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All Hands on Deck: Pharma Meets Packaging Challenges Head-On

Serialization looms large as new technologies prove to be worth their salt

By Doug Bartholomew, Contributing Editor

Once viewed as a mundane part of the business — or in the case of child-resistant closures, a necessary fix — primary packaging of pharmaceuticals suddenly has morphed into a hotbed of creativity. From measured doses of biologic drugs self-administered by syringe, to electronic wearable injectors, to calendarized, unit-dosed blister packs containing multiple pages of patient instructions inside the label, the once-staid business of packaging drugs is evolving into a platform for innovation.

This vastly expanded variety of drug delivery formats has come about largely as the industry has sought to navigate its way through a veritable Scylla and Charybdis of regulatory requirements on the one hand, and security challenges on the other.

Admittedly, some of the latest pharmaceutical packaging trends can be traced to new kinds of drugs — biologics and the new class of biosimilars, for example — that require fresh approaches to the way drugs are administered to the patient, and new technologies that enable them. No one expects the basic plastic pill bottle to go the way the pair of pliers did in dentistry anytime soon, but chances are that most people have already encountered some of these new packaging methods when filling a recent prescription or purchasing an over-the-counter medicine.

This article will examine some of the key challenges having an impact on primary packaging, and how pharmaceutical manufacturers, contract firms and packaging vendors are responding.

An employee at Patheon's Monza, Italy, site conducts a visual inspection of products.

SERIALIZATION

Perhaps the biggest single challenge confronting the pharmaceutical industry from a packaging standpoint continues to be the need to combat the onslaught of counterfeiting that has swamped global pharmaceutical markets. The call for serialization has come about largely in response to this problem.

"The main challenge facing the industry in the United States as well as the EU will be the implementation of the requirement for serialization of all pharmaceutical product down to the smallest unit of sale," points out Rick Seibert, senior vice president for Global Innovation and Technology Services at Sharp Packaging Solutions. "This regulatory-driven change will fundamentally change the way product is packaged, and possibly more importantly, labeled and safeguarded in the future."

Jerry Martin, Pharmaceutical and Life Sciences consultant for the Association for Packaging and Processing Technologies (PMMI), recalls how several years ago he was contacted by a company that had developed a unique 2D barcode system designed to help eliminate drug counterfeiting. But when he approached some pharmaceutical companies with the idea, they weren't interested. "We ran up against a complete denial that there was any prob-

lem," he says. "And the FDA said it was not capable of policing the markets for counterfeiting of drugs."

Finally, the problem got so bad that regulators in Europe and the FDA in the United States issued regulations requiring the serialization of packaging for tamper-proof medications, as well as the establishment of a track and trace system. In the U.S., these regulations go into effect over the next couple of years.

But having the technology to achieve track and trace and manufacture tamper-proof packaging is one thing, and ensuring that the entire global industry adopts the same technologies is another. "Companies are working together to come up with a compatible system for drugs moving through the supply chain," Martin says. "The challenge is to come up with an internationally harmonized system — not unlike the UPC system for consumer products that we have now."

In effect, that means everyone will have to use the same hardware and software to connect seamlessly across the various global supply networks throughout the industry — a tall order, to say the least. But Martin, for one, believes it can be done. "Serialization will eliminate the ability of counterfeiters to put product on the market," he says. "This way, labeling will enable the distribution system to detect counterfeiting before products even get to a pharmacy."

"Serialization will come to different parts of the world at different times," says Carlo Domeneghetti, corporate procurement packaging COE Lead at Patheon in Monza, Italy. "But once in place, serialization, combined with tamper-evident packaging, will be the best way to guard against counterfeiting."

Packagers are likely to take a layered approach to guarantee security and product integrity. "Ideally, there will be additional security features — some covert, some overt — deployed by brand owners as well, offering a tiered/layered program to assure security and product integrity," says Seibert of Sharp.

One packager taking the lead in the march toward serialization is Wheaton Industries. The company's crimp-top vials, which have a plastic coating around the glass the company calls DualFusion, come with a 2D barcode laser-etched on the vial bottom that can be read by a barcode scanner. "Using the scanner, the medical professional can verify that they are giving the right drug to the right patient, because the barcode identifies that drug with that hospital and that patient," explains Wayne Brinster, CEO.

PLASTIC VS. GLASS

The plastic vs. glass debate continues to roil the packaging waters, with the glass camp pointing out their material's benefits and the plastic adherents doing the same for their material.

Workers load auto-injector device components into the machine which takes the drug supplied in an ampule and assembles it into the pen.

At the heart of the dispute is the all-important issue of drug quality — i.e., ensuring that all pharmaceutical substances, especially the expensive biologics, are not reacting with their primary container's material. Glass contains silicon, which can chemically interact with some substances contained in various drugs.

Glass adherents counter with the claim that plastics can react as well. "Plastic water bottles can leach out chemicals, but Type 1 pharmaceutical glass is not going to change a drug," adds David Machak, a consultant at American Glass Research in Butler, Pa.

Even so, the trend is toward plastic, especially for biological drugs. "Due to the potential defects of glass, the market is slowly moving to plastic solutions," says Patheon's Domeneghetti. "Even in syringes, there is a slow trend to move to plastic."

As an example of this shift, West Pharmaceutical Services is using its Daikyo Crystal Zenith vials with its FluroTec stoppers to contain Amgen's FDA-approved oncolytic virus therapy, Imlygic. Manufactured from a cyclic olefin polymer, the CZ vials offer a break-resistant alternative to glass for complex drugs.

Some packagers have solved the problem by marrying glass and plastic. In the case of Wheaton Industries' DualFusion plastic-coated vials, because both the glass and the

plastic layer are fused together, the finished vial can withstand breakage when dropped on a hard surface such as a terrazzo or concrete floor. “The inner layer of organo-silicate eliminates exposure to metals or problems with delamination,” Brinster says.

SELF-ADMINISTRATION

As more biological drugs including biosimilars are being self-administered by patients at home, the dual issues of ease of use and convenience take on greater emphasis than in the past, when such drugs typically would be given in a clinical setting by healthcare professionals. For instance, having primary packaging designed to deliver a consistent injection rate can help ensure that patients taking drugs at home receive the accurate dose for their treatment regimen.

Packaging industry experts caution that self-administration of drugs must by necessity place the emphasis on clear instructions to the patient. “There is a need to provide patient education and training on the devices and delivery systems in addition to the traditional dosing information,” says Seibert. “Coupling these types of programs with the physical package is a solid value proposition we discuss with all clients in the design phase of our project development process.”

INNOVATION

One of the challenges posed by this brave new world of pharma packaging is the need to innovate to avoid falling behind the competition. Among those taking the lead in this area is West Pharmaceutical Services, asserts Martin of PMMI. In July, Amgen received FDA approval for a single, monthly 420 mg dose delivery option for the Repatha cholesterol-lowering drug using West’s hands-free device called the SmartDose electronic wearable injector. The device adheres to the patient’s body, usually on the abdomen, allowing the patient to be hands-free while taking the drug.

“This is clearly an example of differentiation and innovation in pharmaceutical packaging,” Martin says. “The auto-injector makes it easy for patients to take the drug called without having to see the needle. The patient uses a self-contained syringe mechanism with a pushbutton, so everything in the self-administration process is automatic.”

In another example of innovation, Pharma Tech Industries, a contract manufacturer, received approval last January for a novel approach, a drug-device combination consisting of a nosepiece device containing two doses of a common migraine medicine for patients to take the drug in a nasally inhaled form. “The drug is sent to us from the drug manufacturer Avenir Pharma, and we make the product for a distributor,” says Lori Hall, director of quality engineering at Pharma Tech in Athens, Ga.

PATIENT COMPLIANCE

Exacerbated by an aging patient base as

Workers perform subsequent secondary packaging and cartoning of the device.

waves of baby boomers reach the age of seniority, the challenge of ensuring that patients take their prescription medicines in the proper doses and at the proper times looms larger than ever. The global revenue loss to the pharmaceutical industry as a result of the failure of patients to take their medication for chronic conditions alone is estimated to be $564 billion, according to research by CapGemini Consulting.

"A key challenge for the packaging industry is the aging patient base and compliance," Martin says. "Pharmaceutical containers have to be tamper-proof, but they also have to be easy for elderly people to open. I've seen some blister packs that are more difficult for people who don't have the dexterity with their hands that's required to open them. As the baby boom ages, drug containers have to be designed so it's easier for people to take their medicine."

By contrast, he says, the use of auto injectors for biological drugs are an example of easy-to-use packaging. "I envision greater use of devices to ensure compliance," Martin adds. "Already we are seeing more prefilled syringes. Companies are coming out with packaging systems that make it easier for people to self-administer drugs."

Pharmaceutical benefit managers today are requiring results in the form of improved

health outcomes, but the simple fact is that "drugs only work for people who take them," says Eric Resnick, vice president and chief technology officer at West Pharmaceutical Services in Exton, Pa. In the last decade, the 90-plus-year-old company has evolved beyond the traditional approaches, developing new packaging designed to provide both containment and drug delivery mechanisms.

"Simply saying that a device or package has to work is no longer acceptable," he says. "We need to understand why people are not using a specific drug — is the device too complex or too difficult to use?"

West Pharmaceutical Services helps ensure patient compliance through its alliance with HealthPrize Technologies, which integrates a medication adherence and patient-engagement platform with West's injectable drug delivery systems. The combined approach provides a voluntary, electronically connected drug delivery system that tracks when patients take their medication, with patients receiving reward incentives for taking their medication on a regular basis as prescribed.

Additionally, a number of "smart" technologies are entering the pharmaceutical packaging scene. Silicon Valley startup Proteus Digital Health has developed a "smart pill" embedded with an ingestible sensor that sends a signal to a wearable sensor patch when the pill is digested. Patients and doctors get alerts when pills are swallowed, so that doses are not missed. NYC-based startup AdhereTech offers a smart pill bottle that uses wireless technology to collect and send adherence data in real-time. The pill bottle lights up to remind patients to take pills, as well as sends customizable reminders when a dose is missed.

A COMMON PLATFORM?

Today's drug packagers are actively pursuing a host of new solutions to the various challenges they face, including those posed by regulatory, security and new drug therapies. But the jury is still out on how quickly the global pharmaceutical industry will be able to pull together a common technology platform that will enable drug packagers to achieve global serialization, thereby reducing or eliminating drug counterfeiting and diversion.

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Packaging Systems Evolve

Pharmaceutical Manufacturing discusses challenges of today's packaging systems with Jerry Martin, pharmaceutical and life sciences consultant to PMMI, The Association of Packaging and Processing Technologies

What are the major challenges that pharmaceutical end-users experience with their packaging systems?

There are a couple of significant challenges that pharmaceutical manufacturers may experience in selecting and implementing packaging systems. One of these challenges is posed by the growing trend toward prefilled syringes for liquid injectables. Prefilled syringes offer a much higher degree of performance than traditional vials by eliminating the dosage preparation necessary at the hospital. However, the implementation of prefilled syringes expands the validation process for the drug manufacturer.

Another challenge stems from the new standard on the qualification of materials for packaging systems with regard to extractables and leachables. Chemicals that can migrate out of the packaging materials and into the dosage form are a concern. With advancing analytics technology, there is a push from the FDA to understand what risks are posed by packaging ingredient migration. U.S. Pharmaceutical Convention (USP) is actively working on revising its standards for qualifying plastic packaging materials from the raw material to the final format. It's in the process of being finalized and it will be helpful for the industry to follow those standards. The goal is to establish standard evaluation methods and eventually, threshold limits, out of a consensus of experts.

Can you elaborate more on the revision of standards by the USP?

USP has formed an expert committee of volunteers from different reaches of the pharmaceutical and biotech sectors — in-

We're moving into a domain where the drug and the device are a package deal, but assessed by different teams at the FDA.

— Jerry Martin

cluding testing laboratories, drug manufacturers and component or equipment suppliers — to assess the risks and establish an updated, standardized approach to qualifying materials and packaging systems. The first two new standards published late last year addressed the qualification of component materials and final containers made from those materials. The next standards will address the process equipment side — upstream of filling the final packaging. These are currently in draft form and will be finalized by the end of this year. The next step, slated for 2017, is to generate standards for the suitability of packaging in the final dosage form.

When will drug manufacturers be expected to comply with these new standards?

No deadlines are set for compliance. These standards are voluntary. The USP sets the reference standards for the U.S. Food and Drug Administration (FDA). Therefore, pharmaceutical manufacturers that follow the USP standards will not have to go through any extra steps to meet FDA approval. However, pharmaceutical manufacturers that opt not to abide by USP standards will be held accountable by the FDA to provide other proof that the methods of analysis utilized are at least as effective. The USP's guidelines are treated as expectations. If an FDA reviewer questions a practice that complies with USP standards, pharmaceutical manufacturers have a strong scientific basis to stand on.

At this particular juncture in time, what is driving the need for these new USP standards?

Packaging systems are becoming more and more complex. I recently read about a biological that is packaged in an automatically timed, self-injection device that patients can wear on their stomachs. When a packaging system was just a vial in a box, there were far fewer components to evaluate. We're moving into a domain where the drug and the device are a package deal, but assessed by different teams at the FDA. The trend toward more complex delivery systems just doesn't always fit into the

organizational structure of that agency. The FDA addressed this through the Office of Combination Products and new guidance. Creating a standardized set of expectations will make oversight of these increasingly complex packaging systems easier for all parties.

How has this trend toward complex packaging systems affected the general supply chain?

Pharmaceutical manufacturers certainly want to ensure that drugs, especially biologicals, are kept at the right temperature through the course of the supply chain. While we haven't seen many instances where temperature control of the drug has compromised the delivery device, temperature control is becoming more sophisticated with tracers that monitor the temperature and maintain it through electronic signal so that the operators detect any deviation before the product goes bad. The added complexity is bound to necessitate greater utilization of the Internet of Things (IoT) to provide a higher sense of security and environmental control. These methods are being investigated now. On the topic of track-and-trace, sophisticated monitoring devices can help serve to authenticate original products when the threat of counterfeits loom over a drug.

ABOUT PHARMA EXPO

Pharma EXPO (November 6-9; McCormick Place, Chicago, Illinois) will be a resource for insights and solutions on equipment and material solutions to adhere to new USP standards. Co-located with PACK EXPO International, Pharma EXPO is co-produced by PMMI, The Association for Packaging and Processing Technologies and ISPE, the International Society for Pharmaceutical Engineering. Together, the two shows will serve as the largest resource for processing and packaging innovation in North America.

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Trends Driving Liquid Dose Packaging

New compounds, delivery methods, safety and security are the current trends driving liquid dose drug manufacturing.

Liquid dose pharmaceuticals are most often formulated as solutions, suspensions or emulsions. *(Citation: Murthy, RSR and Kar, Ashutosh; Pharmaceutical Technology Volume-I, page 3. -http://www.newagepublishers.com/servlet/nagetbiblio?bno=002130)*. Solutions are a homogeneous mixture where at least once substance is dissolved into another. Suspensions are heterogeneous mixtures with solid particles floating freely in a solvent. Emulsions involve ingredients which are normally immiscible, meaning that they are unblendable or unmixable. Orally administered drugs are traditionally found in glass bottles and delivered through cups, spoons, and droppers. Parenteral drugs, or non-orally administered drugs, are commonly delivered with a syringe that has been filled from a glass vial or ampoule. Many new advancements have been made to deliver more complex formulations beyond these traditional methods with increased shelf life and control over the dose administered.

Many new compounds are complex, large molecule formulations that do not remain stable very long after mixing. Lyophilization, or freeze drying, adds shelf-life to compounds which are unstable as a liquid. In this process, the materials are mixed and filled into a vial, usually in an aseptic, or sterile environment and transported to the freeze-dryers. The freeze-dried product can remain stable much longer which enables extended supply chains and larger inventories where the drug can reliably remain in a status where it is both safe and effective. Often, these products are packaged in a kit with diluent to *reconstitute* the **freeze** dried product. In addition to the increase in freeze-**dried** liquids, there have been advancements that combine delivery methods and packaging.

Aerosols and foams can be used to deliver inhaled and topical drugs. Aerosols are released as a fine spray which is inhaled or applied topically. Foams are a mass of small bubbles. These products require special manufacturing and packaging equipment to combine the drug substance with a propellant and package them under pressure. Commonly used propellants in the pharmaceutical industry such as tetrafluoroethane or dichloromethane are generally not metabolized by the human body which makes them safe for use in drugs like commonly delivered via a metered dose inhaler *(citation: http://metricsinc.com/common-drug-propellants-undergo-insignificant-metabolism-by-body-metrics-scientist-says-in-aaps-poster/)*. Aerosols and foams are commonly self-administered therapies which is another trend in liquid dose manufacturing and packaging.

Self-administered therapies are a driving trend in liquid dose manufacturing. The biggest advancements are unit dose vials and pre-filled syringes. These delivery methods provide pre-packaged doses of liquid products that a patient can administer themselves. Avoidance of office visits increases the likelihood of patient compliance and reduces costs. Unit-dose-vials produced on blow-fill-seal (BFS) equipment. BFS equipment is a single machine were plastic resin is extruded, blown into a mold, filled and sealed. They can be operated in an aseptic environment for opthalmic products or inhalants that can be nebulized. Pre-filled syringes deliver the product in pre-packaged in a syringe ready for patient dosing. The pre-determined doses provides for safe administration of the product.

Safety and security are important considerations for any self-administered product. In addition to the product being safe and effective, the packaging must robust and secure. Anti-counterfeit packaging validates that the product came from the proper source. Tamper evident labels show the consumer that the product has not been compromised after manufacturing and packaging. Additionally, track-and-trace measures will use equipment to apply special labels with coding and, possibly, radio frequency identification (RFID) to ensure that the product can be traced back to the manufacturer.

All drug dosage forms rely upon delivery method and packaging to securely deliver a safe and effective product to the patient. New, life-saving compounds are being developed which require additional manufacturing steps to help them be available on the shelf when they are needed. Innovative delivery methods like aerosols and foams allow drugs to be delivered in novel ways. Self-administered drugs reduce costs and provide for accurate doses. While specialized packaging ensures that the product is what it says it is. All of these factors are driving the trends for liquid dose pharmaceutical manufacturing.

Additional resources

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The State of Pharmaceutical Packaging

Several factors converging at once for the pharmaceutical industry are contributing to the growth and importance placed on packaging

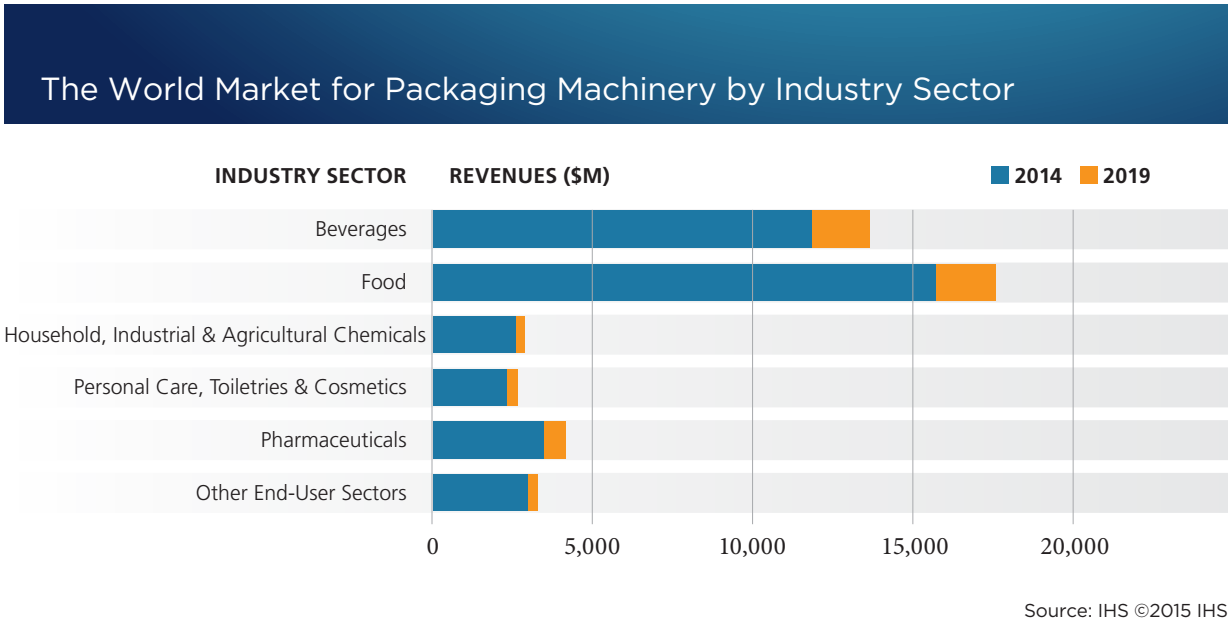
by Jorge Izquierdo, vp, market development for PMMI, The Association for Packaging and Processing Technologies

The global pharmaceutical industry is projected to grow markedly through the decade, reaching $1.4 trillion and 4.5 trillion doses of medicines by 2020[1]. The pharmaceutical packaging market is growing rapidly in kind and is expected to surpass $100 billion globally by 2019[2]. In fact, according to a new study from PMMI, the pharmaceutical packaging sector is expected to grow the fastest among all packaging industry sectors, growing at a five-year CAGR of 3.9 percent through 2019[3].

Several factors are converging at once for the pharmaceutical industry, contributing to the growth and importance placed on packaging. These factors include global demographic shifts, advances in serialization to meet new requirements and the influence of the generics and biosimilars markets.

GLOBAL DEMOGRAPHICS

Many developing regions — including Asia/Pacific, Latin America and much of the Middle East and Africa — will continue to see population growth coupled with economic development. The resultant rise in the middle class will lead to a greater global population that can afford access to drugs. In developed regions where population growth is typically slower, general improvements in healthcare have contributed to an aging population. According to the U.S. Census Bureau, people age 65 and over accounted for around 8.5 percent of the global population in 2015. It is projected that it will reach 12 percent by 2030. This trend is particularly impactful on the pharmaceutical market, as elderly people are large consumers of medicines. Both trends will contribute to an increase in the use of pharmaceutical



The World Market for Packaging Machinery by Industry Sector.

packaging, as well as pharmaceutical packaging equipment, throughout the decade.

SERIALIZATION

The importance and consideration placed on packaging in the world of pharmaceuticals has expanded considerably as a result of serialization requirements. Packaging plays a vital role in ensuring the traceability of products across the supply chain. Several pieces of legislation mandating various serialization requirements have been enacted globally in recent years. In the U.S., the Drug Quality and Security Act (DQSA) has created national, rather than statewide, regulations for serialization. DQSA mandates will come into force for manufacturers in 2017.

The cost and time associated with meeting these regulations can be high. Many manufacturers will require new labeling, coding and scanning equipment to become compliant. Packaging equipment in such categories is expected to see growth prior to serialization deadlines and a downturn immediately following them. For some pharmaceutical manufacturers, installation of new equipment may require an expansion of the packaging line. For those with space limitations, this means potentially turning to robots, where enhanced flexibility offers the capability to handle multiple products in the same space with the same equipment. While working to upgrade their packaging lines to gain compliance with serialization laws, many pharmaceutical manufacturers are turning to co-packers to help fill the gaps in technology and capacity.

Also, proper serialization will require the effective transfer of information among all parties throughout the supply chain. As a

result, demand for improved integrated, software-based solutions has risen, a trend that is expected to continue for the foreseeable future.

GENERICS AND BIOSIMILARS

As patents for several blockbuster drugs expire — known as the patent cliff — the market becomes increasingly competitive with the flood of generics entering the market. Production of the number of pharmaceutical products increase, therefore increasing the number of packaging types employed. Additionally, last year, the FDA approved the use of the first biosimilar product. According to the FDA, a biosimilar is "a biological product that is approved based on a showing that it is highly similar to an already-approved biological product, known as a reference product." Biosimilars are thought to have a comparable effect on the market as generics, potentially increasing competition and the number of packaging types.

As competition steepens, many pharmaceutical companies — particularly original patent owners — are turning to packaging as an important point of differentiation. Packaging technology that can improve convenience and quality, combat counterfeiting or increase patient compliance can set a pharmaceutical product apart.

PMMI, PHARMA EXPO 2016, PACK EXPO

PMMI, The Association for Packaging and Processing Technologies, represents the voice of more than 700 North American manufacturers of equipment, components and materials for processing and packaging. Pharmaceutical manufacturers looking to find the latest packaging solutions can turn to resources provided by PMMI, co-producer of Pharma EXPO 2016 (November 6-9; McCormick Place, Chicago, Illinois) with ISPE, the International Society for Pharmaceutical Engineering. Co-located with PACK EXPO International, the two will serve as the largest resource for processing and packaging innovation in North America. The shows will bring together more than 2,300 suppliers in 1.2 million net square feet of exhibit space to showcase a wide range of processing and packaging solutions to 50,000 attendees.

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A Look Back at Packaging

Packaging does much more than serve as a place for the label

By Emil W. Ciurczak, Contributing Editor

My first job in Pharma was in the Package Materials Testing Group (me) to develop a new (in 1970) approach called "plastic bottles" to replace traditional glass bottles. Another strange, new idea we played with was something called "blister packs." Originally, the reasons for switching from amber glass to plastic bottles were 1) safety (glass breaks, remember?) and 2) cost savings. The blister packs were to replace "strip packages," used by doctors for samples… later found to be good for selling product, as well.

Sounds like an easy switch, but in 1970, interactions between drug products and polymers (and additives) were not known. There is a potential for the API to migrate into the container and, conversely, some of the chemicals (anti-oxidants, mold-release agents, etc.) can migrate into the drug product and either react or "merely" be ingested.

One early example was a trial insertion of the dropper into the bottle of nose drops. Shipping it this way allowed for a smaller package. Since the earlier droppers were glass, for both safety and weight, they were replaced with a polypropylene one. We quickly discovered that the preservative (thimerosal) was absorbed by the dropper, meaning that the first time it was used and replaced, the bottle was an incubator for whatever bacteria came from the patient. A hand lotion, packed in a PVC bottle, extracted the organotin antioxidant from the polymer. Clearly, some R&D was needed.

Switching from glass to plastic also had some physical difficulties, too. The simplest

A hand-held NIR or Raman instrument should be placed in the packaging room for assurance.

was the shape and height of the bottle itself. As tablets are filled at a rapid rate, they bounce off the bottom and ricochet off the curved shoulders. Months of experimentation were needed to determine the correct parameters to keep chipping and breakage at a minimum. And then there was the cap.

Formerly, on glass bottles with metal caps, there was a paper liner that adhered to the glass when the cap was tightened to a predetermined torque. Well, the adhesive used didn't stick to polymers, metal caps didn't work, and plastic "creeps" when torqued to the required tightness, becoming looser with time. Clearly ALL specs needed to be changed. To "ice the cake," so to speak, current labels didn't adhere to the polymers. So they allowed me, a newly minted Physical Chemist, free-rein in the lab.

Fortunately, we had some nice instruments, one of which was an Instron stress measuring device. I used a punch to cut samples from the bottles, along the long and short axes, shaped like mini-barbells. These were clamped into the claws of the device and slowly stretched to the tear-point, determining the tensile strength. An average of several batches were determined, the bottles were then subjected to stability conditions (heat, light, humidity) both empty and with the tablets for which they were intended. As samples were taken at time points, empty and filled bottles had their tensile and tear strengths tested to see if the product affected them.

Also, since the native polymers offered little protection from light, we needed to ascertain the percentage of TiO2 that needed to be added. Less than 3 percent allowed light to degrade the product and more than 3 percent made the bottle brittle, so that's how we chose 3 percent. Then we had to evaluate blister packs for distribution.

A lot of travel was involved, since the technology was not ubiquitous. But as we began

determining what polymers and which coatings were best, someone had the idea that they would also be good for clinical trials. They could be filled by hand and they could all be different, allowing double-blind studies to be run.

One of the recurring problems of pharmaceutical companies (and the cause of many warning letters and recalls) is mislabeling and incorrect drug product in containers. The bulk tablets or capsules arrive in fiber drums or plastic containers, identified by a label, possibly hand-written and certainly hand-attached. The materials are placed in bottles or blisters, based on "faith" that the labels are correct. Since this is often not the case, I have suggested that a simple, handheld NIR or Raman instrument be placed in the packaging room for final assurance that the proper product is packaged. After all the work in developing the package-product marriage, it's the least we can do. Now, nearly 50 years later, these containers are taken for granted, but if you meet a packaging engineer, tell him, "Thank you."