WWW.PHARMAMANUFACTURING.COM

Pharmaceutical MANUFACTURING

THE DRUG INDUSTRY'S VOICE FOR MANUFACTURING EXCELLENCE

PutmanMedia®

Glass vs. Plastic

PACKAGING TRENDS

Innovation & Patient Safety

SPONSORED BY

Catalent

rommelag

WEILER

West

contents

CLASH OF THE TITANS

SUPER-RIVALS GLASS AND PLASTIC SQUARE OFF FOR PATIENT SAFETY

Specifying the best material to serve the primary packaging requirements for a given pharmaceutical used to be pretty easy, considering there was virtually only one champion to call on: Glass. Glass was Pharma's packaging Superman, a hero with well known virtues; strength, purity and transparency. For millennia there were few materials out there that could rival glass's dominance and reputation.

Glass as a material has been around for a long time, but it wasn't until about the 1st century BC, that glass blowing was discovered in the Middle East. This advancement created the industry. Glass vessels could now be mass produced, and more economically than pottery vessels.

And the rest is history as they say. During the ensuing millennia, glass as a packaging material came to dominate the world's food, beverage and pharmaceutical industries; there simply were few or no alternatives. That is, until scientists started uncovering the attributes of organic polymers found first in naturally occurring substances like gum and shellac, then later developing chemically modified materials like galvanized rubber and nitrocellulose. By 1900 the first synthetic plastic Bakelite was developed by Belgian chemist Leo Baekeland. Advances came quickly after that with the likes of BASF, ICI and Dow bringing commercial/industrial ready polymers to market beginning in the '20s.

As we reach the midpoint of this century's second decade, material scientists continue to hyper-refine plastics and glass to enhance positive attributes and mitigate less-than-desired attributes relative to Pharma application and commercial/industrial scale economies. The market for pharmaceutical packaging has become immense and is showing no signs of slowing down; leading market research firms predict demand in the U.S. will grow about 5 percent a year and reach ~ $22 billion

by 2018, representing about a third of the global market which Freedonia Group pegs at $66 billion by 2017 and growing at 6.4 percent annually.

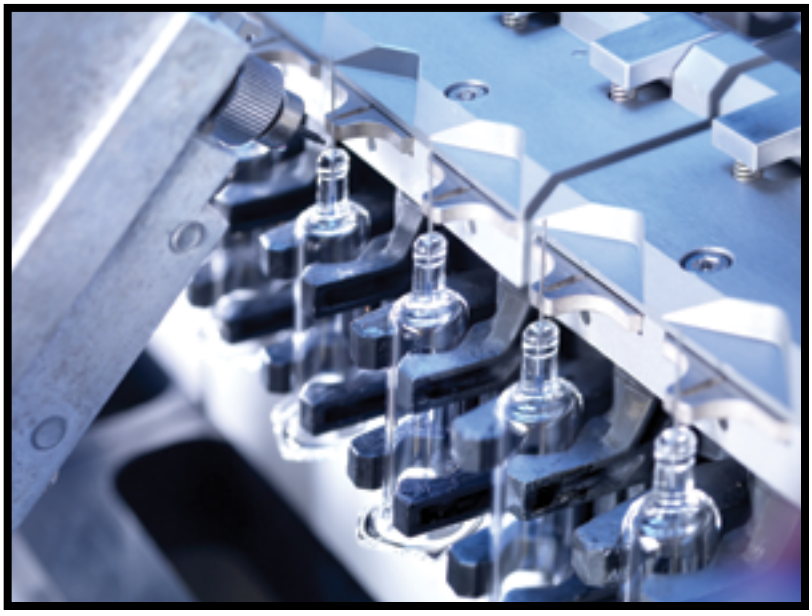
Indeed, glass and plastic have become Pharma packaging's superheroes — both working tirelessly to safely deliver medicines to a world plagued by evil-doing disease. But as our heroes pursue this common cause, packaging's dynamic duo have also become super rivals. However, as far as superhero-to-superhero conflicts are concerned, this one only goes so deep. Suppliers and users understand that any packaging decision is led by the formulation of the drug and ultimately patient safety.

GLASS, THE PROVEN DEFENDER

In an extensive *American Pharmaceutical Review* blog titled "Pharmaceutical Glass Containers: Proven Solution for Primary Parenteral Packaging" Gerresheimer Glass Inc.'s technical and quality managers noted that in 2012, market share for primary packaging of injectables was approximately 98 percent, representing 23 billion primary containers for parenterals. According to Gerresheimer, for the storage of parenterals, borosilicate Type I glass is the material of choice. Borosilicate glass was developed to have superior chemical and temperature properties compared to soda-lime glass; it has a stable matrix that reduces thermal expansion and resists chemical attack. It is inert, chemically stable and nonporous.

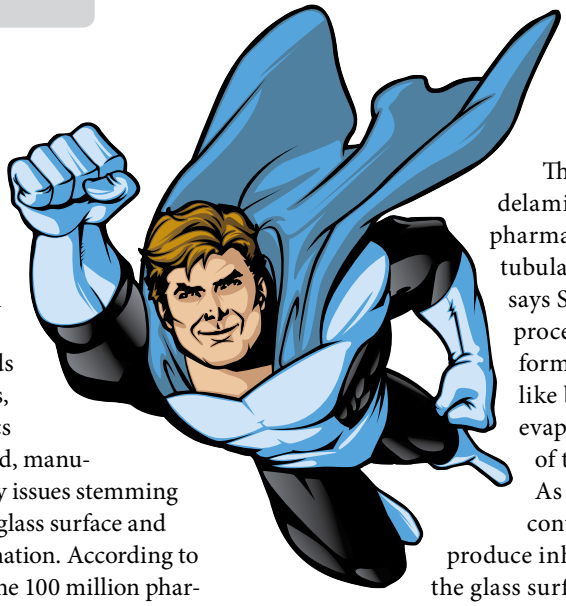
SCHOTT Pharmaceutical Packaging, the industry's leading glass supplier, says it delivers 9 billion containers per year and that includes ampoules, vials and both glass and polymer syringes. "We are working in the pharma industry, so we abide with all regulations," says Anil Busimi, head of global product management syringe business at SCHOTT, "which our customers

GLASS (SHOWN HERE) CONTINUES TO DOMINATE THE PREFILLED SYRINGE MARKET, BUT ADVANCED POLYCARBONATE PLASTICS HAVE GREAT POTENTIAL. SCHOTT IS MANUFACTURING THOSE AS WELL TO PROVIDE ITS CUSTOMERS WITH WHATEVER MATERIAL SUITS THEIR NEEDS BEST.



— like the Pharma companies — have to ensure that their products are produced as per specifications and GMP. I think we follow all the rules." At the same time, says Busimi, SCHOTT ensures Pharma quality standards are met by its suppliers. "SCHOTT is a major producer of glass tubing, [a pre-fabrication form] which is used for [Pharma's] primary packaging containers.

The use of glass pharmaceutical containers remains pervasive, especially for the thousands of well-known, broadly administered and increasingly generic injectable drugs. Materials and production systems are well understood, and in the context of large commercial drug manufacturing operations, there are hundreds of GMP compliant and validated fill-and-finish lines operating out there and a host of reliable glass container suppliers with established supply chains. Data on compatibility and drug/material interactions are both plentiful and accessible to all drug developers and Drug Master Files are kept by regulators. SCHOTT notes that having the technological expertise to support current products when problems come up helps sustain the company and glass's dominance in the category. SCHOTT's scientific advisor Dan Haines explains that, "because most of our products are components within other systems, there can be interface problems. Sometimes there are drug interaction problems. So having the technical expertise to help … is very important." SCHOTT provides this support through its pharma services group as does Gerresheimer and other glass container manufacturers. "In the pharmaceutical industry, it's a [relatively] slow evolution from one drug platform to the next, says Haines, "so there's quite long lead time, which is good. But on the other hand, you pretty much have to have rock-solid solutions when going from the current generation to the next generation."



DELAMINATION, GLASS'S KRYPTONITE

For the most part, and over the last century or so, glass remained impervious to most issues having to do with compatibility. Most formulators took it almost for granted. Most compounds were just fine being contained by glass, but as newer drugs, including biologics with aggressive chemistries introduced, manufacturers were confronted with quality issues stemming from chemical reactions between the glass surface and the drug chemistry known as delamination. According to SCHOTT, between 2006 and 2011 some 100 million pharmaceutical vials were recalled due to glass delamination issues. Delamination became Glass's kryptonite, exposing its (seemingly) one true vulnerability. At its likely nadir, 2010, glass flakes were discovered in nine different drug products resulting in immediate recalls; 30 million vials in one case. Although the phenomenon was recognized as far back as the '50s, the dramatic uptick in recalls forced the industry to react. Unfortunately, recalls continue, with several announced just this year.

The problem with glass delamination, say SCHOTT, Gerresheimer and others is that it may take years to manifest itself. The chemistry behind glass attack by water-based liquids is mainly driven by ion exchange and dissolution.

Gerresheimer says glass delamination is a well-known phenomenon, recognizing that even "upscale" Type I containers are prone to delamination under certain circumstances. Regardless, glass pharmaceutical container manufacturers, as well as industry associations (PDA for example), and regulators all have been galvanized to act and address this serious problem. Over the last several years a number of extensive, thorough studies have been conducted to understand the root causes of delamination and to find ways to eliminate the problem. In its 2011 "Advisory to Drug Manufacturers: Formation of Glass Lamellae in Certain Injectable Drugs," the FDA published that the following conditions were associated with delamination:

- Glass vials manufactured by the tubing process (and thus manufactured under higher heat).
- Drug solutions formulated at high pH (alkaline) and with certain buffers (citrate and tartrate).
- Length of time the drug remains exposed to the inner surface of the container.
- Drug products with room temperature storage requirements.
- Terminal sterilization has a significant effect on glass stability.

The tendency of delamination to occur with a pharmaceutical vial made of tubular glass strongly depends, says SCHOTT, on how the process is controlled during forming. Volatile components like boron and sodium evaporate while the bottom of the glass is being formed. As the production process continues, these substances produce inhomogeneous spots on the glass surface near the bottom that are generally more susceptible to delamination. Active control of this process is possible if the quality of the glass surface and its tendency to experience delamination are monitored during production. According to SCHOTT, this marked the starting point for a new way to test the risk of delamination.

FIND IT OUT FASTER

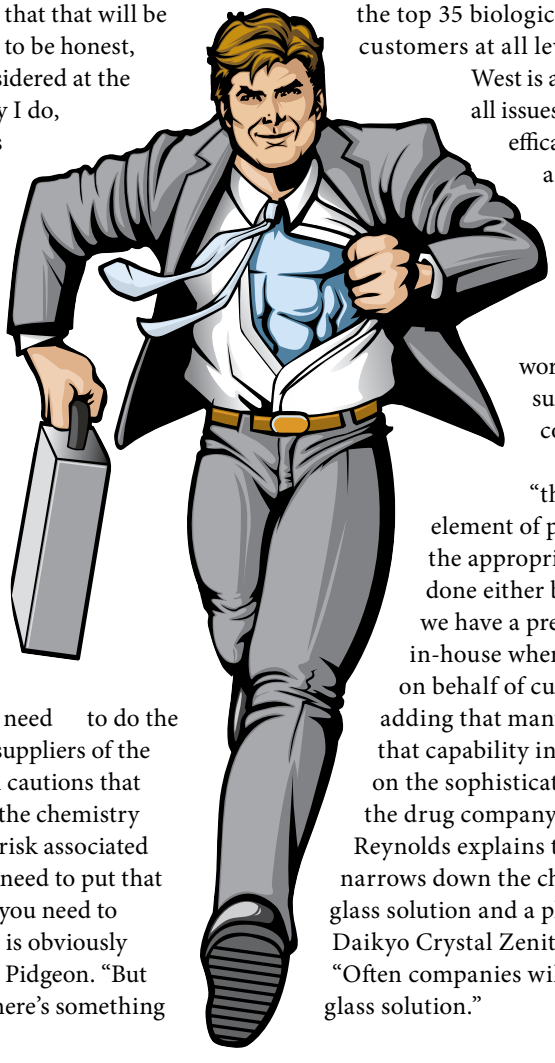
SCHOTT's analysts developed a test that allows pharma glass packaging manufacturers to determine delamination risk within a few hours by applying threshold values. To start the test, the glass surface is gradually attacked locally. Vials removed from the line are stressed inside an autoclave at a temperature of 121 C. In the past, vials were subjected to visual inspections with a stereomicroscope after autoclaving in steam. This method, says SCHOTT, has been replaced by more efficient and effective atomic absorption spectroscopy, a far easier method that can be performed during routine production operations. SCHOTT has received a patent for its in-process Delamination Quicktest, which monitors a threshold value of sodium during manufacturing. To conduct the test, the subject vials are filled with water so the zone where delamination normally occurs is covered slightly. Sodium is extracted inside the autoclave and the amount is determined through atomic absorption spectroscopy. This level correlates with the probability that the vial being inspected will experience delamination eventually.

The bottom line is that SCHOTT and its glass container-making peers, in association with drug makers have worked extra hard to eliminate this issue. Whether through enhanced and refined manufacturing techniques, coatings or better controlled preparation, fill-and-finish operations, delamination of glass containers is becoming less of a threat to operations and supply.

BETTER EARLIER THAN LATER

Tony Pidgeon, applied technology director for finished dose at Patheon explains that from a contract manufacturers' standpoint, their role is to guide primary packaging choices so that regardless of material choices, all aspects of packaging risk are managed to foster all desired outcomes. "The first thing we do is determine what our client's product profile is, in other words 'what are they trying to do' with their product," says Pidgeon, explaining that for many customers, the main motivation is to get the product into its trial in a predetermined time frame, so speed is essential. Often, he says, that means trying to piggyback on existing technologies.

For the drug owner, the decision is based on the fact that glass vials are readily available and for the most part a no-brainer. "People know how to use them," says Pidgeon. "There's an awful lot of data out there about them; people tend to [choose] a Type I glass — they take that as being considerable quality and assume that from a compatibility point of view that that will be fine. Extractable and leachables — to be honest, even delamination isn't really considered at the earliest stage. I must say personally I do, but it depends on the formulations they are coming to us with."



In talking about delamination, says Pidgeon "the general rule of thumb that I tend to follow is that as long as you don't have extremes of pH, then you're normally going to be okay." Regardless of drug formulation, at the beginning stages of the packaging discussion Pidgeon recommends doing comprehensive risk assessment from the very beginning. "That risk assessment will then dictate — or certainly guide — the direction in which you need to go. In other words, do you need to do the standard or get involved with the suppliers of the components themselves?" Pidgeon cautions that just because it's been done before, the chemistry is similar, etc., doesn't mean one's risk associated with packaging is mitigated. "You need to put that risk assessment in place. I suggest you need to do at least some work there, which is obviously unique to your own product," says Pidgeon. "But if it's a generic, for example, and there's something very similar out there, your risk assessment may well suggest that your other data is sufficient. Personally, I would probably be a little bit cautious of this part. I would probably want to have at least some complementary data there, but I would let the risk assessment guide me."

Pidgeon explains that early packaging risk assessment may prompt deeper inquiry — and involvement of packaging suppliers so customer's needs can be better met — in the name of patient safety. "We would speak to West, for example," says Pidgeon, "tell them that our plant is using this product with this kind of formulation and then we would work together to get the client the best service possible."

No surprise that West agrees. "Our core business relates to helping pharmaceutical and biotech companies select the appropriate packaging materials for injectable drugs," says West's vice president of marketing and innovation, Graham Reynolds. "We are currently participating in some way with all the top 35 biologics. We work closely with customers at all levels."

West is also very concerned with all issues that affect drug safety and efficacy. "This area of extractables and leachables has probably become more critical in the last two years as regulatory agencies look for more information on that subject," says Reynolds. West says they work with customers to make sure they have the appropriate container solutions period.

To get there, says Reynolds, "the first phase [includes] some element of prescreening work … to select the appropriate materials. That can be done either by us in our laboratories — we have a pretty extensive laboratory in-house where we can do that testing on behalf of customers," notes Reynolds, adding that many of West's customers have that capability internally. "It really depends on the sophistication and the capabilities of the drug company that we are working with." Reynolds explains that this prescreening exercise narrows down the choices, which may include a glass solution and a plastic solution using West's Daikyo Crystal Zenith cyclic olefin polymer: "Often companies will test a CZ solution and a glass solution."

Other fundamentals, like how the product will be filled and handled, need to be considered, says Reynolds. "Is it in a vial or prefilled syringe? For instance, if a prefilled syringe is going to go into a mechanical autoinjector, you want to make sure to take into account the viscosity of the drug. What forces are going to be necessary? What speed of injection is needed? At that stage, you need to really be considering not only the extractable, leachables and compatibility, but what is the optimal containment system to give the best result for the final drug delivery? That opens up a whole new world of — do I want glass? Do I want CZ? Do I want break resistance? Am I concerned about particles?"

Who gets involved in these discussions? "At that stage, there might be multiple people involved, depending on the complexity of the customer and their approach," says Reynolds. "Typically formulation scientists would be involved to select the materials. You may have packaging development people there saying 'I want it in a vial or syringe or a cartridge,' and what the dose volume would be, for instance. What we're finding now is that even at that early stage, the device people are involved." Kevin Cancelliere, West's marketing director adds, "there are a number of key stakeholders involved in our discussions. We are also seeing considerable interest from marketing. A lot of brand managers are very much interested in the type of primary containers to see if it can get them a competitive advantage in the marketplace."

For West, both Reynolds and Cancelliere say they are seeing a stronger trend toward plastic, prefilled syringes. "It's no doubt that the gold standard legacy is glass containers, but we are seeing a dramatic increase [in the specification of plastic] because of the emergence of the new biologics and the costs associated with them," says Cancelliere. "Drug companies are very concerned with that expensive biologic and how it interacts with primary containers and components. We are seeing an uptick and we really think that these trends are going to continue to grow over time." Part of the challenge says Cancelliere, is overcoming people's comfort level with glass. "Plastic containers are still relatively new. I think as people become more comfortable with them and see the benefits of plastic, we're likely to see an increase in demand."

Prefilled syringes represent one of the fastest-growing packaging and drug delivery segments in Pharma. According to a report published by Transparency Market Research "Prefilled Syringes Market (Glass and Plastic) — Global Industry Analysis, Size, Volume, Share, Growth, Trends and Forecast, 2013-2019," the demand is being fueled by the advantages associated with prefilled syringes, including eased administration, reduced risk of cross

CATALENT'S NEW ASEPTIC PARENTERAL CONTAINER BRINGS ADVANCED PLASTIC BLOW/FILL/SEAL TECHNOLOGY TO ONE OF PHARMA'S HOTTEST CATEGORIES, INJECTABLES.

contamination, less opportunity for overfill, simplified handling and ultimately better patient outcomes. In 2012, the global prefilled syringes market, says Transparency Market Research, was valued at $2.09 billion and is expected to grow at 13.3 percent from 2013 to 2019, reaching an estimated value of $4.98 billion in 2019.

"We've actually been manufacturing pre-filled syringes for many years," says Patheon's Pidgeon. "This year we are validating a brand-new state-of-the-art, pre-filled syringe line at our site in Monza, Italy. It's a big investment for the company and that's where plastics are going to be coming in." Pidgeon explains that while he's aware that glass is still the most popular amongst Patheon's clients, plastics and co-polymers are moving up fast.

SCHOTT's Busimi says his company is working hard to meet the needs of this market. "Definitely we see growth in the prefilled syringe markets," says Busimi. "Having both products in our portfolio with glass and polymer allows us to understand our customer needs and requirements, and then help them try to find the right solution in our portfolio."

PLASTIC IS FANTASTIC

For parenteral, sterile injectables in vials and syringes, glass remains dominant, but advanced plastic materials like West's CZ are making real headway; SCHOTT's move to supply advanced polymer syringes is their hedge. One market research firm noted that market growth for plastic prefilled syringe technologies will be double that of glass from 2013 to 2019. But, as far as the pharmaceutical packaging's universe goes, plastic has clearly become the material of choice across the vast majority of general pharmaceutical container forms. Think about it; most solid dose drugs in quantities of 50 or more come in plastic

bottles with those annoying but necessary child-proof caps. Most sterile liquids, saline, water for infusion, etc., come in plastic bags or bottles, not to mention the bulk supplies of the same.

SUPER INNOVATION

Drug innovation is driving packaging innovation and this is most apparent in the area of dispensing/dosing accuracy, patient compliance and other drug delivery technologies. Whether it's a prefilled multi-dose insulin injector or a dose-metering and counting COPD therapy inhaler, plastics are truly the only choice for designers and engineers fabricating these devices. What's interesting to note is that for some of these devices the medicine is contained in a cartridge — a market niche that both plastic and glass are vying for, but a category where there's a good chance a relative newcomer to the scene, plastic Blow/Fill/Seal (BFS), may soon come to dominate.

In 1963, Gerhard Hansen invented and built the first BFS machine; by May of 1964 he founded rommelag in Switzerland and began to sell his products internationally. The innovation was profound. In a single automatic process, BFS creates containers from thermoplastic granules which are blown into a mold, then inserts the liquid contents (fill) and then closes and seals the container.

Among its biggest advantages, BFS technology does not require the cleaning and sterilization processes that are essential in other kinds of container production and fill-and-finish operations. To provide maximum security in the aseptic packaging of sterile liquids, creams, ointments and vaccines, BFS machines can be equipped with additional modules for quality assurance and monitoring as well as aseptic systems for automatic cleaning and sterilization of lines that come into contact with products.

Customers throughout the world, say rommelag, quickly recognized the advantages of plastic containers, and other enterprising entrepreneurs recognized it as well, including Weiler Engineering who licensed the technology and brought it to the U.S. in the '70s. Its origins may soon be legend because BFS has the potential to truly dominate; not only across most sterile liquids, but for most parenteral injectables as well. Tim Kram, general manager for rommelag USA noted that worldwide interest in the technology is growing, fueled by drug shortage fears that everyone knows are mitigated by high-performing quality management and risk regimes as well as process excellence — something that BFS sterile, class 100 containment brings to fill-and-finish lines.

Describing its rising popularity, Kram points out that in U.S. markets inhalation drugs account for more than 2 billion units, ophthalmic drugs account for 1 billion units and IV solution bottles (worldwide) account for 2.5 billion units. According to Chuck Reed, marketing director for Weiler Engineering, Weiler has machines in over 35 countries producing a wide range of pharmaceutical products which include "everything from generic medicines to vaccines to oral, respiratory therapy, ophthalmic, nasal, otic and nutraceutical applications," says Reed. The market, he says, is growing in every sector due to (among other things) the increasing interest in the sustainability of the BFS process. Citing its low carbon footprint, recyclable base material, high utility efficiency, Reed notes all of these contribute to the success of BFS, not to mention a large movement away from glass, "which continues to be a driver," he says.

For rommelag, Kram says, customers break out this way: 40 percent branded, 35 percent CMO and 25 percent Generic, a spread that may indicate that certain segments are more compelled to adopt the technology's cost and quality efficiencies than others, especially those developing sterile, liquid medicines. Reed notes that "the BFS process provides a significant cost advantage over glass. A complete BFS container is typically less than 1/3 the cost of a similar glass format." Due to the flexibility in container design, Reed explains, "BFS is becoming a preferred format for many combination products due to the changes in device designs. Additionally, BFS can simplify the manufacturing steps to make the end device more cost effective."

Purveyors of our other super packaging hero, Glass, say their customers stay with glass because their processes are validated and for anything new, there are tons of data to draw from to support compliance and risk-management regimes. "The risks and costs associated with validating a

THE FUTURE OF BLOW-FILL-SEAL INNOVATION

Presented by: Megan Johnson, Nephron Pharmaceuticals Corp.

Recent innovation in Blow-Fill-Seal technology means exciting new opportunities in biotech products and vaccines.

This Fundamentals series includes:

- Overview of BFS technology
- Recent innovation in BFS technology
- Comparison of conventional filling to BFS
- Future of BFS technology

click here to view the presentation

new product [with glass]," says Kram, "are better known in the U.S. than with BFS technology." It is understandable, he concedes, that people want to stay with the process that they know. "Thus we try to get onto the packaging option list for new products. We have an extensive knowledge about compatibility that we can offer to new customers, along with test containers made from a selection of plastic resins. Once past compatibility (not guaranteed), the process for validation is similar." There is no difference in validating plastic resins in the same application, says Kram, "the difference stems from the different product regulatory requirements, that is, non-aseptic (preserved) products, aseptic products and terminally sterilized products."

Pharmaceutical manufacturers are embracing the technology. For example, says Kram, Nephron Pharmaceuticals in Columbia, South Carolina, is expanding into injectable drugs with a BFS ampoule. An early adopter was AstraZeneca, which began integrating the BFS process into its nose-drop production environment, installing a rommelag machine in the 1980s. By the 1990s the company ramped up BFS operations in Westborough to support the commercialization of its Pulmicort asthma medication, delivered via an ampoule inserted in a nebulizing device.

Both rommelag and Weiler's marketing and BFS technology development spawned companies that at first demonstrated the technology to potential clients, but over time evolved to provide BFS contract manufacturing services. Catalent (formerly ALP with a shared history with Weiler) offers its customers extensive aseptic, glass-free BFS filling-solution capabilities and capacity with experience providing development through commercial scale manufacturing support covering single- and multi-dose solutions across complex emulsions and suspensions. Since its inception, the company's owners have continuously invested in the facility; currently the 500,000 sq. ft. plant encompasses a total of 38 BFS lines. Catalent says it's made significant capital enhancements in recent years and is about to embark on its next wave of investment to further expand and improve operations over the next three years. In September, Ritedose, formerly rommelag's sister business Holopack, announced a $110 million expansion to its Columbia, South Carolina, facility, planning to add another 80,000 sq. ft. to support enough capacity to meet growing demand, says the company.

Yes, glass and plastic are Pharma packaging's superheroes, but while they are rivals, they continue to develop their respective technical and material attributes to cope with the ever-changing pharmaceutical manufacturing landscape in an effort to win the hearts and minds of drug makers and help fight the battle for patient safety.

Visit us at

ISPE Annual Meeting
Las Vegas - **Oct. 12-15**
Booth **T49**

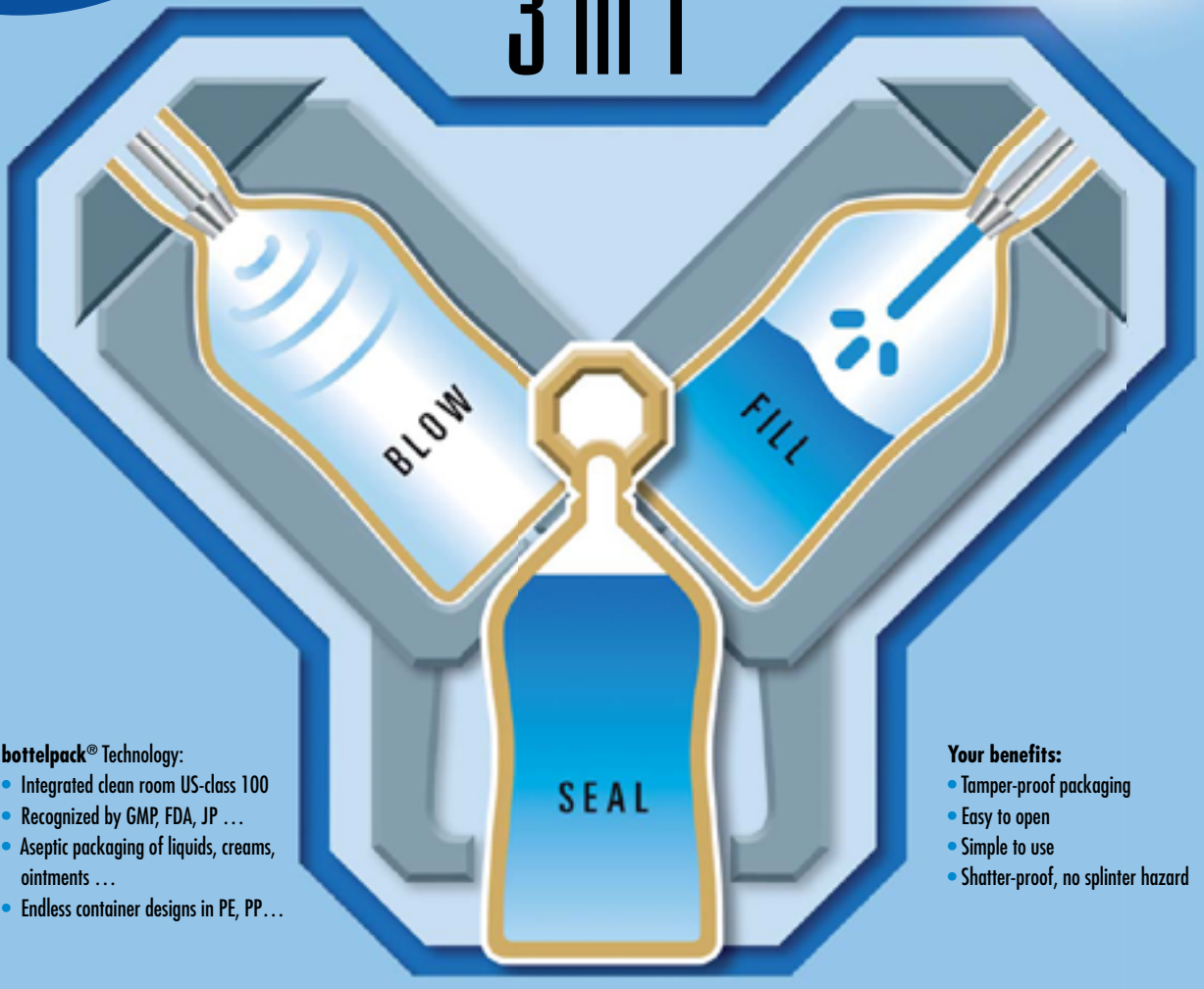
PharmaExpo
Chicago - **Nov. 2-5**
Booth **721**

bottelpack®
BLOW-FILL-SEAL TECHNOLOGY

50 YEARS OF PASSION IN BLOW-FILL-SEAL bottelpack

Advanced aseptic packaging in one operation cycle
Reliable – Simple – Cost-Effective

3 in 1



bottelpack® Technology:
- Integrated clean room US-class 100
- Recognized by GMP, FDA, JP …
- Aseptic packaging of liquids, creams, ointments …
- Endless container designs in PE, PP…

Your benefits:
- Tamper-proof packaging
- Easy to open
- Simple to use
- Shatter-proof, no splinter hazard

rommelag®
www.rommelag.com

rommelag ag
P.O. Box · CH-5033 Buchs, Switzerland
Phone: +41 62 834 55 55 · Fax: +41 62 8345500
E-mail: mail@rommelag.ch

rommelag Kunststoff-Maschinen Vertriebsgesellschaft mbH
P.O. Box 1611 · D-71306 Waiblingen, Germany
Phone: +49 7151 95811-0 · Fax: +49 7151 15526
E-mail: mail@rommelag.de

rommelag USA, Inc.
27905 Meadow Drive, Suite 9
Evergreen CO 80439, USA
Phone: +1.303. 674.8333 · Fax: +1.303.670.2666
E-Mail: mail@rommelag.com

rommelag Trading (Shanghai) Co., Ltd.
Room 1501 Xinyin Building
No. 888 Yishan Road · 200233 Shanghai, P.R.China
Phone: +86 21 6432 0166 · Fax: +86 21 6432 0266
E-mail: romcn@rommelag.com

Container Innovation's PRAIRIE HOME:

Where Catalent Pioneered BFS Packaging for Decades

Catalent's Woodstock, Illinois, facility has been pioneering blow-fill-seal aseptic packaging for decades

By Steven E. Kuehn, Editor in Chief

NESTLED OUT on the prairie about 60 miles northwest of Chicago is Catalent's Woodstock, Illinois, home for Blow/Fill/Seal packaging innovation. Regardless of its sylvan setting, Catalent's been pioneering efficient, sterile aseptic blow-fill-seal methodologies and sustaining its development for more than 25 years and is gearing up for continued success with its global customers from this central-U.S. location.

LEGACY OF INNOVATION

The Woodstock facility has a long history serving the pharmaceutical industry. The original company was founded in 1968 as Automatic Liquid Packaging (ALP) in Elk Grove Village, Illinois. By 1980 ALP headed west to Woodstock, building a new facility to house four BFS lines — intended primarily to demonstrate the efficacy of BFS technology to customers. This eventually created demand for contract manufacturing services, which the company pursued with vigor. The facility's first production runs started in 1982 with approximately 60 employees working three shifts, five days a week to meet the demand. Fast forward to 1999; Cardinal Health purchases the business, and in 2007 Cardinal Health PTS becomes Catalent Pharma Solutions.

Shown here: the redundant sterile filtration and buffer tank that feeds the fill nozzles on the inside of the BFS machine.

As of 2014, Catalent offers extensive aseptic, glass-free BFS filling-solution capabilities and capacity with experience providing development through commercial scale manufacturing support covering single and multi-dose solutions across complex emulsions and suspensions. "For more than 30 years here on site," says David Bricker, Catalent's site general manager, "We've specialized in the 'hard to do' complex molecules — we can do both, but it's really the complex molecules we do well." Bricker explains Catalent has a strong representation in the ophthalmic, respiratory, topical and biotech market spaces.

A main focus for Catalent is in the formulation and development areas. "It's not just the straightforward solutions, but really we are able to simplify the complex molecules and produce them with the same operational excellence as the simple solutions," says Natasha Hults, director of R&D. "For example, we've been successfully producing a biologic in BFS for over 20 years, so we have a long, proven history of how to handle a wide range of molecules, including complex and large molecule products."

Since its inception, the company's owners have continuously invested in the facility and the BFS technology it encompasses. Currently the plant, at some 500,000 sq. ft., encompasses a total of 38 BFS lines. Since 2011, Catalent has invested a significant amount of capital and plans to further expand and improve operations over the next three years. These investments are paying off — especially in the area of quality. Through the guidance and institutionalization of Catalent's Quality Management System, organization and continuous attention to operational excellence, the site's regulatory profile has steadily improved, and in 2013 the company experienced zero FDA 483 observations. Bricker agrees that as Catalent's organizational methods and processes were institutionalized the plant's quality performance has improved markedly.

Inside the isolator room looking at the isolator which is leveraged to insert sterile components into the final container.

OPERATIONAL IMPROVEMENTS ON DECK

It's obvious wherever you observe Catalent and its production assets, whether it's the biotechnologies and biopharmaceuticals, solid dose development or cutting-edge aseptic filling, operational excellence is a priority. For the Woodstock facility, its excellence culture is being manifested in the first phase of its planned multi-million-dollar investment. "There are some things we need to do from an infrastructure standpoint," explains Bricker, "to provide continuous improvement and continue to meet the current and future cGMP standards." Characterizing the first phase as a "nice project," Bricker's description is apt because very targeted dollars are supporting some well-defined, high-value operational improvements. Bricker describes it as a "refresh" with Catalent better aligning the facility to "take advantage, and leverage the BFS technology for [the] injectable marketplace."

The site has a classic feel, after all, its administrative, corporate front and original manufacturing and logistic

Catalent Woodstock Site Capabilities and Facility Metrics

- Over 450,000 sq. ft. of production, laboratory, R&D, packaging, warehouse and administrative space
- Fill volumes range from 0.3 mL to 1 L
- World-class critical utility systems including water for injection
- Cold-storage capabilities
- Solutions for products that are temperature, light-, oxygen-, or delivery-sensitive
- Analytical and microbiology laboratories
- 38 BFS lines running 24/7
- Global regulatory approvals from agencies such as FDA, EMA,PMDA, ANVISA, TGA, etc.

Inside Catalent BFS: the Parison head, the primary functional component of the process.

spaces were built in 1980. But in this case "classic" is relative, more like a vintage car. With 30 years of BFS experience within the context of a nearly continuous history of expansion and infrastructure improvement, Catalent knows a thing or two about leveraging BFS technology within the ecology of its operational footprint. But that doesn't mean opportunities for improvement have all been exploited. Upcoming capital spending is intended, says Bricker, to provide additional administrative and operational control that will support the facility's ability to support BFS process flexibility and market expansion. "When you look at the BFS technology from a parenteral manufacturing standpoint, as well as what has been taking place quality-wise on the traditional glass vial side," notes Catalent's commercial operations director Eric Feltes, "the automatic, aseptic filling technology of BFS addresses many of those root causes of challenges in the parenterals market." Looking at it from a technology standpoint, says Feltes, BFS really has true advantages, especially in other market spaces, outside of ophthalmic and respiratory. So looking at those advances, particularly in the U.S. parenteral space, we see as a growth opportunity for the technology as well as for us as an organization."

PLASTIC AND FANTASTIC

Blow/Fill/Seal technology, pioneered by Weiler Engineering and operationally perfected by Weiler's ALP and eventually Catalent, offers a number of specific advantages over glass injectable drug containers. To a great degree, the process's automated sterile operations reduce opportunities for contamination and drive out risk, "by orders of magnitude," says Catalent. The elimination of human intervention and glass handling prior to fill are huge drivers in this reduction. In particular, there are several different studies that support the drastic reduction of foreign particulates and even a risk assessment by industry experts that

qualify BFS as 100 times lower risk than traditional glass vial filling. "This technology really drives out a lot of the root causes of foreign particulates — even the exposure time that glass containers have — it's minimized; you're controlling or even eliminating it," says Feltes. He explains that BFS, through quality-by-design principles and automation, "drives out, via the design of the process, the different variables that impact quality."

In its pursuit of the sterile injectables market, Catalent recently introduced its ADVASEPT advanced aseptic glass-free delivery solution, a platform that is directly associated with the capital investments being made at the Woodstock facility. Touting enhanced sterility assurance, lower risk and greatly reduced contamination potential of their new design, ADVASEPT vials integrate the stopper and a sealing system that eliminates metal tabs or lids. Catalent says its container system provides high performance characteristics and that the process itself does not impact biologics negatively or affect the stability of biologic compounds tested. Additionally, there is an ongoing study measuring the effects on stability of a monoclonal antibody in glass vs. the ADVASEPT vial that shows comparable results. Catalent has performed controlled extraction studies on ADVASEPT primary and secondary packaging components. Six leachables methods have been validated to cover analysis of any known extractables in both water and saline formulations. Along with the BFS vials, Catalent offers integrated services that will accelerate the conversion from glass to aseptic BFS technology.

Catalent's services include automated back-end operations to speed production including this inline labeler.

OF MOLECULES AND MARKETS

From its role providing flexible BFS packaging and fill and finish operations to critical phase I, II and III and commercial scale-up development support, Catalent's Woodstock facility maintains a leadership role in bringing better operational methodologies to the pharmaceutical industry. Its customers come to the organization to help them meet the challenges they have in bringing their molecules to market while taking advantage of the design freedom of the primary container closer. Catalent's customers are motivated to do business with the company for a variety of reasons, but for many, risk mitigation is an imperative — one that is served well by depending on an experienced operational expert — especially if a client's compounds as well as its customers are better served by safer, more available and less expensive medicines.

We took a cue from Mother Nature.

At Weiler Engineering, our ASEP-TECH® Blow/Fill/Seal packaging machines deliver sterile, aseptic liquid packaging solutions using proprietary technology that ensures safe, tamper-evident environments for your company's most sensitive assets.

What else would you expect from the world's most advanced aseptic liquid packaging system?

Our Blow/Fill/Seal machines integrate blow molding, sterile filling, and hermetic sealing in one uninterrupted operation—a hands-free manufacturing process that ensures your company's parenterals, ophthalmic solutions, respiratory drugs, and other pharmaceutical liquids reach the marketplace in the most cost-effective manner possible—every time.

For more than 40 years, we have set the industry standard for sterile processing development with a continuous commitment to quality and innovation for aseptic technology. We will work with your company to develop a customized approach for each of your products.

See ASEP-TECH® systems in action, visit asep-tech.com/pm

WEILER®
Safeguarding solutions through innovative packaging

©2014 Weiler Engineering, Inc.

TOWARDS A BETTER PREFILLED SYRINGE

West and Vetter look to meet the needs of parenteral manufacturers and regulators demanding safer syringe options.

BY PAUL THOMAS

THE PARENTERAL drug market has long used 1-mL long glass prefilled syringes. While these syringes have experienced success, they have been prone to, for example, breakage or production inconsistencies. Increased regulatory scrutiny of glass syringes, vials, and cartridges, and the way in which they are filled and processed, has led drug manufacturers to search for alternatives.

A few years ago, syringes of Crystal Zenith, a proprietary cyclic olefin polymer from Daikyo Seiko, were introduced. The polymer syringes are said to be not only more resistant to breakage, but are known to have improved manufacturing consistency.

West Pharmaceutical Services and Vetter Pharma partnered to offer 1-mL Crystal Zenith syringes to their clients. Drug manufacturers have the option to conduct the syringe filling within their facility, or to outsource to Vetter. To find out more, we presented questions to West and Vetter. Responses were provided by Graham Reynolds, West's VP for Marketing & Innovation; Mike Schaefers, West's VP for Marketing in Europe; and Vetter Managing Director Thomas Otto.

PhM: What do drug manufacturers need to know about the CZ syringes? Are there new manufacturing issues or validation challenges to consider?

Schaefers: The Crystal Zenith polymer offers many advantages, including glass-like transparency, which permits visual inspection of the manufactured components and of the parenteral products that are delivered to the end user. In addition, the material is highly break-resistant and forms an excellent moisture barrier. Packaging systems based on Daikyo Crystal Zenith have been used for many years on marketed drug products. The 1mL long insert needle syringe system features new enhancements such as automated cleanroom manufacturing, 100% vision inspection (including the needle), and an insert molding process for the needle that eliminates the need for adhesive or tungsten.

Reynolds: We feel the syringe is ideally suited for biopharmaceutical drug delivery. It is sterile, silicone-oil-free and the plunger is laminated with Flurotec film, which

helps to lower protein adsorption and serves as a barrier to leachable substances while enabling effective functionality without the need for silicone oil lubrication. The material's tight dimensional tolerance and consistency of syringe functionality can help to make a delivery system's operation predictable.

PhM: When will commercial-scale filling be available? Do you expect manufacturers of commercialized products to look to switch syringes?

Reynolds: Syringe manufacturing capacity is in place today to support customer stability trials and initial activities, which will be required prior to full-scale commercial launch of a drug. West has sufficient capacity to meet these requirements, as well as initial scale-up, and has plans to introduce more capacity within our Scottsdale, Arizona, facility in the near future. Infrastructure is in place, and additional manufacturing cells will be added to ensure customer needs are met. Vetter has installed capacity to meet initial customer needs for technical trials, stability fills and early-phase clinical fills.

PhM: The solution promises "automated cleanroom inspection and 100% vision inspection." Tell us a about the technology behind this.

Schaefers: West applies 100% vision inspection of the syringe at various stages, including inspection of the needle to ensure integrity. Robotic handling in a classified cleanroom, with minimal operator intervention, contributes to a product of extremely high quality and low particulate levels.

Otto: Vetter will apply the same high standards and systems as used for their filling of glass syringes. In its European facilities, the company has adapted a cleanroom especially for filling the Daikyo Crystal Zenith 1mL long insert needle syringe. Using RABS technology to minimize contamination risk, the line is operating with two filling needles. Meeting cGMP specifications, it has a capacity of up to 3,000 units per hour. All syringes are 100% visual inspected following the filling process.

PhM: How does the prefillable syringe market look in the years ahead?

Reynolds: Drug companies are working closely with drug delivery device manufacturers at an early stage to ensure that there is efficient development of an overall system to enable cost-effective drug delivery. The FDA is placing extra scrutiny on the area of combination products, such as auto-injector systems that use a prefillable syringe, and there is uncertainty about how this may impact drug development. Clearly, regulatory factors will continue to have a key impact on the development of delivery systems.

Schaefers: The prefilled syringe market, estimated at around 2.5 billion units, is likely to continue to grow close to 10% per year. Significant growth will continue for therapies to treat chronic conditions such as autoimmune diseases. Novel systems to enable effective treatment of chronic conditions such as high cholesterol will also grow. In addition, understanding the importance of the drug container as it relates to the integration into the overall drug delivery system will continue to be a key factor.

INTEGRATING QUALITY BY DESIGN FOR DEVELOPMENT OF PREFILLABLE SYRINGE COMPONENTS

Tibor Hlobik, Director, Marketing for PFS Technologies;

Peggy Frandolig, Director, Technical Customer Support


West
Integrating Quality by Design for Development of Prefillable Syringe Components
Tibor Hlobik, *Director, Marketing for PFS Technologies*; Peggy Frandolig, *Director, Technical Customer Support*

CLICK HERE TO DOWNLOAD

Less is More

West
By your side
for a healthier world™

EVERYTHING YOU WANT. NOTHING YOU DON'T.

The Daikyo Crystal Zenith® polymer vial truly delivers an advanced drug containment system. Designed for high-value molecules, it eliminates glass delamination, while helping to ensure the stability and purity of medications. For the life of your product. For the lives of your patients.

Daikyo Crystal Zenith:

- No risk of glass delamination
- High break resistance
- Suitable for cold temperature storage
- Very low extractables
- Used in regulated markets (US, EU, Japan)

www.daikyocrystalzenith.com
(800) 345-9800

DAIKYO
Crystal Zenith®
THE CLEAR SOLUTION

West and the diamond logo and By your side for a healthier world™ are registered trademarks or trademarks of West Pharmaceutical Services, Inc., in the United States and other jurisdictions. Daikyo Crystal Zenith® is a registered trademark of Daikyo Seiko, Ltd. Daikyo Crystal Zenith technology is licensed from Daikyo Seiko, Ltd.

For complete contact information please visit www.westpharma.com.
Copyright © 2014 West Pharmaceutical Services, Inc.

#8792
1014

AVOIDING UNINTENDED INTERACTIONS

Interactions between drug products and packaging are better understood but risks remain

BY THOMAS FEINBERG, PH.D., DIRECTOR, DEVELOPMENT & CLINICAL SERVICES, CATALENT

IF A drug product is contaminated in any way by a chemical derived from its packaging, this can cause real problems for patients. These leachables have caused real-world problems ranging from mild and temporary gastrointestinal symptoms to full-blown immunogenic reactions.

At the less severe end of the symptom scale, in 2009 and 2010 various products reached patients that had a musty smell. This subsequently was identified as 2, 4, 6-tribromoanisole, and eventually traced back to a breakdown product of a fungicide, with which the wooden pallets used in storage and distribution were treated.

More dangerous effects occurred in patients taking Eprex (erythropoietin alpha) after a formulation change. The solubilizing agent, human serum albumin, was replaced with the chemically derived alternative, polyethylene glycol. This change increased the propensity for the new formulation to leach cross-linking agents from uncoated syringe elastomer into the product, which then reacted with the therapeutic protein to cause an antigenic effect.

While such problems are unusual, they do occur, and thus it is essential that all potential interactions between any individual component of a drug's formulation and any part of its packaging are evaluated carefully. Only then can the manufacturer be assured that the packaging will have no deleterious impact on the product's safety and effectiveness.

During the development and registration of every drug product, three crucial variables, drug, device and data, must be considered and understood. By considering each of these variables as the vertices of a formulation triangle, every study can be classified as lying within such a figure. For example, early phase studies of the action of an API in biological systems lie closest to the side connecting the Drug and Data vertices. Device compatibility studies, on the other hand, lie closest to the side connecting the Drug and Device vertices. Device performance testing can be considered to lie between the Device and Data vertices. The ultimate goal for both the developer and regulatory authority is to sample the entire space within the triangle. Only when information is available about all the possible interactions can a packaged drug product be declared safe and effective.

Extractables are those substances that can be extracted from the packaging material in some way, usually requiring the presence of strong solvents, elevated temperatures, or both. Leachables are, essentially, a subset of extractables, and require no unnatural extraction process to enter a drug product, as they are a natural interaction phenomenon between a formulation and its packaging. While both extractables and leachables might be additives that are deliberately incorporated into the packaging material, this is not necessarily the case as they might be low molecular weight fragments of the polymer, such as cyclic oligomers or even unreacted monomers.

The reactions used to make condensation polymers such as nylon are, essentially, reversible, and therefore a condensation polymer backbone can be a source of an extractable monomer created by the back reaction. Monomeric extractables are still reactive, and their free concentrations are usually low. Cyclic oligomers, such as the dimers and trimers of polybutylene terephthalate, are commonly observed extractables from this particular polyester. As long as formulation or any extraction solvent is not in contact with these materials, no observation of complete extraction will ever occur.

This does not mean that such thermoplastics should be avoided as the mere presence of these chemicals may not cause deleterious effects on product quality. In fact it does illustrate that leachables will always be present in drug products and anything packaged in plastic.

The extraction process generally occurs at a solid-liquid interface, although it can occur at a solid-gas interface, particularly if a volatile organic compound is present in the packaging material. The rate of extraction depends on a number of physical and chemical factors, including the permeability of the solvent into the solid, the solubility of an extractable into that solvent, and the temperature and pressure of the system. In the laboratory, there are numerous ways in which to perform extractions. Typical techniques include Soxhlet extraction (diffusion-controlled); boiling point reflux (temperature controlled); equipment that allows elevated pressures above solvent boiling points such as accelerated solvent extraction (temperature controlled); and microwave extraction, to heat a polarisable or dipolar solvent above boiling points (temperature controlled).

Both small molecule drugs and biologics have the potential to be contaminated by extractables, and the direct harm a leachable may cause a patient is the same in either case.

THE IDENTITY OF EXTRACTABLES AND LEACHABLES

Extractables and leachables fall into various chemical groups. Polymer additives are a major class of extractables, and differ both within types of polymers and even grades of the same polymer. They are added to polymers to impart desirable processing and end-use properties such as stability, and while they are not by default bad, there is the potential for them to be extracted or leach into a drug product. They cover a whole range of different functionalities, altering the mechanical, chemical or even electrical properties of the polymer.

Mechanical property modifying additives include nucleating agents that allow polymers to be processed at lower temperatures, cross-linkers that give a polymer mechanical strength and introduce a 3D structure, and fillers that impart both strength and heft. Fillers are typically inorganic substances such as clay, heavy metal oxides or carbon black. Plasticizers, which impart flexibility and give resistance to cracking, are a major class of additives, and may include both natural and synthetic oils, and phthalates. The use of phthalates is now under particular scrutiny.

Cross-linkers can also be classed as chemical property modifying additives, as they create supramolecular structures from the polymer. These larger molecules do not react or dissolve easily in any solvent, imparting chemical resistance. Antioxidants are another common form of chemical additive, and are included if the polymer has a high oxidation potential, typically because it contains many hydrogen atoms. Hindered phenols, or mixtures of these phenols with phosphine compounds, are examples of this class of additives. Flame retardants and clarifiers can also be incorporated into a polymer to make it less susceptible to high temperature oxidation.

Electrical property modifying additives are typically surface modifiers to control static build up. These increase the rate of charge dissipation at surfaces by incorporating a polar group or fixed charge within the additive's molecular structure. Examples include aliphatic amines, amides, quaternary amines or polyol compounds.

Usually, leachables are considered to arise from packaging directly in contact with formulation; i.e. primary packaging. Additionally, extractables in secondary packaging; i.e. materials in contact with the primary packaging, and even from tertiary packaging, may find their way into a drug product prior to the end of its shelf life. These may be present in any part of the entire packaging and delivery system. Examples include components of printing inks, and chemicals such as flame retardants or antifungal agents that might be present in cardboard boxes or shipping containers.

Inorganic compounds can also be found as components of packaging materials. Many of these chemicals will fall into a specific additive class such as filler or, in the case of metal salts of medium chain fatty acids, plasticizers. While rare, it is possible that residual heavy metal catalysts may be detectable in plastics. Fortunately, analytical technology for the detection and quantitation of heavy metals in drug products is fairly well understood, and both the European Pharmacopoeia and the United States Pharmacopeia have well described methods and limits for these elemental impurities.

THE ORIGINS OF EXTRACTABLES AND LEACHABLES

An extractable or leachable may be introduced at any point along the packaging supply chain. While a company

involved in packaging pharmaceutical products will require full disclosure from their suppliers about their processes and any extractable that might have been introduced in their facility, this disclosure requirement does not extend all the way back through the many links of the supply chain.

A pharmaceutical company will source its packaging containers and device components from a moulding shop which converts polymer products, and may add, for example, lubricants and colorants during moulding. The converter sources its materials from a masterbatcher, whose processes could introduce stabilizers, antioxidants, processing aids or antistatic agents. The masterbatcher is supplied by a polymer manufacturer, whose products might contain catalysts, stabilizers, antioxidants or processing aids. The raw materials for polymer manufacture are provided by a company that synthesizes monomers, where bulk chemicals or storage stabilizers might enter the supply chain.

Quality agreements between pharmaceutical manufacturers and their suppliers generally do not cover disclosure beyond the first level supplier. In the US, pharmaceutical manufacturers also have the advantage with first level suppliers because those first level suppliers generally will avail themselves of the Drug Master File (DMF) system. Having a DMF has become a marketing tool for first level suppliers and helps them obtain business from the pharmaceutical industry. The second level and further level suppliers are so far removed from the pharmaceutical industry and do not find the size of the market to be advantageous to their bottom line.

Whatever the form of the packaging, there is always the potential for leachables. Even for typically clean primary packaging, as used for small volume injectables, in cases of long-term storage, inorganics from glass or organic compounds from the elastomeric stopper may be found. If it is packaged in a single-dose pre-filled syringe, there are more potential source components, including the thermoplastic barrel, elastomeric plunger, metal needle, elastomeric needle sleeve, or even the foil pouch or plastic blister that constitutes the secondary container.

The situation is even more complex for products designed to be delivered by infusion. There is potential for long-term storage exposure from the laminate or multilaminates that make up the bag, as well as inks, thermoplastic ports and thermoelastomeric connectors. Further potential sources may come from in-use exposure during infusion, particularly from thermoplastic connectors or elastomeric tubing.

Probably the most complex interaction and, historically, the system of most concern between primary packaging and formulation is the pressurized metered dose inhaler (pMDI). A pMDI has many components that could, conceivably, contribute to the extractables load. These include the metal canister and spring, the valve body, stem and metering chamber, the gaskets on the stem and the valve, and the gathering ring. All of these components will be continuously bathed in an organic solvent (propellant and carrier) for as long as the product is viable.

The leaching of extractables into drug product formulations is inherently a kinetic problem. Intimate mixture between formulation and the packaging will increase the rate of leachables formation. The more similar a formulation is to its primary packaging, the more care should be taken with the choice of primary

CONTAINER CLOSURE SYSTEM COMPONENTS

Primary packaging components, which may be in direct contact with the drug product, and thus may contribute extractables or leachables.

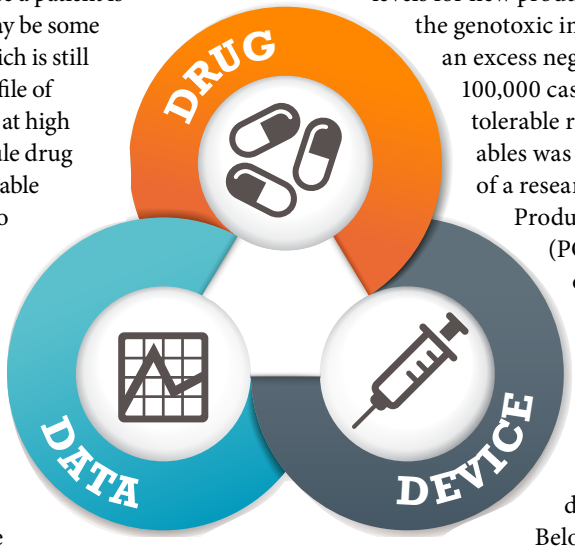
These include:
- Containers (ampoules, vials, bottles)
- Container liners
- Closures (screw caps, stoppers, metering valves)
- Closure liners
- Stopper overseals
- Container inner seals
- Administration ports
- Overwraps

Secondary packaging components, which will not be in direct contact with the drug product, but may still contribute leachables under certain conditions.

These include:
- Container labels
- Administration accessories
- Shipping containers

packaging, and in the design of studies to show its suitability. While there have been recent examples of deleterious leachables in solid oral drug products, the rate of transport of small molecules from packaging onto such dosage forms is generally low. However, it has happened, and should be of concern if there is the potential for volatile chemicals to arise from the primary packaging, or be transported through the primary packaging. Both primary and secondary packaging materials should be screened for volatile organic compounds as part of a systematic characterization of all packaging components.

Both small molecule drugs and biologics have the potential to be contaminated by extractables, and the direct harm a leachable may cause a patient is the same in either case. There may be some dependence on site of action, which is still related to the inherent safety profile of the contaminant. However, even at high concentrations in a small molecule drug preparation, the amount of leachable will usually be small compared to the number of molecules of the drug, and any reactions that might take place between the leachable and the active will not have any appreciable effect on potency. In contrast, the number of molecules of large biologic drugs in a dose is much lower, so any reactions between the leachable and the biologic are much more likely to impact potency. Another issue with biologics is immunogenicity, which is very difficult to predict from chemical structure alone.



Different dosage forms of the same molecular entity will need to be studied separately. It is not possible to state, without carrying out proper investigations, that which is safe for an inhalable formulation, for example, will automatically be safe for an injected drug.

While the identity of extractables or leachables can be unexpected, some cause well known problems, and thus are either best avoided or very carefully tested for. For example, there have been concerns about the migration of benzophenone from labels into ophthalmic products. Benzophenone is a common component of UV-active inks, but is also a potent irritant. Most label suppliers are aware of this link, and offer benzophenone-free options. However, while this individual chemical may have been removed, the irritation potential of the alternative chemicals that are being used instead has not yet been established.

Another well-known problem arises from vial closures. In general, most suppliers have switched their elastomeric closures from natural sulfur-cured latex to other, synthetic, materials. The older materials can contain extremely undesirable chemicals such as nitrosamines and polynuclear aromatic hydrocarbons, which are suspected (or known) carcinogens. It is therefore advisable to use modern synthetic elastomeric polymers for safety reasons.

QUANTIFYING THE RISK

Regulators in both the United States and the European Union have now begun to apply a standard risk level that manufacturers can pair with their respective benefit levels for new products. The tolerable risk level for the genotoxic impurities has been agreed as an excess negative outcome (cancer) of 1 in 100,000 cases. Derivation of a standard tolerable risk level for unknown leachables was one of the desired outcomes of a research project sponsored by the Product Quality Research Institute (PQRI). By comparing negative outcomes from multiple toxicological databases, the toxicologists on the orally Inhaled and Nasal Drug Product PQRI working group derived a common Safety Concern Threshold (SCT) of 0.15µg per day for any exposure compound. Below the SCT, the risk of any unknown leachable has been proposed to be acceptable. This risk can also be understood as an excess negative outcome of 1 in 1,000,000 cases.

Until these quantitative limits were set, regulators would routinely request tests right down to the limits of analytical instrumentation. Analytical capabilities have been evolving to ever lower levels over the past couple of decades, and while this has provided an abundance of information, there is no additional safety margin without the availability of thresholds such as the SCT. Even with these thresholds in hand, formulation compatibility must always be assessed on a case-by-case basis, particularly for biologics. As new and more potent compounds and therapies are introduced to patients, there is a real possibility that lower levels of leachables might cause problems in a formulation. Fortunately, the introduction of risk-based thresholds has provided a level of control of the risks of direct patient exposure that can be measured and, if necessary, managed.

Catalent®
sterile technologies

REDUCE THE RISK OF INJECTABLE FILLING

proven ADVASEPT™ technology: advanced aseptic processing for glass-free injectables.

Our next generation glass-free injectable solution utilizes advanced aseptic processing based on QbD principles to diminish risk for your sterile manufacturing challenges.

DEVELOPMENT DELIVERY SUPPLY

Catalent. More products. Better treatments. Reliably supplied.™
US +1 888 SOLUTION **EU** 00800 8855 6178 catalent.com/advasept

CTLT LISTED NYSE

OVER 95% REDUCTION IN PARTICULATES ▸ STERILITY ASSURANCE THROUGH AUTOMATION ▸ IMPROVED RELIABILITY OF SUPPLY

© 2014 Catalent Pharma Solutions. All rights reserved.

Minimizing the Risk of Sterile Manufacturing Through AUTOMATED ASEPTIC TECHNIQUES

CONTAMINATION EVENTS for aseptic manufacturing have led to product recalls, and even the complete shutdown of manufacturing plants to remediate the issues. This has caused companies real economic and reputational damage. But, fundamentally, the reason why contamination must be avoided at all costs is the potential to harm patients. If a case of contamination is not picked up before the filled product leaves the facility, the risks to patients are obvious.

In recent years, there have been numerous high profile recalls and facility shutdowns after the discovery of contaminated products. Even reading through the FDA's list of product withdrawals there are multiple examples of contamination ranging from glass fragments and other visible particles in vials, to products that caused immunogenic reactions. The severity of contamination risk was highlighted in 2012 when formulations for spinal steroid injections led to hundreds of people becoming infected with fungal meningitis — and caused multiple deaths.[1] Many of these could have been avoided had better manufacturing and control procedures been in place.

Perhaps the biggest challenge to aseptic parenteral filling is the avoidance of microbial contamination. The number one source of microbial ingress into a filling facility is the human operators running the process. If contact between operator and product can be minimized, or even eliminated, then a major potential hazard is instantly reduced, if not removed.

Traditional filling processes offer many opportunities for microbes to enter the filling line. The primary container and closure components have to be cleaned and sterilized ahead of use, but are then exposed to the atmosphere as they rotate on the filling line or stopper bowl. This provides plenty of chances for particulates and other contaminants to be deposited on or in the otherwise sterile components.

Human operators within the filling suite still pose the biggest risk in a traditional filling. They will be physically monitoring the line, straightening vials on the turntable and dislodging stoppers that may have become stuck. This physical contact provides an opportunity for microbe or pyrogen ingress, and even the fact that there are people within the filling suite, breathing and moving around, adds the potential for adventitious contamination.

LEVERAGING ADVANCED ASEPTIC MANUFACTURING TO MINIMIZE CONTAMINATION RISK

An advanced aseptic filling process that leverages blow/fill/seal, or BFS, technology has the potential to reduce these risks. The container is made in situ, and filled in a virtually closed process, with the container being sealed before it leaves the class A/ISO 4.8 environment. This technique has been in common use for the manufacturing of sterile products for decades, and is well established in the filling of parenterals in Europe, South America and Asia. However, surprisingly, in the United States traditional filling techniques for parenterals are essentially exclusive to traditional filling, despite the significant and documented benefits of BFS filling in maintaining product sterility.

BFS has been designated as an "advanced aseptic" technique by regulators. The FDA has established requirements that will render a technique advanced aseptic.[2] Essentially, it is a technique where operators dressed in normal cleanroom garments do not — and cannot — interact with open containers of products or exposed surfaces that come into contact with the product. The advanced aseptic environment of BFS is automated and controlled, with rapid product processing, and the critical control parameters are set and monitored. Other equipment that can be deemed advanced aseptic includes restricted access barrier systems and isolators.

BFS is able to meet advanced aseptic demands because the in situ manufacturing, filling and sealing of the container requires no human intervention, and the line is remotely operated and controlled. In addition, continuous monitoring of parameters, such as the viable and non-viable air in the fill zone adds a further layer of security. In all, its features greatly reduce the potential for microbial and foreign particulate contamination to the product. The FDA deems the design of the equipment, process and operational controls to render it advanced aseptic, with further evidence provided by test results from numerous microbial challenge experiments that were designed to push performance to the limit.

SYSTEM DESIGN

At the heart of the advanced aseptic technology of BFS is the automation and control. The equipment design is rooted in the principles of Quality by Design. The filling process takes place in an ISO 4.8, or Class A, environment, and it takes less than 15 seconds from the start of the container molding process to the final seal being applied to the container. Both the pathway that brings the plastic used to make the container and the pathway by which the product is introduced are virtually closed, with no operator intervention required. A further advantage is the additional level of safety afforded by the high heat and pressure used to melt and process the plastic resin, which inactivates any residual or adventitious microbes or endotoxins that might be present in the plastic.

To make the container, virgin plastic pellets are fed into an extruder through a vacuum line, where the pellets will undergo a phase change with high temperatures and pressures (typically 180 C and 200 atm). The plastic is extruded into parisons, which are long plastic tubes, into a space that meets ISO 4.8 viable air standards, where the maximum number of 0.5μm particles per cubic meter is 3,520, and the maximum for 5.0μm particles is 20. The primary container is shaped via brass and steel 2 stage mold. In the first stage, the mold closes around the parisons and a vacuum is pulled to create the container body. The top of the container is still open and is now ready for filling. Fill nozzles are then activated to fill the container with drug product. Once this is complete, the second stage of the mold closes and seals the product. Again, this entire automated process takes place in an ISO 4.8, or Class A space in the matter of seconds.

Control of the quality of the airspace around the nozzle is maintained and monitored, for both non-viable and viable air. Should the permitted particulate levels be exceeded, the filling machine will automatically shut down to prevent the container and product from being exposed to potential contamination risks. And, as the whole process takes just 15 seconds from start to finish, any risk from exposure to the atmosphere is minimized as the time the container is open is so short.

The fact that the product pathway is also closed in BFS provides further surety of safety. In a traditional filling line, components and equipment are cleaned and sterilized ahead of time and then stored before being assembled and aseptically connected, after which they sit open to the atmosphere within the filling suite. In contrast, in a BFS line all the cleaning and sterilization is done in situ, and thus the product is never exposed to equipment that has been open to the atmosphere or operators assembling it after it has been sterilized.

The ISO 4.8 space that surrounds the filling nozzle is not exposed to human operators. In the unlikely event that an operator does have to enter the closed filling area, the run is stopped and a full re-clean and sterilization procedure will be run, prior to restart. This is much less impactful than in the case of a traditional filling line, as only minimal amounts of product are ever going to be exposed, and the containers simply do not exist until they are extruded.

MICROBIAL CHALLENGE TESTING

It is clear on a qualitative level that vials filled using BFS are inherently much less likely to be contaminated by microbes or pyrogens. However, at the heart of the advanced aseptic designations is the microbial challenge data that supports this designation. Companies such as Advanced Liquid Packaging (now part of Catalent) ran numerous tests, in which various parts of the filling process were exposed to extreme microbial insults.

In order to run these tests, a specific microbial challenge facility was designed with completely dedicated HVAC and exhaust systems, to ensure unplanned contamination was not allowed in, and none able to escape. Microbial loads could therefore be carefully measured, the room safely fogged, and equipment with known amounts of contamination introduced. Several such challenge tests were carried out to form the basis of the advanced aseptic nature of BFS. The three most referenced tests are on the impact of an extreme microbial challenge on the equipment surfaces, the virgin plastic pellets used to make the containers, and the air within the room.

The first of these tests is the equipment surfaces and components test. All of the BFS surfaces were coated with varying levels of up to 108 spore suspension of Bacillus subtilis.[3] The filling process was then run under normal conditions. Even though the surfaces were loaded with microbial contamination, the only surface that created a media failure was the fill nozzle that comes in direct contact with the product. This proves that even if the equipment itself is extremely contaminated and you control the fill nozzles, the final product remains safe.

The challenge test on the raw plastic pellets involved using the loading of up to 108 B. subtilis spore suspension being fed into the extruder.[4] The combination of the heat and pressures utilized in the process created a 10–3 reduction in bioburden. Even though the microbial contamination was far greater than typical resin values, the data provides the benchmark for the critical control parameters for the plastic resin. In addition, this process offers an additional barrier to microbial contamination based on the extreme heat and pressure needed to convert the plastic from a solid to molten liquid.

Finally, the airborne challenge study.[5] The microbial challenge facility was fogged with 102 to 108 of an aerosolized suspension of B. subtilis, with aerosolization continuing throughout the test. Numerous filling runs were carried out under different microbial load conditions, including the activity of the HEPA air shower in the ISO 4.8 space. The tests showed that the contamination fraction was reduced to 10–3, a substantial reduction from the levels that had been introduced. This was directly proportional to the applied microbial load, as was the number of contamination incidents. Clearly, the high levels of B. subtilis introduced are significantly higher than those that are ever likely to be present in the real world, and these results allowed operating and environmental conditions under which the BFS equipment can automatically be guaranteed to meet the sterility assurance level demanded of products that are terminally sterilized, which is set at 10–6.

Now imagine carrying out similar tests in a traditional filling line. Everything within the filling suite — from equipment to consumables — would be covered with microbial contamination if the room were aerosolized with a 107 spore suspension. Virtually every single vial of product would be contaminated — in contrast to those tests leveraging the advanced aseptic process of BFS. Fundamentally, BFS drastically reduces the risk of contamination, which is at the heart of its advanced aseptic designation.

Traditional glass vial filling operations continue to have challenges with aseptic manufacturing that cultivate into contamination issues and product recalls that are leading to drug shortages. It is clear that implementation of BFS to fill parenteral products would reduce the risk inherent in the traditional aseptic filling process by eliminating variables and increasing automation. This could potentially enhance patient safety and product availability due to the decreased risk of contamination. The adage 'Because that's how we've always done it' is not good manufacturing practice, especially when there are alternatives that are safer and more reliable.

References

1. *Update: Multistate Outbreak of Fungal Infections among Persons Who Received Injections withContaminated Medication - Distributed via the CDC Health Alert Network December 20, 2012, 11:55 ET (11:55 AM ET) CDC HAN-0338-2012-12-20-U-N*
2. *US FDA: Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice (2004)*
3. *MCF/2- Effect of Changes in Key BFS Process Variables on Frequency of Vial Contamination. C. Sinclair*
4. *Sinclair and Tallentire (1993) Predictive Sterility Assurance for Aseptic Processing. In: Sterilization of Medical Products, Volume VI, Polyscience Publications, Montreal.*
5. *Parenteral Science and Technology July/August 1990; Bradley, Probert, Sinclair and Tallentire*