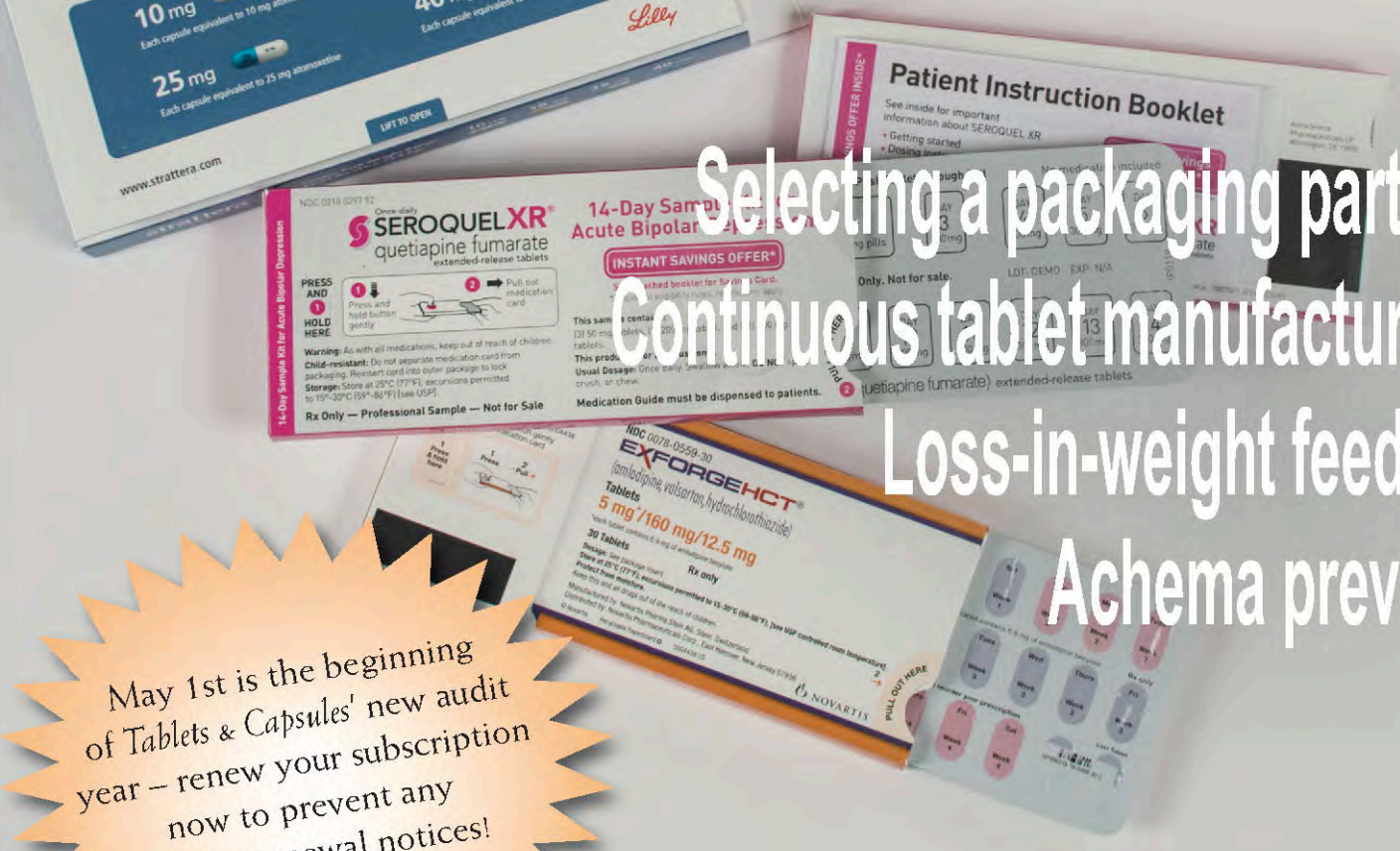
TABLETS & CAPSULES

FORMULATION PRODUCTION PACKAGING

Volume 13 Number 4
May 2015 $15.00



Selecting a packaging partner

Continuous tablet manufacturing

Loss-in-weight feeding

Achema preview

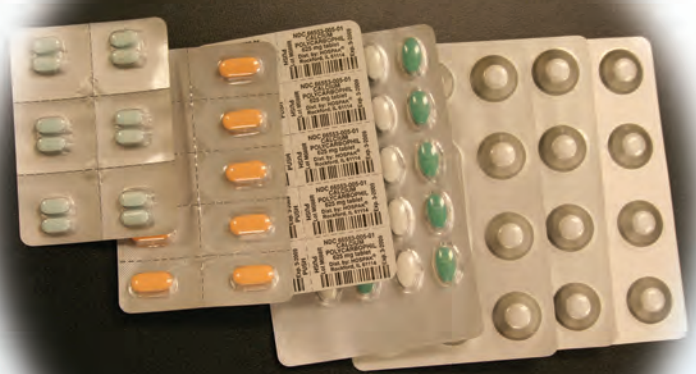
May 1st is the beginning of *Tablets & Capsules'* new audit year – renew your subscription now to prevent any further renewal notices!

Future Pak

Contract Packaging with a Pedigree!

We have been ahead of the curve since 1977...
and we will be ready for track and trace serialization.

SOLID DOSE SPECIALISTS



CAN WE HELP YOU GET THERE TOO?

Call 248.486.0045 or Contact
RBean@Futurepak.com or
DLMalone@Futurepak.com

FUTURE PAK.com

Your Proven Strategic Partner Since 1977

28115 Lakeview Drive
Wixom, MI 48393
248.486.0045 (ph) . 248.486.0086 (fax)
Visit www.futurepak.com

KIKUSUI
Legendary Quality and Reliability

Introducing the **VELA G** — a new state-of-the-art R&D tablet press

VELA G was designed to process small amounts of granulation during product development stages. **VELA G** features turret changeability allowing use of TSM B and TSM D tooling.

- 12 stations TSM-B, and 8 stations TSM-D tooling
- Max pressure 50kN main compression
- Small foot print, W30″ x L18″ x H40″
- User-friendly, easy cleaning
- Compression force data interface available
- Swing-out roller assembly
- Swing-out turret, easy changeover

***VELA G** is the answer to a scientist's desire for a small scale, small sized machine that electronically and mechanically mirrors production machine operation. **VELA G** — perfect for product transfer from R&D to production.*

KIKUSUI USA, INC.
1650 Oak Street • Lakewood, NJ 08701
Phone 732-349-3131 • Fax 732-349-3354
Email: sales@kikusui-usa.com
www.kikusui.com

If you like KIKUSUI tablet presses, you will love the VELA G Quality and Reliability!

TABLETS & CAPSULES

www.tabletscapsules.com

May 2015
Volume 13 Number 4

Cover photo shows winners of the Compliance Package of the Year competition conducted by the Healthcare Compliance Packaging Council. At top is Eli Lilly's Strattera physician sample pack (first runner up) by PCI, Rockford, IL. Next is AstraZeneca's Seroquel XR 14-Day sample pack (Compliance Package of the Year) by MWV, Richmond, VA. Below that is Novartis' Exforge HCT (second runner up) by PCI. Courtesy of HCPC, Bon Air, VA. Tel. 804 338 5778. Website: www.hcpconline.org.

packaging

also in this issue

departments

Tablets & Capsules (ISSN 1549-9928 print; ISSN 1938-9159 online) is published eight times a year in January, March, April, May, July, September, October, and November by CSC Publishing, Inc., 1155 Northland Drive, Saint Paul, MN 55120. Periodicals postage paid at Saint Paul, MN, and additional mailing office. POSTMASTER: Send address changes to *Tablets & Capsules*, 1155 Northland Drive, Saint Paul, MN 55120.

CAPMATIC®
MONTREAL CANADA
SINCE 1964 ...

Built for Life !

STREET FIGHTER™ ...
EVERYTHING COUNTS !

Electronic Tablet & Capsule Counter

Fully efficient on tablet separation, tablet counting and tablet gating directly related to an innovative vibrating system and machine design.

SF-100

No air required allowing for optimized efficiency and complete control of the machine.

Recipe driven quick, repeatable and tool-less changeover through the Allen-Bradley HMI.

Elegant and compact design, 100% Built in North America complying to cGMP & FDA regulations.

Fast & Easy Cleaning procedure by means of special quick release system and design.

Speeds up to One Million tablets/hr per module.

Capmatic Complete Tablet & Capsule Packaging Line

Unscrambler | Electronic Tablet & Capsule Counter | Dessicant & Cotton Inserter | Capping System | Retorquer | Labeler

capmatic.com
+1 514 322-0062, sales@capmatic.com

CAPMATIC® MONTREAL CANADA
Countlab® countlab.com

Street Fighter™ SF series electronic tablet counters including SF-50, SF-100 and SF-200 are designed by Countlab® which is a subbrand of CAPMATIC® Ltd.

TABLETS & CAPSULES

www.tabletscapsules.com

Publishing Office
1155 Northland Drive, St. Paul, MN 55120
+1 651 287 5600 FAX: +1 651 287 5650
e-mail: tc@cscpub.com

Philadelphia Office
800 West State St., Suite 103 Doylestown, PA 18901
+1 215 340 6988 FAX: +1 215 340 6989
e-mail: segenolf@cscpub.com

Achieving new standards in performance takes years of innovative R&D. This is the result.

Vcaps® Plus hypromellose capsules

for pharmaceutical products – true pH and ionic media independence in disintegration for optimized delivery and performance.

Some HPMC capsules are formulated with secondary gelling agents and ionic gel promoters – which may slow down release of active ingredients. Capsugel's Vcaps® Plus HPMC capsules are made through a proprietary manufacturing process that eliminates the need for gelling systems. They disintegrate and release their contents independent of pH and ionic strength of the test media. To discover how Vcaps® Plus capsules can optimize performance, improve product stability, and reduce both variability and timelines in your drug development, download our free whitepaper.

VcapsPlus.com **888-783-6361**

CAPSUGEL®

markets

Report assesses solubility-enhancing excipients for OSDFs

PARSIPPANY, NJ—The market for solubility-enhancing excipients for oral solid dosage forms will grow at a compound annual rate of 13 percent between 2014 and 2024, according to "Solubility Enhancement in Pharmaceutical Oral Solid Dosage Forms: Global Market Analysis and Opportunities." Published by Kline & Company, the report also assesses processes that improve API solubility, including size reduction, chemical modification, spray drying, hot-melt extrusion, and lyophilization.

www.TABLETSCAPSULES.com

industry news

Mylan pursues Perrigo; Teva offers $40 billion for Mylan

NEW YORK, NY—Two weeks after generic drug maker Mylan offered $29 billion to acquire Perrigo of Dublin, Ireland, the company rejected the offer, and Mylan became the target of a takeover bid by Israel's Teva. Teva, the world's largest manufacturer of generics, offered $40 billion and said the combination would help it manufacture softgels and other difficult-to-make products.

TGA considers adopting EU guidelines

SYMONSTON, Australia—The Therapeutic Goods Administration is discussing adopting European Union guidelines in Australia. Under consideration are ICH Q9 and Q10, as well as guidelines on stability, active substances, clinical pharmacology and pharmacokinetics, biosimilars, and others.

Lung cancer pill shows promise

LONDON, UK—New findings from an ongoing clinical trial show that AstraZeneca's AZD9291, administered at one 80-milligram oral dose per pay, delays the progression of a specific lung cancer by as much as 13.5 months. The company is expected to file a new drug application (NDA) for the molecule later this year.

IPEC issues position paper on excipient standard

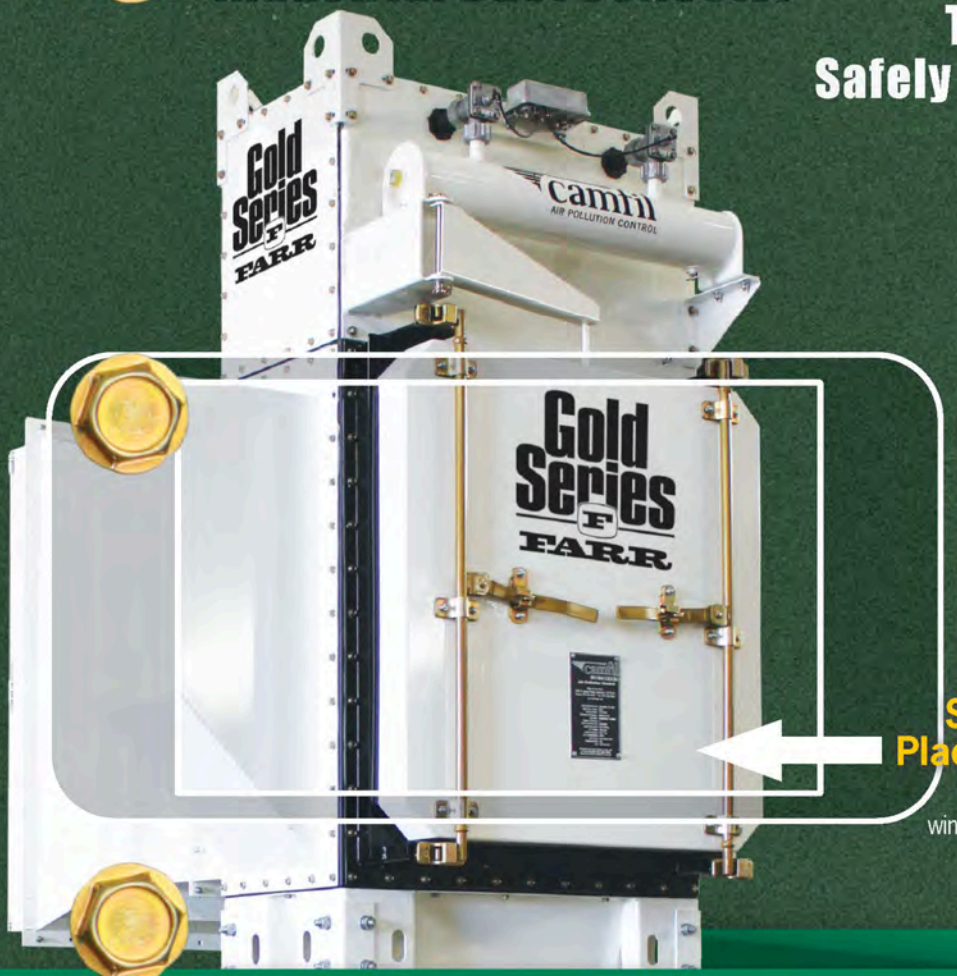
ARLINGTON, VA—Members of IPEC-Americas' GMP Committee finalized its position paper, "Implementation of the NSF/IPEC/ANSI 363-2014 Excipient Standard." Though not suggesting a specific deadline for implementation, IPEC recommends that all excipient suppliers have an implementation plan in place by the end of third quarter 2015.

GENERAL VENTILATION
TABLET PRESSES
GRANULATING
TABLET COATING
FILLING & PACKAGING
MIXING & BLENDING
LOCAL EXHAUST
DRYING
CENTRAL VACUUM
AND MORE

DUST PROBLEMS SOLVED

Farr Gold Series®
Industrial Dust Collector

Total Containment Safely and Economically




Bag-In Bag-Out

Scan QR Code, Place Phone Here

Turn your phone into a window to actually see inside the Farr Gold Series.

LOOKS LIKE A SAFE BECAUSE IT'S

BUILT LIKE A SAFE™

866-696-6266 www.camfilapc.com

camfil
AIR POLLUTION CONTROL

packaging

Selecting a contract packaging partner

Scott Garverick
Pharma Packaging Solutions

Partnering with a contract packaging company gives manufacturers the expertise to comply with serialization requirements and the flexibility needed for global pharmaceutical logistics.

The global pharmaceutical sector is reshaping itself to be leaner and more responsive to market demands. That's because, as always, manufacturers are seeking to reach global markets more quickly. To do so, they must navigate myriad new regulatory requirements across many countries. In short, new regulations and regulatory uncertainty have placed the pharmaceutical industry in a challenging and uncharted landscape.

Among the drivers of these changes is merger and acquisition (M&A) activity, layoffs, patent expirations and a fluid regulatory environment. Overall, M&A activity in 2014 increased by 4.1 from 2013, reaching $378.2 billion, and the number of deals rose by 37.5 percent to 153 [1]. In most M&As, supply chains also merge, and that alone is a complex process that must be well managed. When you add layoffs and patent expirations, the challenges grow larger as companies focus on cost cutting. These changes can lead to delays in delivering drug products, poor customer service, security and compliance risks, and a host of missed opportunities.

Meanwhile, the intricacies of logistics and the complexities of new regulatory requirements persist. Logistics—

from the time the product is produced, packaged, and labeled to its ultimate distribution—requires special care in terms of product shelf life, temperature control, storage, and shipping. From a regulatory standpoint, different governments take different views of drug products, their components, and how they must be handled and documented.

Using a contract packager

Contract packagers allow pharmaceutical companies to focus on their core competencies of developing and marketing needed drugs. When identifying the right contract packager, pharmaceutical companies need to consider compliance, capacity, and capabilities. There are many contract packagers to choose from. According to a 2013 technical market research report, the global market for pharmaceutical and biopharmaceutical contract manufacturing, research, and packaging was valued at $219.9 billion in 2012 and is expected to reach nearly $374.8 billion by 2018, which equals an annual growth rate of more than 9 percent [2].

Outsourcing packaging is a beneficial business strategy because it enables pharmaceutical manufacturers to transfer non-core activities to external partners, allowing manufacturers to restructure their distribution networks, make better use of internal resources, and intensify their focus on research and development. Meanwhile, contract pharmaceutical packagers can focus on incorporating packaging innovations, which "are expected to create a major change in the way drugs will be packaged," according to a 2014 report form Frost & Sullivan [3]. In many cases, outsourcing has improved supply chain management; it can also reduce total supply chain costs by 25 to 50 percent [4].

Seek a contract packager that can handle large and small batches and whose equipment can package drug products in different formats.

Serialization

The most critical issue today for people working in the pharmaceutical supply chain is serialization, also known as track and trace. It's an area that continues to grow to fight drug counterfeiting, which is a multibillion-dollar industry. While its exact extent is unknown, in some areas of Asia, Africa, and Latin America, counterfeit medical goods constitute as much as 30 percent of the market, according to Interpol. In a single operation last year, its agents seized 9.4 million doses of fake medicines [5].

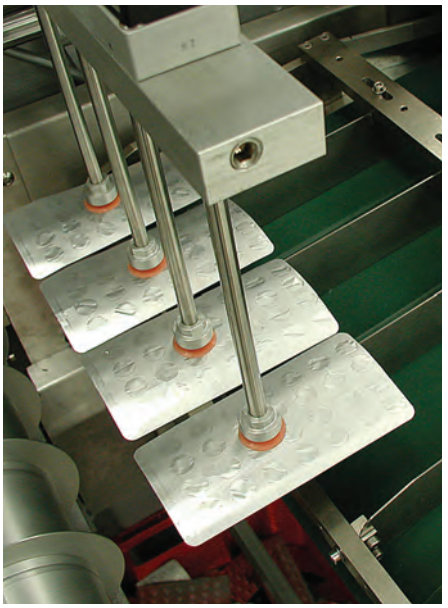
By 2018, track-and-trace regulations—including the Drug Supply Chain Security Act (DSCSA) in the USA—in the EU, China, Brazil, Korea, and Argentina, and other countries will be in force and apply to more than 75 percent of global medicines. Already in January 2015, more than 20 markets have in place or have pending pharmaceutical serialization requirements [6]. Instituting serialization, product tracing, product verification, and government reporting systems that comply with all these requirements is a complex undertaking, and the risk of missteps is high.

What to look for in a serialization and contract packaging partner

Every pharmaceutical company should be studying how it will meet serialization requirements, especially those with global reach. Today, serialization is front and center as the means to ensure the quality and safety of drug products as they move through the supply chain. Make sure the contract packagers you consider are well versed in that area. They should also understand bright-stock labeling, which can help streamline drug product distribution in countries beyond where the drug product was manufactured. Every contract packager under consideration should also offer production flexibility in terms of packaging lines that can handle a variety of products and batch sizes.

Whenever drug products are shipped internationally, government agencies must be confident that you're shipping exactly what you claim. That minimizes the risk of contamination and counterfeits, thereby promoting quality and patient safety. When the DSCSA became law in November 2013, it tasked the FDA with developing a means of tracking drug products throughout the supply chain. To that end, all pharmaceutical companies must add serial numbers to their packages in the next 4 years. Package labels must be upgraded to electronic codes by 2023 so that ownership can be traced to the original manufacturer or repackager.

Pharmaceutical companies should ensure that their contract packagers have a complete serialization program in place, one that tracks a given product's chain of custody from the manufacturer to the point of dispensing and securely stores that history, known as an e-pedigree. Additionally, the e-pedigree should provide data about the batch from which the drug product was manufactured. That means contract packagers should affix a unique and traceable serialized number to every package,



A marshalling device transfers completed blisters to the conveyor for further packaging.

The practice of labeling products immediately after manufacture is disappearing. More often, the package bears only an expiration date and tracking info until just prior to shipment, when compliant language is added.

bundle, case, and pallet associated with that drug product. That way, at each leg of the product's journey from the manufacturer to the consumer, the serial number can be scanned and added to a database in order to document the product's official chain of custody. These standards, used mainly to reduce counterfeiting, require that contract packagers understand how the requirements differ, often subtly, from country to country.

No matter where you plan to sell your products, every contract packager you consider should offer flexible production. That means operating several lines that run your product, not just one. It also means the company's equipment should handle large and small batches and adapt easily to package your drug products in different formats. There are several additional factors to consider:

Project management. Ask the contract packager to describe its project management system in terms of who is handling your project, the expected turnaround time, and whether there will be a line dedicated to your product's run for as long as it's needed. Look for a plan that defines the requirements of each new project and describes how they will be met. Ideally, project management includes team planning and weekly or bi-weekly meetings.

Packager profile and history. Look at the experience of the management group and the team's knowledge. Its employees should be confident in what they propose and should back up their proposals with documentation. Can the group provide turnkey solutions under one roof? That typically provides tighter control over the supply chain. How long has the packager been in business?

Regulatory capabilities and track record. Ask about FDA audits and how the contract packager performed. Find out when the last audit occurred, whether the site complies with current GMP, and if any 483s (warning letters) have ever been issued. If the company is involved in packaging dietary supplements, check its regulatory status. You need to know that the company has undergone an FDA audit and is registered with the DEA to handle your pharmaceutical products.

Dedicated resources. Depending on how many lots you anticipate running, the packager should be able to tell you whether they have the equipment and tools needed to produce your product and manage your project. Verify it during a plant visit.

Rest-of-world packaging and bright-stock labeling

Contract packagers can also help pharmaceutical companies extend the reach of their new drug products by helping them comply with the regulations in markets outside of the USA, Europe, and Japan. This can be done using the rest-of-world (RoW) packaging concept. With RoW, products specific to the country in which they will be consumed are held in inventory and, as needed, the contract packager labels the goods with the required information in the correct language. It's similar to the concept of bright-stock labeling.

In fact, the practice of labeling products immediately after manufacture is disappearing. More often, drug products are manufactured in large batches and stored in unlabeled primary containers that bear only expiration dates and tracking information. These containers then receive compliant labeling in the language appropriate to their destination just prior to shipment. This is called bright-stock labeling and it's beneficial to manufacturers of prescription and over-the-counter products because it allows companies to operate on a "just-in-time" or "made-to-order" basis, typically in cooperation with a contract packaging company that maintains the manufacturer's inventory. (The term "bright stock" comes from the food industry, where it referred to metal cans of vegetables, soup, or other products that had yet to be labeled.)

Using the bright-stock approach, a US-based contract packager might receive filled and capped bottles of tablets from Europe and simply add a label and insert that suit the

market where the drug product will be consumed. Bright-stock labeling also eliminates many of the complications and costs of labeling and packaging the product at the time of manufacture. In addition, by labeling and completing the product's package closer to shipment time, manufacturers can forecast inventories more accurately. This prevents an underestimate of sales from leading to a shortage or an overestimate causing expiration-dated products to languish at the retail level. The logistical simplicity of bright-stock labeling also supports the goal of delivering drug products to the patients most in need.

Conclusion

Pharmaceutical companies want to make drug products, sell them quickly, and get the right product into the patient's hands. Those are their core competencies. As the pharmaceutical industry has become enmeshed in a global supply chain, meeting those goals has become more challenging. A contract packager can eliminate many complexities and ensure that your company's objectives are achieved. *T&C*

References

1. Pharmaceutical and Life Sciences Deals Insights Quarterly, Q4 2014. PricewaterhouseCoopers, London, UK. February 2015. http://pwchealth.com/cgi-local/hregister.cgi/reg/pwc-pharma-deals-insight-q4-2014.pdf. Accessed April 12, 2015.

2. Global markets for contract pharmaceutical manufacturing, research and packaging. BCC Research, Wellesley, MA. August 2013.

3. New technologies that will impact the global pharmaceutical packaging industry. Frost & Sullivan, San Antonio, TX. December 9, 2014.

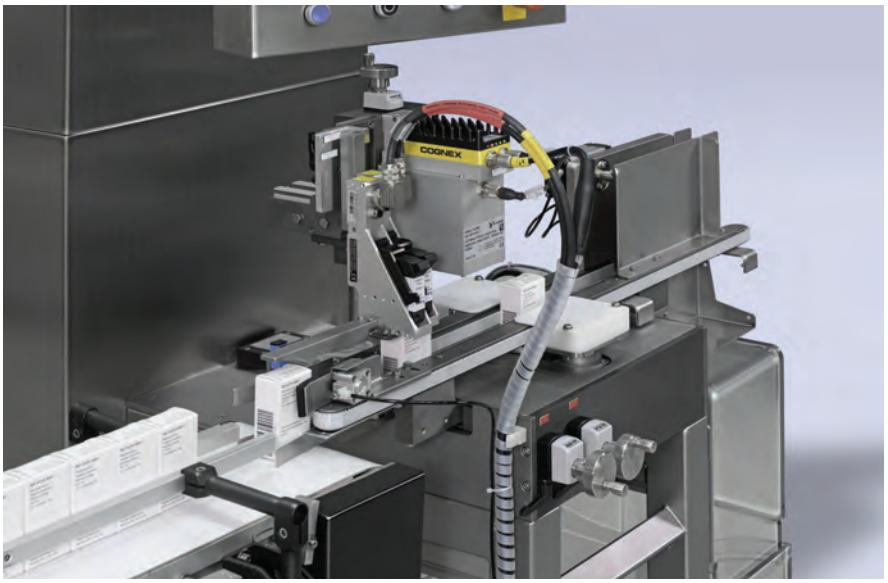
4. Building New Strengths in the Healthcare Supply Chain: Pharmaceuticals and Medical Products Operations. McKinsey & Company, New York, NY. January 2013.

5. "Thousands of illicit online pharmacies shut down in the largest-ever global operation targeting fake medicines." Interpol, Lyon, France. May 22, 2014. http://www.interpol.int/News-and-media/News/2014/N2014-089. Accessed April 12, 2015.

6. White paper on traceability data architecture. Rx-360, Washington, DC. March 14, 2015. http://rx-360.org/. Accessed April 12, 2015.

Scott Garverick is vice president of business development at Pharma Packaging Solutions, 341 JD Yarnell Industrial Parkway, Clinton, TN 37716. Tel. 800 533 7744. Website: www.PharmaPackagingSolutions.com. The company is a turnkey contract packager, offering commercial packaging, product launches, stability services, cold chain packaging, and product retain services to the regulated healthcare industries.

Issue focus packaging



Track-and-trace printing

CPS series equipment prints and verifies as many as 400 folded cartons per minute. Printing module accepts marking systems (e.g., inkjet, laser) from all common brands to apply serial numbers, 1D and 2D codes, batch data, and expiration dates in plain text and/or machine-readable codes. Unique serial number is assigned to each package and verified by camera. Adjustable conveyor belts let you secure cartons for printing on side flaps from front and/or rear, as well as top and/or bottom. Quick, tool-free changeover lets you reposition printer and camera easily and attach multiple print heads for simultaneous printing. Expandable architecture lets you add modules for checkweighing, applying tamper-evident seals, and labeling. All operations are controlled from interface that integrates with your company's IT for complete serialization and aggregation management.

Bosch Packaging Technology, Minneapolis, MN.
Tel. 763 424 4700
www.boschpackaging.com

Counter-fillers

Countlab Street Fighter series electronic counter-fillers fill as many as 250 100-count bottles per minute and handle round, square, hexagonal, or odd-shaped tablets, hard capsules, and softgels. Keyed parts, modular design, and snap-latch connections ensure quick, tool-free changeover. Allen-Bradly touch-screen interface eases recipe programming and machine operation; software meets 21 CFR Part 11. No compressed air is required, promoting efficiency while preventing cross-contamination. Vacuum cleaning system eliminates dust, reducing downtime. Counters have small footprint and meet or exceed cGMP and FDA requirements.

Capmatic, Montreal, Quebec.
Tel. 514 322 0062
www.capmatic.com

Packaging services

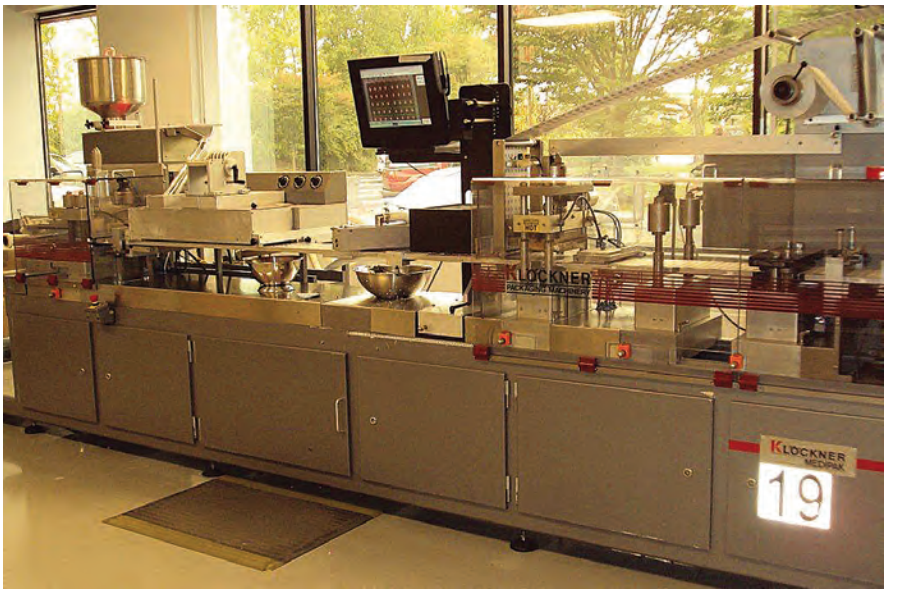
Company offers branded and private-label packaging to pharmaceutical and dietary supplement industries. Services including bottling, blistering, wallets (heat-sealed carding), cartoning, and deblistering. Services comply with FDA, DEA, and MHRA (UK) requirements and abide by cGMP. Capabilities include globally compliant packaging, serialization, and GDUFA compliance. Facilities in Clinton, TN, and Shelby, OH, comprise more than 260,000 square feet.

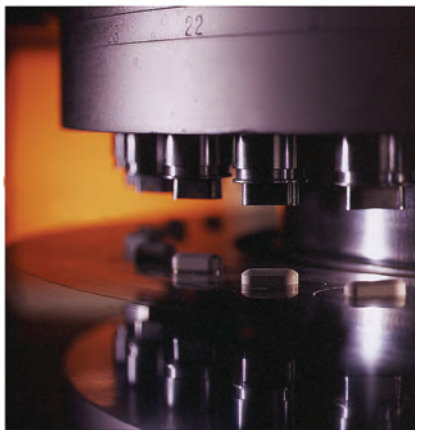
Pharma Packaging Solutions, Clinton, TN.
Tel. 800 533 7744
www.pharmapackagingsolutions.com

Blister packaging services

Company provides automated solid-dosage blister packaging from product development and stability testing to full-scale production. All thermoform barrier films are available, as well as aluminum-aluminum. Packaging lines use positive-placement feeding, vision verification, and inline carton filling. Operations serve pharma and dietary supplement industries and comply with cGMP; facilities are registered with FDA and DEA (Schedule III to V). Company also offers high-speed strip packing, bottling, multiple-color inline printing, and sample packaging. It also offers tabletting, capsule filling, blending, and other solid dosage processing.

Future Pak, Wixom, MI.
Tel. 248 486 0045
www.futurepak.com





Packaging services

Company manufactures and packages gelatin and vegetarian softgels, hard shell capsules, tablets, powders, teas, and probiotics. Turnkey services include R&D and product formulation, manufacturing , custom packaging , laboratory analysis, and stability testing. Packaging facilities include high-speed automated bottling and powder filling lines, and pill-pouching equipment. Company's 120,000-square-foot FDA-inspected facility holds California drug license, and NSF and NPA GMP certifications; organic, kosher, and halal designations are available.

Best Formulations, City of Industry, CA.
Tel. 626 912 9998
www.bestformulations.com

Pouch filler

V 600 series multiple-product pouch filler combines as many as eight different products (tablets, caplets, capsules, and/or softgels) per pouch at 320 pouches per minute using 6- or 12-inch-wide web. Additional features include servo drive, on-the-fly product fill change, sequential filling that alternates one combination of products for morning and another for evening, in-line printing and print registration, Ethernet connectivity, and IQ/OQ/PQ documentation.

Wrapade Packaging Systems, Fairfield NJ.
Tel. 973 773 6150
www.wrapade.com

Belt conveyor

SureClean belt conveyor integrates with bottle fillers, electronic counters, cappers, labelers, and other packaging machines. Sloped surface beneath belt prevents product residue from accumulating. Unlike other conveyors, unit can be cleaned without completely disassembling it, allowing faster changeovers. Raised conveyor track wipes down easily, and internal wire channel eliminates exposed cables. Conveyor is available as stand-alone unit or as part of complete packaging line. Standard lengths are 4, 8, and 16 feet; various speed ranges are available.

Service Industries, Rolling Meadows, IL.
Tel. 847 392 1652
www.serviceindustries.biz

Packaging equipment and services

Company supplies slat and electronic counter-fillers; conveyors; container handling equipment; container sealers; and surge, accumulation, and unscrambling tables. Line integration services include remote monitoring and data collection to determine overall equipment effectiveness. Other services include project review and scope analysis, project management, equipment sourcing, purchasing guidance, training, validation, and maintenance.

Modular Packaging Systems,
Randolph, NJ.
Tel. 973 970 9393
www.modularpackaging.com

Packaging services

Contract packager nearly doubled its capacity in 2014, adding three Bartelt-style pouch machines (photo), four Videojet printers, and one automatic shrink-wrapper. Company also acquired five powder fillers. Recent projects include launching product packaged as eight tablets per blister, 15 blisters per four-color tray and sleeve, as well as packaging almost one million pouches per week for another customer. Company ensures project and product confidentiality and on-time delivery. Standard packaging includes blisters, bottles, pouches, and strip-packs. Customers work directly with owner of company, which is registered with FDA and New York State Board of Pharmacy.

Ruspak, Lyons, NY.
Tel. 315 946 9777
www.ruspak.com

AEM

A Division of Wilson Tool

RESHAPING THE WAY WE SHAPE TABLETS.

Welcome to better. Advance Engineering and Manufacturing is now part of Wilson Tool – a global leader in precision tooling. Fortified by Wilson Tool's engineering expertise and lean manufacturing methodology, AEM now delivers even greater performance to customers and establishes a higher standard for the industry. Contact us now to advance your tablet tooling with the new AEM.

800.467.8444 www.advanceeng.com

feeding

Accurately and safely dispensing pharmaceutical and high-value powders with an automated loss-in-weight feeder

Sharon Nowak
Coperion K-Tron

This article explains how an automated loss-in-weight feeder can accurately and safely dispense pharmaceutical and other high-value powders in continuous feeding and batching applications, eliminating the dangers and inefficiencies of conventional manual loading.

Difficult-to-handle, toxic, and/or highly reactive powder ingredients are regularly used in chemical and pharmaceutical processes, yet dispensing them into blenders, granulators, extruders, reactors, or other process vessels presents major challenges: The powders must be dispensed accurately to meet process or batch set-points, and they must be fully contained during the process to protect workers.

A good way to overcome the challenges of dispensing these tough-to-handle powders is to select an automated loss-in-weight (LIW) feeder with high-accuracy load cells, advanced controls, and a contained, easy-to-clean feeding device. By working with the supplier to choose a feeder that has these components and is suited to your powder's characteristics, your total batch size, the process's upstream and downstream equipment, and your application's other unique requirements, you can ensure that the feeder meets your accuracy and safety goals.

Some LIW feeder basics

A LIW feeder, as shown in Figure 1, typically consists of a hopper with a feeding device (such as a single- or twin-screw feeder or vibratory feeder), a weight-sensing device with high-speed load cells, and a controller. The feeder can be suspended from a weight-sensing frame mounted with three load cells (Figure 1) or can rest on a platform scale with one load cell. For continuous feeding applications, the operator programs the controller to dispense powder at a pre-determined continuous feed rate (set-point), and for a batching application, the operator programs it to dispense a predetermined batch weight within the desired batching time.

In operation, the feeding device discharges powder from the hopper at a speed determined by the controller. The weight-sensing device continuously reports the powder weight in the hopper to the controller. In a continuous feeding application, the controller determines the actual rate of weight loss and compares it to the feed rate set-point; in a batching application, it determines the measured (or absolute) weight loss and compares it to the batch weight set-point. The controller then increases or decreases the feeding device's speed to increase or decrease the powder weight change in the hopper, matching the feed rate or batch weight to the set-point.

The controller regulates the feeding device's speed to compensate for non-uniform material flow characteristics and bulk density variations, providing high feeding or batching accuracy. The LIW feeder is most accurate when it uses high-resolution, high-speed load cells that are immune to vibration and temperature fluctuations. [**Editor's note:** For information on how a LIW feeder can be better suited to a batching application than a gain-in-weight (GIW) feeding system, see the sidebar "Comparing LIW batching with GIW batching."]

Selecting a LIW feeder to handle a toxic or reactive powder

Let's consider two examples showing how LIW feeders can be selected for dispensing a toxic or highly reactive powder.

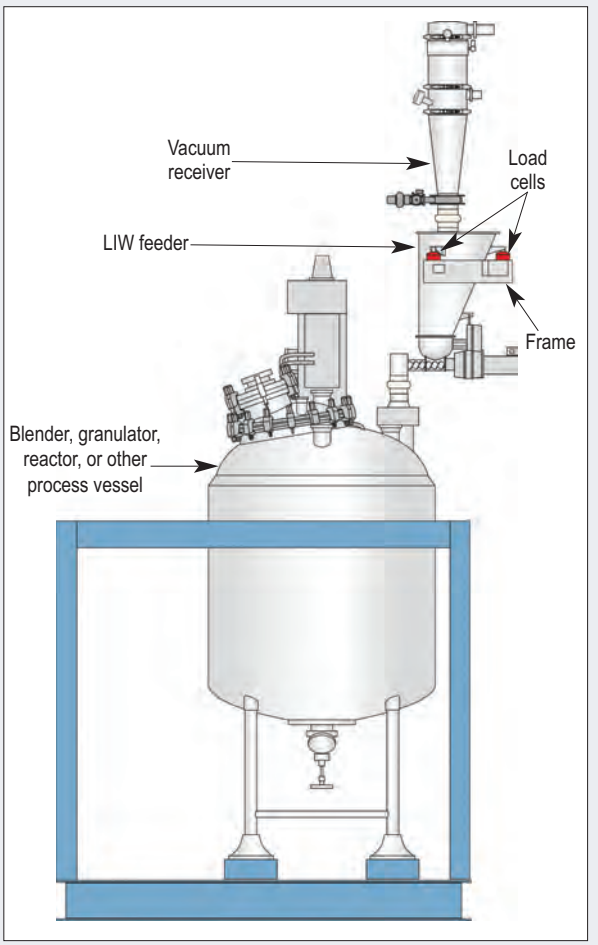
Single LIW feeder dispensing powder from vacuum conveying system. This batching application requires one LIW feeder, as shown in Figure 2a. A large quantity of a highly reactive powder in a supply vessel on one floor is transferred by a vacuum conveying system to the LIW feeder on the floor above. The powder is completely contained as it discharges from the conveying system's vacuum receiver into the feeder's hopper.

Figure 1

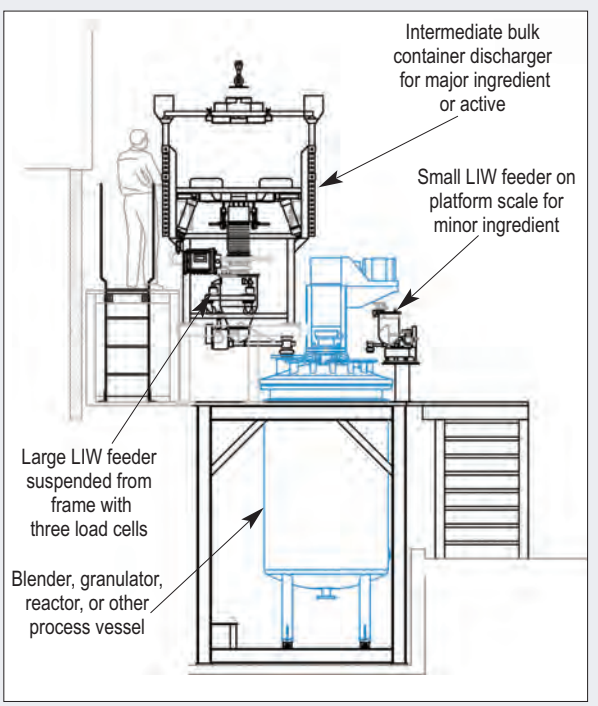
LIW feeder

Figure 2

LIW feeders in two batching applications



a. Single LIW feeder dispensing powder from a vacuum conveying system



b. Two LIW feeders dispensing two powders into one vessel

Comparing LIW batching with GIW batching

Both LIW feeders and GIW feeding systems can be used in batching applications, but they work in fundamentally different ways. These differences typically make the LIW feeder better suited for dispensing powder actives or other ingredients with high accuracy requirements.

The LIW feeder is suspended from or rests on high-speed load cells and dispenses powder into a granulator, blender, or other process vessel at a rate based on sensing the feeder's loss in weight. The LIW feeder's weight-sensing device provides high-speed, high-resolution weight-loss measurements of the powder in the feeder hopper. An example of an LIW batching application with two LIW feeders simultaneously dispensing ingredients into a process vessel is shown in Figure A.

FIGURE A

LIW batching

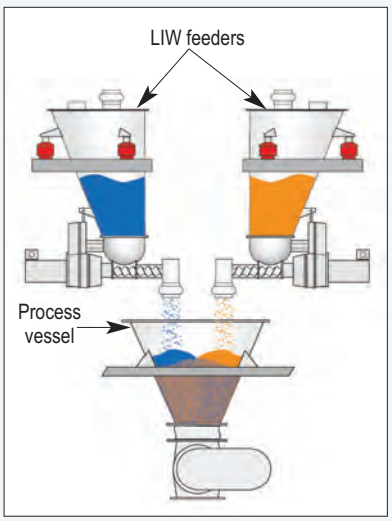
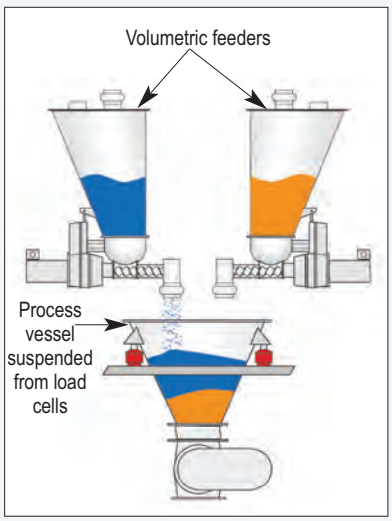


FIGURE B

GIW batching



The GIW feeding system includes one or more volumetric feeders above a process vessel that's suspended from high-capacity load cells or rests on a high-capacity floor scale. Each volumetric feeder sequentially dispenses powder at a rate based on sensing the gain in weight of the entire vessel and its contents. In the GIW batching application shown in Figure B, two volumetric feeders sequentially dispense ingredients into the process vessel.

Which feeder type is best for your batching application depends on several factors, including the total batch size, the number of ingredients in the batch, your desired batching time, each ingredient's flow characteristics, and your application's accuracy requirements. When the batch ingredient is an active pharmaceutical ingredient, feeding accuracy can be a critical factor in determining whether the LIW or GIW batching method is best.

Here's why: With a GIW feeding system, a volumetric feeder dispenses powders into a vessel mounted on load cells, which must detect the weight of that powder addition as well as the full weight of the vessel and the powder it already contains (called the full scale capacity). Because most high-capacity load cells and floor scales don't have enough speed or resolution to detect the weight of a small amount of powder relative to the much larger overall weight of the vessel and its contents, a GIW system's expected batching accuracy is typically ±0.5 percent of the full scale capacity. However, the LIW feeder can achieve batching accuracies of ±0.1 percent of the batch set-point. This is because the LIW feeder's operation depends on sensing only the weight of the ingredient being fed rather than the much larger weight of the vessel and all of its contents, and the LIW feeder's high-speed load cells provide very high resolution (typically one part in four million).

The LIW feeder can also speed your batching operation. When a GIW system handles an application with multiple ingredients, multiple volumetric feeders (one per ingredient) must dispense ingredients one at a time into the vessel, because the vessel is weighed for each ingredient. In contrast, multiple LIW feeders can all dispense their ingredients at the same time into the vessel, because each ingredient is weighed as it's dispensed. This significantly cuts the total batching time.

Be aware, however, that using LIW feeders for all the powders in a multi-ingredient batch can be expensive. A cost-saving alternative is to select a batching system that includes both GIW and LIW equipment. The GIW system can handle the lower-cost ingredients that have lower accuracy requirements. The LIW feeders can dispense the more costly ingredients, such as actives, that have higher accuracy requirements or can dispense ingredients required in a large quantity, thus cutting the total batching time. —*S.N.*

The feeder is located above a blender, granulator, reactor, or other process vessel and is suspended from a frame with three load cells to handle the large batch size. The load cells are connected to the feeder's controller. The controller is programmed to control the feeder to meter the powder at a high-speed (or bulk) flow rate into the vessel below it until the controller determines that the dispensed powder is within 90 percent of the powder's batch set-point. Then the controller automatically slows the feeder to a trickle (or dribble) rate to ensure that the feeder accurately delivers the desired batch weight.

Two LIW feeders dispensing two powders into one vessel. In this batching application, two LIW feeders—one large and one small—each dispense a powder into a process vessel, as shown in Figure 2b. In this process, the final dosage form includes a large quantity of active, which is supplied in intermediate bulk containers. The large LIW feeder is suspended from a frame with three load cells and located below a discharger, which provides fully contained discharge through an airtight connection into the feeder's hopper.

LIW feeders are a must for continuous manufacturing. In batch operations, they can feed two or more ingredients, reducing cycle times.

The small LIW feeder receives a minor ingredient supplied in small bags; because this feeder handles less weight than the large LIW feeder, it rests on a platform scale with one load cell. Each small bag of powder is manually emptied into the small LIW feeder's hopper.

Both feeders are connected to a controller that automatically controls the feeder speed at fast and trickle feed rates to accurately meet both ingredients' batch set-points. The LIW feeders allow simultaneous batching of both ingredients, reducing the overall batch cycle time. The feeders are also mounted on casters that roll on tracks, allowing the feeders to be rolled in and out of place as needed for cleaning.

More about the LIW feeder's weighing system

To provide the feeding control and performance required for accurate batching, the LIW feeder's controller must receive accurate high-speed measurements of powder weight changes from the load cells. This weighing system (that is, the load cells and controller) must also filter out measurement errors caused by plant vibrations, non-uniform powder flow, or bulk density variations and remain stable despite changes in the temperature of the ambient air or powder. The higher the resolution of the load cell weight measurements and the faster the measurements are taken, the better the information going to the controller and the better its control and vibration-filtering algorithms will work.

LIW feeders typically use analog strain gauge or digital load cells based on advanced weighing technologies. Work with your LIW feeder supplier to choose load cells that provide the speed, resolution, vibration-filtering capability, and stability your application requires. [**Editor's note:** For detailed information on load cells for LIW feeding and batching applications, contact the author.]

LIW feeder options

Your LIW feeder's components can be fabricated of various materials to suit your pharmaceutical or high-value powder. The components can also be designed to safely contain your powder while simplifying inspection, cleaning, and changeovers. Which components are best suited to your LIW feeder will depend on your powder's characteristics.

For example, equipping the feeding device's outlet with a split butterfly valve (which combines active and passive components to provide maximum containment) will ensure that your powder is completely contained when the feeder is moved away from the process vessel after batching is completed.

You can also select a feeder (and the hopper or receiver that discharges powder to it) with a retractable wash- or clean-in-place (WIP or CIP) spray system that eliminates many labor-intensive steps, thus ensuring fast changeovers and minimizing contamination between runs while protecting workers. The spray system also can pre-wet the feeder's interior before it's opened, thus wetting the dust and preventing it from becoming an airborne hazard to workers. Even a feeder equipped with a WIP/CIP system will still need to be disassembled for inspection from time to time, so look for feeding devices that give you quick, easy access.

Consult your LIW feeder supplier for advice on selecting the components that suit your powder's characteristics and containment requirements, as well as your expected inspection, cleaning, and changeover frequencies.

Maximizing your LIW feeder investment

Using a LIW feeder to accurately weigh and deliver pharmaceutical and other high-value powders to a process without manual intervention can provide several advantages. These include achieving better product quality, reducing manufacturing costs, and obtaining maximum yields. The feeder supplier can help you not only design the feeder to accurately and safely handle your tough powder, but help you combine the feeder and upstream and downstream equipment into a system that reduces your operating costs while maximizing your process efficiency and product quality. *T&C*

Sharon Nowak is global business development manager at Coperion K-Tron Pitman, 590 Woodbury Glassboro Road, Sewell, NJ 08080. Tel. 856 256 3119. Website: www.coperionktron.com. She holds a BS in chemical engineering from Rutgers University, New Brunswick, NJ, and has 24 years' experience in developing process equipment for the pharmaceutical and other process industries.

production technology

Arden House conference: Continuous manufacturing gains momentum

Matthew Knopp
Editor

The allure of continuous manufacturing—better product quality, more flexibility, higher efficiency—coupled with supportive regulators, is persuading more manufacturers to adopt methods that are commonplace in the food, chemical, and other industries.

For more than a decade, the FDA has urged, encouraged, and enticed pharmaceutical companies to modernize their manufacturing methods. But in a regulated industry where missteps are costly, the majority of manufacturers saw more risk than reward and preferred the known over the new. But as blockbusters dwindle and generics grow, the innovator companies are re-thinking their reluctance.

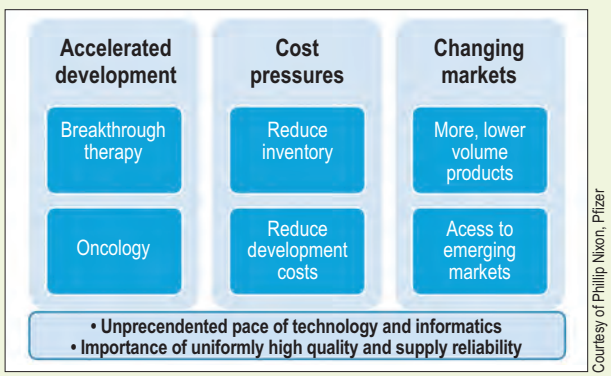
"The pharmaceutical industry is going through a period of dramatic change, and incremental improvement to the decades-old batch manufacturing paradigm is no longer sufficient," said Phillip Nixon, the executive director of Pfizer's PharmaTherapeutics PharmSci Technology & Innovation Group. He said it is no longer a question of if the pharmaceutical industry will adopt continuous manufacturing, only of when, how, and to what extent.

Those were the ideas Nixon and nearly 150 attendees discussed at the 50th Arden House conference, held March 16-18 in Baltimore, MD. The event focused on oral solid dosage forms and featured 21 speakers, each of whom gave 45-minute presentations and answered questions. There was also a poster session.

Nixon, who chaired the event, spoke first. The business factors driving companies to adopt continuous manufacturing include the need to accelerate development and lower costs, address changes in the markets, and find better ways to make low-volume products. Continuous processing allows manufacturers to use the same equipment for product development and commercial manufacturing, which reduces the effort, cost, time, and risk associated with technology transfer (Figure 1).

FIGURE 1

Evolving business needs of the pharmaceutical industry



Courtesy of Phillip Nixon, Pfizer

While continuous manufacturing may seem "disruptive," Nixon said, it doesn't require new or unknown technologies. Much of the uncertainty centers on process integration, process control, and regulatory acceptance. It also requires the use of predictive computational models and other analytical tools. Pfizer's approach is to use continuous "mini-factories"—an approach dubbed "portable, continuous, miniature, and modular," or PCMM—that replace large fixed-size batches and reduce manufacturing time to minutes. Scaling up production would no longer entail using larger equipment, only running the process longer. With PCCM, the process equipment is enclosed in an autonomous "pod" that can be shipped to any location and quickly installed in a "gray-space" warehouse to create a fully functional GMP space.

The need to raise quality also favors continuous manufacturing, and most solid dosage operations operate at two or three sigma quality, Nixon said. "We optimize our settings and then don't move them. Thus the variability of the inputs, such as excipients, lead to variable results." A better idea is to use a process that can adjust to variable inputs.

Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research (CDER) and acting director of CDER's new Office of Pharmaceutical Quality, was next to speak. Her talk was mostly about the FDA's drive to modernize the industry and itself. She addressed continuous manufacturing specifically at a 2014 event [1].

After her remarks, an attendee noted that continuous manufacturing generates a large amount of data and asked how much of it the FDA will want to see. "FDA shouldn't ask for all the data that you generate on continuous," she replied. "Tell us your algorithms and how well you're doing with that. We will have to decide how much control data we will want to see, so there will be a struggle over that." She said that any company that attains six-sigma quality would face less scrutiny. "But for those that don't shift over [to six sigma], we can't insist on that." She said the FDA was still considering how continuous manufacturing would affect recalls, specifically on "how to put boundaries on where the problem lies." She said that the biggest problem with batch processes is that the Agency "can't find out what went wrong."

Jim Wetzel, director of global reliability at General Mills, discussed how his company moved to continuous production of Cheerios. Until 1966, every box of Cheerios was made in batches using an explosive process that puffed the cereal. He said it took 20 years of R&D for the company to develop a continuous process to do that. And while it continues to operate garage-sized dryers, the continuous puffing equipment is only as big as two conference tables, he said. It saves the company many millions of dollars each year.

Wetzel said one the "biggest leaps" in managing its processes and plants around the world was standardizing on the company's information technology platforms instead of its engineering or other platforms. It now gathers information about the variability of its ingredients before they reach the factory, enabling the facility to prepare for them. He said General Mills handles 700 billion data points a day and, thanks to its sophisticated controls, attains 0.25 percent accuracy on operations that process a million pounds per day.

Kris Schoeters is in charge of the continuous manufacturing business of GEA, a multinational supplier of equipment and systems to the process industries. He said the company began developing its ConsiGma continuous processing equipment in 2007, when two major manufacturers inquired about continuous wet granulation. That process was developed in cooperation with the University of Ghent. Since that time, the company has added feeders, mixers, mills, dryers, tablet presses, and film coaters to its continuous portfolio.

Today, the company has 35 different projects installed worldwide, Schoeters said, most of which are R&D operations. But some customers are manufacturing commer-

cially, including GlaxoSmithKline, AstraZeneca, and Jannsen in Europe. In Mexico, generics manufacturer Chinion makes three products with GEA's equipment. The company also has three or four installations in South Korea and six or seven in Japan, including at Diaichi Sankyo. The equipment is also used at Vertex of Boston, MA, and in Pfizer's PCCM approach.

Several questions about cleaning arose. Schoeters said running the system empty, what he called a dry rinse, was the first step. Next, the components must be removed and cleaned offline. One customer runs its tabletting line for 2 or 3 weeks before cleaning and reassembling the components, which takes 2 days. He said the job could be done faster if everything were done simultaneously instead of having one person clean the parts one by one.

Aditya Vanarase, a research investigator at Bristol-Myers Squibb, spoke about the key role of loss-in-weight feeders and blenders in solid dosage continuous manufacturing. Advantages of continuous mixing include less risk of particle segregation, less post-blending powder handling, and the potential to avoid roller compaction/wet granulation. She presented case studies about optimizing feeder refill and dealing with cohesive materials in continuous mixers.

Vanarase also covered the practical aspects of feeder selection, including desired feed rate, feeder scale, capacity, nozzle size, gear ratio, powder properties, type of screw, and discharge screens. A case study examined how the feeder responded to variation in material properties. Development challenges of the future include implementing advanced process control, rejecting off-spec material, modeling predictive controls, and designing formulations suitable for continuous processes.

Eric Jayjock of Janssen Pharmaceutical, Horsham, PA, performed his graduate studies at Rutgers University, where he was a part of the Center for Structured Organic Particulate Systems (C-SOPS). His presentation addressed fundamental engineering principles of continuous manufacturing and compared its "by-design" equipment and processes to legacy practices.

He recommended using virtual designs that account for the characteristic times of existing unit operations and processes. He said to scrutinize—both experimentally and virtually—the process for events that push it outside the steady state and to validate and produce your product within a "control state."

Feeding powders will always include some "noise," and in continuous processing that noise can threaten product homogeneity if not properly measured and addressed. He highlighted the opportunity to design process robustness into continuous manufacturing systems, and offered as an example designing back-mixing into a blender to account for the variability of the feeding step.

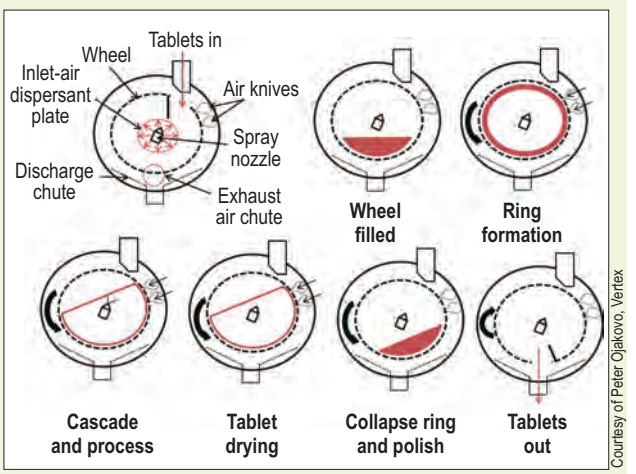
James Litster, professor of chemical engineering and professor of industrial and physical pharmacy at Purdue University, West Lafayette, IN, devoted his talk to continuous granulation in twin-screw granulators. They are used at high throughputs to make detergents, but are also good for developing and scaling low-throughput applications such as pharmaceuticals. Furthermore, they simplify online measurement and control, and allow design optimization through regime-separated operation.

He discussed twin-screw system variables, which include the powder feed rate, formulation composition, liquid feed rate, granulating liquid composition, method of adding liquid feed, screw speed, shaft length, and screw configuration, which can include conveying, mixing, dispersive, and distributive elements. Litster explained how the different elements affected granulation and how to develop a design model.

Peter Ojakovo, a formulation scientist at Vertex Pharmaceuticals, discussed how he and his team developed a commercial coating process for its continuous tabletting line using GEA's Omega semi-continuous coater (Figure 2). Unlike traditional pan coaters that rotate slowly and stir a tablet bed, the GEA coater spins quickly (~115 rpm) and the core tablets form a ring around the pan's outside wall. The speed is then reduced to ~92 rpm, and two air knives dislodge the tablets, causing them to cascade through a center-mounted spray. As the coating builds, the rpm can be adjusted, which is handled by software linked to a Raman device that tracks the reduction in signal for the API and the increase in signal for the coating material. To polish the coated tablets, the speed is reduced to ~30 rpm.

FIGURE 2

How GEA's Omega coater works



Courtesy of Peter Ojakovo, Vertex

Ojakovo said coating takes less than 20 minutes and typical weight gains are 2.9 to 3.1 percent. RSD variation of coating thickness is 1 percent. The Omega coater handles tablets gently, but uses higher-temperature air than conventional pan coaters. Ojakovo said flat tablets were difficult to form into a ring, but the addition of gripper-bars resolved the issue.

Robert Meyer, who leads Merck's innovation and technology efforts for small-molecule oral drug products, summarized his team's experimental and operational testing of GEA's CDC-50. The tests focused on residence

Solutions for Poorly Water-Soluble APIs and Pharmaceutical Mixing

NETZSCH

Agitator Bead Mill
DeltaVita®

Laboratory Homogenizing Mixer
KappaVita

NETZSCH *DeltaVita*® mills offer innovative solutions to poorly-water soluble APIs through the nanonization of drug substances to increase surface area, increase dissolution velocity and ultimately increase bioavailability.

NETZSCH *KappaVita* homogenizing mixers offer integrated CIP/SIP design and can process highly viscous substances. Both systems are offered for aseptic processing.

NETZSCH Premier Technologies, LLC
125 Pickering Way – Exton, PA 19341
Tel: (800) 676-6455
Fax: (610) 280-1299

be productive

Ask us about our laboratory testing capabilities!

www.netzsch.com/gd

time distributions, PAT, and process control. He noted that some aspects of the system would require optimization before it could be used for production, but it satisfied long-term operational requirements under the conditions tested. The system is designed to produce 50 kilograms per hour, and that is where results were best. At 90 kilograms per hour, the RSD variation of tablet weight was 5 percent. "When pushed to the extremes of operation, all operating conditions resulted in acceptable tablets for all three formulations," Meyer said.

Daniel Blackwood of Pfizer provided more details about the company's integrated PCMM system, which uses a pod to house all the process equipment and control systems necessary to continuously manufacture tablets from direct-compression blends or wet granulations. The modules can be deployed worldwide, allowing the company to begin manufacturing quickly and at lower cost compared to establishing a traditional facility, especially in emerging-market regions. The week before the conference, Pfizer had "brought to life" six modules of the pod at its Groton, CT, site. (The company uses POD enclosures supplied by G-Con Manufacturing of College Station, TX.)

The FDA is encouraging manufacturers to adopt continuous manufacturing, which can streamline QbD development and NDA submission.

Blackwood emphasized the importance of gravimetric feeders and blenders in developing a continuous manufacturing system. He said that continuous powder mixers should be installed as close as possible to the tablet press. He described a prototype vertical mixer made in-house a few years ago that sits inside the tablet press enclosure. The mixer's design has since been commercialized as part of the PCCM program. After his prepared remarks, Blackwood responded to a question about variable materials by saying there is an "untapped opportunity for NIR probes, which can be used for more than just potency signals." One example is to check whether other quality attributes, such as those of excipients, are at the high or low end of specification, he said.

Jeff Katstra of Vertex discussed how his company developed and implemented a continuous manufacturing system simultaneously with its development of a new drug product to treat cystic fibrosis. He said continuous manufacturing streamlines QbD development and NDA submission. And while there is a presumption of regulatory difficulty, authorities encourage new technology. Breakthrough therapies offer a good opportunity for companies to work closely with the US regulators.

The project began with using individual unit operations in the development and manufacture of clinical formulations in discontinuous mode. Next, Vertex installed a GEA ConsiGma-25 and qualified it for "continuous clinical batch manufacture." The final step was the creation of its development and launch rig that can use multiple processing technologies. The rig, installed at a CDMO in the UK [2], is equipped with PAT devices for process monitoring and control and real-time release. It also has two segregation points, one after milling and another after compression. He said it takes 2 or 3 days to do a major cleaning. The bottleneck is usually the sink, and the company is seeking to add washroom capacity. The company also operates a continuous manufacturing system in Boston.

Philippe Cappuyns, a research fellow at Johnson & Johnson, London, UK, addressed switching legacy products from batch to continuous manufacturing. He presented a case study in which an existing product made using a conventional fluid-bed granulation-dryer was moved to a continuous process using GEA's ConsiGma-25. The study compared granule and tablet properties and tested the stability and repeatability by performing three consecutive production runs. It also monitored process outcomes and granule and tablet properties as a function of process time.

The project required 6 to 8 weeks of work at GEA to develop a process worthy of in-depth assessment and 2 years of further study. The company has introduced continuous direct compression at a site in Puerto Rico and is in the midst of launching continuous wet granulation at a site in Italy. He stressed the importance of selecting the right type of mill screen in order to obtain the desired particle size distribution and to avoid overheating. He also said it's important to run long trials for issues to become visible.

Xiaoyu Zhan, a senior research scientist at Eli Lilly in Indianapolis, IN, discussed her team's experience using PAT tools to monitor and control continuous manufacturing processes. She said continuous processing changed how her company develops products and requires more and earlier collaboration among formulators, analytical experts, and data managers. Her team conducted an 11-run DoE to optimize drug load and process parameters in 2.5 hours using just 2 kilograms of API. The same effort using a batch approach would have taken 3 weeks and required making three to four batches per week. She described in detail how her team designed and built a system that automatically samples and analyzes individual tablets using NIR. Standard tablet shapes are analyzed in 15 to 45 seconds; complex shapes can require 1.5 to 3 minutes.

Marianthi Ierapetritou is a professor and chair of the Department of Chemical and Biochemical Engineering at Rutgers University. The title of her talk was "Taking continuous processing from good to great: The application of advanced process controls and real-time analytics." Topics included flowsheet modeling, design space evaluation, process flexibility, and feasibility. It is important to know how much uncertainty a process can tolerate and how to assess the effect of uncertainty, she said. She also discussed integrating a material properties database and how to reuse accumulated information to better under-

stand and/or make predictions about the process. She outlined a model for controlling a continuous tablet manufacturing process.

Dora Kourti of GlaxoSmithKline, London, UK, spoke about control strategy considerations and concerns when using advanced process control/PAT with continuous manufacturing. During her talk, she cited earlier meetings, presentations, and articles that addressed how to control continuous manufacturing operations [3-5].

Sean Bermingham of Process Systems Enterprise, London, UK, described how the pharmaceutical industry could adopt the model-based approaches of the chemical industry to develop and optimize products and processes. He recommended that experiments be used to optimize a model (not the process) and to derive an accurate model that can be used to optimize the process. He also said the pharmaceutical industry has done well with models, but they should be applied more routinely and earlier in process development, before conducting experiments.

Models are critical to continuous manufacturing and must be made accessible to non-experts.

A mechanistic model can be used to design experiments and maximize information. When used as the basis for development, a mechanistic model can reduce timelines from 6 months to 6 weeks. Models should also be made more accessible to non-specialists. "It is possible to do amazing things with mechanistic models, but how many people in the world are able to use" them? "Models [...] need to be maintained by and made accessible to a wide range of stakeholders to realize their potential."

Panel discussion

At the end of Tuesday's prepared remarks, speakers from the first 2 days were invited forward to take questions.

Should batch and continuous manufacturing be developed in parallel? Nixon said it's a business decision, but "Those of us close to [continuous manufacturing] technology think it will work and that we don't need to do that." Another panelist noted that Vertex filed its last NDA with its continuous rig.

How do you handle post-approval changes? "It depends on the specifics," said Cappuyns. He said his company is in contact with authorities in Japan and China about switching some products from batch processing. "They are aware of continuous manufacturing technologies and capable of evaluating the changes we're proposing," he said.

What are the main technical obstacles to twin-screw wet granulation?

"I'm not sure there are obstacles," said Litster. "It's more flexible to use because it can operate over a range of properties that other equipment cannot."

How do we get management to buy into continuous manufacturing?

"We made slides and showed them the feasibility, but what sold them was that we built it," said Merck's Meyer. "We told them that we could supply the US from this 120 square feet of space." Nixon said to point out the inefficiency of "all those bins sitting around with in-process material." He also cited risk management. Others suggested demonstrating the long-term savings, the supply-chain benefits, and the feasibility by doing a "killer experiment" to get data and/or assembling a continuous manufacturing line using old equipment and a shoestring budget.

Final day

Rapti Madurawe is acting division director of the FDA's Office of Process and Facilities. She discussed the opportunities and challenges of continuous manufacturing from a regulatory standpoint. "The FDA is an advocate of continuous manufacturing," she said. While there are no specific FDA guidances about continuous manufacturing, it is consistent with QbD, ICH, PAT, and the FDA's push for the pharmaceutical industry to modernize.

She stressed the need for a control strategy that addresses all factors that affect variability and several times cited the need to understand how disturbances could propagate in the system and affect critical quality attributes. Other topics included ensuring the traceability of raw materials, how to define a "batch," and handling nonconforming materials. She said the FDA is open to conducting pre-operational reviews. When asked about modifying SUPAC to address continuous manufacturing changes, she said the document is likely too prescriptive and that a risk-based approach would be better.

Martin Wunderlich of Hoffman-LaRoche discussed the "perfect marriage" between continuous drug development and PAT and QbD. His talk focused on continuous wet granulation, which the company began studying in 2010 and pursued in 2011 after a promising product reached Phase III. It acquired a ConsiGma-25 from GEA, but the project ended when the product was withdrawn from clinical trials. Next came collaboration with the University of Ghent to gain process understanding and control. In closing, he said the lack of blockbusters means many companies have excess capacity, and it is thus difficult to persuade risk-averse managers to invest in continuous manufacturing. He called for more data and experiments to make the case for adopting the new process, which will need to have a backup system for every critical measurement. He called Vertex a "role model" for its work with regulators.

Hayden Thomas, vice president of formulation at Vertex, gave his perspective on the future gaps and challenges for the continuous manufacture of oral solid dosage forms. The company's products treat cystic fibrosis, and it plans to file an NDA in July for a product developed in parallel with its continuous manufacturing system. "Going through multiple scales doesn't fit our business model." Thomas said, and the Vertex approach "is easier to sell to the industry and regulators if they can see it and touch it. There are no regulations that prevent us from taking this continuous manufacturing approach."

As for improvements, he suggested seeking alternatives to loss-in-weight feeders to increase accuracy at low feed rates; adding web-enabled technology and anti-fouling windows to PAT gear; and boosting run times by facilitating in-service maintenance, such as de-blinding fluid-bed screens. Changeover could also be improved. He said it takes several days to disassemble, clean, and reassemble the system. He also discussed establishing a sampling plan, responding to variations, and adding redundant systems in case instruments go "blind" during cleaning.

He directed his final comments to vendors: "Define the space you want to play in. Will it be soup-to-nuts integrated systems or specialty equipment? Form partnerships with others. Adapt learnings from other industries. Look for plug-and-play solutions. Look for opportunities to lower costs and risks. Look at solutions to retrofit."

T&C

References

1. MIT-CMAC International Symposium on Continuous Manufacturing of Pharmaceuticals, Cambridge, MA. May 20, 2014. Website: https://iscmp.mit.edu/sites/default/files/documents/ISCMP2014_Keynote_Slides.pdf. Accessed April 12, 2015.

2. Ross, David. Continuous tablet manufacturing: Faster development and greater efficiency. Tablets & Capsules 12:6, pp 18-22, September 2014.

3. AAPS Workshop: Advances and Opportunities in Drug Product Manufacturing - A Look at Continuous Manufacturing Process. September 20 - 21, 2010 Sheraton Inner Harbor Hotel Baltimore, MD.

4. Swinney, K. and Warman, M. Ensuring data availability to support a fully integrated control strategy. IFPAC, January 21-24, 2014, Arlington, VA.

5. Allison, G. et al. Regulatory and quality considerations for continuous manufacturing. J Pharm Sci 104:3, 803-812, March 2015.

October 6-8, 2015 Atlanta, GA

Three power-packed days for you to plug into vitally important dry bulk processing issues, concerns and technology.

Scores of manufacturers and service companies displaying their latest powder processing and handling expertise, ready to answer your toughest challenges.

POWDER 15 THE POWDER SHOW™

2015 Southeast Powder Show™ & Conference

This is the only dry solids handling & processing show held in Atlanta.
Next one will be in 2018 — don't wait three years!

For details visit: pbepowdershow.com

powder transfer & containment

A survey of what's available

Synthetic filter

HemiPleat filter is made of lightweight, spun-bond polyester media that resists moisture, accepts heavy dust loads, and handles hygroscopic and sticky dusts. Its widely spaced pleats maximize filter surface area, minimize pressure drop, and release dust easily during pulse-cleaning. Washable media withstands operating temperatures to 160°F. Standard media is rated MERV 11. Addition of company's eXtreme nano-fiber layer increases rating to MERV 15 and creates pre-filter that enhances surface loading and extends service life. Filters fit Farr Gold and most other cartridge dust collectors.

Camfil APC, Jonesboro, AR.
Tel. 870 933 8048
www.camfilapc.com/pharma

Level detectors

Dynatrol detectors sense when powders, tablets, capsules, or other bulk solids reach high-, intermediate-, and low levels in bins, hoppers, or feeders. Detectors have no moving parts, gaskets, or seals, and require no calibration. Combining detectors with company's EC-501A control unit lets you activate process controls, alarms, or indicator lights. Detectors sense solids of less than 0.5 pounds per cubic foot to more than 60 pounds per cubic foot.

Automation Products, Houston, TX.
Tel. 713 869 0361
www.dynatrolusa.com

Powder receiver-conveyer

P30 receiver-conveyor uses vacuum sequencing to pneumatically convey pharmaceutical powders and other bulk solids. Applications include loading hoppers and refilling loss-in-weight feeders. Unit has integral polyester filters with automatic jet-pulse cleaning, disassembles quickly, and uses all stainless steel components. Gaskets are made of FDA-approved materials, and steep cone angle of 30-liter vessel ensures complete discharge. Throughput—up to 1,800 kilograms per hour—depends on material characteristics, conveying distance, plant layout, and discharge valve used.

Coperion K-Tron, Sewell, NJ.
Tel. 856 589 0500
www.coperionktron.com

Tablet press loaders

Vacuum loaders transfer material directly from drums, boxes, storage containers, and process vessels to tablet press hopper. Loaders eliminate manual loading and mishandling and use level sensor to automatically initiate conveying cycle when hopper runs low. Made of 316L stainless steel, loaders make dust-tight connection between receiver and press hopper and include automatic pulse-jet filter cleaning. Units are powered by low-maintenance venturi or high-efficiency electric blower. Throughput is 200 to 250 kilograms per hour. Four quick-release clamps allow tool-free disassembly to simplify cleaning.

Vac-U-Max, Belleville, NJ.
Tel. 973 759 4600
www.vac-u-max.com

Pneumatic conveyors

PPC series vacuum conveyors' one-piece, gap-free construction prevents residue from accumulating, and they dismantle without tools for easy cleaning. Units integrate with sieves, feeders, tablet presses, capsule fillers, mills, weighing systems, and other process equipment. Discharge is via hygienic butterfly valve. GMP-compliant, CIP-ready units are ATEX-certified for zones 1, 2, 21, and 22 and can be equipped with WIP systems. Company also offers validation support services.

Volkmann, Bristol, PA.
Tel. 609 265 0101
www.volkmannusa.com

Achema

a preview

PAT a centerpiece of international congress

The triennial Achema World Forum exhibition and congress for the chemical engineering and process industries returns to Frankfurt, Germany, June 15-19. The 30th congress in 2012 attracted 167,000 attendees from nearly 100 countries, with 3,773 exhibitors from 56 countries. Organizers of the 31st event expect a comparable or better turnout in 2015.

The 5-day exhibition is organized into 13 categories: research and innovation; engineering; pharmaceutical packaging and storage techniques; laboratory and analytical techniques; mechanical processes; thermal processes; instrumentation, control, and automation techniques; materials technology and testing; pumps, compressors, valves, and fittings; literature (information, learning, and teaching aids); industrial and labor safety; biotechnological equipment; and environmental protection.

Education

One of the educational themes is Process Analytical Technology (PAT), and the PraxisForum lecture series, "Innovative Process Analytical Technology" begins Wednesday, June 17. The first presentation is "Analyzer device integration: The power of analytical data." Wednesday's lectures also include: "In-line particle-size measurement of pellet fluidized-bed coating in laboratory and pilot-scale," "PAT in bioprocess development: A strategy for more efficiency and higher product quality," and "In-line particle-sizing probe as a PAT tool in high-shear and fluid-bed processes."

Thursday's lectures include "Data analysis and process control: Big data analytics and its application in plant asset management," "Taking advantage of PAT and process control for 'golden batch' strategies," and "Status and challenges of process analytics."

According to Achema organizers, this year's emphasis on PAT evolved naturally and by necessity: "Precise, real-time process analytics is indispensable to future chemical production, which has to comply with increasingly higher standards in terms of individualization, quality control, and process efficiency. Since automation has conquered all areas of the process industry, the call for innovative solutions from online analytics has made it into the next round."

Other events

Throughout the week, a number of guest organizations and experts will address process technology topics, including:

What?

Achema

Who?

Professionals involved in chemical engineering, environmental protection, biotechnology, and all varieties of process technology

Where?

Messe Frankfurt, Frankfurt, Germany

When?

June 15-19

Exhibition:
Register online at www.achema.de.

Conference:
10:30 am to 5:30 pm on June 15-18
10:30 am to 12:30 pm on June 19

General Exhibition:
9:00 am to 6:00 pm on June 15-19

For more information:
Dechema
Tel. +49 69 7564 750
www.achema.de

Accommodations:
Reserve rooms online at www.achema.de.

Automation in Dialogue. NAMUR, a chemical industry standards organization, and others will host this joint forum all 5 exhibition days. In addition to panel discussions, attendees can participate in "Meet the Experts," which will feature informal discussions in the foyer. Topics include modular automation, IT security, and energy and resource efficiency, as well as new developments in Industry 4.0 (optimization of production by cyber-physical systems) and the "Internet of Things." The experts will also address evergreen topics such as asset information management, explosion protection, and functional safety.

Labor and Process Safety Technology. The European Process Safety Centre will conduct educational sessions on Tuesday morning (June 16); the Center for Chemical Process Safety will hold additional sessions Wednesday; and the International Sanitary Supply Association is presenting a 2-day workshop June 17-18. All lectures and discussions will be given simultaneously in English, German, and French.

Powder and Nanotechnology. The Society of Chemical Engineers, Japan, will host this forum. *T&C*

Exhibitors

The following companies and organizations are among those exhibiting at Achema on June 15-19 in Frankfurt, Germany. Advertisers in this issue are listed in boldface. For a complete, updated list, visit www.achema.de.

Company	Hall and booth
A	
ACG Pharma	3.0 D73
Ackley Machine	**3.1 E69**
Adamus	3.0 H73
Advantest	4.2 P36
B	
Beckman Coulter	4.2 E49
LB Bohle	3.2 D49
Bonfiglioli Engineering	3.1 C70
Bosch	4.2 A79
Brabender Technologie	6.0 B50
Brookfield Engineering	**4.2 E64**
C	
CEIA	3.0 F96
Camfil APC	**5.1 B17**
Coperion K-Tron	5.0 D34
Countec	3.1 G69
Crown Iron Works	5.1 D78
D	
DMR Prozesstechnologie	5.1 C100
Dott. Bonapace	3.0 J73
Driam	3.0 B99
E	
Elizabeth	3.0 A50
Evonik Industries	5.1 C17
F	
Fargo Automation	3.0 J58
Fette Compacting	3.0 F3
Freund-Vector	4.0 B1
G	
GEA	4.0 F46
Gabler	3.0 F99
Glatt Pharmaceutical,	F1
H	
I Holland	3.0 H100
Horiba	11.0 A28
Hosokawa	3.1 A27
Huber	4.2 B49
K	
Kaiser Optical	11.1 C27
Kikusui	**3.1 F31**
Kilian Tableting	3.0 B49
Körber Medipak	3.1 J72
Korsch	3.0 A49
Krämer	3.0 C17
L	
Lubrizol	8.0 E72
N	
Natoli Engineering	**3.1 F15**
Netzsch	**6.0 B6**
O	
OCS Checkweighers	3.0 D95
O'Hara Technologies	3.0 B100
P	
Particle Sizing Systems	4.2 D62
Pharma Technology	3.0 F26
Pharmapack	Forum Fo_0 D9
Pharmaworks	Agora A7
Powder Systems	5.1 C31
ProCepT	4.0 C33
Q	
Qualicaps	Forum Fo_0 C1
R	
Röltgen	3.0 F2
Russell Finex	6.0 C75
S	
Scanware	3.1 A55
Sepha	3.1 C64
Solvay Specialty Polymers	9.1 C83
Sotax	4.1 H77
T	
Thomas Engineering	3.0 A24
U	
Uhlmann	3.0 F25

CombiLac®.
Best of both: compactibility and disintegration.
From Meggle.

Certified

MEGGLE's world's first high-functionality triple co-processed excipient is a monodisperse combination of alpha-lactose monohydrate, MCC and starch. It is specifically designed to ease oral solid dosage form development and manufacture and highly appropriate for direct compression (DC). The benefits speak for themselves. And for CombiLac®:

- **Excellent compactability**
- **Excellent flowability**
- **Fast, hardness-independent tablet disintegration for effective API release**
- **Low friability**
- **Overcoming individual ingredient compacting and handling limitations**

CombiLac® from MEGGLE:
Combining best of both.

MEGGLE USA:
www.meggle-pharma.com
customer.service@meggle.com
Phone +1 844 4MEGGLE
(+1 844 463 4453)

HEAD OFFICE GERMANY:
www.meggle-pharma.de
service.pharma@meggle.de
Phone +49 8071 73 476

MEGGLE
EXCIPIENTS & TECHNOLOGY

eye on excipients

David Schaible and Louis Mejias
JRS Pharma

Lubricants can have a negative impact on tablet hardness and other critical quality attributes. In this edition, our guest columnists discuss the results of a study that compared how blends made using silicified microcrystalline cellulose and microcrystalline cellulose and two different lubricants performed on a tablet press.

In decades of troubleshooting formulations for customers, some of the most common issues we've encountered involve lubricant sensitivity of microcrystalline cellulose (MCC) and, to a lesser extent, other excipients. Lubricants often cause problems during development, scale-up, and production. In many cases, these problems could have been avoided by using high-functionality excipients (HFEs). These may be defined as excipients which: serve more than one function (e.g., both binder and glidant or binder and disintegrant); have inherently high functional performance allowing larger batch sizes and/or higher drug loading even at relatively low usage levels; require no complex processing; and, impart their desirable performance characteristics to the overall formulation. Likewise, a more comprehensive understanding of the tablet-making process—as the FDA's Quality-by-Design (QbD) initiative is intended to foster—would also have helped avoid formulation performance problems.

Defining the critical quality attributes (CQAs) of tablets or capsules is integral to QbD, and identifying the elements that could put CQAs at high risk is part of the QbD design space. Historically, blending and compression rank among the high-risk operations. To assess risk and devise ways to mitigate it require a thorough examination of these operations and their effects on the process and final product. That is the only way to acquire the data needed to determine whether tabletting or capsule filling has a negative effect on the CQAs. If it doesn't, we can consider the formulation robust.

While risk assessment in QbD merits an article unto itself, here we are simply defining it as a measure of the likelihood that a process will yield excessive CQA deviation, with an eye on what we know about the variables in the process and what control measures are in place.

Effect of lubricants

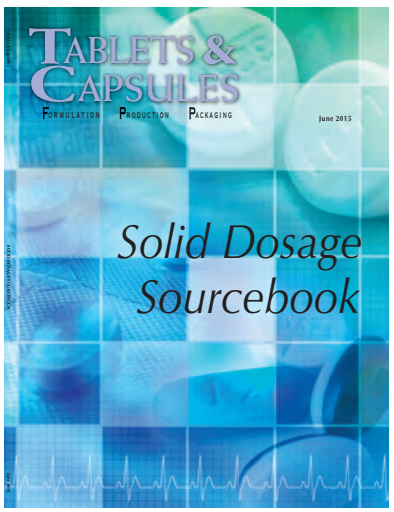
Magnesium stearate (MgSt), a ubiquitous tablet lubricant, diminishes tablet hardness when used with MCC. Its effects vary with the amount of lubricant used and the duration of blending [1].

Studies show that blends of MCC and MgSt exhibit greater lubricant sensitivity and are more sensitive to tablet press speed than blends of silicified microcrystalline cellulose (SMCC) and MgSt [2]. On the other hand, compared to MgSt, sodium stearyl fumarate (SSF), another popular lubricant, produces minimal negative effects with respect to amount and blend time when blended with MCC [3]. Studies of SSF-SMCC and MgSt-SMCC blends show that the SSF-SMCC combinations form superior capsule plugs [4]. Studies by Muzíková demonstrate that this effect holds true when various lubricants are combined with SMCC in placebo tablets [5]. In short, using HFEs such as SMCC in combination with SSF can reduce risk and dramatically simplify the design of experiments during formulation development.

Surprisingly, there are few studies available like the one detailed in this article, which incorporate a model API into the evaluation of how lubricants (MgSt and SSF) and binders (MCC and SMCC) affect one another with respect to excipient amount and blend time (Table 1). The data from this study indicate that using quality materials such as HFEs prevents problems and simplifies risk-mitigation studies, leading to superior dosage forms with less development time required. The placebo data suggest general trends, and the model API formulation with chlorpheniramine maleate (CPM) reinforces the patterns identified in the placebo models.

The results of tests on the SMCC placebo formulation (Figure 1) illustrate the effects of lubricant amount and blend time on tablet hardness.

Coming in June



The T&C Solid Dosage Sourcebook — Spotlighting the top companies that supply equipment, materials, and expertise to manufacturers of pharmaceuticals and dietary supplements.

TABLE 1

Specifications and methodology of study

Placebo methods:

- 20-mesh screen; varying levels of lubricant; blend with MCC or SMCC; mix using Turbula blender for varying amounts of time.
- Amounts of lubricant used: 0.5, 1.0, and 2.0% MgSt.
- Blending times: 5 minutes, 20 minutes.*
- Materials compressed with instrumented rotary tablet press that recorded compaction and ejection forces.
- Tablets analyzed for hardness/crushing strength.

API model methods:

- 20-mesh screen; lubricant; blend with MCC or SMCC and 20 percent CPM; mix using Turbula blender for varying amounts of time.
- Amounts of lubricant used: 0.5% MgSt or 0.5% SSF.
- Blending times: 5 minutes, 20 minutes.*
- Materials compressed with instrumented rotary tablet press that recorded compaction and ejection forces.
- Tablets analyzed for hardness/crushing strength.

* Note: In this study, blend times denote the period that the formulation spent undergoing blending in a high-energy lab-scale Turbula-style blender. In a production setting, true blend times and the shear applied are often difficult to measure. Furthermore, blending actually continues as the formulation is transported, transferred, and fed through the hopper onto the turret. It only really ends when the tablet is compressed. While blending time is usually held constant over the lifespan of a formulation, equipment and manufacturing sites may change, causing the shear force and true blend time to vary, which could lead to failures.

The same trends are evident from the tests of the MCC formulation, except tablet hardness is much lower (data not shown). Similar trends are evident in a placebo formulation that used SSF as the lubricant, but there wasn't as much reduction in tablet hardness (data not shown).

Baseline functionality of an excipient matrix in placebo formulations is useful, but the addition of APIs and how much is added dictate ultimate functionality. Likewise, studies with model APIs can help you identify issues to anticipate when manufacturing with comparable APIs. Figure 2 shows that SMCC formulated with a model API (CPM) and lubricated with MgSt has a substantially better compaction profile than a formulation that includes premium spray-dried MCC, regardless of the blend times. Note that tablet hardness increases consistently with compaction force in the SMCC formulation, while doubling the compaction force applied to the MCC formulation improves hardness only negligibly and somewhat unevenly. It is noteworthy that the SMCC profiles have steeper slopes, suggesting harder tablets are achievable.

The same methods and equipment were used to compress formulations that included SSF instead of MgSt (Figure 3). Once again, the SMCC formulations had substantially better compaction profiles than the MCC versions. (All formulations had acceptable ejection forces.) As Figure 4 shows, combining SMCC and SSF produced very robust formulations, with a fivefold or greater increase in tablet hardness. This suggests that these excipients offer a broad design space without compromising CQAs.

While the characteristics of a formulation depend upon the specific API(s) used, this study using a model API reflects the same trends seen in the placebo studies. Understanding these trends may help you substantially reduce development time, require less material, and simplify risk-mitigation studies.

In sum, the evidence examined in this study supports the assertion that the cost of failures and delays associated with scale-up and production using common excipients outweighs the higher costs of HFEs. T&C

Figure 1

Compaction force vs. hardness of SMCC compacts lubricated with MgSt

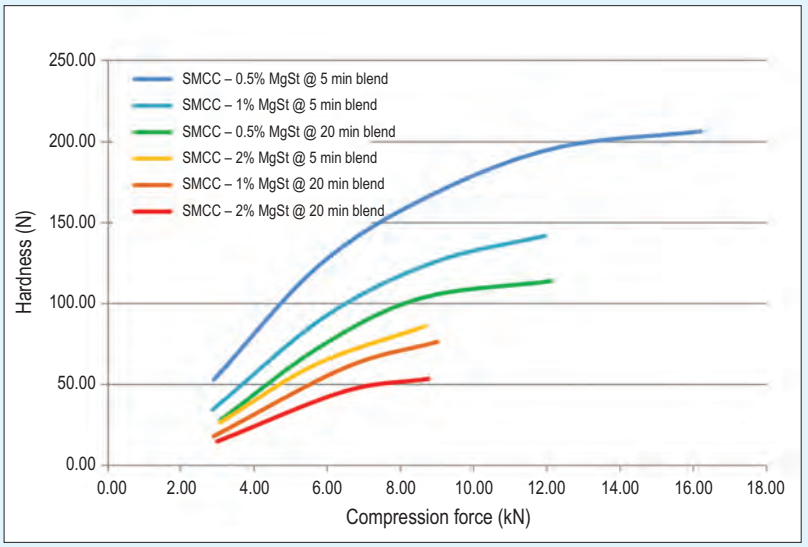
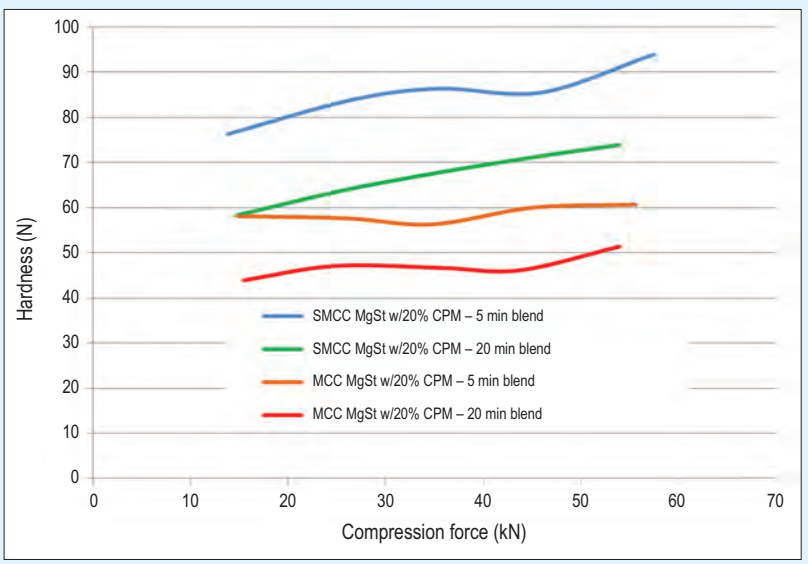


Figure 2

Compaction force vs. hardness of SMCC and MCC compacts lubricated with MgSt



References

1. Doelker, E. et al. Comparative compaction properties of various MCC types and generic products. Drug Dev. Ind. Pharm., 19: 2399-2471, 1993.

2. Hwang, R., and Peck, G.R. A systematic evaluation of the compression and tablet characteristics of various types of microcrystalline cellulose. Pharm. Technol., 24: 112-132, 2001.

3. Schindler, B., Zeleznik, J., and Renak, J. Sodium stearyl fumarate: An effective tablet lubricant to avoid slippery situations. JRS Pharma. AAPS Annual meeting poster presentation, Nashville, 2008.

Figure 3

Compaction force vs. hardness of SMCC-MCC compacts lubricated with SSF

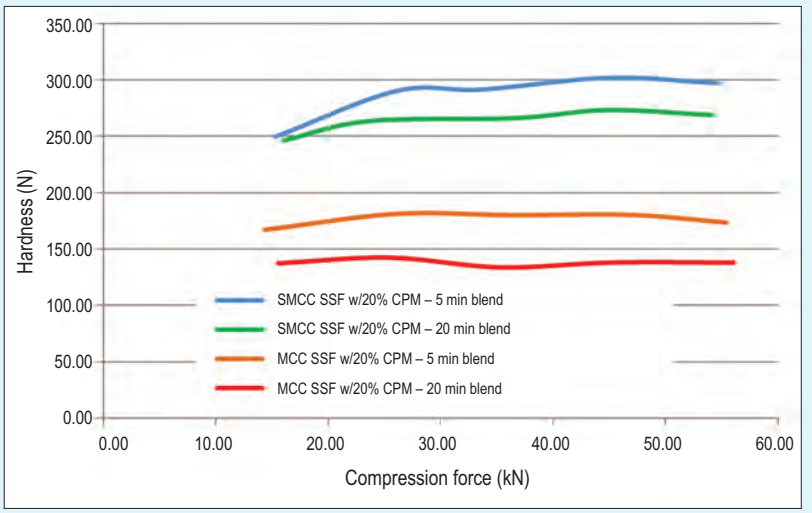
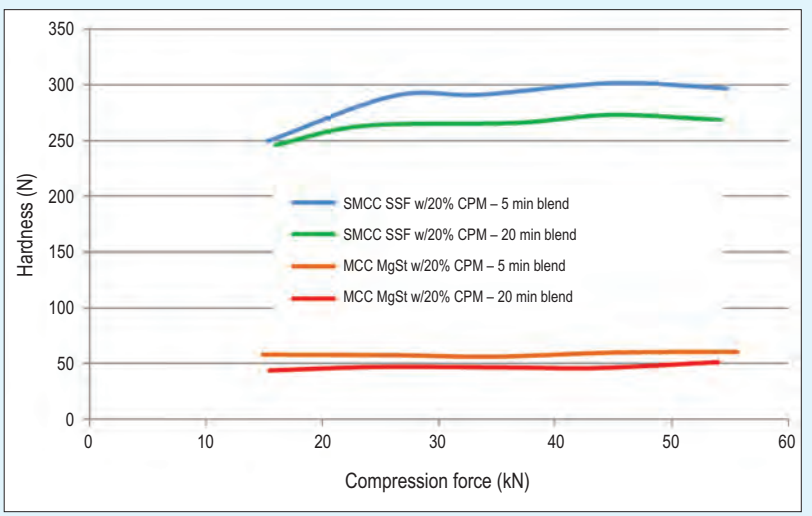


Figure 4

Compaction force vs. hardness of SMCC-SSF tablets and MCC-MgSt tablets



4. Guo, M., and Augsburger, L.L. Potential application of silicified microcrystalline cellulose in direct-fill formulations for automatic capsule-filling machines. Pharm Dev. Technol. 8(1):47-59, 2003.

5. Muzíková, J., and Nováková, P. A study of the properties of compacts from silicified microcrystalline celluloses. Drug Dev. Ind. Pharm. 33(7):775-81, 2007.

David Schaible is a principal scientist and manages R&D and Louis Mejias is scientist II at JRS Pharma, 2981 NY-22, Patterson, NY 12563. Tel. 845 878 3414. Website: www.jrs.de. Schaible specializes in API-excipient co-processing and development of high-performance excipients; he has been awarded several patents for development of co-processed excipients.

particle size: reduction, separation & analysis

A survey of what's available

Powder flow tester

PFT powder flow tester requires only 43 cubic centimeters of powder to determine flow function, time consolidation, and wall friction. Data indicates flow index, arching dimension, rat-hole diameter, hopper half angle, gravity chute angle, and bulk density curve. Benchtop unit includes Powder Flow Pro software and is easy to operate. Company can perform IQ/OQ/PQ certification for you or you can self-certify using company's IQ/OQ/PQ document with step-by-step instructions and calibrated reference powder. Self-certification kit is available worldwide.

Brookfield Engineering, Middleboro, MA.
Tel. 800 628 8139
www.brookfieldengineering.com

Bead mills

DeltaVita series bead mills reduce particles to 200 nanometers or less, increasing surface area and improving dissolution and bioavailability of poorly soluble APIs. Better bioavailability reduces amount of API required, production costs, and risk of side effects. GMP-compliant units produce batches of 15 milliliters to 4,000 liters. Laboratory mills accept grinding chambers in range of sizes, use grinding media of 0.05 to 2 millimeters, and separate media from product using centrifugal force. Company supplies test and qualification documentation and FAT, IQ, OQ, and PQ validation. Clean-in-place and sterilize-in-place systems are optional for pilot- and production-scale mills. Data recording and formulation management are also available.

Netzsch Premier Technologies, Exton, PA.
Tel. 800 676 6455
www.netzsch.com/gd

Particle size analyzer

SALD-2300 laser-diffraction particle size analyzer allows you to test wet and dry samples simply by changing flow cells. With batch cell, sampler with flow-through cell, and cyclone injection unit, you can analyze wet or dry samples of 0.1 parts-per-million to 20 percent particle concentration range. Highly concentrated samples can be measured without dilution, preventing dispersion or agglomeration. Instrument's range is 17 nanometers to 2,500 microns. It uses one sensor to detect side-scattered light and five others to detect back-scattered light in real time at minimum of 1-second intervals. Wing Sensor II has 78 concentric detector elements that can acquire data with multiple peaks. Software automatically calculates appropriate refractive index based on method used to reproduce light-intensity distribution. You can analyze data from various angles using statistical processing, time-series analysis, and 3D graphs Operation log stores measurement data and instrument contamination status.

Shimadzu Scientific Instruments, Columbia, MD.
Tel. 800 477 1227
www.ssi.shimadzu.com

Annual Meeting and Exposition of the Controlled Release Society

a preview

Delivery science conference heads to Scotland

The Controlled Release Society (CRS) is taking its annual meeting to Edinburgh, Scotland, July 26-29. This year's theme is "Creating Value Through Customized Delivery." Organizers anticipate 1,250 or more attendees—roughly half from industry and half from academia—from 45 countries. Networking opportunities are plentiful with the Consumer & Diversified Products Division luncheon, President's banquet, Preclinical Sciences & Animal Health networking get-together, Women in Science luncheon, Young Scientist Mentor/Protégé meet-and-greet, and the Young Scientist networking event.

Delivery science specialists from a variety of disciplines will be on hand, including drug delivery, dissolution testing, R&D, formulation, nanotechnology, business development, regulatory affairs, and particle design.

Scientific sessions

The educational program features 20 scientific sessions based on abstracts submitted to CRS pertaining to its 10 core areas. Each session will include two invited speakers, five research highlight talks, and a moderated discussion with the speakers. Session topics include: "Drug Delivery to the Brain," covering strategies to overcome the blood-brain barrier to treat tumors, traumatic brain injury, and degenerative diseases; "Formulating Oral Solid Dosage Forms to Enhance Drug Delivery," focusing on APIs with poor solubility and complex stability challenges; "Modulated and Responsive Delivery Systems," aimed at zero-order release profiles, and "Oral Drug Delivery," which examines advances beyond traditional matrix tablets using technologies such as 3D printing, lipophilic pro-drugs, polymeric nanoparticles, and gastroretentive delivery systems.

Plenary sessions

Plenary speaker sessions feature "Customized Drug Delivery: A Personal Odyssey," in which noted professor of medicine, Dr. Vincent H.L. Lee, shares how his personal struggle with Parkinson's disease sharpened his awareness of why drug delivery advances, both scientific and regulatory, are needed to meet patient needs. Another session, "Polymers and Nanomedicines: The Promises and Pitfalls of New Materials," looks at promising developments with responsive materials for drug, gene, and cell delivery—and the hurdles yet to be overcome.

Technology Forums

Technology Forums are both educational and promotional opportunities for companies to present their latest technology in a small group setting. Catalent and BASF will co-present "Formulation Solutions Using Hot Melt Extrusion for Poorly Soluble Drugs." Evonik Industries will host "Case Study: Developing Complex, Extended-Release Products from Feasibility to Production."

Pre-meeting workshops

Half-day, full-day, and 1.5-day workshops are scheduled for Saturday and Sunday, July 25-26. They include "Introduction to Encapsulation and Controlled Release Technologies," covering the latest microencapsulation techniques used for controlled-release applications, including atomization, spray coating, co-extrusion, and emulsion-based technologies. *T&C*

Exhibitors

The following companies and organizations are among those exhibiting at the Annual Meeting and Exposition of the Controlled Release Society on July 26-29 in Edinburgh, Scotland. For a complete, updated list, visit www.controlledreleasesociety.org.

Company	Booth
B	
BASF	701, 801
Bend Research-Capsugel	601
Buchi Labortechnik	303
C	
Catalent	400
Colorcon	200
D	
Dissolution Technologies	N/A
E	
Evonik	201
F	
Freund-Vector	401
G	
Gattefossé	402
M	
Merck Millipore	403
S	
Shin-Etsu	305
Sotax	702

What?

Annual Meeting and Exposition of the Controlled Release Society

Who?

Professionals dedicated to the delivery of actives, including delivery scientists, engineers, clinicians, and technical professionals

Where?

Edinburgh International Conference Centre, Edinburgh, Scotland

When?

July 26-29

Registration & Accommodations:
www.controlledreleasesociety.org/meetings/annual/RegHotel

Conference:
8:00 am to 5:30 pm on July 26-28
8:00 am to 11:00 am on July 29

General Exposition:
Grand Opening: 5:30 pm on July 26
9:30 am to 5:30 pm July 27
9:30 am to 4:00 pm July 28

For more information:
Controlled Release Society
Tel. 651 454 7250
www.controlledreleasesociety.org

Pharmapack North America

a preview

Track-and-trace compliance, other regulatory issues central at packaging expo

Pharmapack North America returns to the Jacob Javits Convention Center in New York, NY, June 9-10. The conference and exhibition is part of a co-located advanced manufacturing conference that also includes Medical Device Design and Manufacturing East, East Pack, and Atlantic Design and Manufacturing. Registering for one event grants you admission to all.

The exhibition hall, open from 10:00 am to 4:00 pm Tuesday and Wednesday, will feature technologies and services from suppliers representing the many facets of pharmaceutical packaging, including child-resistant/adult-friendly packaging, barrier packaging, blister packaging, compliance packaging, serialization/track-and-trace, patient safety, package integrity, container closure systems, inserts and outserts, labeling design, and supply-chain sustainability.

Conference: Tuesday

Educational opportunities begin Tuesday morning with a keynote address, "Recent Changes and Proposed Changes to USP Packaging Chapters," from Dwain L. Sparks, a 39-year veteran of Eli Lilly and now an independent consultant on Chemistry, Manufacturing, and Controls (CMC) regulatory affairs and pharmaceutical packaging regulations. Immediately following is a roundtable discussion with subject matter experts on how USP changes will affect economics, risk, and product development and how to prepare for these changes, manage new challenges, and benefit from arising opportunities.

Afternoon sessions focus on innovations in pharmaceutical packaging, starting with an overview of the fast-growing combination products sector and the regulations that pertain to them. A later session examines how advancements in packaging—including the integration of digital audio, Bluetooth devices, and sensors—can improve patient education and training and thus improve compliance and reduce errors.

Another session looks into the future of pharmaceutical packaging and labeling in general, with insights on applying objective, research-based principles that help you design and evaluate labels to improve compliance and patient outcomes. An industry-wide session tailored to all co-located conference attendees ponders "mass customization"—the concept by which manufacturing retains the efficiency of mass production while offering a range of options that satisfy a wide customer base.

Conference: Wednesday

Wednesday's keynote, "Method or Magic?" features Nancy Limback, manager of packaging innovation and development at Sanofi. She will discuss key principles of package differentiation, including a study of several

What?

Pharmapack North America

Who?

Professionals involved in the purchase and development of packaging, pharmaceuticals, and drug delivery systems

Where?

Jacob Javits Convention Center
New York, NY

When?

June 9-10

Exhibition:
Register online at
www.pharmapackna.com

Conference:
9:30 am to 4:00 pm, June 9-10

General Exhibition:
10:00 am to 4:00 pm, June 9-10

For more information:
UBM Canon
Tel. 310 445 4200
pharmapackna.com

breakthrough packaging examples. A representative from the Consumer Product Safety Commission will present an update on child-resistant packaging requirements. Next is a roundtable titled "Packaging Technologies for Driving Patient Adherence, Convenience, and Safety," followed by a question-and-answer session on whether patient-friendly child-resistant packaging is truly feasible.

Afternoon sessions are aimed primarily at supply chain security and counterfeit prevention. The first delves into how pharmaceutical counterfeiters infiltrate legitimate supply chains and what you can do to detect, deter, and defeat their efforts. The next session reviews best practices pertaining to serialization standards and guidances. Then comes "From Master Data to In-spec GS1 Data Matrix Symbols," which provides insights on how to successfully implement item, bundle, and case-level serialization and 2D barcode marking. Other sessions include "Creative Packaging Designs for Drug Serialization," which offers start-to-finish tips on how to integrate creative packaging designs and enterprise systems with new serialization and traceability regulations. *T&C*

Exhibitors

The following companies and organizations are among those exhibiting at Pharmapack North America, June 9-10 in New York, NY. For a complete, updated list, visit www.pharmapackna.com.

Company	Booth
A	
Amcor Flexibles	1338
B	
Bemis Healthcare	1950
K	
Körber Medipak	4151
M	
Multisorb Technologies	4209
T	
Tekni-Plex	4215

industry *innovations*

Pin mill

CIM-18-S316 pharma-grade pin mill grinds friable powders, flakes, and granules into controlled particle sizes, either coarse or fine. Outer and inner discs swing away from unit on cantilevered arms, providing full access to both sides of each disc and mill housing for rapid cleaning and sanitizing. High-speed rotation of inner disc creates centrifugal force that accelerates material passing through central inlet of opposing stationary disc. As material travels at high speed from center to periphery of discs, it passes through five intermeshing rows of rotating and stationary impact pins. Rotor spins at a few hundred rpm to 5,400 rpm to perform deagglomeration, coarse grinding, and fine grinding (400 mesh). Unit is made of type 316 stainless steel and features sanitary butterfly valve on air intake, sanitary fittings at material intake and discharge, and wash-down motor.

Munson Machinery, Utica, NY.
Tel. 315 797 0090
www.munsonmachinery.com

High-speed capsule filler

GKF 2600 capsule filler encapsulates powders, pellets, tablets, liquids, and combinations at speeds as high as 2,600 capsules per minute. Modular unit uses proven and new technologies, including micro-dosing wheel that meters 2 to 30 milligrams. Features include automatic troubleshooting function, user-friendly controls, and easy-access filling stations. Options include KKE 2600 checkweigher and feedback loop that automatically regulate over- and underfilling, as well as x-ray unit that inspects weight and quality. Machine also accepts upgrades to meet your containment requirements.

Bosch Packaging, Minneapolis, MN.
Tel. 763 424 4700
www.boschpackaging.com

Moisture-barrier coating

Opadry amb II immediate-release film coating protects moisture-sensitive formulations. Fully formulated PVA-based coating is first of its kind without polyethylene glycol or soy lecithin, reducing impurity and allergen concerns. Low-viscosity, high-productivity coating imparts robust, glossy finish and well-defined logos without affecting dissolution. It preserves stability, mechanical integrity, and shelf-life of loose tablets, such as those packaged in bottles or removed from primary packaging. One-step dry powder mixes with water and is ready to use in 45 minutes. It comes in clear and pigmented forms, and recommended weight gain is 4 percent.

Colorcon, Harleysville, PA.
Tel. 215 256 7700
www.colorcon.com

calendar

May

Pharmaceutical Dissolution Testing: A Hands-on Course. May 26-28 in London, UK. Conducted by Pharma Training. Tel. +44 11 5912 4249. Website: www.pharma-training-courses.com.

Hands-on Course in Tablet Technology. May 31-June 5 at University of Mississippi, Oxford, MS. Tel. 662 915 7283. Website: www.olemiss.edu.

June

International Industrial Pharmaceutical Research & Development ("Land O'Lakes") Conference. June 1-4 in Madison, WI. Presented by University of Wisconsin-Madison School of Pharmacy. Tel. 608 262 3132. Website: ce.pharmacy.wisc.edu.

Outsourcing Pharmaceutical Operations. June 1-2 in New Brunswick, NJ. Conducted by the Center for Professional Advancement. Tel. 732 238 1600. Website: www.cfpa.com.

Rx-360 Symposium: Fighting Fakes. June 2-3 in Washington, DC. Hosted by Rx-360. Tel. 202 230 5607. Website: www.rx-360.com.

Encapsulation Defects Symposium. June 3-4 in Cleveland, OH. Conducted by Techceuticals. Tel. 216 658 8038. Website: www.techceuticals.com.

Good Manufacturing Practices. June 8-10 in Malvern, PA. Conducted by Center for Professional Innovation & Education. Tel. 610 688 1708. Website: www.cfpie.com.

Packaging of Pharmaceuticals. June 8-10 in New Brunswick, NJ. Conducted by the Center for Professional Advancement. Tel. 732 238 1600. Website: www.cfpa.com.

Pharmapack North America. June 9-10 in New York, NY. Conducted by UBM Canon. Tel. 310 445 4200. Website: www.canontradeshows.com.

Scale-up: Transferring Products to Production. June 9-11 in Schopfheim, Germany. Conducted by Bosch Packaging Academy. Tel. +41 586 746 593. Website: www.boschpackaging.com.

Process Validation for Packaging of Pharmaceuticals and Medical Devices. June 11-12 in New Brunswick, NJ. Conducted by the Center for Professional Advancement. Tel. 732 238 1600. Website: www.cfpa.com.

Best Practices for an Effective Cleaning Validation Program. June 11-12 in Malvern, PA. Conducted by Center for Professional Innovation & Education. Tel. 610 688 1708. Website: www.cfpie.com.

Achema. June 15-19 in Frankfurt, Germany. Conducted by Dechema. Tel. +49 697 564 254. Website: www.achema.de.

Compaction Simulation Forum. June 16-17 in Copenhagen, Denmark. Website: www.compactionsimulation.com.

Excipient GMP Auditor Workshop. June 16-18 in Atlanta, GA. Presented by IPEC-Americas. Tel. 571 814 3449. Website: www.ipecamericas.org.

Pharmaceutical Packaging Systems, Parts 1 & 2. June 16-18 in Vienna, Austria. Conducted by the European Compliance Academy. Tel. +49 6221 84 440. Website: www.gmp-compliance.org.

Design of Experiments (DoE) for Process Development and Validation. June 18-19 in Seattle, WA. Conducted by the Global Compliance Panel. Tel. 800 447 9407. Website: www.global-compliancepanel.com.

Active Pharmaceutical Ingredient & Drug Product Specifications: From Clinical Development to Market Approval. June 22-23 in Los Angeles, CA. Conducted by Center for Professional Innovation & Education. Tel. 610 688 1708. Website: www.cfpie.com.

21 CFR 111 Dietary Supplement GMP Overview. June 23 in Chicago, IL. Conducted by NSF. Tel. 734 769 8010. Website: www.nsf.org.

Advanced Compression. June 24-26 in Cleveland, OH. Conducted by Techceuticals. Tel. 216 658 8038. Website: www.techceuticals.com.

Hands-on Tablet Development Including the Principles of Pre-formulation, Formulation, and Process Development. June 24-26 in Penge, UK. Conducted by Pharma Training. Tel. +44 11 5912 4249. Website: www.pharma-training-courses.com.

July

Current Industry Trends and Rethinking on QbD. July 9-10 in New Brunswick, NJ. Conducted by the Center for Professional Advancement. Tel. 732 238 1600. Website: www.cfpa.com.

Drug Product Stability and Shelf-Life. July 13-15 in New Brunswick, NJ. Conducted by the Center for Professional Advancement. Tel. 732 238 1600. Website: www.cfpa.com.

World Nutraceutical Conference and Expo. July 13-15 in Philadelphia, PA. Conducted by OMICS Group International. Tel. 650 268 9744. Website: www.pharmaceuticalconferences.com.

21 CFR 111 Dietary Supplement GMP Overview. July 14 in Denver, CO. Conducted by NSF. Tel. 734 769 8010. Website: www.nsf.org.

Basics of Tablet Manufacturing and Troubleshooting. July 14-16 in St. Charles, MO. Conducted by Natoli Engineering. Tel. 636 926 8900. Website: www.natoli.com.

The New GDP and Track & Trace Regulations in Europe. July 14-15 in Jersey City, NJ. Conducted by the European Compliance Academy. Tel. +49 6221 84 440. Website: www.gmp-compliance.org.

Tablet Pro. July 15-17 in Cleveland, OH. Conducted by Techceuticals. Tel. 216 658 8038. Website: www.techceuticals.com.

Drug Processing, Labeling & Packaging. July 20-22 in Beijing, China. Conducted by OMICS Group International. Tel. 650 268 9744. Website: www.pharmaceuticalconferences.com.

Pharmaceutical Process Development. July 20-22 in Burlingame, CA. Conducted by the Center for Professional Advancement. Tel. 732 238 1600. Website: www.cfpa.com.

Controlled Release Society Annual Meeting & Exposition. July 26-29 in Edinburgh, Scotland. Tel. 651 454 7250. Website: www.controlledrelease.org.

21 CFR 111 Dietary Supplement GMP Overview. July 28 in Dallas,TX. Conducted by NSF. Tel. 734 769 8010. Website: www.nsf.org.

back page

The impact of M&A on innovation

Every week or two, another merger or acquisition—either between pharma companies or their suppliers—is in the news. Last year saw a surge in deals, some driven by tax benefits and others by a new strategy. The attempt of Pfizer to acquire AstraZeneca and of AbbVie to buy Shire foundered only because the USA tightened its tax code. That rewrite also shifted the M&A game, and companies are now pursuing new and more narrow therapeutic areas because they offer more opportunity to dominate a particular disease and maximize ROI.

As mergers continue, in-house R&D will shrink and many companies are tightening their focus and invoking the term "measurable results." Many are also divesting in-house manufacturing, and only a handful of drug or biopharma products are made solely within a company's vertical infrastructure. It's now common to outsource the APIs, product manufacture, and packaging. That's good for contract manufacturers, which are growing, but the combination of more M&A and outsourcing doesn't bode well for innovation.

Worldwide, pharma companies are flush with cash, much of it kept overseas to avoid US taxes. But the cash isn't idle. It's invested in promising discoveries, offshore manufacturing, and foreign-based clinical trials and development. That reduces investment in R&D here and diminishes our industrial infrastructure. As a result, the remnants of our domestic companies are now sales and marketing units. Discovery and innovation are left to others. Perhaps Valeant's business strategy is the new model: Focus on acquisitions that expand the portfolio and avoid the need for research.

Generic manufacturers are not immune to this change, and many of them have been acquired and consolidated into companies based in the USA, Israel, India, and China. While many generics bear the name of a marquee domestic company, all the manufacturing and packaging were done overseas.

Contract manufacturers grow

The rise of new and larger contract manufacturers is another trend. The acquisition of Anderson Brecon by Packaging Coordinators (PCI) is one example. The big contract manufacturers (PCI, Sharp, Patheon, Catalent, etc.) offer not only packaging, but also API manufacturing, clinical trial support, and compounding. The result, I predict, will be less innovation in pharma, fewer new packages, and supply chains that are more susceptible to problems.

Yet innovation in both drug discovery and packaging is sorely needed to address the chronic ailments of aging populations in the USA, Europe, and Japan. Too many drugs are still delivered in packages developed 75 years ago, and those are difficult for aged patients to use and don't allow physicians to monitor their patients' progress over extended periods.

Smart packaging—which has yet to reach the mainstream—offers new opportunities to improve treatment outcomes. How much better would healthcare be if pharma packaging enriched communication between the patient, pharmacist, and physician? Adherence-promoting packaging—pouches or blisters that hold multiple drugs and describe the dispensing regimen, for example—is available, but hasn't been adopted. Has M&A activity caused companies to shift their focus from the patient and clinical outcomes to revenue optimization and internal efficiency?

The new drugs targeting specific therapeutic areas, such as hepatitis C, require an extended course of treatment. But these new treatments will likely be packaged using old technologies, just as the treatments for Crohn's disease, HIV, and other major ailments are. A good deal of the packaging technology used today is 10 to 15 years old. Forthcoming treatments for fibrotic diseases, cancers, and other afflictions should use innovative packaging to improve delivery, adherence, and outcomes.

In fact, we need to break the outdated packaging mold, but I see no evidence that anything new is in development. Sadly, I foresee an extended period of only incremental improvement in packaging and drug delivery. *T&C*

*[*Editor's note: To comment on the Back Page, visit www.tabletscapsules.com.]

Edward J. Bauer, author of The Pharmaceutical Packaging Handbook, *held global responsibility for packaging at Abbott (Ross Products Division), Wyeth, and Bausch and Lomb before he retired in 2011. Today, he consults in association with Packaging and Technology Integrated Solutions, Havi Global Solutions, 3500 Lacey Road, Suite 600, Downers Grove, IL 60515. Tel. 269 806 4566. Website: www.ptisglobal.com. His article, "Packaging's contribution to patient adherence and cost containment," appeared in the May 2014 issue.*

supplier news

Nisso increases HPC capacity

NEW YORK, NY—Nippon Soda (Nisso) added several production lines dedicated to hydroxypropyl cellulose (HPC) at its Nihongi, Japan, facility. The new lines manufacture Nisso's SSL-SFP low-molecular-weight, fine-powder HPC. In the October 2014 issue, Nisso's Ryan Cheng discussed how the new HPC, even at low usage levels, improves the solubility of APIs and helps formulate immediate-release tablets and films.

Metrics adds elemental impurities testing equipment

GREENVILLE, NC—Metrics Contract Services augmented its analytical laboratory capabilities with the purchase of a Thermo Scientific mass spectrometer and a Milestone UltraWave single reaction-chamber digestion vessel. The equipment, which cost about $200,000, will speed testing for elemental impurities as required by the ICH Q3D international guidelines and by the general chapters <232> and <2232> that USP is scheduled to implement in January 2018.

Jet Pulverizer acquired by Rice Industries

RICHMOND, VA—Rice Industries purchased Jet Pulverizer, Moorestown, NJ, a supplier of spiral jet mills and size reduction toll processing. Rice also owns Ancos, which offers polymer enhancements (polymerization, crystallization, grinding, and blending) and material handling services.

Catalent completes Kentucky plant expansion

SOMERSET, NJ—Catalent Pharma Solutions completed a 2-year, $52 million expansion of its Winchester, KY, manufacturing facility, creating 140 new jobs. The expanded site, with additional fluid-bed capacity and analytical laboratories, has produced more than three billion tablets and capsules per year since it opened in 1992.

Aenova debuts contract packaging services

MIAMI, FL—CDMO Aenova Group now offers packaging services for solid dosage forms. The new offering follows its September 2014 acquisition of Contract Packaging Resources, Greensboro, NC.

L.B. Bohle opens continuous processing center

ENNIGERLOH, Germany—L.B. Bohle opened a technology center here dedicated to continuous tablet production. The process accommodates direct-compression blends and dry and wet granulations.

Klöckner Pentaplast opens film technology center

GORDONSVILLE, VA—Klöckner Pentaplast's pharmaceutical films division unveiled its "kp i.center" in Charlottesville, VA. The center, located in the University of Virginia's Research Park Emerging Technology Center, houses the company's expanded BlisterPro Xcel suite of consulting, design, stability, and prototyping services.

classified

position available

advertiser index

TABLETS & CAPSULES

Welcome to **Tablets & Capsules** magazine!

Tablets & Capsules is the only technical publication devoted exclusively to readers involved in the tablet and capsule processing industries. Our aim is to provide practical information that readers will use in daily operations of their businesses. Our articles and bonus sections provide the most up-to-date information in the industry.

Upcoming issues focus on Excipients, Tabletting, Quality: Validation and Regulatory Compliance, and the Annual Buyer's Guide.

The best part of **T&C** is that all of this valuable information comes to you in a subscription that is **FREE**!!

So fill out the form on the reverse side of this card and send it back to start your subscription to **T&C** today!!

You can also subscribe online at **www.tabletscapsules.com**.

fold on this line

PLACE
STAMP
HERE

CIRCULATION DEPT
CSC PUBLISHING INC
1155 NORTHLAND DR
SAINT PAUL MN 55120-1288

Pass this on to a co-worker so they can get their own subscription to Tablets & Capsules

Do you wish to receive (continue to receive) ***Tablets & Capsules***? ☐ **Yes** ☐ No
How do you wish to receive ***Tablets & Capsules***? ☐ Print ☐ Digital

What is your company's **primary** business? (check only one):

21. ☐ Pharmaceutical Manufacturing
22. ☐ Nutraceutical Manufacturing
23. ☐ Vitamin Manufacturing
24. ☐ Food Manufacturing
25. ☐ Chemical Manufacturing
26. ☐ Contract Manufacturing/Packaging
27. ☐ Consulting Engineering
28A. ☐ Educational Institutions
28C. ☐ Pharmaceutical Materials
28G. ☐ R&D Labs
28. ☐ Other _____

Do you currently manufacture tablets at this location?
☐ Yes ☐ No

Do you currently manufacture capsules at this location?
☐ Yes ☐ No

SUBSCRIBER

If you qualify, ***Tablets & Capsules*** will be sent to you without cost or obligation. Please note: unless **all information** is given, magazine cannot be sent.

Principal job function (check only one):

1. ☐ Process/Production Engineering
2. ☐ Validation
3. ☐ R&D
4. ☐ QC/QA
5. ☐ Plant Management
6. ☐ Operations Management
7. ☐ Corporate Management
8. ☐ Consulting Engineering
9. ☐ Packaging Management

Numbers of employees at this location:

10. ☐ 1,000 or more
11. ☐ 500-999
12. ☐ 100-499
13. ☐ 50-99
14. ☐ 20-49
15. ☐ Under 20

CSC Publishing will use mailing information, phone, fax and email to ensure delivery and maintain your FREE subscription.

Name _____ Title _____

Company _____

Business Address _____ Mailstop _____

City _____ ST _____ Zip _____

Business Phone _____ FAX _____

E-mail _____

Signature _____ Date / /

TC	BI	JF	PS

Please sign and date. Affix postage and mail or fax to 651/287-5666 or 651/287-5650.
You can also subscribe online at **www.tabletscapsules.com**.

QUALITY.

NATOLI leads the industry in tablet compression tooling.

At Natoli Engineering Co., we're proud to engineer punches and dies of superior quality. We use the highest quality steel paired with the latest manufacturing innovations, and all of our materials are tested for quality by our in-house metallurgist and an independent lab. Can your tooling supplier document steel quality like Natoli can? Find out at **natoli.com.**

NATOLI

YOU DEMAND. WE DELIVER.