellulose acetate butyrate, fiberglass, latex, natural gum rubber, polyacrylates, and PVF. The following showed color changes and signs of physical

Figure 1: Oxygen piping system decontamination connections.




changes such as oxidation and pitting: bronze, galvanized malleable iron, nickel-copper, silver, and titanium. The material most adversely affected by chlorine dioxide was sorbothane, which demonstrated some disintegration and became very sticky and gummy after the final dosage [26].

## DECONTAMINATING A SYSTEM

An oxygen piping system was found to be contaminated with a bacillus strain of organisms at several point-of-service locations, thus requiring decontamination. The oxygen system was fed by an outside tank that feeds 39 points of service stations inside the laboratory. To decontaminate the oxygen system, gaseous chlorine dioxide was injected into the system at high concentrations, > 22 mg/L, and held for 30 minutes. The system was then flushed with oxygen gas to purge the chlorine dioxide gas. The process was successful, as determined by post-exposure swabbing that was found negative for any biological contaminates.

The chlorine dioxide gas generation process used for this process passes a low-level dilute chlorine gas (2% chlorine/98% nitrogen) over solid sodium chlorite, which yields pure chlorine dioxide gas. An additional benefit of chlorine dioxide gas is that it has a color, which allows it to be measured by a photometric device that analyzes certain wavelengths and measures absorbance. This absorbance can then be used to calculate the concentration (mg/L). This allows the process to be tightly controlled and very repeatable.

The typical chlorine dioxide gas decontamination process for spaces is to humidify the target chamber to 65% RH and hold this for a conditioning time. Once that is complete, chlorine dioxide gas is injected in the charging step to reach the target concentration. The typical concentration for rooms is 1 mg/L and for small chambers, such as isolators, it is 5 mg/L. This concentration then sits in exposure until a dosage of 720 ppm-hours is achieved for normal space decontaminations. For example, 1 mg/L for 2 hours of exposure accumulates a dosage of 720 ppm-hours.

1 mg/L ≈ 360 ppm
360 ppm × 2 hrs = 720 ppm-hours

Dosage is the accumulation of concentration over time and with chlorine dioxide gas it is referred to as ppm-hours. Studies have shown that a dosage of 720 ppm-hours at varying concentrations (0.3, 0.5, 1, 5, 10, and 20 mg/L) demonstrated a 6-log reduction of spores [27]. This dosage or contact time, concentration accumulated over time, is based on the conditioning step at 65% RH. Humidity helps condition the spore walls and helps the sterilant achieve its effect [28, 29]. In this application, RH or moisture can be an issue, so it was decided to forgo the RH injection or conditioning step. If steam was injected into the piping system at room temperatures (21°C), condensation would form and introduce unwanted moisture into the system. Previous studies have shown that high concentrations or dosages can achieve log reductions with low RH of 30%-40% [30]. In this study, it was found that a 3,000 ppm-hour dosage achieved a 6-log reduction of spores. The dosage was calculated from the cycle with a chlorine dioxide gas concentration of 100 mg/L for 5-minute exposure.

1 mg/L ≈ 360 ppm
100 mg/L ≈ 36,000 ppm
(36,000 ppm) × (5 min/60 min/hours) = 3,000 ppm-hours

Using this as a criterion, a minimum target dosage of 3,600 ppm-hours was determined for this application. Before arriving onsite to perform the decontamination, it was critical to identify each and every drop or point-of-service location. If any location is missed, then the decontamination might not be successful and the contamination will continue to linger.

## MATERIALS AND METHODS

The following materials were used for the study:

- 1 chlorine dioxide gas generator
- 1 CSI chlorine dioxide cartridge
- 1 gas cylinder (2% chlorine/98% nitrogen) with CGA 660 valve
- 2 EMS chlorine dioxide gas sensors on carts
- 6 rolls ¼-inch polyethylene tubing (green)
- 2 ATI PortaSens II low-level sensors, 0–5 ppm
- 2 BSC scrubbers with hoses
- 2 ladders
- Piping distribution system with 39 points of service

The oxygen system is supplied by a 304 stainless steel tank outside the building. The oxygen tank supplies the gas to a 304 stainless steel regulator that reduces the pressure to the operating pressure (50 PSI). This regulator then feeds a copper trunk line, which is made up of 1-inch piping with seven branches that go off to service various stations in the laboratory (see Figure 1).

Each branch has a bronze ball valve (B1–7) to isolate it if necessary repairs/additions are located in a service area. Each point-of-use valve was a 304 stainless steel ball valve located inside the lab. Upon arrival to the site, the first step was to ensure all the point-of-service valves were closed with tubing fittings installed, oxygen feed valve (F1) was closed (to isolate the oxygen tank), and each branch valve was opened. The oxygen tank was not part of the decontamination plan. Once the valve states were verified, the chlorine dioxide gas generator was connected to the system at the oxygen fill valve (F2).

Once chlorine dioxide gas injection connection was made, the oxygen isolation fill valve (F3) was opened to inject CD gas into the trunk. The objective was to fill the trunk with high concentrations of chlorine dioxide gas and then get the gas to each point-of-service valve. To do this, a tube was connected to V39 and bought to the EMS CD gas sensor (see Figures 2 and 3).

After the tube was connected, the valve was opened. V39 is on branch 7 and is the valve the farthest on that branch and farthest from the chlorine dioxide gas injection.

By opening this valve first, the trunk line was filled with high concentrations of chlorine dioxide gas (≈ 100 mg/L). Once the reading at the valve was > 22 mg/L the valve was closed and the next valve was opened (V38). The maximum reading of the chlorine dioxide gas sensor was 22 mg/L, At this point, a second team started the same process by opening (V6), which is the farthest point-of-use valve on branch 1 (B1). Once V6 reached concentration (> 22 mg/L) the valve was closed and V5 was opened. This process was repeated until all point-of-service valves were opened and concentrations measured, and then the vales were closed. After closing the valves, the gas was allowed to sit or expose to achieve the desired kill.

To achieve a target of 3,600 ppm-hours, the exposure time needs to be:
22 mg/L × 360 = 7,920 ppm
(3,600 ppm-hours/7,920 ppm) × 60 min/hour = 27 minutes

Based on this calculation, the target exposure time was set for 30 minutes. After a minimum of 30 minutes of exposure, the oxygen fill valve/gas injection valve (F2) was closed and the oxygen feed valve (F1) was opened. At this time, the tubing from V39 was brought to an exhaust point and the valve was opened. Figure 4 shows multiple point-of-use tubing running to an exhausting biological safety cabinet to remove the chlorine dioxide gas from the piping. Tubing (green) from each point of use was brought to exhausting biological safety cabinets, fume hoods, exhaust point, or scrubbers—this depended on whichever was closest to the point of use valve.

The concentration was then measured using the ATI PortaSens II low-level chlorine dioxide sensor at the tubing exit (see Figure 5). Once the concentration was measured as 0.0 ppm, the line was considered purged and the valve closed and tubing removed, the valve was closed, and the next valve (V38) was opened until the concentrations were at 0.0 ppm.

**Figure 2:** Connection point and tubing from the point-of-use valve.

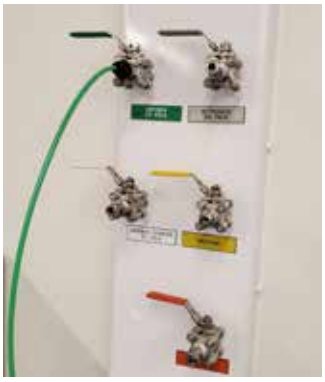


**Figure 3:** Connection points for EMS sensor.




**Figure 4:** Removing CD gas from the piping.



**Figure 5:** ATI PortaSens II aeration measurement.



At this point, the second team brought the tube connected from the point-of-service valve (V6) to an exhaust point, then opened the valve and measured the concentration until the reading was 0.0 ppm. After this the valve was closed and the team moved to the next (V5). This process continued with both teams, until all valves were verified to be completely aerated and measured 0.0 ppm. After this was completed, the chlorine dioxide gas generator and all equipment were removed and packed up, and the facility was exited. The entire process of setup, (connections made; valves opened/closed as needed; chlorine dioxide gas injected, exposed, and gas aerated/removed; and disconnections) took approximately 8 hours.

## RESULTS

After the decontamination event was completed, follow-up testing demonstrated the process was successful in eliminating the contamination issue. All swabs taken from several locations showed no growth for any bacillus species. The dosage of each point-of-use valve was calculated by noting the time the concentration was > 22 mg/L and when the concentration was down to 0.0 ppm. This determined the number of minutes that the concentration was exposed at the point-of-use valve. The dosage was calculated using the following equation.

$$\text{Dosage (ppm-hours)} = 360\ \text{ppm} \times 22\ \text{mg/L} \times (\text{number of minutes}/60)$$

The actual minimum dosage in the system was measured/calculated at 6,106 ppm-hours in branch 4. The maximum dosage achieved was 31,723 ppm-hours in branch 1. Branch 1 had the highest dose because this was one of the first sections that chlorine dioxide gas was injected into. Branch 4 was the last section to inject chlorine dioxide gas so it had the lowest overall dosage. No corrosion was noted on any parts immediately after the decontamination or a few weeks later.

## DISCUSSION

There was significant variation of dosages within the system. The lowest dosage was 6,106 ppm-hours, whereas the highest dosage was 31,723 ppm-hours. The low dose of 6,106 ppm-hours was much larger than the target dosage of 3,600 ppm-hours. This was easily attributed to lunch (longer than expected). All the gas lines were filled with chlorine dioxide gas and then allowed to sit for minimum of 30 minutes. At this time, lunch was taken and was a little longer than 30 minutes, which accounted for the extra dosage. The large dosage of 31,723 ppm-hours was attributed to it being the line that had the gas in it the longest. This was measured in V6 of branch 1. In this application with the materials used, no corrosion was noted on any parts either immediately or few weeks later after the decontamination. The concentrations in the piping were measured at 22 mg/L.

As noted previously, this was the maximum reading for the EMS chlorine dioxide gas sensor. The actual generation concentration is known to be 100 mg/L, so it can be assumed to be 100 mg/L in the lines. To be conservative, the maximum reading (22 mg/L) was used for all calculations and all assumptions. Additionally, during the purging, several point-of-use valves were opened at the same time. When doing this, the pressure in the system dropped. This necessitated a maximum of four to five point-of-service valves to be opened at any one time to maintain pressure in the system. This was also a contributing factor to the higher dosages in the system. The oxygen supply tank was not part of the decontamination process. It was determined that this was not the source of the contamination, so decontamination of this equipment was deemed not necessary. The oxygen purge to remove the chlorine dioxide gas was the final step of the process.

No follow-up cleanings were done because little to no residues were expected with a dry gas. Studies have shown no detectable residues (chlorine dioxide, chlorite, or chlorate) on potatoes (high organic load) with chlorine dioxide in the gaseous phase [31]. Chlorine dioxide gas does not condense on surfaces and is maintained as a gas through the whole process and as such residues are not expected on hard, nonporous surfaces like a piping system. Little organic load was expected in the process for residues to form, as would be expected with potatoes in the reference given previously.

## CONCLUSION

The decontamination service of oxygen piping was successful, as the target dosage of 3,600 ppm-hours was exceeded. More important, it was successful in that there were no follow-up positive swabs for any bacillus strain of organism. The lowest dosage achieved was 6,106 ppm-hours and the maximum dosage achieved was 31,723 ppm-hours. This lowest dosage is 1.7 times the target of 3,600 ppm-hours and 8.5 times greater than the normal dosage to achieve a 6-log reduction (720 ppm-hours). It has been demonstrated that a dry gas can be used to remediate a contaminated piping system.

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