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# PACKAGING TRENDS



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# Packaging Delivers

By Steven E. Kuehn, Editor in Chief

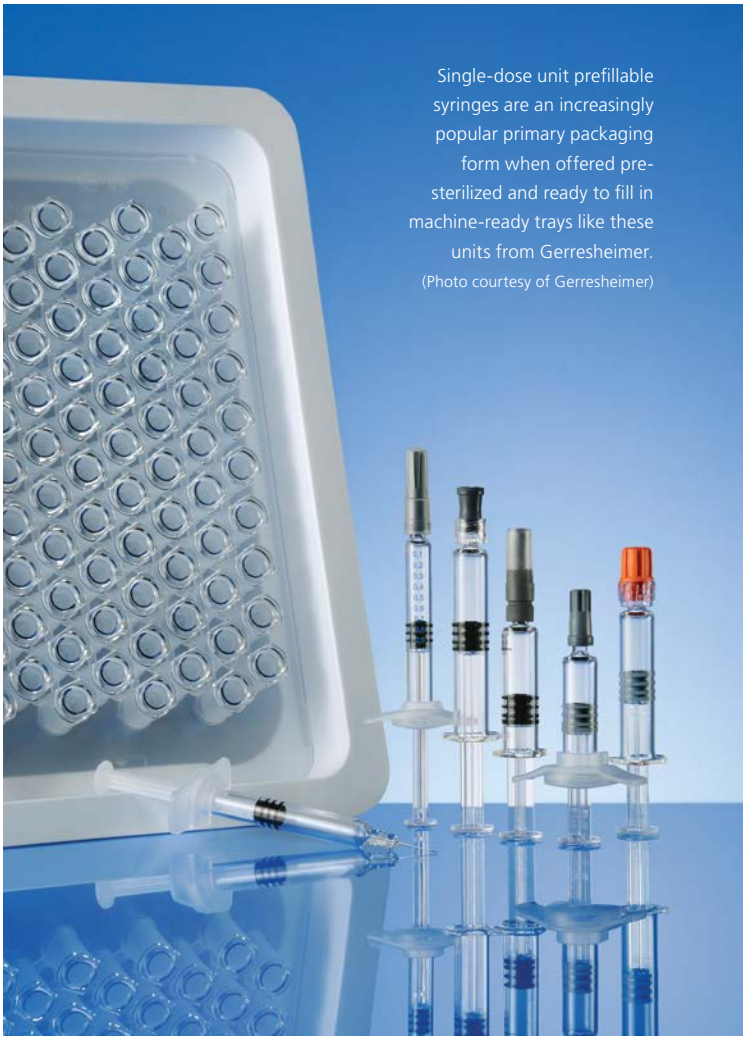
**IT'S HARD** to understate the critical role pharmaceutical packaging plays in ensuring the efficient distribution and eventually, the safe consumption of the world's drug supply. Much of where the category is today (and all that it brings to Pharma) stems from an amazing confluence of operational and technological wisdom gained from years and years of applicational experience across all sectors of the industrial landscape.

Seriously essential, packaging has always delivered, but in 2015 it's being asked to deliver even more to meet Pharma's ever-expanding demand for packaging solutions. From the materials and science associated with primary packaging, to the increasing sophistication and integration of drug delivery platforms and single-dose-unit forms, packaging is playing an increasingly integral role supporting the medical success of a given compound.

World pharmaceutical packaging demand, says The Freedonia Group, will increase 6.4 percent annually to $90 billion in 2017. According to Freedonia's "World Pharmaceutical Packaging" report, "Based on the operation of extensive and diverse drug-producing industries, Western Europe, the U.S. and Japan will account for nearly 60 percent of this amount." Not surprisingly, the report notes countries like India and China will experience the fastest product demand growth from "rapidly expanding pharmaceutical manufacturing capabilities, burgeoning drug exports, and the phasing-in of an extensive government program designed to upgrade the quality and integrity of nationally produced medicines." Who's coming up the fastest? Brazil, Mexico and Turkey were identified as fast-growing pharmaceutical packaging product markets.

**For Pharma, what's on the outside counts as much as what's on the inside**

As per usual, the U.S. will remain the largest market for pharmaceutical packaging "as its advanced drug-producing sector introduces new, sophisticated therapies with specialized packaging needs." Freedonia notes growth in West European demand will reflect government standards requiring unit-dose, high-barrier and security packaging for many types of medications. Japan, says the report, will also continue to provide a large, diverse market for pharmaceutical packaging.



Single-dose unit prefillable syringes are an increasingly popular primary packaging form when offered pre-sterilized and ready to fill in machine-ready trays like these units from Gerresheimer. (Photo courtesy of Gerresheimer)

### FAST GROWTH PREDICTED FOR PREFILLABLE SYRINGES

Global demand for primary pharmaceutical containers, says Freedonia's analysts, will increase 6.6 percent annually to over $57 billion in 2017. Prefillable syringes, notes the report, will be in high demand, and the list of suppliers and vendors pursuing the potential revenue from this category are becoming legion; Becton Dickinson, Gerresheimer, SCHOTT, Vetter and West (to name just a few top players) are all positioning themselves strategically and operationally to deliver solutions to meet this burgeoning demand.

Demand for prefillable, injectable, single unit dose forms is being driven by a number of factors but Freedonia and others point out the advances in the biotechnology sector will mean a steady stream of parenteral therapies requiring prefillable solutions to deliver these therapies to consumers. West Pharmaceutical Packaging Systems' Mike Schaefers notes his company is seeing growing demand from customers for pure, high-quality packaging components for injectable biologics and biosimilars. "Many biotech and sensitive drug products have unique requirements, and polymer systems provide key solutions for patient safety and compliance," says Schaefers. "There are a variety of products on the market that can help mitigate these risks, including barrier films for elastomer components that help to reduce potential extractables and leachables formation," he says, but "for materials that are sensitive to glass, cyclic olefin polymers can be molded into a variety of shapes and sizes to accommodate not only the drug product, but also large-volume doses. In addition, cyclic olefins can be molded to suit innovative delivery devices, offering differentiation in the market." Ultimately, says Freedonia, that megatrend will also fuel "above average growth" in demand for parenteral vials and ampoules because the category will increase demand for those vessels as well.

### MESSAGE IN THE BOTTLE

Despite increasing competition from highly engineered, unit-dose and prefillable solutions, plastic bottles will "remain the most widely used package globally for oral drugs distributed in bulk," notes Freedonia's report. Plastic bottle's penetration into Over-the-Counter (OTC) packaging will continue because many OTC medicines are sold in oral solid dose forms and in quantities of 50 or more.

Blister packaging is a rising star and Freedonia's study confirms this. Blister packaging of single doses are at the forefront of how Pharma is responding to the market and regulator's demand to improve dose compliance and therefore safety — not to mention the overall efficacy and improved outcomes of therapies administered this way. "Blister packs are becoming more popular as they can improve patient compliance and can be customized to fit a product design due to the availability of a broad range of materials and multiple configuration options," notes Gordon Haines, Rottendorf Pharmaceuticals' CEO. Rottendorf packages more than 3 billion tablets, capsules and pills a year on nine blister lines and two bottle lines. "Blister packs also protect product integrity,

West's SmartDose system is an excellent example of how West collaborates with biotech companies to offer fully integrated drug delivery systems designed to meet patient needs.

(Photo courtesy of West)

allowing patients to select one pill at a time while leaving the others untouched," says Haines, "as opposed to bottles where a patient might dump out a handful of pills in order to select just one."

Freedonia's report says it has become the second-largest selling group of primary pharmaceutical containers "and will generate above average growth in demand based on adaptability to unit dose and clinical trial formats with expanded label content, high visibility, and built-in track and trace features."

Tee Noland, CEO of Pharma Tech Industries (annual sales ~$80 million) notes customers are looking for innovation from a cost and quality perspective. "We are … seeing a lot of interest in unique delivery systems as line extensions, says Noland, "and more emphasis on single-dose forms from a portability and ease-of-use perspective." Noland also notes his customers are showing more interest in vertically integrating production points like packaging, manufacturing and molding, as well as onsite testing.

Prefillable inhaler's stock is rising, too. Due to the increasing number of patients diagnosed with COPD, chronic asthma, and allergy related respiratory symptoms, Pharma's introducing and regulators are approving new inhalable therapies at a pretty good pace. Further, some of these medications are going off-patent and Generic Pharma will not be ignoring the potential in this category any time soon.

West Pharmaceutical Delivery Systems' vice president Graham Reynolds illuminates how Pharma, and more importantly consumers, are pushing for increasingly sophisticated delivery modalities. "Historically," says Reynolds, "the primary focus of pharmaceutical manufacturers has, appropriately, been on the efficacy and safety of their drug product. However, with more drugs coming onto the market as combination products — drug products paired with delivery devices — pharmaceutical companies are paying closer attention to the design, function and efficacy of integrated delivery systems." Reynolds says a successful integrated system will combine the needs of the patient at a variety of stages during the patient journey with the drug, its primary containment system and its delivery system.

## SECURITY FROM THE OUTSIDE IN

Beyond packaging's broadening role as the means and medium if you will, to provide both physical and virtual security in the supply chain, packaging is also being called on to help solve the knotty problems of dose compliance. According to the Healthcare Compliance Packaging Council, pharmaceutical noncompliance is a tremendous problem in the U.S.: "Estimated annual costs [associated with] patients not taking their medications approaches $300 billion. It is also estimated that 125,000 Americans die annually (342 people every day) due to poor medication adherence and 10 - 25 percent of

(Photo courtesy of Pharma Tech Industries)

Tee Noland, CEO of Pharma Tech Industries (packaging line operator shown here) notes customers are looking for innovation from a cost and quality perspective.

hospital and nursing home admissions are also caused by people's inability to take their medications as prescribed."

Tom Hubbard, the New England Healthcare Institute's VP of Policy Research noted in a PMP.com report last year "There is no question that packaging is a part of the overall strategy to addressing medication adherence," noting medication adherence is a metric in the quality ratings for Medicare drug plans. "Payers and providers are thinking more strategically about adherence, said Hubbard, "Healthcare plans are trying to figure out the right mix of steps to keep patients adherent and head off overall medication spending. Packaging is part of that response."

Mike Schaefers, also a marketing VP with West Pharmaceutical Packaging Systems, says his company is seeing strong growth in creative collaborations between drug manufacturers and packaging and delivery systems manufacturers much earlier in the drug development process. "To achieve the best possible patient outcomes, pharmaceutical companies developing injectable therapies must consider how the drug product will interact not only with the primary container, but also with the delivery system and the patient to help ensure compliance to prescribed regimens and loyalty to specific brands," explains Schaefers. According to Schaefers, by partnering with a component manufacturer early in the drug development process, pharmaceutical manufacturers can identify and mitigate many of the risks associated with hasty or poorly vetted containment selection.

## SUPPLY CHAIN SECURITY OFFICER

Packaging is also being tasked to deliver improved supply chain security. "Implementing a Pharmaceutical Serialization and Traceability System in the United States," a study by consultancy Booz | Allen | Hamilton, noted in its executive summary that the U.S. pharmaceutical supply is considered one of the world's safest and the distribution system was well regulated. But on the other hand, critics note that the bulk, wholesale distribution of medications to and through pharmacy distribution networks, while proven safe and effective in the past provide an antiquated system that just isn't up to the task of interdicting the activities of very bad and sophisticated actors looking to profit from the nefarious trafficking of counterfeit, substandard and outright fake drugs.

Last year Walter Berghahn, The Healthcare Compliance Packaging Council's Executive Director, offered testimony before a House Energy and Commerce Subcommittee Hearing on Supply Chain Security. In his letter, he concluded that supply chain security should include the "patient" and noted the following about packaging's role in drug security and safety:

Blister packs, says Gordon Haines, Rottendorf Pharmaceuticals' CEO, are becoming more popular as they can improve patient compliance and can be customized to fit a product design due to the availability of a broad range of materials and multiple configuration options.

- Driving the serialized container through the pharmacy to the patient will virtually eliminate dispensing errors that occur regularly in today's "count, pour, lick and stick" environment.
- Putting an original manufacturer's container in patient's hands will allow them to authenticate the package.
- That same container, or more appropriately the serial barcode, will allow patients to link to a variety of compliance tools which will allow them to track their individual performance and link them to a variety of reminder tools.
- Serial numbers could create the opportunity for direct-to-consumer notification of recalls, unlinking the dependency on pharmacists to track the lot and then research which patients' scrips were filled from that lot, etc.
- Serial numbers could be used in reverse logistics to prevent the re-issuance of a container that was already delivered into the market place and left the care of a professional controlled environment.
- Serialized containers would ease the process of reverse logistics, returns. No more diverted returns.

Vetter, a well-known contract manufacturer and complex secondary packaging specialist, offers serialization at the carton (sales unit) level and aggregation at the carton (sales unit), shipping case, and pallet levels. Like others in its peer group, Vetter recognized that fundamental serialization services at the point of secondary packaging operations is something its existing customers need right now and something potential customers will likely want well into the future. Vetter says its serialization and aggregation services are seamlessly integrated into its primary packaging processes. Vetter says this service helps its clients establish "the 'parent-child' relationships among components and understand the exact contents of a product package at any point."

The point is, most of the physical aspects of serialization, the marking of primary and secondary packaging, and most of its associated data are gathered at this point in Pharma manufacturing operations. It's here where enterprise data and the physical manipulation of the products meet and the point where the handoff to logistics providers and others take possession of these goods. The prevailing wisdom is that there is much opportunity to optimize supply chain operations. Serialization, explains UPS Healthcare marketing director Robin Hooker, offers Pharma tremendous opportunity. "Every bottle will have its own birth certificate, passport and social security number, and in essence, once that happens you've got a tremendous way

of visualizing the supply chain." Hooker explains that "if this transaction data gets handed off through every supply chain actor from the manufacturer, to UPS Freight [and on] to a distributor, then from distributor to drug retailer or specialty pharmacy, those handoffs and that visibility and that information is going to do amazing things for supply chain optimization."

### FUNCTION JUNCTION

It's at this junction where the integration of data and production systems simply cannot be an afterthought. Most MES platform suppliers including Rockwell, Siemens, SAP, Werum and others know that information technologies, well integrated with packaging line production equipment, all married to machine vision and marking and labeling technologies will deliver efficiency gains that have far-reaching positive effects operationally.

### CONTRACT PACKAGERS

Across Pharma's operational landscape, contract manufacturing organizations (CMOs) are doing the heavy lifting associated with packaging and packaging operations. For many drug owners, there's plenty of incentive to bring in contract packaging solutions providers from both a design and commercial packaging operations standpoint.

"Our customers want a reliable, high-quality operation that will help them meet new serialization requirements without having to make the capital investment themselves," says Rottendorf's Haines. To accomplish this, he says, Rottendorf works consultatively to design packaging to cost targets, "by providing more cost effective and efficient materials and operations," notes Haines.

"Consumers want a package that is easy to use and straightforward," says Pharma Tech Industries Noland, "you are seeing this with some of the new virtual companies that are developing certain OTC products. In terms of our organization, we have made more investment into our unit-dose capability suite to support these opportunities."

West's Schaefers explains that everything in the value chain cannot be a core competency, "so outsourcing makes sense on many levels. Quality expectations are increasing, and as a result customers seek solutions to improve product quality and ensure drug integrity." Schaefers says West continues to make significant investments in vision inspection systems as more customers demand 100 percent inspection of components.

### THE EARLIER THE BETTER

With packaging playing such a significant role in the commercial success of today's pharmaceuticals, it makes tremendous sense to include CMOs and contract packagers in on product development as early as possible. "Packaging choices can have a significant impact on the finished cost of a product," says Haines. "If packaging suppliers are involved early in the process, appropriate packaging can be designed and optimized for dependability and cost." Yet it's not all peace and harmony out there, he says. "While the mindset of companies is starting to change, many pharma companies still treat packaging as an afterthought. We try to make our customers aware of the potential impacts of incorporating packaging design early, to try to move it up on their list of priorities, but practice is still behind where it needs to be."

"In some cases," says Noland, "we are seeing this collaboration at the early part of the drug development cycle because packaging can comprise a significant part of a product's cost. Not only are we looking at specific packaging projects, but also technology transfers of entire operations or even entire sites. These more strategic activities allow our customers to rationalize their supply chain and simplify their business exponentially."

### LET'S GET RATIONAL

The complexities of Pharma's supply chain, its limitations and its contributions to drug safety are well recognized by the industry, its contract services providers and its technology suppliers. Best practice involves getting resources and technologies aligned early for best effect. Noland's comment regarding rationalizing the supply chain has everything to do with successfully fielding well-integrated packaging operations and leveraging them to answer the halo of issues associated with supply chain security and dose compliance by consumers. Yes, packaging is bringing a lot to Pharma, and it appears it is ready to take delivery.

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# Prepare Now for DSCSA Serialization

More than putting numbers on a bottle, looming regulations will have a profound impact on enterprise IT architecture, operational processes and supply chain readiness

By Brian Daleiden, Vice President, TraceLink

**SERIALIZATION AND** related track and trace regulations are now a strategic requirement. For pharmaceutical companies, the supply partners they work with to produce life-saving medicines, and the distribution trade partners that ensure these medicines get to the patients who need them worldwide, track and trace requirements are rapidly becoming a daily part of normal operations in the pharmaceutical supply chain. Propelled by a growing counterfeit drug threat that kills more than 100,000 people annually, regulations for drug serialization, supply chain traceability, and government reporting will affect almost 80 percent of the world's drug supply by the end of 2018. From the United States and the European Union to China, Brazil, and more, over forty countries will have instituted serialization and other traceability regulations in four short years.

In the United States, the 2013 Drug Supply Chain Security Act (DSCSA) was designed to help combat these patient safety threats. Lot-level traceability, product and transaction verification, and unit-level serialization will be instituted in phases starting in 2015, and will converge into end-to-end unit-level traceability in 2023. The 2017 DSCSA serialization deadlines will mark the first time that many pharmaceutical companies and their supply chain partners will have to implement serialization and manage serialized product inventory.

What has been learned by those who have already started? What are the key issues to master in preparing for DSCSA serialization deadlines? And, why should you start now to understand your true readiness timelines and build your strategic plan, particularly in the context of the global regulatory environment?

## DSCSA REGULATIONS & TIMELINE

The Drug Supply Chain Security Act's ten year timetable outlines critical steps to build an electronic, interoperable system to identify and trace prescription drugs from manufacturer to dispenser across the supply chain serving the United States market. Implementation of the forty pages of complex DSCSA regulations can be broken down into three general phases:

2015: Lot-level traceability and verification of products and transactions
2017-2020: Serialization of drug products and enhanced verification of serialized product identity
2023: Unit-level traceability

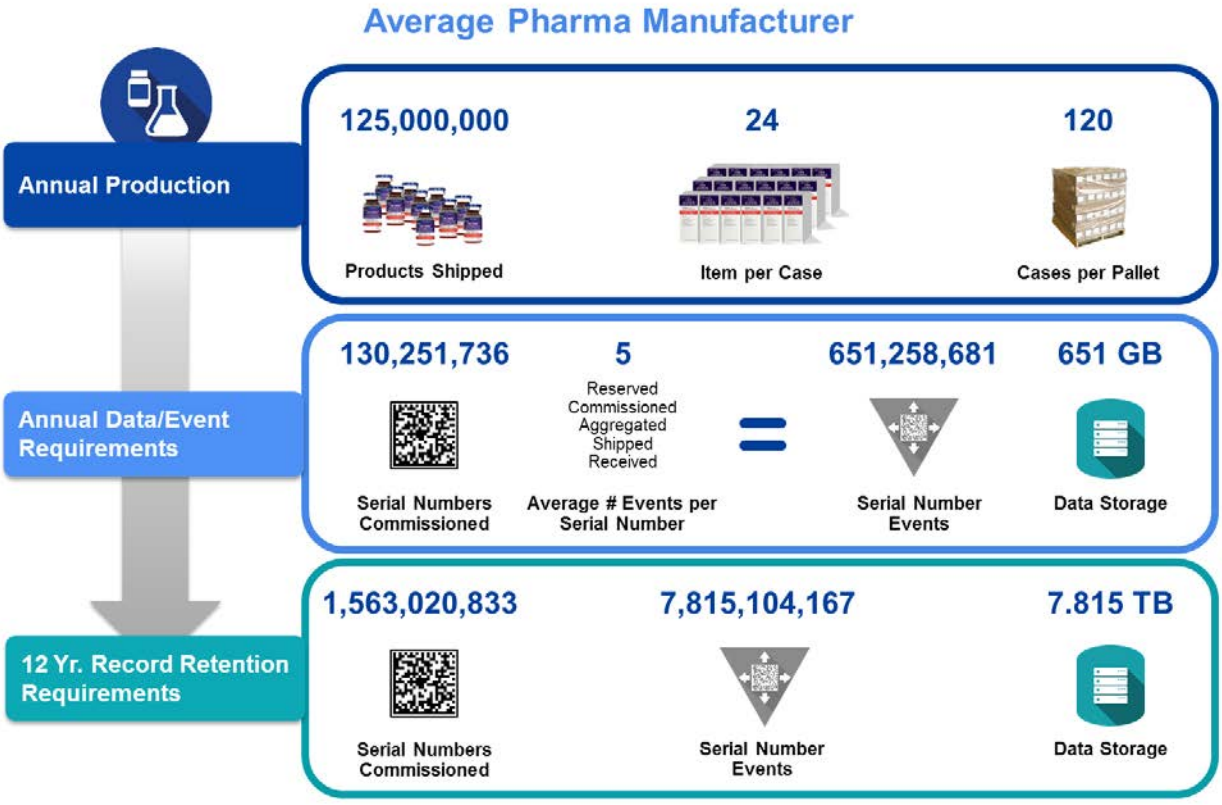
On the surface, preparing for the 2017 DSCSA serialization deadlines doesn't seem that challenging – at least in comparison to other global serialization regulations. Pharmaceutical companies and their CMO/CPO partners must generate serial numbers for each saleable unit and sealed homogeneous case of drug product produced. The serial numbers with associated National Drug Codes (NDCs), lot numbers, and expiration dates need to be encoded into 2D data matrix barcodes (for units) and either 2D data matrix or linear barcodes (for cases) following generally recognized industry standards. If you just look upon serialization as "putting numbers on bottles," it can be very tempting to put off planning for DSCSA serialization. However, it's more complex than that.

To understand the full complexity of serialization readiness, here are five key issues that pharmaceutical companies need to consider as they build their serialization programs and ask themselves: "When do I need to start?".

*1. Serialization is More than Putting a Number on a Bottle*

Current and proposed serialization and barcoding regulations create a complex, strategic data management challenge. While U.S. DSCSA data requirements are fairly straightforward, globally there is a highly diverse serialization ecosystem to contend with:

- Coding: 2D data matrix or linear barcodes may be used incorporating global GTINs or country specific NTINs
- Formats: GS1 standards predominate while China's EDMC and Brazil's IUM differ significantly in length and format
- Sources: Manufacturers can create their own serial numbers except in China where they are requested from the government
- Attributes: Serial numbers may be randomized or sequential and uniqueness may be required within a product line or across all products
- Packaging hierarchies: Serialization may be required at the unit level (EU), unit and case level (US) or all levels below pallet (China)




- Aggregation: Aggregation may be a legal requirement or a potential trade mandate
- Master data: Company, partner and product data related to serialization requirements varies widely from country to country and across trade partner relationships

So, unless your company will only serve the U.S. market and none of your supply or trade partners does business in other markets, it is critical to understand the diversity of the serialization regulations and how they potentially impact your enterprise IT architecture, your operational processes or the readiness of your supply partners to serve you when you need them.

*2. Serialization Forces Supply and Trade Partner Networks to Evolve*

You have to understand all potential network connections (internal, supply, trade, governmental) over which serialization information needs to flow, not just internal packaging site or CMO/CPO links, to understand the regulatory and business data flows your infrastructure needs to support. The serialization infrastructure you develop will probably have to support a surprising diversity of data types, connection methods, business preferences and regulatory interpretations across your various network relationships.

For DSCSA, you'll need to manage serial number requests and responses with the different packaging line systems you and your supply partners work with. Commissioning events must be captured and potential aggregation data exchanges managed as product travels from packaging line to packaging site warehouse, through internal warehouses and into 3PL facilities. Shortages, damaged product and other exceptions need to be dealt with in new ways where serialized product is involved.

Downstream, you may have to send aggregation data to direct trade partners and capture and respond to SNI verification inquiries from any entity that has the product in their possession. Each of these partners may have its own preferences, system capabilities or interpretations which can impact how the serialization system is designed and how the packaging lines are deployed.

*3. Serialization Creates Unprecedented Scalability Challenges*

The data generated and the transaction events created are orders of magnitude beyond what companies in the pharma supply chain are used to.

A mid-sized pharmaceutical company that produces 125 million units a year will now, under serialization, be faced with creating more than 130 million serial numbers a year across multiple packaging hierarchies. These serial numbers need to be provided to dozens

of internal and external packaging lines and related commissioning, aggregation and other related serialization events from numerous systems and partners across the supply chain need to be captured. Each serialized product unit may spawn a net average of 5 serialization events across packaging, internal movements and supply chain transactions.

Annually, this company will need to capture and manage more than 650 million serial number events. At a typical size of 1 kilobyte per serialization event, this represents more than 650 gigabytes of data per year. Across a 12 year record retention period and at steady state, that exceeds more than a billion serial numbers generated, almost 8 billion serialization events managed and almost 8 terabytes of compliance data to store. Since this data is not just compliance data but also used for daily operational needs, this demands a complete rethink of how information is captured and managed across your business.

*4. Serialization Fundamentally Changes How Your Company Conducts Business*

Serialization and the management of serialized inventory fundamentally changes how your company conducts business. It's crucial to reach out across the organization, from quality and artwork, to supply planning, trade relations and commercial operations, to understand how corporate functions are impacted by serialization. Continuous education on serialization regulations and their implementation rules, data standards and industry implementation trends across the organization is important so that you can gain informed feedback on organizational needs, preferences and requirements to inform your serialization planning. For example, good distribution practices in the warehouses may conflict with the needs to maintain aggregation relationships across the organization.

Most companies will undergo a transition from lot-level identified to serialized product over time. So your systems, processes and connections to supply and trade partners will need to be flexible in managing both serialized and lot-level product throughout your organization and network.

*5. Serialization Preparation Timelines are Always Longer than They Appear*

Serializing packaging lines and serialization enabling a packaging site is a long and complicated project which may take from 12-18 months to complete from hardware acquisition to live site validation. But the true serialization readiness timeline must incorporate many other factors.

Depending on product stock levels and velocity through the supply chain, it may take months to bleed out existing lot level product from internal warehouses and external distribution sites. Existing supply plans need to be incorporated to determine how often production runs are executed, how long they take and when existing production lines can be idled for retrofit.

Rarely can all serialization lines be upgraded in parallel due to cost or resource constraints. So, projects must be staged in phases. As each line and site is being serialization-enabled, it must be integrated into the internal serialization architecture linking the enterprise systems, warehouse management systems, edge devices and trading partner systems across which serialization data and serialization events must flow. This places a requirement on the business to understand how this architecture should be developed well in advance of line deployment.

Working back from the deadlines, most companies find that their serialization start date for U.S. DSCSA serialization is several months to more than a year before they expected, not accounting for the lead times required for other serialization regulations.

## WHY START NOW?

The approach to serialization must be staged. Or, as we like to say the "big bang" approach just doesn't work.

Serialization decisions are tightly intertwined with numerous other corporate functions, so starting now helps identify dependencies in supply planning, IT architecture, operational processes and even product commercialization programs.

Starting early also lets you uncover issues and mitigate risks before full-scale serialization and network implementation. For example, does your 2D barcode content match event data? Is serialization data consistently maintained in repository? Do network integrations maintain serialization data?

As you've seen, there are many issues to master in preparing for DSCSA serialization deadlines. The requirements far exceed just putting numbers on bottles, as those that have started serialization projects can attest. Start early, understand your true readiness, and build a strategic plan to meet both DSCSA and global regulatory requirements.

## ABOUT THE AUTHOR:

*Brian Daleiden is Vice President of Industry Marketing at TraceLink. In this capacity, Brian leads the company's thought leadership, global regulatory analysis and market education programs that help industry stakeholders understand and respond to emerging regulatory, business and technical requirements. Brian guides the TraceLink Cloud Community of industry leaders from across the global life sciences supply network. Brian holds an MBA from Vanderbilt University and a BS from the University of Wisconsin.*

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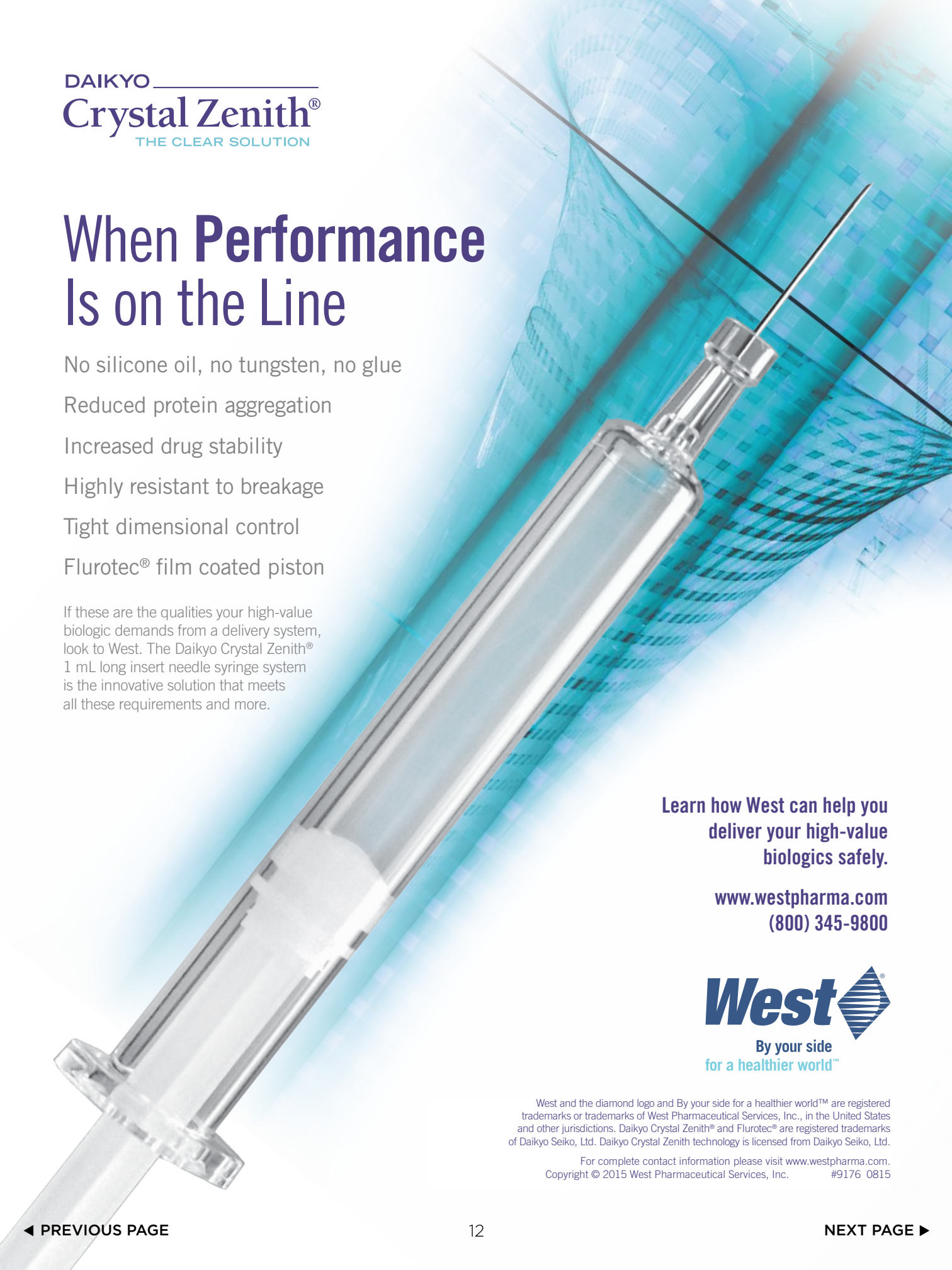

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Humans invading your sterile processes? Advances in aseptic processing technologies aim to keep their risk and contamination at bay.

# no man's land

By Steven E. Kuehn, Editor in Chief

Before the rise of aseptic processing technologies, horribly contaminated humans, shedding clouds of particles roamed controlled spaces, invading Pharma's sterile processes. Sure, gowning, booting and hair-netting the contaminated helped tame the beasts and manage the risk, but their presence could not be denied … That is until now. Over the last 10 years advancements in aseptic processing equipment have been arming pharmaceutical manufacturers with the defensive systems they need to create a true "No Man's Land" where human intervention and its risk are banished forever.

It's pretty hard to understate the multiple layers of risk that need to be managed to successfully and compliantly accomplish aseptic drug processing. Drug safety and regulatory imperatives dictate drug makers create intensive, pervasive and verifiable systems to assure sterility in aseptic processing environments.

According to the Food and Drug Administration's (FDA) 2004 "Guidance for Industry Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice," in aseptic process: "the drug product, container and closure are first subjected to sterilization methods separately, as appropriate, and then brought together."

Because there is no process to sterilize the product in its final container, says the FDA, it is critical that containers be filled and sealed in an extremely "high-quality" environment. The FDA guidance generally recommends that before final assembly the individual parts of the final product should be subjected to various sterilization processes. For example, says the FDA guidance, glass containers might be subjected to dry heat; rubber closures subjected to moist heat and liquid dosage forms subjected to filtration. As most are aware, each of these processes requires validation and control. To think that legitimate sterile drug manufacturers would ignore the risks to public health and its bottom line and willfully manufacture nonsterile product is a stretch, but the path to perdition is often paved with good intentions. Poorly instituted cGMP conditions can, says the FDA, "ultimately pose a life-threatening health risk to a patient."

U.S. regulators note for each process there is the potential to introduce errors that ultimately lead to product contamination. "Any manual or mechanical manipulation of the sterilized drug, components, containers or closures prior to or during aseptic assembly poses the risk of contamination and thus necessitates careful control."

(photo courtesy of AST)

Advanced isolator technology is becoming an affordable but higher-quality alternative to barrier systems.

Aseptic processes should be designed to intrinsically minimize exposure to potential contamination hazards that come from (relatively) routine manufacturing operations. To achieve a high assurance of sterility, regulators recommend drug makers take some pretty logical steps like optimize process flow, limit the duration of exposure of sterile product elements, provide the highest possible environmental control, and configuring equipment to prevent the entrainment of low-quality air into the Class 100 (ISO 5) area.

Further, to prevent unnecessary activities that increase the potential for introducing contaminants, FDA guidance notes personnel and material flow, the layout of equipment and incumbent operator ergonomics should all be optimized to limit the number and duration of personnel present in an aseptic processing environment. Essentially, best practice calls for limiting the frequency of entries and exits made into and out of aseptic processing rooms and their critical areas, including isolators.

To be clear, drug manufacturers now understand that any intervention, delay or stoppage during aseptic processing greatly increases contamination risk. The design of equipment used in aseptic processing, says FDA, should limit the number and complexity of aseptic interventions by operators. "For example, personnel intervention can be reduced by integrating an on-line weight check device, thus eliminating a repeated manual activity within the critical area. Rather than performing an aseptic connection, sterilizing the preassembled connection using sterilize-in-place (SIP) technology also can eliminate a significant aseptic manipulation. Automation of other process steps, including the use of technologies such as robotics, can further reduce risk to the product."

Preceding the section outlining the above in its guidance, the FDA offered a caveat noting that the design concepts discussed were not intended to be exhaustive (read prescriptive). They did, however, declare "appropriate technologies that achieve increased sterility assurance are also encouraged." Encouragement is one thing, but at the time, their vision of GMP-refined aseptic manufacturing — where human interventions become the exception rather than the rule — was a reality challenged by many factors, driven by both internal and external forces buffeting the industry.

Few have observed more closely the trends driving the uptake of advanced aseptic processing technologies than Sterling Kline, vice president of design at IPS, a

processing systems integrator that's been at the forefront of aseptic process design for decades. "The trend over the past 10 years has been very dramatic," says Kline, "and it has been driven by the regulatory agencies." He explains that historically the technology was not quite ready commercially to enforce regulation standards: "In the past decade, the technologies have finally caught up with where regulators want to be in the industry."

From a regulatory standpoint, says Kline, there are two prime factors driving the industry currently. "One is separation. As in separating the operators who are the prime source of contamination from the product and separating potent compounds from the operators." Kline notes that this separation is much more accessible nowadays because of continuing development of barrier systems that have proven, he says, to work very well. The most prominent being restricted access barrier systems (RABs) and isolators, the more formidable (to contaminants) and favored by regulators.

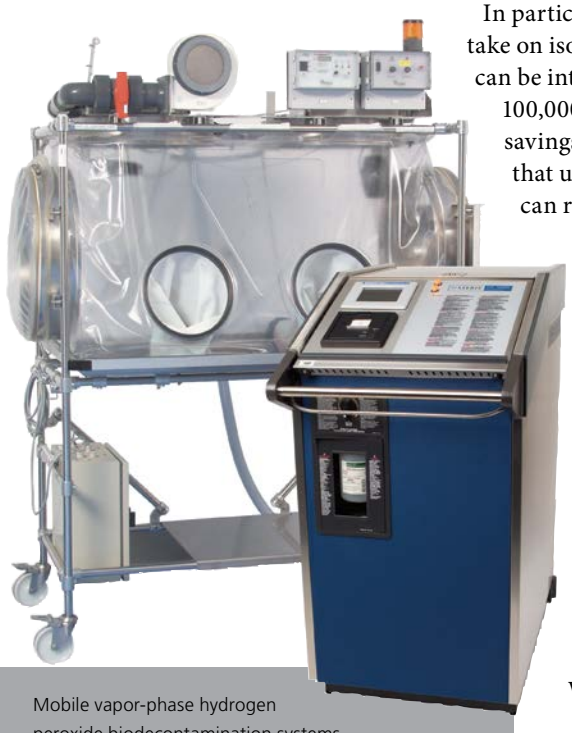
Josh Russell, product manager for the Life Sciences business segment of AST, another of the industry's most trusted and experienced aseptic systems integrators, echoes Kline's assessment. "To a certain extent, there has been somewhat of a longstanding understanding that the agency has extended regulatory relief to the industry in regards to integrating isolators with their aseptic processes," notes Russell, citing that specifically, this relief is characterized by the amount of media fills that drug makers can do on an annual basis.

Regardless, both Kline and Russell agree that both RABs and isolators have become very prominent over the past decade. "Historically," says Kline, "there were about 2,000 aseptic facilities of traditional design that did not have the barriers. Over the past decade, it's gotten to the point where it's down to about a thousand of the old, traditional facilities, with isolators and RABS making up the remainder." The acceptance of these straightforward technologies is now pretty much a foregone conclusion. According to Kline it's becoming more and more prominent with most, if not all, new facilities implementing isolators or RABS. "The older technologies are not being produced even in third-world countries at this point and developing nations," observes Kline. "India has lagged and is a bit behind, but has now picked up on the technology dramatically." The majority of the facilities are isolator and RABS controlled space, he says, noting that there are more RABS in India, but in the U.S. isolators are now beginning to really take off.

Russell and Kline agree that developed, proven technologies are finally available and now more economically accessible by the world's drug processors. "It's similar to computers or cell phones," says Kline. "As the volume goes up, the price becomes more affordable and the technology has become dramatically better." Noting that cycle times for vapor-phase hydrogen peroxide (VHP) systems have dropped off, typically down below two hours and that, Kline explains, puts the turnaround time for an isolator at par with RAB systems.

From an economic standpoint, says Kline, in most of the Western nations the capital cost for isolators is absolutely cheaper than RABS. The difference is slight, he notes, because head to head, isolators cost more than RAB containment. "But the RABS facility costs substantially more than an isolator facility," he says, "even where you have very inexpensive construction, such as India."

In particular, Russell says, offering his take on isolator economies, "isolators can be integrated into a grade D or class 100,000 cleanrooms. That's substantial savings that a pharma manufacturer that uses isolator-based technology can really employ." There have been several great studies done, notes Russell, "where it's actually shown that end-users can save upwards of a million dollars per year between the cleanroom cost, turnaround costs, personnel utilization and equipment downtime; the list goes on and on." From an operating cost standpoint, both Kline and Russell assert isolators are absolutely less expensive to operate and have lower lifecycle costs, no matter where you are in the world.



Mobile vapor-phase hydrogen peroxide biodecontamination systems like this one from Steris offer the flexibility users need to support this critical task within aseptic processing environments. (photo courtesy of Steris)

## ISOLATOR ADVANCEMENTS

Russell characterizes isolators as the "Cadillac" when it comes to protecting the product from contamina-

tion. The game changer, he says, is the isolator's ability to be bio-decontaminated using VHP. "That repeatability, being able to decontaminate the line quickly and consistently, offers end-users a great advantage over traditional aseptic process lines with RABS integrated onto them."

Both Kline and Russell say they rely on isolator solution builder SKAN, to create the VHP-enabled isolator systems they need to satisfy their customers' decontamination requirements. "SKAN," says Russell, "has really developed the technology and its practical implementation. For example, SKAN is able to guarantee a six log bio-burden reduction within two to three hours. That is a huge improvement (in terms of isolator decontamination technologies) from even five years ago, where oftentimes it took anywhere between eight to sixteen hours for isolators of similar size and shape."

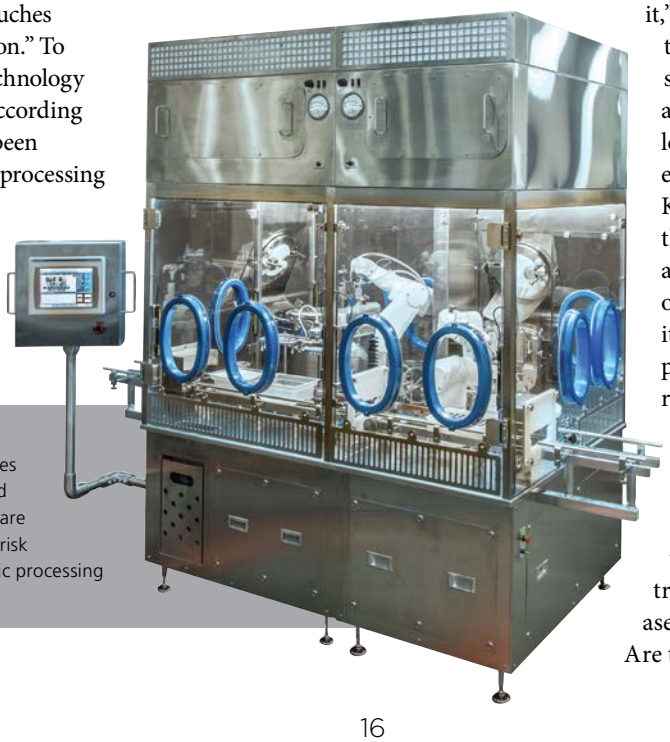
Vapor-phase hydrogen peroxide decontamination has become extremely popular because it's been recognized for its efficacy, compatibility and flexibility, as well as its utility. Arthur B. Papineau, VHP solutions manager for STERIS Corp., finds that regulatory trends, as well as global health crises are responsible as well. "I think that there is a lot more focus right now on infection prevention in general given the FDA's current investigations into the Pharmaceutical Compounding market and USP 797 as well as with the heightened awareness caused by the Ebola outbreak with the potential of other outbreaks," explains Papineau.

STERIS first introduced VHP to the market in 1991 and since then, the technology's effectiveness, Papineau explains, has helped it expand into other markets: "We actually see a push for the technology into aseptic-type food and beverage packaging, particularly for dairy products and especially most things in foil or pouches not requiring refrigeration." To Pharma, it seems, the technology has been heaven-sent. According to Papineau, "VHP has been embraced by the aseptic processing community due largely in part to its ease/robustness in validation and re-validation; high level of effectiveness against organisms; wide range of material compatibility; ambient condition process; and a process that is safe for both the environment and user.

The other area of great interest, he says, is in the application of VHP for the terminal sterilization of prepackaged medical devices, especially pre-filled syringes. Terminal sterilization has never been practical for most pharmaceuticals for obvious reasons. "This solution," says Papineau, "offers users a tremendous amount of design flexibility for their facility, manufacturing processes and validation protocol. It is only achievable because of the low temperature and material compatibility of the VHP process."

AST's Russell offers this bit of color commenting on how biotechnology products are really starting to flourish and fill today's drug pipeline — and that is fueling demand for advanced VHP capabilities. "Biotechnology drugs really have a lot of unique properties that have to be safeguarded against as you manufacture them. Most of these biologics are proteins and monoclonal antibodies, which are sensitive to vapor phase hydrogen peroxide." Russell explains some manufacturers need to safeguard the products against the oxidizing aftereffects of VHP. He says isolator vendors are now coming up with rapid VHP technologies using catalytic converters and other methodologies that introduce VHP into the chamber to quickly decontaminate the chamber, but also as quickly aerate and diminish residual VHP levels down to 30 parts per billion or less.

"In the past three to four years," Kline says, "the greatest advance in isolator technology [has been] the introduction of catalytic converters," a technology initiated by SKAN he says. "Now all of the companies are using it," says Kline. The issue with the vapor hydrogen peroxide sanitization comes with the aeration cycle, which can take a long period of time to cycle the exhaust operation completely. Kline explains that during the exhaust cycle operators are trying to get the VHP out of the machine and exhaust it out, but that can cause the pressure differential in the room to go negative, which, like the longer cycle time is not desirable. Catalytic converters speed up cycle time." For biologic products, the catalytic converter is a tremendous improvement to aseptic operations, says Kline. Are there any other isolator



(photo courtesy of AST)

Isolators and highly integrated process technologies within, including advanced robotics and automation, are dramatically reducing the risk of contamination in aseptic processing operations.

technologies worth mentioning? Kline points to isolators now being engineered for clinical scale operations: "There now is a modular isolator, SKAN has one and other companies are now introducing them as well. That drops the price, so if you can reproduce a module, it drives the cost down and makes it much more affordable."

### PROCESSING FLEXIBILITY

Faster decontamination cycles from advanced VHP offer drug makers a number of operational economies, but Russell maintains just as important is the flexibility companies need from their aseptic processing lines to address a variety of high-value, low-volume drugs — as Russell put it, "personalized in nature." However, that is not to say that drug companies processing parenterals and other common compounds in commercial volumes aren't clamoring for the flexibility advanced aseptic processing technologies can deliver. "These lines need to be highly flexible, able to adapt to both current manufacturing needs and regulatory demands, as well as be able to forecast and address future manufacturing and new regulatory challenges that they may be faced with. Especially with fill line purchases — often multi-million-dollar system integrations — it's key that these systems are able to address the long-term needs of the organization."

Kline mentions isolator modularity as a path to aseptic process line flexibility and cost efficiency — a well-understood technical response to the often "bespoke" and expensive nature of filling and other systems custom-engineered to create a site-specific solution. The availability of effective, mass-produced off-the-shelf technologies are making an affordable difference and manufacturers are also following suit, designing fill-finish and similar systems to fit into relatively standardized isolator real estate. "We've actually put a freeze dryer in one of the modules," says Kline, extrapolating that aseptic drug processors could use one for staging, for example. "A number of companies have done that … so if somebody buys a single module for one application, there is nothing to prevent someone from buying three or four modules and put them together for a specific process; regardless, it's still cheaper than building custom filling lines."

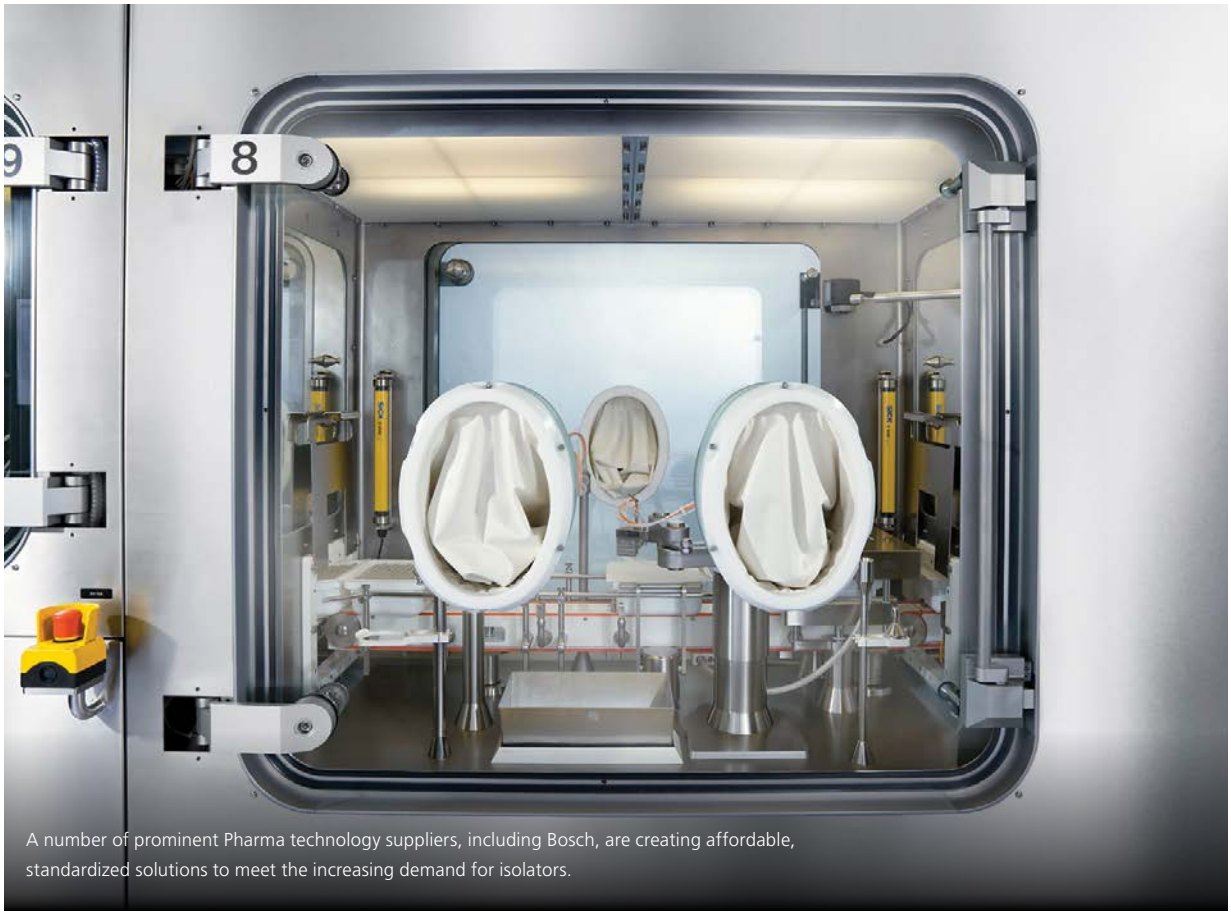
AST says it clearly sees the trend towards clinical scale isolators as well as the implantation of interchangeable filling machines. "We're definitely seeing that there are a lot of advantages to having a standard isolator platform like the SKAN PSI, which stands for pharmaceutical safety isolator." Russell says SKAN has cut out the backside of the isolator to allow for docking different trolleys with traditional filling equipment into the isolator. "What that's done, according to Russell, "is it's really driven down the cost of technologically advanced isolators. But systems integrators may not be getting all the flexibility they can affordably purchase," Russell explains. "What you're buying is a flexible isolator, but a not-so-flexible filler. What AST is doing is putting together the best of both worlds by combining a flexible filler with a flexible isolator." Russell explains that such a scheme allows the end-user to have a single trolley that performs all the fill-finish operations for vials, syringes and cartridges, and then it can be removed with another trolley for other activities placed within the isolator and used. One simple advantage of this is that the operators can remove the filling system trolley from the isolator for maintenance. "That way," says Russell, "you don't have to do it within the clean space of the isolator."

Isolators work phenomenally well with the traditional filling lines, says Kline, in terms of keeping operators away. He explains that it's not just putting an isolator on an old filling line: "The technology of all the filling [systems] companies have gone up dramatically in the last few years. The filling lines are much narrower — a design feature so that people can reach with the gloves to all the appropriate locations inside the filler."

Kline also points out that the electromechanical, automated aspects of filling, capping — essentially technologies that manipulate and convey products to and through process operations — have improved as well. "From that standpoint, there's not the glass breakage or the tippage that we had years ago," says Kline, so [there's been] incredible improvement, which reduces the interventions that folks have to do."

Regardless, even if manual interventions are required, the increasing implementation of isolators means operators are doing it through gloves and not by opening doors. "Another great advancement in isolators that help in terms of the turnaround and also for cleaning from one product to another," says Kline, "is single-use product contact parts." Kline explains that by installing pre-sterilized contact parts, the cost savings can be significant. According to Kline "probably 90 percent of our customers that we design facilities for use this technology, so it's driven the cost of the single-use disposable contact parts down dramatically and reduces the cleaning time." Kline says that for potent products, it's really the only way to go. "You don't risk contaminating one product with the next product — the technology has worked out incredibly well." Talking about potent products, Kline notes isolators have now transitioned into formulation operations. "When you're formulating potent products, all the additions into the tanks, etc., are done through isolators at this point and provide a much safer environment for operators."

According to Russell, process flexibility sprouts from the fertile soil of contemporary technological advances in automation, control and robotics. "We're seeing a couple different approaches. The approach that AST has adopted is leveraging robotics — to create a truly flexible aseptic




(photo courtesy of Bosch)

A number of prominent Pharma technology suppliers, including Bosch, are creating affordable, standardized solutions to meet the increasing demand for isolators.

platform. We use a robot to be able to fill and finish, pre-sterilize vials, syringes and cartridges. It's ideally suited for companies that are looking for the ability to fill multiple formats in a low- to mid-volume production setting."

## LOWER RISK, HIGHER REWARD

When it comes to advances in aseptic processing technologies, the cost curve is being driven down and along with that, a lot of risk. Drug makers need to a have very high degree of confidence in the sterility of their processes, and technology is making that happen. "Yes, absolutely," agrees Kline, "and risk is the key driving word here. Everything in terms of designing aseptic facilities is based on risk management. One could drive to zero risk, but your costs go up exponentially, thus it's not a viable project. The economics don't work out; there is a delicate balance to be maintained," says Kline.

Kline explains that beyond segregation (FDA's term) regulators are seeking high levels of isolator contained process line integration. "It's not just the filler. It's isolating transport to capping machines, or the conveying into and out of loading and unloading of freeze dryers. They're looking for fully isolated manufacturing in a continuous process via tunnels." He explains that traditional back-end process systems and operations like vial washing, then manually transferring vials to drying and transport to the filler is becoming a thing of the past. "So the risk has dropped off dramatically through separation and integration, and the cost of the technology has now dropped dramatically. It's also reduced the number of operators. So there are significantly fewer operators on an isolator filling line or a RABS traditional line.

The conversation with Kline and Russell continued, ranging from the upside and downside of blow-fill-seal technology and the numerous benefits of creating highly collaborative relationships with both the users and the aseptic processing technology builders. Risk is also being driven out by advances in production-related control and automation, as well as information systems and remote monitoring and service via the cloud. Aseptic manufacturing environments are also being well managed by similar applications of advanced control technologies across building automation and HVAC elements of controlled space. Ultimately, it is the systems integrators' task to deliver on regulators' vision for efficient, cost-effective and safe aseptic drug processing, and drug maker's equal need to achieve the same to stay in business. For sure, AST and IPS are creating a no man's land in controlled Pharma space, and that's how it should be.

# ascent of the robots

Robots are ideal for when potent compounds need to be handled in isolator containment. They also do not shed particles like humans and achieve ISO 5 standards.

Josh Russell, AST's Life Science project manager, has been an advocate for advancing aseptic processing through the use of robot technology for years, writing about its benefits and exploring their application in their customer's solutions. According to Russell, aseptic manufacturing generally entails often repetitive activity that requires a high degree of reproducibility in order to create a high-quality product. He asserts that robots are the ideal platform to perform the highly accurate, repeatable operations demanded by aseptic processing operations. These non-organic automatons have the distinction of being able to operate where no man should or can. "This becomes particularly important in applications that require containment of highly active and potent compounds." Not only that, but our electromechanical friends won't ever shed the clouds of particulates humans do because they generate no viable and extremely low levels of non-viable particulates, making them ideal for ISO 5 aseptic environments.

"What we've seen in particular is that more robotics' manufacturers are coming to the table to offer truly viable solutions to this challenge," says Russell. Most importantly, life science oriented designs that are VHP "proof" are now available. "Staübli Robotics is there – with a complete line of six axis robotic arms compatible with vapor phase hydrogen peroxide decontamination. With Staübli's wide portfolio of VHP compatible robotic systems solutions providers like AST don't have to compromise on payload and reach because the system exist for us to provide the optimal solution with our products." He says suppliers offer robots that can complete the span of automated tasks required by commercial aseptic processing; robotic options for everything from aseptic vial processing to lab automation to freeze dryer loading and unloading applications.

Commercially available robotic automation is well developed and extremely accurate with repetitive pick-and-place maneuvers and precise positioning tasks and Russell agrees. "Absolutely they do, and it's being expanded. For example, we like to use robotics for manipulating syringes and cartridges. We found that it offers several advantages to that process that just aren't found in traditional filling lines." He notes that other companies, like Kawasaki, have introduced a seven-axis, stainless steel VHP compatible robot. "It provides even more flexibility than what we've seen in the past," says Russell. "Other companies have been developing their own robotics for their own solutions. We've just seen the market really proliferate with a lot of various options that are geared to meet the challenges within the industry."

For example, Denso recently announced the introduction of its new compact, high-speed, VS-050 six-axis aseptic robot. It features an ISO 5 cleanroom rating and incorporates specially designed coverings, for applications, says the company, where intensive biocontamination control is required.

Peter Cavallo, robotics sales manager for DENSO Products & Services Americas, explains, "We created the VS-050 aseptic robot because of rapidly increasing demand in the pharmaceutical, medical and life sciences sectors. Now our customers in those areas with sterilization requirements can benefit from the high speed and other outstanding features of the VS Series."

Denso's robot offers a protective outer coating and sealed joints that allow the VS-050 to be safely sterilized with hydrogen peroxide or UV light. According to the company, the smooth, rounded exterior of the robot keeps dirt, dust or other contaminants from adhering to its surface. Among other things, Denso internally embeds wires up to the flange and locates the control-cable connector at the bottom of the robot, further streamlining the arm and facilitating cleaning.

Russell says the economics are right and right now. "I would say that integrating the robotics into life-science aseptic applications is very affordable, especially when you take it in the context of not having dedicated automation that would be required to perform the same assembly task or application." He says that it's actually even more affordable, especially given the amount of flexibility and adaptability that robots can provide. "There's less complication. In terms of aseptic manufacturing, they're easy to clean, easy to program, highly repeatable and reproducible." He explains that when lines have many isolators, robots can eliminate the ergonomic challenges associated with traditional fill lines if glove ports are not adequately planned prior to isolator integration. "And then you can decontaminate them very, very simply by articulating them during the bio-decontamination process."

Programmability is advancing, too, and Russell notes that in terms of the systems that AST provides, they go to great measures to make sure that they integrate robotic technologies that truly allow end-users to be able to support and program the equipment on their own.

By Richard Moody, laboratory manager, 3M Drug Delivery Systems

# Efficient Development of Generic Metered Dose Inhalers

## Inhalable therapies require a systems approach to optimize MDIs

**LIKE MANY** drug delivery technologies, development of Metered Dose Inhalers (MDIs) is a technical challenge. Formulators must ensure that the finished product is safe and efficacious for the duration of the product shelf life, and that it complies with the requirements of the current regulatory landscape.

There are many factors that need to be assessed and brought together to successfully formulate a new product. MDIs are made up of a number of sub-systems, which are required to work with each other to ensure that the finished MDI product operates appropriately. These sub-systems can be broadly summarized as the formulation, container closure system, actuator and secondary packaging. The development of MDIs must therefore use a total system approach to fully design and optimize these products to be robust and reliable during patient use. Other considerations must also be adhered to, including regulatory and quality requirements.

In light of these rigorous processes and requirements, development of a generic equivalent to a current marketed product brings immense challenges. Companies that seek to develop a generic inhalable therapy are likely to need an experienced partner to develop the delivery technology. Doing so helps ensure the smoothest possible path to commercialization and maximize return on investment. During the development of any generic MDI product, there are various distinct areas that need to be investigated and characterized. Following are six areas of focus that frame the process of robust generic MDI development:

### 1 ANALYTICAL METHOD DEVELOPMENT

Analytical methodology must be phase appropriate and fit for the purpose. Analytical method development and validation is typically delivered via the Quality by Design paradigm, applied from feasibility through product launch.

The concept of a lifecycle model described in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines is applied; the analytical method is the "process" and the process output is the reported result. All methodology has a defined Analytical Target Profile (ATP) and is subject to risk management and continuous

improvement processes. The concept of an ATP parallels that of a Quality Target Product Profile (QTPP), as defined in ICH Q8. An ATP is a predefined objective that stipulates the method performance requirements.

Suitable risk management tools such as Fishbone diagrams, Cause & Effect matrices and Failure Mode Effect Analyses identify controls and required experimentation, for each method variable. The critical variables are investigated by designed experiments to understand the performance of both the Innovator and generic products. This allows method robustness to be inherently built in, rather than challenged towards the end of the method and product development lifecycle. Finally, the capability of each method is reviewed throughout its lifecycle to deliver continuous improvement.

## 2 REVERSE ENGINEERING

To properly base-line and determine the working design space of a generic product, it is critical to gain a thorough understanding of the physical make up and pharmaceutical performance of the innovator product. To achieve this, the current delivery device must be closely evaluated for general design, primary/secondary packaging and additional features like a dose counter. Measurements are taken of hardware parameters that may influence product performance, including actuator exit orifice and jet length, and the impact of altering these parameters is determined. Also, the design and construction of the container's closure system may provide insights into its formulation characteristics and stability. For example, if a coated canister is used, there may be potential for drug deposition or an interaction with the base material of the canister.

In the case of a suspension product, visually assessing the emitted dose provides information on the particle size of the Active Pharmaceutical Ingredient (API) and an indication of the route-of-manufacture or size-reduction technique. Understanding and matching the particle size distribution of the marketed product is critical in producing a generic product that meets both the in-vitro and in-vivo regulatory requirements.

A further visual assessment of the formulation offers insight into the suspension characteristics and formulation composition. The rate of creaming or sedimentation is useful to understand when developing robust analytical methods.

Base-lining the marketed product for pharmaceutical performance offers a working target specification. In addition, base-lining of the marketed product is done to understand its batch-to-batch performance and performance over its shelf life to establish targets for key performance indicators. These factors will include characterizing key dosing parameters across multiple batches. Key pharmaceutical performance tests are assessed, including delivered dose and Aerodynamic Particle Size Distribution (APSD). When formulating an MDI product, these base-line parameters ensure that the product is developed to match the current marketed product.

## 3 PRODUCT FEASIBILITY

During the initial product feasibility stage, all public domain information is reviewed, and an assessment of project risks is initiated. This ensures that all prioritized factors are included in the work plan. In scoping a project, it is vital that all factors within the plan are considered. While not all options will be required and/or desirable for a given project, the rationale for not performing a certain area of work should be considered.

Following an initial screening, pre-formulation activities are required. These will include a thorough characterization of the API and any other excipient candidates. Studies may also be required to match the particle size distribution of the API to that of the marketed product. Once a suitable API is attained, formulation-based activities are required to assess and optimize the propellant and formulation system. These studies will include several approaches. The experienced formulator will design a study based on the requirements of a single program. In general terms, activities to be carried out during this phase will include assessing the solubility of the API in formulation compared to the marketed product. This will include aspects to assess the physical (e.g., Ostwald Ripening) and chemical compatibility of the API in formulation.

After the systems are further categorized, more detailed formulation activities are required in order to optimize the test product with that of the innovator. Typically a Design of Experiment (DoE) approach may be employed in order to assess a whole raft of responses compared to the innovator product, with the aim to match as closely as possible. When an acceptable match is achieved, this should be assessed to observe the effect, if any, over time. Typically a short-term informal stability assessment will be included for this purpose.

| DEVELOPERS | CONSIDER THESE ELEMENTS FOR PRODUCT SCALE UP | |
|---|---|---|
| ❑ Design | ❑ Lab scale manufacture | ❑ Process scale up |
| ❑ Prototype | ❑ Toxicological (TOX) supply | ❑ Stability manufacture and set up |
| ❑ Assembly | ❑ Pilot manufacture | ❑ Technology transfer |
| ❑ Manufacture | ❑ Phase I to phase III Clinical Trial (CT) supply and support | ❑ Data analysis |
| ❑ Test new products from concept phase through product and process development | | ❑ Final product commercialization |

## ACTUATOR DESIGN

Actuator design takes place in parallel with other areas in the process. During this time, the marketed product is evaluated on key parameters such as mouthpiece design, spray cone, and orifice and expansion chamber geometry. These listed parameters and variants of the design space are then incorporated into the actuator and mould actuators on a single cavity actuator tool. The actuator variants are tested with the given product to evaluate the performance compared to the marketed product. From testing, the key actuator geometries are determined, which are then implemented into an optimal device to be used in the stability and clinical program. Upon successful completion of this program, the selected actuator is then scaled up for commercial manufacturing.

The valve variant is also evaluated to ensure compatibility with the integrated dose counter (DC) or dose indicator (DI), if applicable. This assessment evaluates if the selected valve, when paired with the DC/DI, will tend to fire after the dose counter has committed to its count to eliminate undercounting and potential patient misuse. If this evaluation shows that further optimization is required, then this can be achieved with modification to the given actuator.

## DEVELOPMENT/BIOEQUIVALENCE

European Medicines Agency (EMEA) and Orally Inhaled Products (OIP) guidelines stipulate that product performance has to be within specified tolerances relative to the marketed product. These factors include, for example, the same active substance, target delivered dose within ± 15 percent and for aerodynamic particle size distribution (APSD), it may be considered acceptable to demonstrate therapeutic equivalence by using comparative APSD in-vitro data only, if the product satisfies all of the other criteria outlined in the guidelines.

The APSD data is deemed to be therapeutically equivalent if the calculated 90 percent confidence intervals for the observed in-vitro differences of the test and reference products are within ± 15 percent (average bioequivalence). Outside of these limits, a pharmacokinetic and pharmacodynamic assessment must be made to determine that the test product is equivalent to the marketed product.

## PRODUCT SCALE UP

Product and process development should be carefully scoped from start to finish, from feasibility to launch, and marketed product support. A capable development partner should have the ability to provide an off-the-shelf development service or a more bespoke plan to suit various project requirements.

Manufacturing technology should provide pressure and cold-fill manufacturing options from small to large scale as well as final packaging facilities. Manufacturers should also have the capability of custom equipment design and on-site qualification to suit specific project requirements.

High quality service and an excellent standard of manufacture should be ensured. The principles of QbD, ICH and current regulatory guidelines, Current Good Manufacturing Practice (cGMP) and manufacturing best practices should be implemented from the very start of a project, continuing right through to the day-to-day routine manufacture, testing and packaging.

As this overview illustrates, development of generic MDIs is a technically challenging process that requires significant expertise. The growing market trend toward lower cost generic products means that companies need experienced partners to develop robust generic products that meet the requirements of the current regulatory landscape. The most qualified partners will be able to demonstrate significant experience formulating, developing and gaining successful registration of multiple MDI products.

With the application of innovation, scientific know-how, state-of-the-art technology, product design expertise and business acumen, pharmaceutical companies and their partners can ensure a smooth and timely project and a robust submission package.

# The Forgotten Segment in PAT

What can a PAT program bring to the packaging party?

BY EMIL W. CIURCZAK, CONTRIBUTING EDITOR

**EVER SINCE** the U.S. FDA embraced the idea of PAT (even prior to its 2002 Draft Guidance), many, including myself, have attempted to define exactly where PAT begins and ends in a Pharma process. My personal view is that EVERYTHING about the process of making and delivering a quality product is covered, including packaging.

At my first Pharma job in 1970, I was hired to determine, with methods I was supposed to devise, the interactions between pharmaceutical dosage forms and polymeric materials. The industry was moving to distributing drugs in plastic bottles, not knowing what kinds of polymers to use, how thick the walls, or what shape the bottles should be, and what additives were safe or could protect the polymers.

I was guided by regulators to use "best scientific judgment" (cGMPs were not yet in effect) to measure interactions. Vapor transmission (both water and organic solvents) was one simple test, followed by light transmission (adding TiO2 wasn't for esthetics), shoulder angles (to avoid chipping or cracking during filling), and cap tightness. We also needed to see what went into and is extracted from the polymer; plastics were suggested to save money and improve safety. A plastic dropper for nose drops was chosen. After initial success with testing, it was decided that the dropper could be packaged in the bottle. Eureka! We had a smaller and lighter package — what could possibly go wrong?

Well, no one thought of testing the preservative (thimerosal) over time with the dropper in the bottle. As it turns out, thimerosal went into the plastic rather rapidly at room temperature. So after using the dropper and inserting it back into the bottle, the remaining solution became a petri dish for cold "germs." Another instance involved hand cream. The bottle's PVC antioxidant was tetraethyl zinc … which migrated into the cream over time and ultimately killed the product.

Though this was happening in the '70s, as recently as two years ago a major Pharma company was forced to recall its products because of "an organic odor." It was discovered that the wooden pallets the bottles were stored on emitted fumes from the preservatives used on them. These emissions permeated the bottles and "adulterated" the products. Unfortunately, the company also had a spate of recalls for shipping mislabeled batches of product, all of which finally brings us to what PAT can bring to the packaging party.

It seems that even a company with a thriving PAT program (i.e., well monitored and documented) can make some false assumptions. At one outfit, we had labels specially made for high humidity climates with "heat seal" mucilage and "wet seal" for dry climates; on several occasions these were mixed, ultimately causing the batch to be rebottled. Another case involved a bi-layer polymer that was heat-sealed to the base of a blister pack. We found that if the polymer is wound on the roll upside down, the polymer will melt onto the heated roller that seals capsules to the packs. What a mess.

**A SMALL NIR OR RAMAN UNIT COULD** DETERMINE ID AND POTENCY OF A PRODUCT **AS WELL AS CHECK PLASTIC SEALING.**

Such problems may be obviated by simply conducting a last-minute check in the packaging area. A small NIR or Raman unit could determine the ID and potency of a product, as well as to ascertain that the plastic sealing material is correct. That simple step brings packaging into the PAT paradigm of the company.

Keeping sterility is a major problem when packaging liquids, since the drug product is a solution and by definition, homogeneous, confirming content uniformity is generally a matter of weighing the containers. One interesting approach is Blow Fill Seal (BFS) technology, often used for volumes from 0.1mL to >500mL.

If you are not familiar, the basic concept of BFS is that a container is formed, filled and sealed in a continuous process without human intervention, in a sterile area inside the machine. BFS reduces personnel intervention making it a more robust method for the aseptic preparation of sterile pharmaceuticals. Generally, the containers are polyethylene (PS) and polypropylene (PP). PP is more commonly used to form containers which are further sterilized by autoclaving as it has greater thermostability. Notably, the plastic containers can be easily checked with a Raman monitor, thus allowing them to remain sealed and sterile.