WWW.PHARMAMANUFACTURING.COM

VOLUME 15, ISSUE 3

Pharmaceutical MANUFACTURING

THE DRUG INDUSTRY'S VOICE FOR MANUFACTURING EXCELLENCE

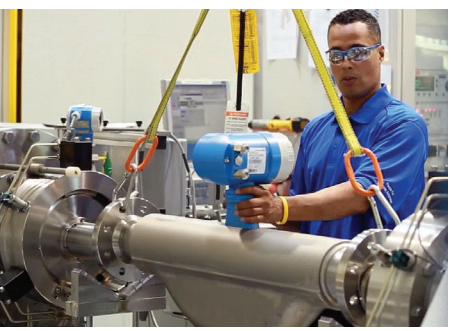
On Solid Ground

OSD manufacturers may not be reinventing the wheel – but they are fine-tuning it

APRIL 2016

PutmanMedia®

Our calibration is worth its weight in gold



Improve your operations and save money

Best practices for flow calibration management

Thanks to advances in flowmeter diagnostics and instrument management software, the increasing availability of nearby calibration labs and portable calibration rigs, and the willingness of instrument vendors to help users with calibration, setting up a flow calibration plan based on best practices is much easier than in the past. Once set up, the flow calibration plan will improve operations and save money by making sure all flowmeters are calibrated only when necessary.

When you need calibration, Endress+Hauser is the partner you can depend on:

- Calibration for flow, temperature and pressure - **on all manufacturers' instruments**
- **A2LA accredited field and laboratory calibration** services available in accordance with **ISO 17025**
- Clear and concise **calibration certificates**
- **NIST traceable** master flowmeters

A2LA ACCREDITED
Cert #1897.01/3041.01/3041.02

Download our white paper on calibration best practices:
www.us.endress.com/flow-calibration

Endress+Hauser, Inc
2350 Endress Place
Greenwood, IN 46143
info@us.endress.com
888-ENDRESS
www.us.endress.com

Endress+Hauser
People for Process Automation

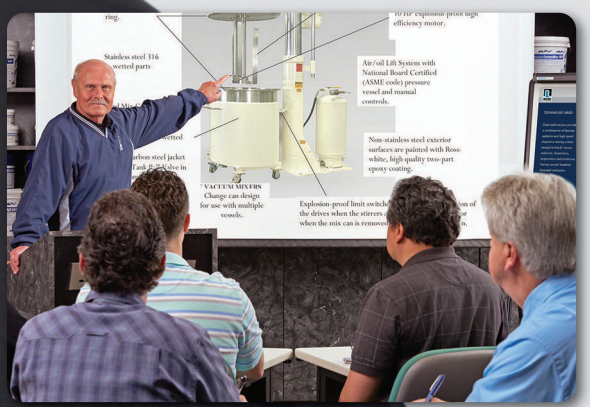
“My job is all about leadership, not just taking orders.”

Ross Regional Sales Managers are full-time, salaried mixing experts who apply decades of experience to every application. Manufacturers throughout the U.S. process industries rely on the insights they can provide to boost production and improve end-product quality.

With the world’s widest selection of technology and equipment designs for mixing and blending, a Ross Regional Sales Manager can help optimize your process, too.

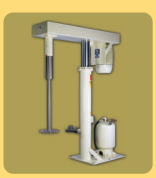
Contact Ross today to put our experience to work in your plant.
Call 1-800-243-ROSS or visit mixers.com

Try our Knowledge Base & Product Selector web app: mixers.com/web-app



Tom O’Shaughnessy
Regional Sales Manager
33-Year Ross Veteran
Employee Owner

Scan to learn more.



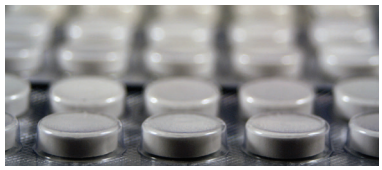




ROSS





LUBRICANTS FOR THE PHARMACEUTICAL INDUSTRY WITH

THE POWER TO PROTECT

YOUR MACHINERY, YOUR PRODUCTS AND YOUR CUSTOMERS

Lubriplate NSF H1 Registered Lubricants do more than keep your machinery running at its best. They free you from the potential chemical hazard risks posed by conventional lubricants. In fact, using 100% Lubriplate H1 Lubricants throughout your plant can significantly simplify your HACCP program by completely eliminating lubricants as a potential chemical hazard.

High Performance Synthetic and Pure USP White Mineral Oil-Based Lubricants.

NSF H1 Registered Food Machinery Grade for Safe, Non-Toxic Lubrication.

NSF/ISO 21469 Certified

FDA COMPLIANCE - With Regulations 21 CFR 178.3570, 21 CFR 178-3620, 21 CFR 172-878, 21 CFR 172.882 & 21 CFR 182 G.R.A.S.

NSF H1 REGISTERED · Certified Kosher Pareve · HALAL · NSF ISO 21469 Certified · ISO 9001 Registered

To Learn More About Lubriplate H1 Lubricants Call 800-733-4755 or visit www.lubriplate.com

"It's the Film." PREVENTS WEAR and CORROSION LUBRIPLATE SUPER-LUBRICATION

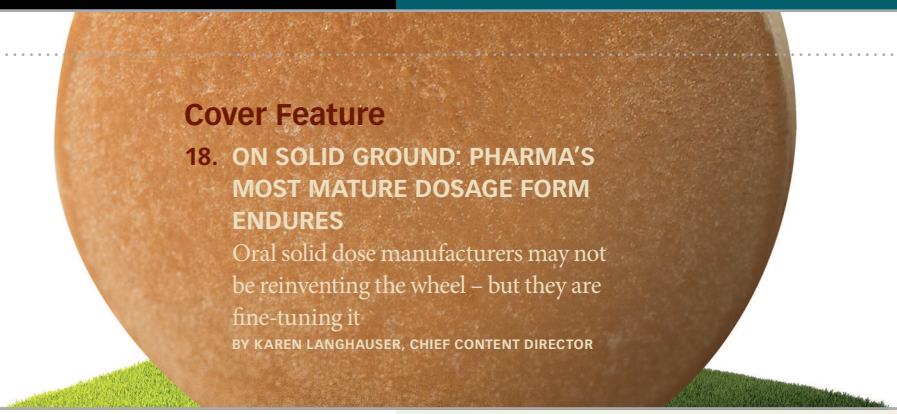
Lubriplate® Lubricants

Newark, NJ 07105 / Toledo, OH 43605 / 800-733-4755
www.lubriplate.com / LubeXpert@lubriplate.com

Backed By: Lubriplate® ESP

Complimentary Extra Services Package

Plant Surveys / Tech Support / Training
Color Coded Lube Charts & Machine Tags
Lubrication Software / Follow-Up Oil Analysis



Cover Feature

18

Features

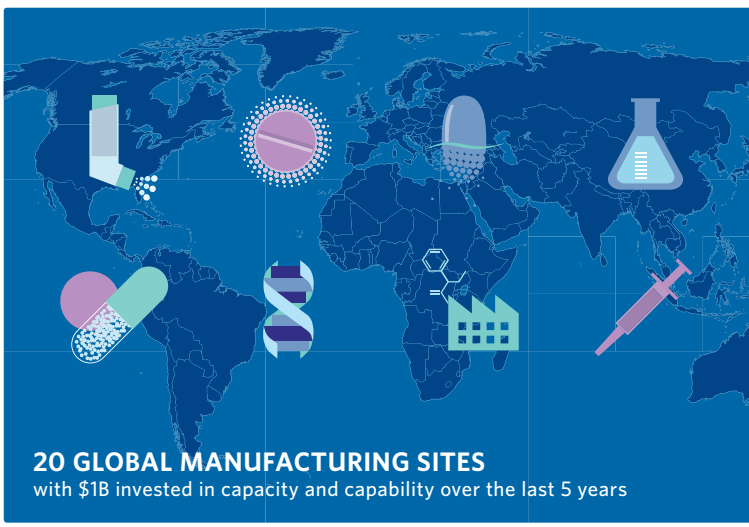
35

Departments

Pharmaceutical Manufacturing (USPS number 023-188) is published monthly by Putman Media Inc. (also publishers of Food Processing, Smart Industry, Chemical Processing, Control, Control Design, Plant Services and The Journal), 1501 E. Woodfield Road, Suite 400N, Schaumburg, IL 60173 (Phone: 630-467-1300 Fax: 630-467-1179). Periodicals Postage Paid at Schaumburg, IL and additional mailing Offices. POSTMASTER: send change of address to Pharmaceutical Manufacturing, Post Office Box 3431, Northbrook, IL 60065-3431. SUBSCRIPTIONS: To receive a complimentary subscription go to www.pharmamanufacturing.com. Subscription rate for non-qualified U.S. subscribers is $68/yr. Single copy rate is $15.00. Other international is $200/yr (airmail only). Canada Post International Publications Mail Product Sales Agreement No. 40028661. Canada Mail Distributor Information: Frontier/BWI, PO Box 1051, Fort Erie, Ontario, Canada L2A 5N8.. Subscriptions/Customer Service: (888) 644-1803

flexible manufacturing.
customized solutions.
reliably supplied.

Catalent®



20 GLOBAL MANUFACTURING SITES
with $1B invested in capacity and capability over the last 5 years

80+ YEARS OF EXPERTISE
in product development to commercial manufacturing

500 NEW PRODUCTS
currently in development, with 165+ products launched annually

70B+ DOSES
manufactured annually, across multiple delivery technologies

TECHNOLOGY TRANSFERS
A proven track record of product launches in multiple markets, with the analytical, development, project management and operational expertise to support successful technology transfer.

SPECIAL HANDLING
Ability to support potent and controlled substances from development to commercial supply, with 300+ potent, cytotoxic and hormone compounds handled across our global network.

CUSTOM SUITES
Established infrastructure and business models for providing unique manufacturing solutions for complex formulations, with the flexibility to design customized or dedicated suites.

NETWORK SOLUTIONS
A global footprint with the capacity, regulatory expertise and technical capability to provide large-scale, integrated manufacturing services in support of product or network strategies.

DEVELOPMENT DELIVERY SUPPLY

Catalent. More products. Better treatments. Reliably supplied.™

US + 1 888 SOLUTION (765-8846) **EU** + 800 8855 6178 catalent.com/manufacturing

PutmanMedia®

1501 E. Woodfield Road, Suite 400N, Schaumburg, IL 60173
Phone: (630) 467-1300 • Fax: (630) 467-1179
www.putmanmedia.com
Subscriptions/Customer Service
(888) 644-1803 or (847) 559-7360

EDITORIAL TEAM

KAREN LANGHAUSER — CHIEF CONTENT DIRECTOR
klanghauser@putman.net

KATIE WEILER — MANAGING EDITOR
kweiler@putman.net

KEITH LARSON — VP, CONTENT AND GROUP PUBLISHER
klarson@putman.net

TONY D'AVINO — SALES AND PUBLISHING DIRECTOR
tdavino@putman.net

EDITORIAL ADVISORY BOARD

ALI AFNAN, Step Change Pharma
JIM AGALLOCO, Agalloco & Associates
CARL ANDERSON, Duquesne University
JAMES BLACKWELL, Bioprocess Technology Consultants
JOHN BLANCHARD, ARC Advisory Group
TOM CAMBRON, P&G Pharma
JAMES CHENEY, Celgene
BIKASH CHATTERJEE, Pharmatech Associates
EMIL CIURCZAK, Doramaxx Consulting
ROBERT DREAM, HDR Company
ERIC LANGER, BioPlan Associates
ROBBE C. LYON, FDA
IVAN LUGO, INDUNIV, Puerto Rico
GIRISH MALHOTRA, Epcot International
FERNANDO PORTES, Stevens Institute of Technology
GARY RITCHIE, Consultant

DESIGN & PRODUCTION TEAM

STEPHEN C. HERNER — V.P., CREATIVE & PRODUCTION
sherner@putman.net

MICHAEL ANNINO — ASSOCIATE ART DIRECTOR
mannino@putman.net

RITA FITZGERALD — PRODUCTION MANAGER
rfitzgerald@putman.net

ADMINISTRATIVE TEAM

JOHN M. CAPPELLETTI — PRESIDENT/CEO

JACK JONES — CIRCULATION DIRECTOR

In Memory of Julie Cappelletti-Lange,
Vice President 1984-2012

USPS number (023-188)

Team OSD Has Staying Power

Oral solid dose continues to dance in March

'TIS THE season for basketball clichés and analogies, so I figured I might as well give it a shot (see what I did there?)

As I was thoughtfully filling out my bracket for this year's March Madness pool during non-work hours, of course (March Madness activities apparently cost employers close to $4B in lost productivity, fyi), Internet-induced attention deficit disorder got the best of me and I started reading about the history of basketball.

Basketball was invented by athletic instructor Dr. James Naismith in 1891, who was tasked with devising a game that students could play indoor during winter months, in a small amount of space. The first basketball game used a soccer ball and two peach baskets as equipment. Naismith created 13 rules, and oddly enough, a large number of those original rules still apply in modern day basketball.

So, as it turns out, the basic infrastructure of the original rule set created 125 years ago is still pretty much intact today. What else do you know with that kind of staying power?

While historians have found evidence of "pills" since BC, the invention that paved the way for the mass manufacture of medicines in the form that most patients know them today came centuries later.

The Scientific Revolution, which continued into the late 1700s, brought sweeping developments in mathematics, physics, biology and chemistry. The end of this period crossed over with the beginning of the Industrial Revolution — which brought us machines and the advent of modern manufacturing practices — creating a perfect, stage-setting collision of science and manufacturing.

The lines started blurring between the chemical industry, textile industry and apothecaries (Bayer, for example, started as an innovative dyestuffs factory in Germany) — which, at the time, made sense from a research angle, but in present day seems somewhat frightening. But what emerged from this was what most claim to be the start of the pharmaceutical industry as we know it today.

The real game-changer came in 1843, when British inventor William Brockedon patented an invention that compressed sodium carbonate and potassium carbonate in a tube, to form solid tablets. Eliminating the need for moisture to bind ingredients in the pill-making process, Brockedon's invention enabled the mass production of "compressed pills." This basic oral solid dose manufacturing methodology is quite similar to the OSD manufacturing used today (which you can read about in our cover story on page 18).

Oral solid dosage remains the form of choice for thousands of drugs and billions of patients. Over the past three years, 37 new tablets and 22 capsules have been approved by the FDA.

As the mature dosage form adapts to a changing landscape that involves higher potency products, generics, and the push to change to continuous manufacturing processes, we see OSD manufacturers fine-tuning their processes and equipment, and truly staying in the game.

Oh, and for the record, I had Villanova to win it all in my pool…how did I do?

BY KAREN LANGHAUSER, CHIEF CONTENT DIRECTOR
KLANGHAUSER@PUTMAN.NET

Critical Cleaning • ***Professional Technology***

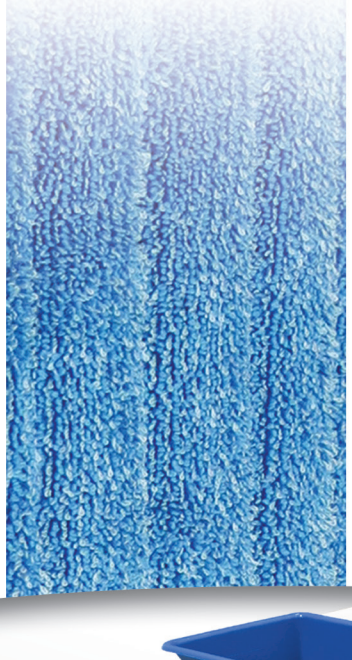
PERFEX — Innovative Cleaning Tools — For Controlled Environments — Since 1994

Innovations for the highest standards of hygiene

- *TruCLEAN Anti-microbial Mop:* micro-filaments significantly reduce bacterial growth on any surface
- *TruCLEAN Microfiber Mop:* remove and retain solid particles quickly and effectively without use of chemicals
- *TruCLEAN Cleanroom Mop:* looped-end design conforms to any shape, very low particulate levels with mop-to-dry performance

TruCLEAN ANTI-MICROBIAL

TruCLEAN MICROFIBER



TruCLEAN CLEANROOM

ALL NEW website!
www.perfexonline.com

The ORIGINAL CLEANROOM SPONGE No. 22-34

TruCLEAN ProXL *- The Ultimate Cleanroom Mopping System*

Control contamination more efficiently using multi-bucket technology!

For over 90 years, Perfex has provided the highest quality and most reliable cleaning tools for the critical cleaning industry. TruCLEAN Mopping systems are constructed entirely of autoclavable components. Change mop heads easily with quick-release stainless-steel mop frame. TruCLEAN products work together to provide optimal cleaning results. Endless configuration possibilities help cater to your facilities specific cleaning needs.

TruCLEAN Pro
Triple Bucket

TruCLEAN Pro
Double Bucket

TruCLEAN 2
Bucket-in-Bucket

Perfex Corporation • Poland, New York • **Customer Service:** 1-800-848-8483 • **perfex@perfexonline.com**

HPAPI Market to Reach $25 Billion by 2023

High Potency Active Pharmaceutical Ingredient market to register 7.8% CAGR over the next eight years

BY KAREN LANGHAUSER, CHIEF CONTENT DIRECTOR, AND KATIE WEILER, MANAGING EDITOR

ACCORDING TO a new market report published by Transparency Market Research, "High Potency Active Pharmaceutical Ingredient (HPAPI) Market - Global Industry Analysis, Size, Share, Growth, Trends and Forecast 2015 - 2023," the global HPAPI market was valued at $12.6 billion in 2014 and is projected to reach $25.1 billion by 2023 at a compund annual growth rate of 7.8%. The report compares contract versus captive HPAPI, synthetic versus biological, and branded versus generic.

High potency active pharmaceutical ingredients — molecules that are effective at much smaller dosage levels than traditional APIs — are used in targeted therapeutics. These APIs are difficult to manufacture and require technological expertise and sophisticated manufacturing setup. The report says the HPAPI market currently accounts for a small portion of the overall API market, however, is a rapidly growing segment. The global HPAPI market covers oncology, anti-diabetic, cardiovascular, central nervous system, musculoskeletal and others.

According to the report, oncology leads the market with more than 50 percent market share and is also the fastest growing segment. Patent expiry of blockbuster cancer drugs will create new opportunities for generic drug manufacturers and contract manufacturing organizations (CMOs). Avastin (bevacizumab), Herceptin (trastuzumab), Synagis (palivizumab), Erbitux (cetuximab), Humira (adalimumab), Remicade (infliximab), and Rituxan (rituximab) are some of the major drugs going off patent in the near future.

Most high potency API manufacturing is confined to captive production to avoid risk of patent infringement, the report said, and increasing cost of drug development and commercialization adds to the financial burden. With developing regulatory and legal framework, outsourcing proved to be the most optimal option for HPAPI manufacturing. Hence, outsourcing production is expected to grow rapidly in the near future.

Mimicking biological drugs is challenging, and technology and ability for producing cost effective, high-quality HPAPI lies in the hands of a few major players, the report says. Also, as no regulatory and standardized process policy exists, there is a little guidance for new entrants. CMOs are gaining technological expertise and are building assets to become ready for the HPAPI market.

The report profiles key players in the market including Alkermes plc, Cambrex Corporation, Dr. Reddy's Laboratories, Lonza Group, Novasep, Sandoz International GmbH, Pfizer, Inc., Sigma-Aldrich Co. LLC., and WuXi AppTec.

For more information on the High Potency Active Pharmaceutical Ingredient report, visit www.transparencymarketresearch.com/high-potency-active-pharmaceutical-Ingredients-market.html. Also, don't miss the article on p. 30 of this issue, discussing Catalent's holistic approach to high potency API operations.

FUNNY PHARM

"Wow, that 'Patent Expiration' setting is really fast!"

— John Iverson

Funny Pharm comics, drawn by professional cartoonist Jerry King, appear on PharmaManufacturing.com. Readers submit suggested captions. Above is January's cartoon and winning caption.

PITTCON 2016 MAKES $25.8M IMPACT

PITTCON 2016 — the 67th Conference and Exposition for Analytical Chemistry and Applied Spectroscopy — ended on March 10, in Atlanta, Georgia, with an economic impact to the city estimated at $25.8 million.

This year's event brought together nearly 13,000 conferees and exhibitor personnel, with 37% of conference attendants being first-time Pittcon attendees.

Global attendance remained strong with 24% of attendees being from outside the United States. The top countries by attendance (excluding the U.S.) were Japan, China, Canada, Mexico and the United Kingdom. Attendees include lab managers, scientists, chemists, researchers and professors, from industrial, academic, and government labs. They represent an equally broad number of scientific disciplines including life science, food science, drug discovery, environmental, forensics, nanotechnology, water/wastewater, energy/fuel, agriculture and bioterrorism.

The 409,740-square-foot exposition floor consisted of 847 exhibitors from 37 countries occupying 1,539 booths displaying the latest innovations in instrumentation and technology used in laboratory science. This year, there were 119 first-time exhibitors. There were two specialized areas on the exposition floor — the New Exhibitors and Laboratory Information Management (LIMS).

New this year were the Live Demos where leading exhibitors presented pre-scheduled interactive presentations of a product, technique or service in two designated areas on the show floor.

Pittcon offered more than 2,000 technical sessions presented in 64 symposia, 14 awards, 86 oral sessions, 24 contributed sessions, five workshops and 53 poster sessions. About 40 percent of the presentations focused on life science topics. The 31 networking sessions provided an opportunity for conferees from around the world to meet in an informal setting to discuss topics of mutual interest. The facilitator-assisted sessions discussed techniques, solutions to challenges and innovative concepts.

FDA ANNOUNCES NEW OPIOID LABELING

The Federal Drug Administration (FDA) announced enhanced warnings for opioid pain medications that will affect 141 generic and 87 innovative immediate-release opioid products, which account for about 90 percent of all prescription opioids.

The new boxed warning details the risks of misuse, abuse, addiction, overdose and death. FDA said labeling was updated due to the increasing number of reports of abuse and misuse.

The updated information clarifies that, because of those risks, IR opioids should be reserved only for patients suffering severe pain for whom there are no other treatment options. Dosing information also will be more detailed.

WEBWATCHER

Read full stories on PharmaManufacturing.com

- AstraZeneca Blood Thinner Fails Pivotal Trial
- China Vax Scandal Widens; Pharma Cos Investigated
- Novartis Pays $25M to Settle Bribery Charges
- WHO Puts a Hold on TB Drugs from India
- Bristol-Myers Squibb Buys Padlock Therapeutics
- Vetter Breaks Ground on $79M Production Building
- Hospira Recalls One Lot of Sodium Bicarbonate Injection
- Valeant CEO Out; Investor Ackman In as Board Member
- FDA Cites Lupin Plant Following Inspection
- GSK CEO Witty to Retire
- Bayer to Open Biotech Innovation Center in Massachusetts
- Teva Pharma Says Allergan Generics Deal Delayed
- Amgen Wins Patent Lawsuit vs. Sanofi, Regeneron
- Gilead Stops Six Trials Due to Adverse Events, Death
- Valeant Cuts Forecast; Stock Plummets by Half
- Sun Pharma Recalls Osteoporosis Drug in U.S.
- Indian Court Grants Pfizer Temporary Injunction on Corex Ban
- FDA Advisors Question Abbott's Dissolving Heart Stent
- India's Lupin Completes GAVIS Buy, Gains First U.S. Plant

COMBUSTIBLE DUST PUTS YOUR MOST VALUABLE ASSETS AT RISK.

MORE EXPERTISE. MORE TECHNOLOGY. MORE SOLUTIONS.

When it comes to managing your combustible dust, Donaldson Torit® expertise, technology and product options can help you design the best risk mitigation solution, as well as support your compliance efforts and performance needs. Customers have relied on our high-quality dust collectors in over 250,000 installations. Now, more companies look to us to integrate their dust control systems with fire and explosion protection equipment and strategies. Your Donaldson Torit representative can listen to your needs, work with you to identify options and implement a customized dust management solution unique to your plant's requirements.

Donaldson® Torit®

DonaldsonTorit.com
800.365.1331

Go with Donaldson Torit and get
EXACTLY WHAT YOU NEED.™

LEARN MORE
Visit **donaldsontorit.com/combustibledust**

Harnassing the Power Potential of the Sun

How RAM Pharma reduced energy costs by installing a solar steam generation system

BY MARTIN HAAGEN, INDUSTRIAL SOLAR GMBH

INDUSTRY CONSUMES around one-third of the total primary energy demand. From that, around 2/3 of this industrial energy demand is used for process heating. Thus, sustainable solutions for industrial heat supply — like solar process heating — are needed for a transition towards manufacturing without carbon emissions.

At present, solar thermal energy isn't typically applied in industry, for a variety of reasons. First, the legislative framework for renewable energies in most countries can be seen as somewhat biased toward power generation. Second, industry is often not aware of the opportunities of solar thermal technology and tends to invest its innovative capacities more on its products than its energy supply. Third, there is a lack of successful showcases proving the technology. Nevertheless, due to the continuous growth of industry — especially in emerging markets — and limited availability of fossil fuels, solar energy will need to cover an increasing share of the industrial heat demand.

ENERGY CONSUMPTION IN PHARMA

In both primary (fermentation, organic chemical synthesis and biological and natural extraction) and secondary processing (drying, molding, coating and sterilization), substantial amounts of energy are used for the production of pharmaceuticals. While the exact distribution of thermal and electric energy within pharmaceutical industries depends strongly on the specific profile of a company, in most cases process heating is the major energy consumer. In sunny regions, a large share of this heat demand can be provided by the sun. Typical process temperatures range between 60° C and 120° C. However, in most cases, heat is supplied via a central heating system, mainly steam, which commonly operates at 140-180° C. The differentiation between process and supply temperature is crucial for the integration of solar thermal collectors as they differ in respect to their maximum temperatures.

IT'S POSSIBLE THAT THE INCREASING SHARE OF THE PROCESS HEAT DEMAND IN THE PHARMACEUTICAL **SECTOR WILL BE COVERED BY THE SUN.**

SOLAR THERMAL COLLECTORS FOR INDUSTRIAL APPLICATIONS

Non-concentrating solar collectors, like flat plate or evacuated tube collectors, are the most common solar thermal collectors. They are mainly applied for space heating and domestic water heating and can achieve temperatures of around 100° C. Concentrating solar collectors can supply more than 400° C and are thus mostly applied on solar thermal power plants where they provide steam for a turbine to generate power. To achieve these temperatures, concentrating collectors use large reflective areas to concentrate the direct sunlight onto an absorber where these high temperatures can be achieved. The sunlight is comprised of a direct and a diffuse part (deflected from particles in the air), whereas only the direct part can be concentrated. While non-concentrating collectors are limited in respect to their maximum temperature, the application of con-

Fresnel installation at RAM Pharma in Jordan. (Copyright: Anders)

centrating collectors is spatially constrained to regions with high direct irradiation. Besides the temperature, available space, load profile and integration are major factors in designing a solar thermal system for industrial purposes. In respect to integration, there are three major concepts (see illustration):

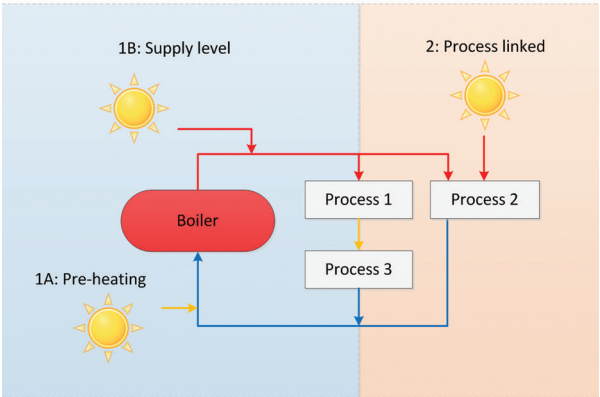
- **Pre-heating of Boiler Fed Water**
  Non-concentrating solar collectors are integrated in the return line of the heat supply and pre-heat the fed water in the boiler, while reducing its fuel demand. While this is the easiest integration, its application is limited as mostly the return water is still above 90° C, which reduces the efficiency of the collectors. Moreover, most energy is needed for the evaporation.
- **Direct Integration into a Specific Process**
  The advantage of the direct integration into a specific process is that the operating temperature can be adjusted accordingly, and thus the efficiency of the solar collectors increases (lower temperature, less heat losses, higher efficiency). However, the integration to a specific process reduces the flexibility in case the process is stopped or altered.
- **Integration on Supply Level**
  As the supply level temperature in the pharmaceutical industry is commonly between 140 and 180° C, integration on supply level is only possible with concentrating solar collectors and thus only in regions with a high share of direct sunlight. Yet, where it is possible, it is the optimal integration as it can provide the highest solar share (solar energy/total energy) and provides the greatest flexibility in respect to changes in the production process.

A REAL-WORLD EXAMPLE: SOLAR STEAM GENERATION AT RAM PHARMA

Established in 1992, RAM Pharmaceuticals is a pharma company in Jordan, located approximately 25 miles from the capital Amman. It is mainly active in the production of penicillin-, hormone- and cephalosporin-based formulations.

As Jordan imports more than 90 percent of its energy, fuel demand and costs for industry are high, especially in comparison to the gulf countries. Thus, energy costs are a growing challenge for industrial companies. At the same time, Jordan has a very high solar irradiation (power per unit area produced by the sun in the form of electromagnetic radiation), which even exceeds the neighboring countries.

To reduce its energy costs, RAM Pharma decided to install a solar steam generation system on the roof of its facility. A Fresnel collector with an aperture area — which is the glazed portion of the collector designed to trap the solar radiation — of almost 400m² (4,300 sq. ft.) and a peak capacity of 223 kWth from Industrial Solar was installed. Installation began in November 2014 and was completed in March 2015.



General integration opportunities. (Source: Industrial Solar GmbH)

The Fresnel collector was selected because it is well suited for industrial applications due to its high ground space efficiency, and it can be installed on most industrial rooftops. It operates parallel to the existing diesel fired steam boiler and reduces its consumption during sunshine hours and increases the supply security. The Fresnel collector is a concentrating solar collector with uniaxially tracked primary mirrors that reflect the direct irradiation onto an absorber tube installed above the mirrors.

To balance fluctuations from supply and demand, a 2m³ buffer storage was installed as well. From there, the steam is directly fed into the existing distribution network at around 160° C (320° F). Due to the buffer storage, the system also stabilizes the pressure within the network and smooths the operation of the fuel fired steam boiler. Since March 2015, the fully automatic collector has been operating smoothly, and during midday can provide almost the whole steam demand of the factory. The Fresnel system provides steam to the main steam pipe of the factory and thus reduced the demand of diesel for the fuel boiler. Over the course of a year, the collector saves almost 8,000 gallons of diesel.

This project proves the opportunities for solar process heating in the pharmaceutical sector. Other projects with different collector technologies and integration concepts have also been realized already. With increasing energy costs and stricter regulations on carbon emissions, it is possible that the increasing share of the process heat demand in the pharmaceutical sector will be covered by the sun.

CDMO Market Continues to Expand

Recent survey results indicate that outsource spending has nearly tripled, with further future spending expected

BY GUY TIENE, DIRECTOR OF STRATEGIC CONTENT, THAT'S NICE LLC / NICE INSIGHT

RESPONDENTS TO Nice Insight's annual survey of outsourcing-facing pharmaceutical and biotechnology executives expect spending on outsourcing to increase for the fourth year in a row. This result fits well with estimates that the global contract pharmaceutical manufacturing market is growing at an average annual rate of 7.5%. There are many factors driving this growth in 2016 — increasing consumption of medicines around the world; a more robust pipeline of drug candidates and an increasing rate of FDA NDA/BLA approvals; the increasing focus on biologic drugs, including by traditional pharma companies that lack biotech expertise; the entrance into the market of numerous small, virtual startups that have no manufacturing capacity; the rise in patent expiries and increasing generics competition, which is driving a greater need for cost efficiencies and access to novel, proprietary technologies for achieving product differentiation; and the increasing complexity of both small- and large-molecule drugs such as antibody-drug conjugates and highly potent compounds.

DRAMATIC INCREASE IN SPENDING

This strong growth is supported by the results of Nice Insight's 2016 CDMO Outsourcing annual survey of professionals in the pharmaceutical and biopharmaceutical industries; participants have indicated that their companies have dramatically increased year-over-year spending on outsourcing for the last four years.

Most notably, while the percentage of respondents whose companies spent more than $50 million on outsourcing remained fairly stable at 24 to 23% from 2012-2014, the number of respondents nearly tripled to 71% in the new 2016 Nice Insight CDMO Outsourcing survey of nearly 600 outsourcing-facing pharmaceutical and biotechnology executives. Meanwhile, the percentages of respondents whose companies spend less than $10 million and $10 to $50 million on outsourcing both decreased from 2015 to 2016 from 16% to 3% (down from 43% in 2010) and 62% to 23%, respectively. Likewise, manufacturing equipment needs are shifting; as seen in the Nice Insight 2015 Pharmaceutical Equipment Annual Study, 54% of respondents (n=560) indicated that their companies spend over $100 million on equipment per year.

Survey results also indicate that further spending can be expected. Nearly 95% of respondents expect that their companies will either maintain (18%) or increase (75%) their spending on contract development and manufacturing services over the next five years. Furthermore, while three-quarters of respondents currently use 0-10 CDMOs and/or CMOs, 7% use 11-20 and 5% use 21-30, 69% of participants in the 2016 CDMO survey expert to increase the use of CDMOs and CMOs going forward, with 29% expecting the number of manufacturing partners to remain the same, and only 1% expecting to decrease the number of partners.

EMERGING MARKETS, VALUE-ADDED GENERICS AND BIOSIMILARS WILL PROVIDE **POTENTIAL OPPORTUNITIES FOR GROWTH.**

These numbers reflect the robustness of pharmaceutical pipelines and an overall greater need for support. Slightly more than half (56%) of respondents to the 2016 Nice Insight CDMO Outsourcing survey indicated that an expanding R&D portfolio is driving their increasing use of CDMOs and CMOs. Survey participants also indicated that their companies are increasing the use of outsourcing as part of their manufacturing strategies (60%) due to the need to address patent life issues, the need for novel delivery forms and other specialized capabilities, and a desire to increase decentralization for greater flexibility. Companies are also expanding the use of service providers because they have had positive experiences with outsourcing to CDMOs and CMOs in the past (59%).

Interestingly, outsourcing is not highly focused at any one particular development stage, although the percentage of respondents outsourcing Phase II projects (63%, up from 42% in 2014) to CDMOs and CMOs is slightly higher than those using manufacturing services for Phase III (54%, up from 29% in 2014), Phase I (53%) and pre-clinical, including discovery phase, (51%) projects. The distribution is fairly even, however, and is another reflection of the robust drug pipeline resulting from significant investment in innovation; many candidate

drugs are now steadily moving toward commercialization. Phase IV/Post-Launch projects are outsourced by 39% of survey respondents; the lower level of outsourcing compared to those at earlier phases reflects the attrition that occurs as safety and efficacy are evaluated. However, the number is nearly double that for outsourcing on Phase IV/Post-Launch projects in 2014 (22%). The much higher percentages of respondents outsourcing phase II, III and IV projects strongly suggest that new programs designed to weed out unlikely candidates as early as possible in the development process and well before they enter into clinical trials are achieving the desired results.

WHO WILL BE THE WINNERS?

Not all contract manufacturers will benefit from the increased spending anticipated by the participants in this year's Nice Insight CDMO Outsourcing survey. Indeed, the percentage of respondents that elect to work with "Preferred Suppliers" rose to 43% from 35% last year, while the preference for tactical suppliers dropped from 35% to 31%.

What does it take to be preferred? Such firms tend to have more global footprints, large-scale capabilities for greater cost efficiencies, a broad range of service offerings including development and final formulation/drug delivery in addition to API manufacturing, and access to advanced technologies. In particular, successful CDMOs make it possible for drug manufacturers to more efficiently and cost effectively develop and produce increasingly complex drug candidates and extend the product lifetimes of off-patent products using novel, proprietary technologies. Consequently, technological capabilities will equate directly to competive advantage as drug manufacturers continue to pare down their vendor numbers and establish preferred/strategic partnerships with fewer, integrated suppliers.

It should also be noted, however, that preferred suppliers must continually earn their position with ongoing high levels of performance. For instance, half of the 2016 Nice Insight CDMO Outsourcing survey respondents indicated that they would switch CDMOs if

SURVEY BACKGROUND & METHODOLOGY

For the first time since That's Nice began gathering data on the pharmaceutical and biopharmaceutical contract services markets, in 2016 the original Nice Insight CRO/CMO outsourcing survey was divided into two separate surveys in order to focus on the differing aspects of the contract [development and] manufacturing (CDMO) and contract research markets (CRO/Clinical Services). In addition, in recognition of the key trend in this sector toward companies that provide integrated development and manufacturing offerings, the new manufacturing survey specifically explores the use of CDMOs and CMOs for both drug substance and product.

The Nice Insight 2016 CDMO Outsourcing Survey includes responses from 587 outsourcing-facing pharmaceutical and biotechnology executives.

Importantly, the majority (39%) of survey participants are key decision-makers (executive/management positions) in their organizations. Professionals with positions in R&D, formulation and analytical (18%), development, production and manufacturing (13%), and operations and engineering (10%) functions are also well represented. As a result, the survey is quite balanced with the opinions of both company leaders and those in the trenches. The new CDMO survey is also truly global in nature, with 56% of respondents from North America, 28% from Asia, and 16% from Europe.

These statistics clearly suggest that the results of the 2016 Nice Insight CDMO Outsourcing survey should be highly indicative of the conditions in the global pharmaceutical contract development and manufacturing sector. Initial analysis of the data also indicates that survey participants utilize contract services in all key pharmaceutical and biopharmaceutical markets around the world.

The Nice Insight Contract Development & Manufacturing Survey is deployed to outsourcing-facing pharmaceutical and biotechnology executives on an annual basis. The 2015-2016 report includes responses from 587 participants. The survey is comprised of 225+ questions and randomly presents ~50 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions of the top 123 CDMOs servicing the drug development cycle. Four levels of awareness, from "I've never heard of them" to "I've know them very well" factor into the overall customer awareness score. The customer perception score is based on six drivers in outsourcing: Quality, Innovation, Regulatory Track Record, Affordability, Productivity and Reliability.

% Of Respondents Who Outsourced Specialized Services With CDMOs/CMOs

Regulatory Expertise and Support Services	High-potency Compounds Capabilities
52%	51%

Sterile/ Contained Manufacturing	Controlled Substances Capabilities	Parenteral Manufacturing/ Packaging	Cytotoxic Compounds Capabilities	Lyophilization Services
50%	46%	44%	40%	36%

they do not continually meet quality and on-time delivery expectations.

So where will the opportunities lie for CDMOs in 2016? Companies with truly integrated offerings and unique technical capabilities will enter into collaborative capacity management and long-term, multiproject relationships. Emerging markets, value-added generics (so-called supergenerics), and biosimilars will provide other potential opportunities for growth. Those that are positioned to leverage these opportunities will survive the more competitive contract manufacturing marketplace.

To learn more about Nice Insight, contact Guy Tiene at guy@thatsnice.com or visit www.niceinsight.com.

A New Door Opens.

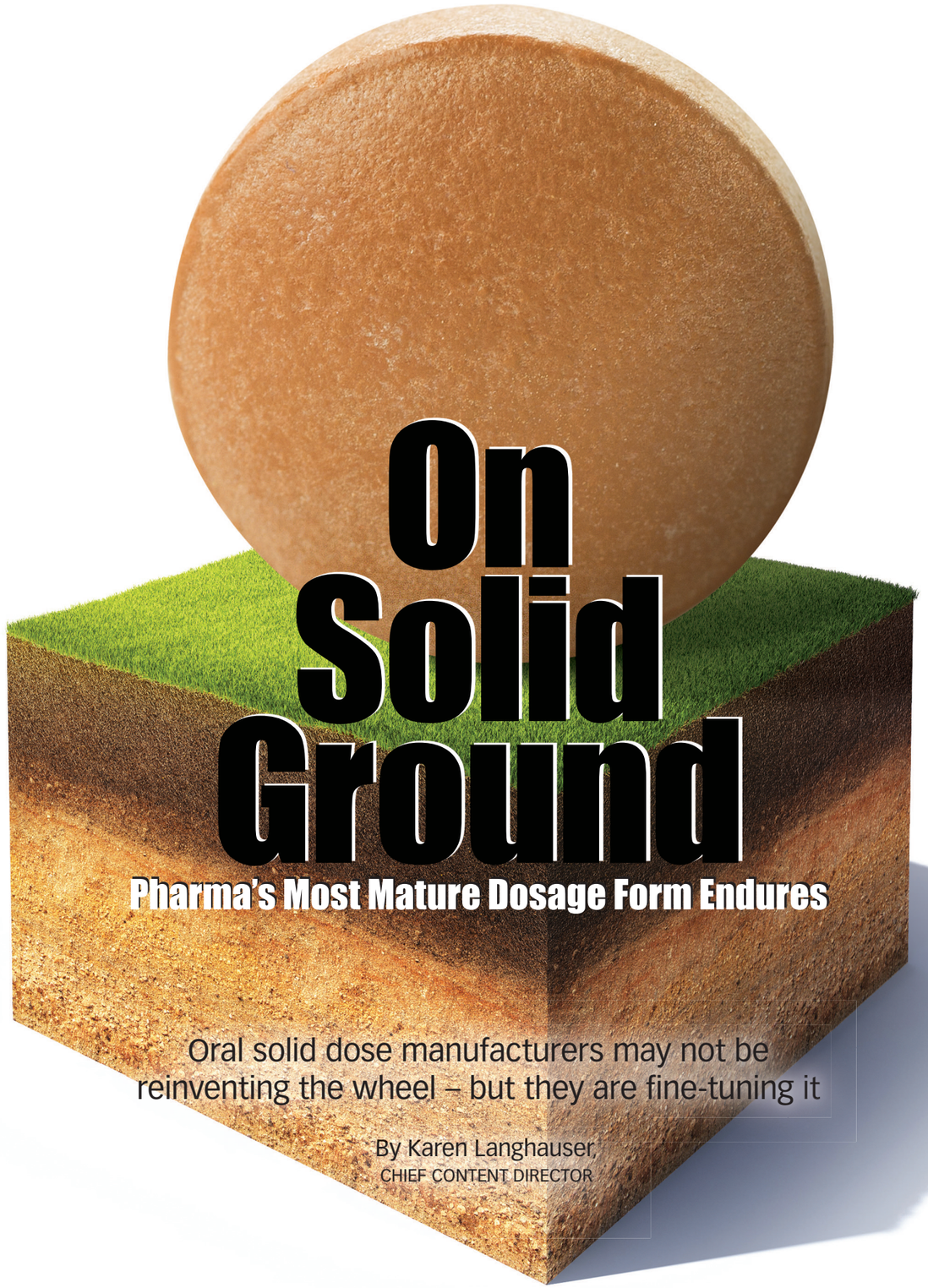
CLEAR, INDELIBLE MARKING FOR THE GLOBAL PHARMACEUTICAL INDUSTRY.

NEW TRI-STAR COLD LASER. THE REMARKABLE MARKER.

Prepare to be astounded by the capabilities of Tri-Star's new high-speed Cold Laser Marker. Employing proprietary technology, it offers the assurance of clear, permanent, tamper-proof marking on tablets and gelatin capsules of any size. It creates high-resolution text, barcodes and graphics, assures accurate track and trace, 100% verification. Complete DQ, IQ, OQ validation package for equipment. Control system fully compliant with GAMP 5 and 21 CFR Part 11. And we service what we sell, 24/7, worldwide.

TRI-STAR TECHNOLOGIES
A Carlisle Company

CONTACT US AT: www.tri-star-technologies.com • alex.kerner@Carlisleit.com • 310-536-0444



On Solid Ground

Pharma's Most Mature Dosage Form Endures

Oral solid dose manufacturers may not be reinventing the wheel – but they are fine-tuning it

By Karen Langhauser,
CHIEF CONTENT DIRECTOR

LOOKING BACK on the history of the pharmaceutical industry, it's very much an evolving practice, with new knowledge bringing continuous improvements. Copious trial and error has brought us an industry very different from that of 150 years ago. And yet, one methodology has survived the decades essentially intact. The basic oral solid dose manufacturing methodology used today is very similar to the OSD manufacturing of the past — and that's not necessarily a bad thing.

In 1843, British painter/author/inventor William Brockedon patented an invention that compressed sodium carbonate and potassium carbonate in a tube, to form solid tablets. Eliminating the need for moisture to bind ingredients in the pill making process, Brockedon's invention ushered in a completely different type of "pill" — one that could be mass produced in different dosage forms.

And while the dosage form has not seen what OSD subject matter expert Dave DiProspero calls a "silver bullet change," the sector has continued to stay relevant.

Recent FDA numbers lend support to this relevancy. If you look at the 2015 new drug approvals, 51 percent of the new molecular entities (NMEs) approved by the U.S. Food and Drug Administration were solid dosage products — a slight increase from the previous year. In 2014, 19 of the 41 NMEs were solid dosage products (46 percent); while in 2015, 23 of the 45 NMEs were solid dose products. Over the past three years, 37 new tablets and 22 capsules have been approved by the FDA.

In terms of oral-solid-dose facility construction, DiProspero, a senior consultant for CRB Consulting Engineers and also a leading committee advisor for ISPE's Oral Solid Dose Community of Practice, notes that changes to the OSD sector have been "more along the lines of moderate upgrades and improvements to the process/facility. Not a lot of significant changes."

"Over the past few years there has been a slowdown in 'new' OSD facilities. We are not seeing a lot of greenfield, let's-build-a-100,000-square-foot-OSD-facility type projects (though there are a couple). However, renovating and upgrading of processes and technologies in OSD remains relatively strong. Companies are still investing in projects and working to upgrade existing facilities," says DiProspero.

Despite the solid dose slowdown, and the noticeable attention being given to newer, flashier biologics initiatives, pharma is still investing in solid dose capabilities. Capsugel, for example, recently completed construction on a $25 million spray-dried dispersion (SDD) commercial facility in Bend, Oregon (read the details on page 42 of this issue). Capsugel, now with the largest SDD facility in North America, is solving a number of different formulations and stability challenges faced with capsule and tablet dosage forms. In another example, prescription opioid pioneer Purdue Pharma invested big in the construction of a new 190,000-square-foot, oral-solid-dosage manufacturing plant in Durham, N.C., in 2014. The company is currently expecting to file for full manufacturing approval from the FDA in the second half of this year.

OSD GENERICS

With the large number of oral solid dose drugs plunging off the inevitable patent cliff, generic solid dose products have stepped in, poised to compensate for any future decline in OSD NMEs. As the role of generics in the OSD sector continues to grow, so does the regulatory scrutiny of generic solid dosage products. With 86 percent of all prescriptions in the United States now filled by a generic drug products, the Office of Generic Drugs began to notice that many ANDAs were being submitted to the FDA with tablets and capsules that were much larger in size than the reference product. While the generic formulations of these drug products are required to be both pharmaceutically and therapeutically equivalent to a reference listed drug (RLD), the agency was concerned that differences in physical characteristics of solid dose

generics (size, shape, weight) would affect patient compliance and cause medication confusion.

In response to these concerns, FDA released a draft guidance document of "nonbinding" recommendations in 2013, which was finalized in June 2015. The "Size, Shape and other Physical Attributes of Generic Tablets and Capsules" guidance pushes generic OSD manufacturers to take a closer look at the same factors brand manufacturers have been dealing with for decades. This guidance implies that as the FDA reviews new generic drug applications, physical characteristics will start being considered alongside pharmaceutical equivalence and bioequivalence.

Natoli's rotary tablet press can deliver up to 5,500 tablets per minute with increased size and weight.

For generics manufacturers, this means making adjustments to compression equipment, staying current with OSD technologies and just a general "stepping up" of OSD techniques in regards to determining and regulating the measurements of tablets and capsules.

CONTAINMENT CONSIDERATIONS

According to DiProspero, in an industry where so much emphasis and regulatory focus is on the quality of the final product, it's important to remember that there are "other factors aside from the final dosage form that need to be closely examined from the manufacturing standpoint." Two such factors are environmental and operator protection during the manufacturing process.

Growing demand for more potent active pharmaceutical ingredients, as well as for toxic APIs for hormone and oncology drugs, means containment issues continue to be a crucial aspect of solid dosage manufacturing. According to GEA Pharma Systems, containment is an issue in 9 out of 10 cases of solid dosage form production. As the industry's knowledge of potent and toxic compounds increases, with that comes the responsibility of monitoring and limiting exposure to manufacturing personnel.

Containment strategies need to address both operator exposure and cross-contamination issues. For the OSD sector, this means sophisticated equipment, such as containment technologies, HVAC systems and airlocks, proper facility design, protective equipment for workers, and comprehensive training and SOPs.

Last year, CMO giant Catalent further expanded its highly potent handling platform with an investment in contained oral solid manufacturing at its Somerset, NJ, headquarters. Catalent's high potency containment strategy (discussed in detail on page 30 of this issue) starts with API categorization. The Catalent compound categorization code, developed in partnership with Safebridge Consultants, is applied across all global Catalent sites. When Catalent receives a new compound, operators determine which of the four categories it fits into, and this, in turn, informs all handling requirements.

CONTINUOUS DEBATE

The ongoing discussion regarding the degree to which continuous manufacturing should be applied to the manufacturing process is healthy in the oral solid dose sector.

The need to improve process efficiency, cut costs and improve quality is undeniable. "If you look at it from an operational efficiency standpoint, OSD manufacturing has a long way to go in comparison to other industries. Pharma needs to find ways to eliminate the many sub-step/no-value added operations and the many quality holds in its processing methods," says DiProspero.

But is continuous manufacturing the cure-all? There are certainly benefits to CM, including a greater control over the quality and consistency of the products. Additionally, concerns associated with material handling, scale-up and production floor space commonly found in a batch process are largely resolved by continuous operations. But most experts agree that it's just one tool in the efficiency arsenal.

"I see continuous manufacturing being an element of OSD facilties of tomorrow — not necessarily replacing traditional processes, but in addition to, the way we currently operate," confirms DiProspero.

Gilad Langer, director of automation & MIS for NNE PharmaPlan, is more hesitant. "Before we latch on to a golden notion, we need to think it through. There

NOVEL DRUG APPROVALS

2015

23 of the 45 NMEs were solid dose products (51%)

15 tablets, 8 capsules

2014

19 of 41 NMEs were solid dose products (46%)

10 tablets, 9 capsules

2013

17 of the 27 NMEs were solid dose products (63%)

12 tablets, 5 capsules

*Information courtesy of U.S. FDA

needs to be a compelling business case for continuous manufacturing — it's a huge investment and highly specialized."

The continuous manufacturing paradigm continues to face manufacturing and development-based challenges. A primary discriminating parameter in the decision to go continuous is associated with production volume. Production of large volumes of solid material in a pharmaceutical environment is a challenge for batch and strongly points toward adapting a continuous processing solution, whereas manufacturing smaller volumes of multiple products in the same production facility on shared processing equipment introduces challenges for continuous processing.

There is a growing amount of real-world evidence that continuous processing is a viable approach to manufacturing OSD therapies, however. Last year, Janssen Pharmaceuticals and its corporate parent, Johnson & Johnson, announced production of daily HIV med Prezista would transition from batch processing to continuous manufacturing at its Gurabo, Puerto Rico, plant. Firmly committed, Janssen aims to manufacture 70 percent of "highest volume" products using CM within eight years, increase yield by reducing waste 33 percent, and reduce manufacturing and testing cycle times by 80 percent.

AUTOMATION BALANCE

Continuous manufacturing can't exist without automation, but automation does certainly exist even in plants that have not made the leap to continuous. Batch manufacturing is still the norm is oral solid dose production, and the individual automation of stages allows the overall process be maintained with minimal risk.

Fully automated tablet presses, paired with automated in-process tablet inspection, have brought greatly improved product consistency and quality to the process. Automated inspection systems facilitate greater process control. By capturing a continuous stream of data about products in real-time, this technology enables OSD manufacturers to improve both upstream operations and streamline downstream processes, immediately — a key necessity for the integration of Process Analytical Technology (PAT) initiatives.

Reduction of manual tasks means less chance of errors, but in specific scenarios, some argue it can also mean surrendering a level of adaptability. In a market where agility and operational flexibility are key, OSD manufacturers are searching for the right balance between manual and automated processes. Langer cautions against the notion of blanket automation: "You first have to clearly understand what your objectives are — then you can decide what level of automation is needed and how much flexibility you need to build into the process."

Manufacturers producing high-volume, high-potency solid dose products have realized the benefits of more elaborate automation. With the growing number highly potent OSD products being manufactured, automation is critical to operator safety, limiting operator exposure to toxic ingredients.

A classic example is Pfizer's NEWCON facility at Illertissen, Germany, winner of the overall 2008 ISPE Facility of the Year Award. To accommodate growing demand for smoking cessation drug Chantix, Pfizer designed a facility for processing highly potent pharmaceuticals. High process automation and online PAT technologies resulted in a manufacturing facility that Pfizer reports has 44 percent lower production costs and 66 percent less staff. The plant's production equipment is located in a dedicated processing module

and is automated to ensure that no dust from the highly potent Chantix production can escape from the manufacturing area. All of the process stages are controlled and monitored from a separate control room so that employees do not come into contact with dust. According to ISPE in 2008, "This extent of automation has not previously existed in containment production anywhere in the world."

SERIALIZATION & DATA OVERLOAD

Drug counterfeiting remains a growing challenge facing the oral solid dosage sector. High-value products that can be duplicated with relative ease make OSD forms a prime target for counterfeiters.

With the 2015 DSCSA "phase-one" launch date passed, and the 2017 "phase-two" deadline looming, serialization efforts are well underway across the supply chain. Beginning in November 2017, pharmaceutical products must be "marked with a national drug code, serial number, lot number, and expiration date in machine-readable and human-readable form" — and most manufacturers report being ready to meet this deadline.

The 2016 RxTrace U.S. Pharma Traceability Survey, which polled companies across the U.S. pharma supply chain and their solution providers, indicated that the majority of respondents were ready for the deadlines they had faced in 2015 and were feeling confident that they have enough time to take action to meet the next deadline.

As manufacturers arm themselves for a new level of traceabilty, many are opting for off-the-shelf control and information technology — such as vision, printing and checkweighing equipment, MES software and information-enabled programmable controllers — that will not complicate the information transfer needed for new serialization legislation.

Ramping up automation, moving towards continuous manufacturing and striving to meeting serialization mandates all result in huge volumes of data, which means data management is more important than ever before.

Langer points to the DIKW (data, information, knowledge, wisdom) Pyramid in order to explain the importance of data management. This concept stresses the need to elevate data to information, and then giving this information context to form knowledge that can be acted on. "Manufacturers need to pull data from equipment and give it context, elevating data to information, and using that for operational excellence."

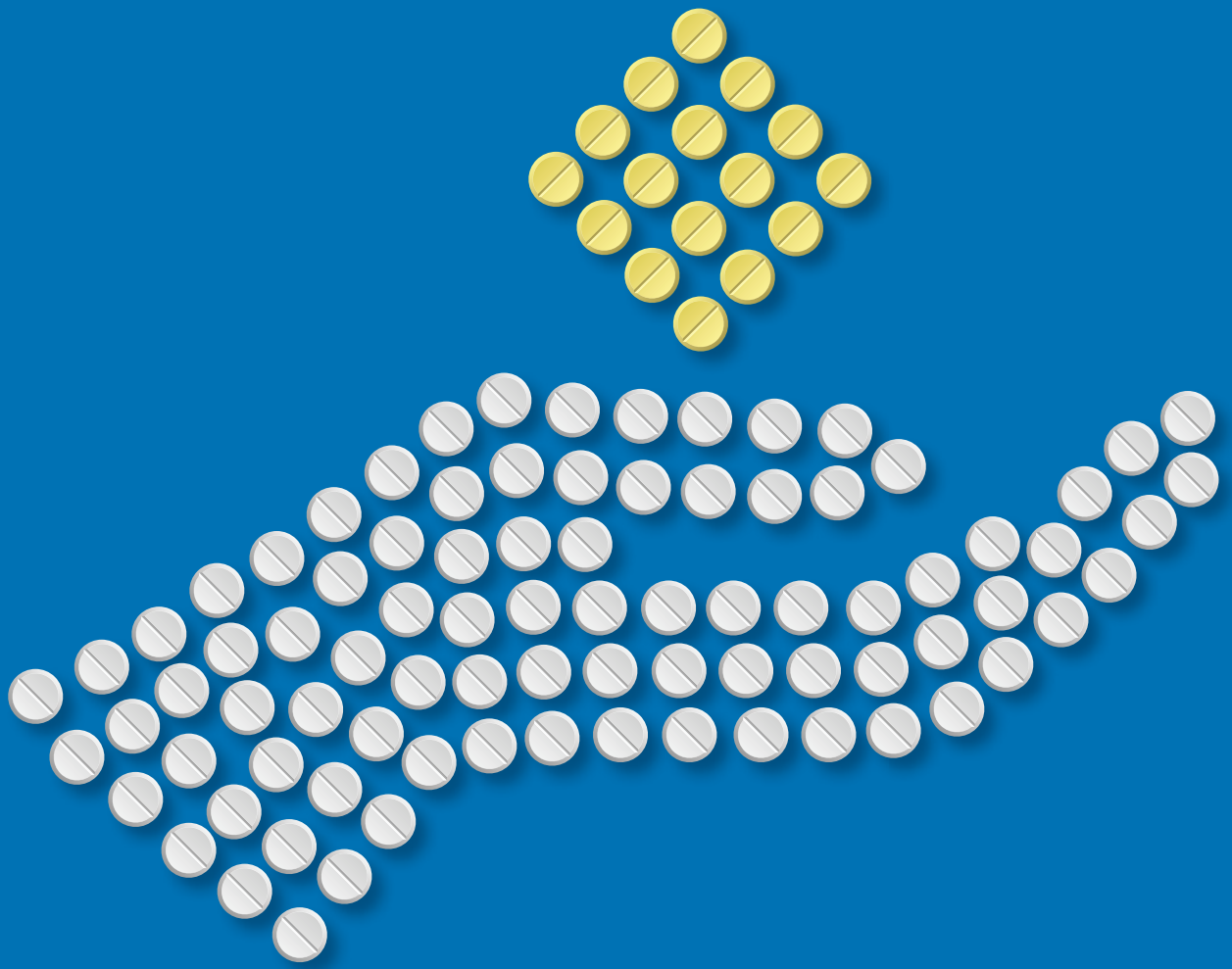
OSD OF THE FUTURE

The challenges faced by biologics in terms of development and production costs, drug delivery and a more complex biosimilar approval process, equate to continued relevancy for oral solid dosage drugs. In order to best capitalize on opportunities, OSD manufacturers are recognizing a universal need to ramp up efficiency and reduce waste.

According to Langer, "What's driving all these moments is operational excellence. Manufacturers need, from a business perspective, to operate much more efficiently. The reality is that manufacturers can get much more out of what they have in place already."

Even if processes do not achieve full continuous manufacturing as industry defines it, steps in that direction — taken by both brand and generic OSD manufacturers — are proving to be of significant benefit across the industry.

Concludes DiProspero, "I am frequently asked about what the OSD facility of the future might look like. I believe that The Facility of the Future is going to be much more agile, flexible and efficient than it is today. How do we do that? Innovative design concepts, new technologies and unique solutions: pull that together – perhaps in the context of continuous manufacturing – and you've got something to take OSD into the next generation."



“I need a CDMO that I can TRUST.”

With Rottendorf Pharma as your CDMO, you can be sure we will protect your profits, allow you to focus on your pipeline, keep you informed, and keep you compliant. Need someone you can trust with your solid oral doses? Rottendorf owns it.

For more information, visit www.Rottendorf.com/trust

ROTTENDORF PHARMA

MANUFACTURING • PACKAGING • FORMULATION DEVELOPMENT • ANALYTICAL METHODS

STEPS TO ENSURE THAT REMEDIATION REALLY WORKS

If not handled properly, remediation efforts can become sizable and expensive; fortunately, companies can draw on the structured remediation experiences of other companies who have emerged from crisis

By Ted Fuhr, Evgeniya Makarova, Janice Pai and Camilo Rueda, McKinsey & Company

QUALITY PROBLEMS are rising in the pharmaceutical industry, often to the point of crisis. But remediation is no simple matter. If not handled effectively, it can be extremely cumbersome and expensive, often without even fully meeting its main goal: reducing patient risk. Delayed or ineffective efforts can also bring on drug shortages, which hurt patients and the industry as a whole — not to mention creating greater financial risk.

It's time for companies to devote more attention to effective remediation initiatives. Empirical evidence demonstrates that an intensive investment early on, following a structured approach to problem solving and project management, can make remediation run much more smoothly. Indeed, properly managed remediation efforts can not only restore operations to normalcy, but also strengthen a company's quality systems and operating culture to help forestall future crises.

The good news is that companies entering a remediation can learn from those that have navigated their own quality crises. The leaders of those successful pharmaceutical companies have found ways to implement focused and time-sensitive fixes while laying the groundwork for better quality systems for the future. We've distilled seven foundational principles from the successes of those companies (Exhibit 1).

1. ALIGN & COMMIT THE WHOLE ORGANIZATION

To ensure successful remediation, the entire organization must be committed to the effort. Typically, quality and compliance problems that are large enough to require remediation are complex, with root causes that are difficult to identify and resolve. Sophisticated solutions cannot be implemented solely by the quality staff or even the entire operations organization. Successful remediators make it a company-wide commitment, requiring the wholehearted engagement of top management, the allocation of necessary organizational resources, and cross-functional collaboration focused on finding and eliminating the root causes.

A remediation program requires significant resources. Without intervention from the top, managers are stuck with the untenable burden of carrying out remediation activities and simultaneously completing day-to-day tasks. So companies should identify the necessary resources from the earliest stages of any remediation program. At a minimum, they should establish a strong project management office (PMO) tasked with coordinating remediation activities, tracking progress and measuring key performance metrics. For larger and more complex remediation efforts, it is prudent

to set up an entire remediation organization led by a senior executive with sufficient technical and management resources on hand — including targeted infusions of staff from other divisions or from external contractors, when needed.

The hard work of remediation starts with a structured approach to root-cause problem solving — not simply by jumping on first- or second-order diagnoses. Ideally, the problem solving should be cross-functional. In one company, the sessions included personnel not only from the engineering, manufacturing and quality groups, but also from HR. That inclusive approach helped to pinpoint the fact that some production workers were not following established operating procedures.

Cross-functional collaboration is just as important once the root causes are clear. Quality and manufacturing must align on solutions and adjust their operating priorities consistent with the remediation program. Procurement and other functions might need to get involved, too. IT may need to step in to build systems that can capture more data or better analyze trends. And it may even be valuable for the R&D group to join in, postponing unrelated work in order to focus on solutions that change the product lineup, for instance.

2. MAKE PERFORMANCE MANAGEMENT TRANSPARENT

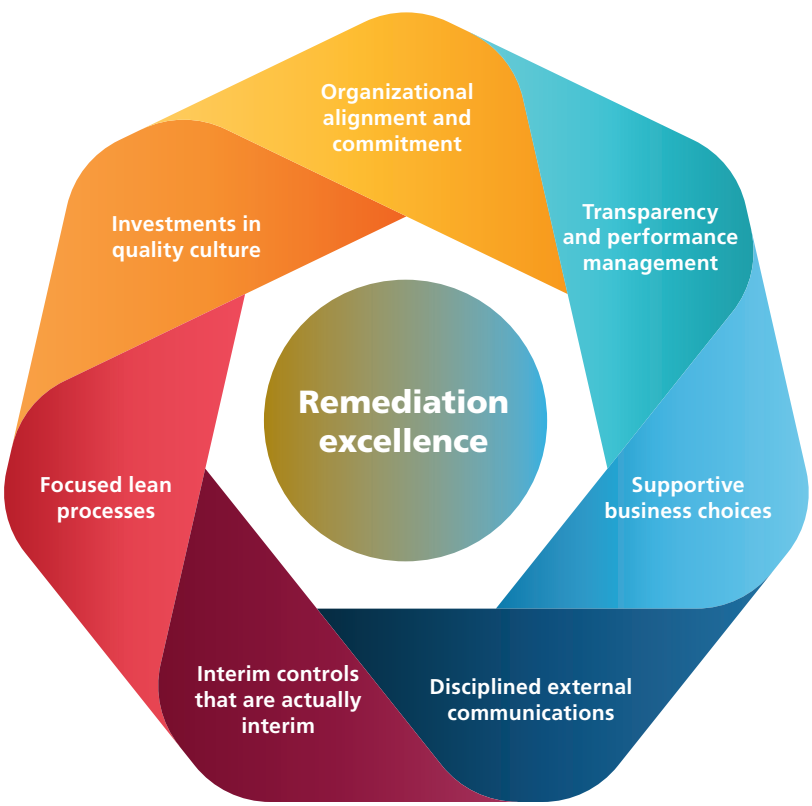
The work of remediation differs so much from that of the core business that it requires a very different approach to managing performance. The most successful companies establish balanced scorecards to track remediation activities and overall company metrics; they also create a robust forum to properly review this performance, and they aggressively manage the performance of third parties such as remediation consultants brought in to provide interim controls.

Balanced scorecards are essential to provide visibility into both the remediation efforts and key day-to-day activities — and to shine a light on the performance of all of those activities. This requirement seems simple, but many companies fail to carry it out. They may lack the available data to be able to set up a scorecard; they may not have the resources needed to collect and manage the metrics. The companies that do commit to tracking performance management should set up simple scorecards that include such measures as remediation activities completed, regulatory external commitments met, first-pass quality, deviation and CAPA closure, and amount of back ordered product (Exhibit 2).

The PMO can be the appropriate forum for tracking performance as well for helping to coordinate and execute remediation activities. But we have found that the most successful remediation initiatives establish a fully equipped "control tower." This is a dedicated, cross-functional forum for leaders at both the corporate and plant levels that can track improvement projects, make fact-based decisions, and drive the collaboration needed for cross-project initiatives.

The best remediators also make a point of aggressively managing the performance of third parties. In one scenario, a large company set up a remediation control tower at one location to manage a cross-

Exhibit 1: Successful companies have included seven key elements in their remediation programs



Source: McKinsey analysis

continental program involving nearly 1,000 contractors. The project managers had the tough job of remotely managing remediation initiatives and contractor activities across as many as 20 sites. The control tower provided transparency to all the PMOs so that the managers could easily track progress and performance. Control tower staff were able to rapidly escalate site-level concerns to project owners for resolution. Furthermore, the control tower facilitated regular communications and flagged key challenges on remediation progress to senior executives.

3. ENSURE THAT OTHER BUSINESS CHOICES SUPPORT REMEDIATION

Done properly, remediation can require not just extensive resources and management attention but also R&D and production capacity. To free up those elements without impairing the drivers of corporate revenue, companies have to be disciplined about setting priorities for a host of other activities. Cross-functional collaboration is essential here, too — with help from the strategy staff to make sure that the inevitable changes are consistent with corporate goals.

We're pleased to report that we've seen many companies come together with business choices that are truly supportive of the remediation efforts. We've observed project managers working closely with the commercial function to simplify product lines, and manufacturing teams drawing on wider networks to shift production to other locations (either the affected product itself or close replacements for it) and expediting production to build up inventory before shutting down a production line. We've also seen some companies shifting important resources and talent from across the globe to support the location where remediation is needed most. That's a meaningful sacrifice not just for the sourcing locations, but also for the individuals who must uproot and live away from home in order to support the remediation activities.

At one company, product managers quickly rationalized several SKUs. By shutting down production of a number of high-risk legacy products, they not only freed up resources, but also reduced demand for remediation work. Additionally, these managers delayed some marketing plans in order to free up space in plants. They could do this only because they were fully aware of the trade-off in value, and they used their business judgment to distinguish between the short-term gains available to them and the long-term success of the organization.

4. COMMUNICATE WITH THE OUTSIDE WORLD IN DISCIPLINED WAYS

Remediation requires communication — and plenty of it. It is not something that can be dealt with by hunkering down and improving internal operations while ignoring the outside world. Pharmacos that try to "keep a lid" on remediation activities can soon find themselves embroiled in public relations crises. Open up any major news service after a big quality issue in the industry and you will find piercing headlines that grab the attention of the affected pharmaco's customers and investors. The concerns ripple outward: Consumers will question the safety of the affected brands, while distributors and retailers will fret about the company's reliability.

So a vital component of every remediation effort must be the ability to work well with external parties and communicate with them clearly, crisply, continually and proactively. Having a clear

Exhibit 2: A remediation scorecard provides a balanced view of performance

Safety and people

- Incident rate
- OSHA reportable incidents
- Training index
- Perfect attendance %

Compliant processes

- First-pass quality
- ERs created vs. closed
- ER aging
- CAPA closure without extension
- Recalls
- Customer complaint aging
- Meeting regulatory external commitments
- Meeting customer external commitments

Production processes

- Customer service (e.g., order fill rate)
- Manufacturing schedule adherence
- On-time deliveries
- Aged batches in quarantine

Financial indicators

- Back orders
- Inventory loss
- Total inventory
- Variance to monthly operations forecast
- Variance to monthly commercial forecast

WHAT ONE ORGANIZATION LEARNED

The experiences of one large pharmaco show what's needed to handle remediation relatively well:

THOROUGH ASSESSMENT OF THE PROBLEM. It wasn't enough for the company to issue general calls to take remediation seriously. It was able to shift its culture toward embracing quality only by increasing organizational accountability . As one manager proudly stated, "We have created a system where people can't find loopholes [so they] have to do the right thing."

Managers were able to take immediate steps, such as taking difficult-to-manufacture products off the market for either remediation or elimination. The organization also benchmarked against external best practices to dig deeply into quality issues. "Answering 483s only touches the surface," recalled a manager. "Without structured problem solving, we would never have gotten to the root cause."

However, some elements of the remediation program were not handled in the most effective ways. The new quality system was not simple to use. There were persistent skill gaps affecting operation of the system, and the company suffered from a shortage of subject matter experts.

ORGANIZATIONAL COMMITMENT. The company wisely assigned a new leadership team to remediation — a team whose members were comfortable with critiquing the status quo. As one manager said, "It's hard to get the architect of a system to change it; you have to place people in charge of the transformation who don't have strong ties to the system in place."

The new team worked to address key issues in a timely and efficient manner, with clear decision rights within the steering committee. The team members also demonstrated the willingness to make tough decisions, while fostering an open culture that made people comfortable with raising difficult issues. "We truly shut down R&D and focused all of our resources toward the initiative," noted one member. "This sent a positive message about how serious we were." And throughout, they kept the teams under them focused on solving the quality problem, without being sidetracked by related issues.

Nevertheless, some elements of effective governance did fall short. Decision rights weren't so clear below the level of the steering committee, and individual remediation projects weren't integrated enough. The remediation teams also had limited two-way learning with quality experts from other divisions. And leadership was fragmented at the various sites that were affected by the remediation initiative.

COMMUNICATION. The company did significantly better at communicating compared with its earlier compliance programs. It had a disciplined and targeted external communications strategy. Customers got important updates, but the company held back from providing guarantees. Regulators, however, got special attention. As one manager said, "Taking the lawyers off the front line was critical to building our relationships with the FDA."

Internally, the company pressed forward with more open communication. Management appointed guides to speak about the program, and sessions for specific employee groups helped to pass along further detail. As the remediation projects unfolded, though, communication became more of a challenge. The program management office initially treated messaging as a secondary staff duty; the office had no communication professionals. "House message boards" drew a mixed response. Here again, the accelerated schedule left little time to prepare for change management in advance.

communication strategy is essential in working with regulators, shareholders, the media (including social media) and, of course, customers facing drug shortages.

In fact, we contend that it is absolutely crucial to establish a productive dialogue with regulators. Agency officials should receive continual updates on remediation plans and progress against those plans. Pharmacos must resist the temptation to merely send reports; instead, they should engage in a two-way conversation on how best to emerge from the crisis. At one pharmaco, the chief executive made it a top priority to personally communicate with the company's regulatory agencies. In addition to the company's delivery of concise quarterly reports on progress and challenges, the CEO scheduled multiple meetings to keep the regulators entirely up to date with the remediation effort.

Shareholders are the other constituency that must be kept in the loop. Communication with them should include not just the immediate operational challenge for which remediation is necessary, but also a vision of how the remediation

investment will help the company become stronger, operationally and financially. Companies that have successfully navigated remediation have been upfront with shareholders about the required investment. They've also provided clear road maps on how costs will stabilize and what the post-remediation organization will look like.

5. INTERIM CONTROLS

Remediation is a sign that the company's existing quality controls have failed and must be rethought. Until new procedures are in place, regulatory agencies often require pharmacos to install temporary controls that provide greater margins of safety. These "interim controls" ensure sufficient oversight over quality in the company's ongoing operations.

In addition to the added oversight, such controls signal how seriously the company's leaders are viewing the remediation activities. In effect, the measures are saying, to both internal and external constituencies, "We know there's an issue and although we don't fully understand it yet, we're acting immediately to protect patient safety and our overall reputation."

In some cases, a company can administer the interim controls itself, but more often it will hire third-party consultants experienced in collaborating with regulators on these measures. Regardless, it is vital to clearly define the role and scope of the controls so that employees are more likely to break out of their usual work habits when problems arise. They might need to escalate quality issues to senior quality leaders much faster than they usually might or ensure double inspection for documentation. Controls should include metrics so that staff can be confident of which steps to follow during this unusual period.

However, interim controls should be just that: stop-gap measures. They should specify the time line over which a company can phase them out. Otherwise, companies can find themselves saddled with ongoing costs and burdensome procedures that become entrenched in the quality system.

On top of covering all of these functional needs, companies will also want to design the controls to generate knowledge about underlying issues in quality and compliance. This might require additional people or resources, of course. But the intensive oversight that comes with such controls can yield valuable information that would never surface in the course of normal quality practices — and at just the time when the organization is establishing a new quality system.

6. PRACTICE LEAN PROCESSES

The actions taken after a quality and compliance incident are not expected to be highly efficient. The priority is to react fast and implement interim controls as quickly as possible amid considerable uncertainty. Remediation brings unfamiliar requirements that can easily slow down employees and production lines by creating new bottlenecks. Approvals that were dealt with quickly in the past may now require multiple new handoffs as well as sign-off from senior managers.

So it might seem counterintuitive to say that remediation is an ideal time to think and act "lean." The focus should be on implementing requirements in efficient ways and ensuring that additional controls are adding quality to the process.

In one instance, a pharmaco assessed the performance of a remediation group assigned to investigate a quality problem. The company found that less than a third of the work actually was productive — in that it identified and eliminated the root cause of the problem. Other activities were wasteful, including a slew of auxiliary paperwork and excessive time spent fact-finding. With an understanding of the drain on time, the company took immediate action to add extra administrative support. Now, the group could focus on the main work: streamlining approvals and standardizing data collection processes.

7. A CULTURE OF QUALITY

Remediation is a shock to an organization, and some employees will see it only as a time-consuming ordeal that they must tolerate. Employees are eager to move on as soon as possible and "check the necessary boxes" so that they can get back to operations as usual. Yet remediation can also be a golden opportunity to alter the way that the organization approaches day-to-day quality issues. Leaders can take advantage of the experience to instill a renewed quality mindset, to ensure that the company doesn't find itself in another quality crisis a few years later.

Transforming quality can start with a "quality maturity" assessment that establishes a baseline for the current-state culture, highlighting the current quality mindset and the management and process gaps. Once the gaps are understood, specific interventions, initiated by employees and supported by leadership, can begin to change the quality culture.

The good news is that there are already many successful remediation stories out there. By incorporating these seven key principles into their remediation programs, and with the sincere support of leadership teams, companies that are launching remediation initiatives can be more confident that they can regain their footing — without any noticeable negative impact on everyday business activities.

Discover the Disinfection **Power** of **Cold Plasma** Activation

Interphex | Booth 3835

Technical Theater

Wednesday, April 27th

3:00-3:30pm on Stage 6, Booth 1677

TOMI™ ENVIRONMENTAL SOLUTIONS | STERAMIST™ POWERED BY BINARY IONIZATION TECHNOLOGY®

DOWNLOAD CASE STUDIES

Case Study Compilation: Global Pharmaceutical Manufacturers Validate Disinfection Protocols Utilizing SteraMist™ Powered by Binary Ionization Technology (BIT™)

www.tomimist.com/pharmastudies

LEARN MORE AT WWW.TOMIMIST.COM | 800.525.1698

CATALENT'S HOLISTIC APPROACH

TO HIGH POTENCY API OPERATIONS

How Catalent's approach to containment mitigates cross-contamination risk and regulatory issues, ultimately safeguarding patients

By Karolina Narczykiewicz, Operations EHS Manager, Catalent

THE MORE potent a drug substance is, the more stringent the handing requirements throughout the manufacturing process. Occupational health must be taken into account across the board, from the time any potent material enters (or is made in) the facility, to the time it leaves as a final dosage form. A careful consideration must be made of any environmental impact that might result if something goes wrong, such as air pollution or water contamination. The safe and proper handling of waste must be considered, too.

Regulatory compliance and quality also play an important role in ensuring safety within a facility that handles potent and highly potent compounds. These functions help to ensure there is no cross-contamination and assist in the development of appropriately designed vessels that are easily cleaned. This is particularly important in a multipurpose plant where the vessels are not dedicated to one specific product.

COMPOUND CLASSIFICATION

Any company that works with highly potent compounds must have a rigorous system in place for classifying the potential hazards and risks of each individual product. Many different factors are taken into account, such as the lowest

Table 1 - All APIs assessed to a 4-band system developed in partnership with Safebridge.

Categorization Code	OEL Band Vapors/Gases	OEL Band Solids	Definition
1/4	≥ 100 ppm	≥ 100 µg/m³	Pharmaceutical compounds that have a high Occupational Exposure Limit (OEL) as evidenced by a low to moderate pharmacological activity.
2/4	< 100-10 ppm	< 100-10 µg/m³	Pharmaceutical compounds that have an intermediate Occupational Exposure Limit (OEL) as evidenced by a moderate pharmacological activity.
3/4	< 10-0.1 ppm	< 10-1 µg/m³	Pharmaceutical compounds that have a low Occupational Exposure Limit (OEL) as evidenced by a high pharmacological activity
4/4	< 0.1 ppm	< 1 µg/m³	Pharmaceutical compounds that have a very low Occupational Exposure Limit (OEL) as evidenced by a very high pharmacological activity.

therapeutic dose, the compound's bioavailability, mode of action, and an understanding of its overall pharmacological activity. Are there any known target organ toxicities? Is it a known mutagen, carcinogen or genotoxic agent? Is it a sensitizer? Does it exhibit any warning properties?

The occupational exposure limit, or OEL, may already have been determined for the compound, and this can be an important starting point for compound classification as it represents the maximum acceptable concentration in workplace air. Before deciding whether to use that OEL, it is important to know whether it is based on human data, and what studies were performed to determine it.

The Catalent compound categorization code is laid out in Table 1. It was developed in partnership with experts at Safebridge Consultants Inc., and it is used across all of its sites around the world. When Catalent receives a new compound, they determine which of the four categories it fits into, which informs all handling requirements. Class 1 is the least potent, and corresponds to an OEL band of >100µg/m^3. Typically, they do not consider those that fall into classes 1 and 2 to be potent. Those in class 3 are potent, and class 4, corresponding to the OEL band for solids of < 1 µg/m^3, are highly potent.

If data are lacking, which is often the case in the early stages of a product's development, the company will default to a conservative banding, and assume that it is potent. This does increase cost, and thus it is important to reassess its categorization in the light of new data as it becomes available.

RISK ASSESSMENT AND CLASSIFICATION

To determine whether a compound is compatible with a facility, a full risk assessment and classification must be carried out, taking into account hazard, exposure and risk. Hazard is the potential for a compound to produce harm. For exposure, we look at the potential for the compound to be absorbed via inhalation, ingestion or skin absorption; the compound's physical state and how it is handled can affect how it behaves. Risk is the probability that the compound will produce harm under the specified exposure conditions. These factors all lead to an understanding of the acceptable risk level, which is the probability of exposure occurring, and the harm that may result. This must be as low as is reasonably practical, but still tolerable.

The scope of manufacture also drives facility compatibility. For example, some sites cannot handle beta-lactams, antibiotics, hormones or cytotoxic molecules. Is it reactive or inflammable, or does it create an explosive dust? Are we able to develop suitable cleaning methods to prevent cross-contamination and carryover, and is the facility layout and available equipment in line with minimizing risk? We will also need to review quality agreements and site licenses to ensure the compound class is not precluded. If it is a controlled drug, additional requirements may add complexity to containment, and more operators may need to be involved.

This is all part of a formal onboarding process for compounds and projects. As Catalent may handle many different products and projects in their multipurpose facilities, they need to mitigate the risk of cross-contamination, and the attendant risk to patient safety. Not only do they have to comply with both regulatory and license requirements, but clients may have their own specific requirements that could preclude Catalent working with certain other classes of compounds within the facility. Onboarding is very important from an Environmental, Health and Safety (EHS) point of view, too, when determining the containment strategy. It also helps reduce the risk to business and client relations by ensuring everything works as it should, and that they only work with appropriate material for the site's capabilities.

FURTHER CONSIDERATIONS

The level of flexibility required must also be determined. Can (or must) the process be run from start to finish with no stoppages, or can it be broken down into different segments? If it can, the company also needs to identify the points of intervention, such as intermittent cleaning or pausing to take a sample, and how this fits into the overall containment and control strategy. Batch size is also important, as this determines the equipment scale. Cleaning requirements will vary depending on the containment that is used. A fixed containment system will have to be cleaned; disposable containment is thrown away, removing the need for this level of cleaning intervention.

Effective cleaning is essential, and at Catalent, they develop cleaning master plans for all sites to ensure carryover and cross-contamination are prevented. For example, in their oral solids manufacturing facility in Somerset, N.J., the plan consists of two parallel pathways. In one, environmental, health and safety data are collated, and studies are carried out to determine the acceptable residue limit, or ARL, based on the maximum allowable carryover for the compound. In parallel, tests are run to identify the optimal cleaning agent. These two activities culminate in the development of an analytical method, and the validation of the cleaning process.

The starting point for exposure control is the facility infrastructure. Is the HVAC system single pass or recirculating air? The former is more appropriate when

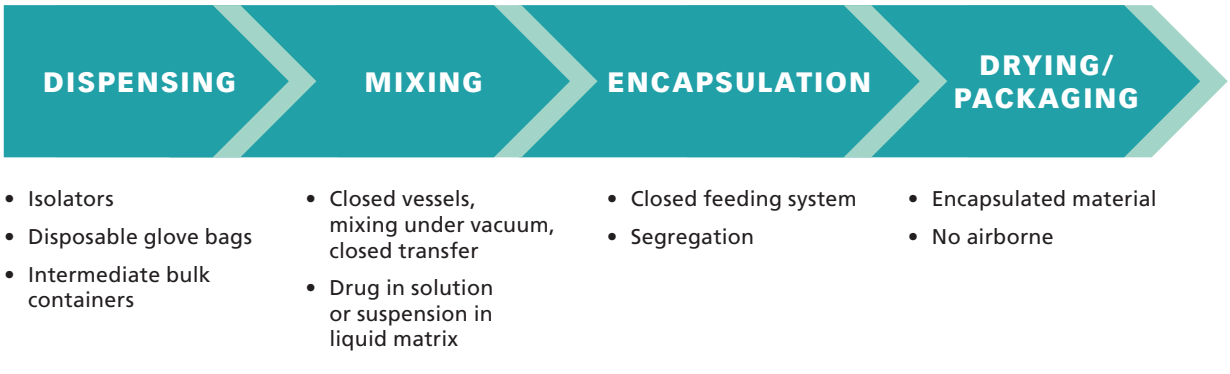


Table 2. Containment measures and controls — "Softgel example"

handling potent compounds. How many air changes an hour is the room designed for? Again, higher numbers are preferred for potent compounds. Are the rooms equipped with airlocks that allow for a unidirectional flow of personnel, and a separate flow of materials and equipment? This is important for reducing the potential for cross-contamination. And is clean-in-place possible? Manual cleaning adds an additional point of exposure potential for the workers.

The decision on containment approach is between containing hazardous compounds at the source, and running an open process with personal protective equipment (PPE) to safeguard the operators. The nature of the containment type that is selected — fixed hard-shell or disposable — will depend on the application. Transfer systems such as split butterfly valves can have containment advantages over flexible systems like continuous liners.

It may also be appropriate to use additional PPE even if containment is in place. Catalent typically uses powered air purifying respirators as a failsafe, and some specific processes might require items such as special gloves or suits.

The effectiveness of containment is verified by performing industrial hygiene studies. These will typically be carried out via surrogate monitoring, using compounds such as naproxen or lactose in place of the potent compound itself. Air-monitoring samples for the personnel working within the operation will be taken, along with area samples to give a picture of how well the containment is working, alongside the level of containment that can be achieved. If a surrogate has been used in a particular area before, it is advisable to run background samples to ensure there is no carryover that could skew the results. In environments with routine cleaning procedures this should not be an issue, but it is still worthwhile. Wipe tests may also be carried out.

Ongoing monitoring is carried out at set frequencies, according to an industrial hygiene plan. This is used to inform decisions on whether altered protocols, additional controls or different containment equipment are required.

Table 2 shows an example of containment and control from Catalent's softgels business. As they move from dispensing through mixing to encapsulation, drying and the final packaging of the softgels, containment requirements are much higher in the early stages — with isolators and disposable glove bags for dispensing — than at the final packaging stage, where there is little chance of airborne contamination so containment requirements are minimal.

THE IMPORTANCE OF ADAPTABILITY

It is important to recognize that there is no single approach that fits all applications when working with potent compounds. Risk assessment is essential, and must be done before manufacturing or onboarding compounds to ensure the best solution for that particular case is chosen. Tailoring the approach to the process is key, with hazard, exposure, controls and understanding of acceptable risk all important factors in making the correct decision. Flexibility may cost more, but for small batches it can be a more cost-effective solution.

Selecting the right approach to containment when working with potent and highly potent compounds carries with it many benefits in terms of safety and environmental protection. Containment reduces the risk of cross-contamination and, when matched with the correct cleaning methods, leads to a reduction in regulatory risk, and further down the line, minimizes the risk to patients.

Think about what went into producing this capsule.

We'll help you get more out of it.

Recovery and refining of PGMs from spent pharmaceutical catalysts ...

When you're ready to change out your PGM-bearing API processing catalysts, we'll recover and refine their precious metals with highest possible returns without environmental concerns. We've done this for seven decades and for hundreds of organizations around the world— ***and we do it better than anyone else.***

Full details at sabinmetal.com

SABIN METAL CORPORATION
70th
PLATINUM ANNIVERSARY • 1945-2015

sabin
METAL CORPORATION

‘Future-Proofing’ Serialization Solutions

The key to creating an optimal implementation strategy is to select a serialization solution that has strong capabilities at all levels of technology

By David Carpentier, Founder & CTO, Adents; and James Cumming, VP Americas, Adents

THE COMPLEXITIES surrounding product serialization for pharmaceutical and medical device companies are immense. While current serialization requirements are limited to marking the unit of sale with a unique data carrier, by 2023 the process will require a product to be traceable through the entirety of its journey — from the individual package through the carton/pallet to its final point of distribution. In the United States, the Healthcare Distribution Management Association (HDMA) is suggesting that pharmaceutical companies begin to support this level of serialization, called aggregation, now. Around the world — in Europe and Asia in particular — disparate track and trace practices are incrementally moving toward a global standard that will, undoubtedly, be more stringent than today’s differing benchmarks.

How can companies manage this transformation with the greatest degree of success while also minimalizing business disruption? The key to creating an optimal implementation strategy is to select a serialization solution that has strong capabilities at all levels of technology. It’s also important to choose a solution that enables multi-phase implementation and provides business benefits beyond compliance.

FOUR LEVELS OF TECHNOLOGY

There are four main levels of technology involved in the delivery of an effective serialization solution:

- *Level 1: The Device Level* — Includes line level systems such as printers, scanners, cameras, code readers and controls.
- *Level 2: Line Level Control Systems* — Includes software that controls data, serial number management and aggregation of data across all Layer 1 devices on a specific packaging line. These real-time controls and software supervise, monitor and control the physical processes, human-machine interface (HMI) and data acquisition.
- *Level 3: Site Level Software and Hardware* — Includes software systems that send and receive information to multiple Level 2 systems within each site and that connect to Level 4 software, which is often hosted outside the company firewall, or in the cloud. There is typically one Level 3 system for each packaging facility. These systems manage production workflow to serialize the desired products: Master data such as customer, product and work order information are generally managed in this layer and distributed out to

Level 2 systems in a one-to-many distribution model. Centralized configuration at Level 3 provides an enhanced level of governance and robustness in today's fast-changing environment.

- *Level 4: Business Logistics Systems* — Level 4 encompasses the software that manages connectivity to the greater pharmaceutical company and connects all Level 3 site level systems across all sites. Level 4 Electronic Product Code Information Service (EPCIS) systems typically interface with Enterprise Resource Planning (ERP) systems along with other track-and-trace related systems in order to provide comprehensive use of serialized and operational data. Level 4 systems manage the business-related activities of the manufacturing operation, such as establishing the basic plant production schedule, material use, shipping and inventory levels.

The most effective and comprehensive serialization solutions will support the requirements of all levels of technology, connecting challenges at the shop floor and plant levels with the enterprise level.

The most effective and comprehensive serialization solutions will support the requirements of all levels of technology, connecting challenges at the plant level with the enterprise level.

IMPORTANCE OF LEVEL 3 APPLICATIONS

There is no denying the importance of Level 3 applications for serialization solutions — the software that resides at the manufacturing or packaging plant site level above the packaging lines and machines/devices (Levels 1 and 2), and below Level 4 enterprise applications.

ISA-95.00.01-2010 is an international standard for the development by global manufacturers of an automated interface between enterprise and control systems (Levels 3 and 4). It is meant to be applied in all industries and all sorts of processes, such as batch, continuous and repetitive processes.

The goals of the standard are to increase uniformity and consistency of interface terminology, and to reduce the effort associated with implementing new product offerings so that enterprise and control systems can easily integrate and smoothly interoperate.

While there are no definitions for serialization in ISA-95 for objects, attributes, interfaces, etc., the overall architecture and concepts can be leveraged in designing and implementing serialization systems.

As defined by ISA-99.01.01, implementation of a Level 3 system above all Level 2 systems is a critical element in securing corporate infrastructure through a conduit and zoning model, where a zone is defined as a grouping of logical or physical assets that share common security requirements, and conduits are defined as a logical grouping of communication channels connecting two or more zones. As most serialization systems are implemented in response to counterfeiting or brand protection programs, it should seem obvious that following best practices security guidelines would be a basic requirement.

One of the primary goals of Level 3 applications is the provision of critical isolation of automation and production devices from enterprise applications at Level 4.

This separation provides:

- Governance
- Network traffic management and security
- System access management and control
- Data domain establishment at the site level

Level 3, in its most basic construct, is an element of an architectural design pattern that does not cover capabilities, functionality, capacity, implementation methodologies, or any metrics that could be applied to an application to create some sort of baseline. In simplest terms, if you stick a PC with a hard drive at the plant level and make a Windows share or FTP mount point on it, you could technically classify it as a Level

3 architectural system. Simply put, ISA-95.00.01 Level 3 Model only defines its architectural level — but nothing about the functionality of the application itself. (For serialization systems, Parts 2-6 do not directly apply.)

DEFINING KEY FUNCTIONALITIES

The following are key functionalities for a useful serialization Level 3 application, and an examination of what a complete Level 3 solution should ideally include for each Level 2 functionality category.

Key Functionality Categories:

1. Configuration Management
2. Data Exchange
3. Reporting
4. Change Management Support
5. Validation Support
6. IT Governance

1. CONFIGURATION MANAGEMENT

Unfortunately, there exist large gaps in the benefits offered by many widely used Level 3 solutions. Many have only partial configuration capabilities, and some offer no configuration whatsoever; they are simply generic middleware platforms providing a one-to-many communication function for data transfer.

A more complete Level 3 solution would provide a multitude of additional functions, including:

- Performing all configuration at Level 3
- Not requiring configuration work at each and every line level controller
- Being 'self-aware' in that it would broadcast its information so that the solution's upstream components would 'discover' it
- Involving no chance of human error

Let's consider a hypothetical, yet typical, scenario: One plant with 15 lines, four levels of aggregation and five rework stations.

Assume we need to prompt the operator for a new piece of data per each new regulation. In most systems this would require making at least 65 configuration changes. In fact, in some systems, there would need to be corresponding changes at Levels 2 and 3, causing this number to rise to 130 configuration changes at the line level, taking each line out of service for a period.

In addition to the incredible waste of time and energy needed to replicate a simple change across all of those configuration points, there would be a 65- or 130-times greater chance of entering something wrong.

A complete Level 3 solution would require making just one change in the default general parameters section, which would then reflect that change throughout the serialization enterprise.

That is 1/65th or 1/130th of the work for each and every change. This clear savings in time and labor is compounded exponentially in the validation, governance and change management support functions, to be discussed later. A related scenario: Let's assume a mistake is made at the outset, such as the last number being left off in some value. One quick change would fix it instantly, for a total of two changes versus 130, or 260, or more.

Today's serialization solutions must be outfitted to meet tomorrow's demands, which will require more exacting track and trace practices, documentation, and data sharing capabilities.


THE DIFFERENCE BETWEEN A SOLUTION AND
THE RIGHT SOLUTION.
Breadth and depth of proven technologies and capabilities. Technology selection and formulation methodologies based on extensive scientific investigation and modeling. Through the integration of Capsugel, Bend Research, Encap Drug Delivery, Xcelience and Powdersize, we bring the expertise needed to meet bioavailability and other target product profile requirements. Our strengths span design, development and manufacturing – an integrated process to take your product from start to finish, all under one point of contact, to meet your commercial objectives while minimizing costs, time and risk.
To find your solution visit www.Capsugel.com/DFS or call +1.541-312-CAPS.
CAPSUGEL®
Dosage Form Solutions
Better medicines through science and engineering.

What this amounts to is a distribution of configuration changes. In this far more preferable arrangement, configuration change elements are distributed across the complete solution in the same "delta" methodology used in Enterprise Master Data Management platforms and ERP systems. This provides an extremely high performing solution that keeps systems up to date with the latest configuration changes, all with zero downtime.

2. DATA EXCHANGE

A major element of a proper Level 3 application is managing communications from both a data transmission and security access approach.

Recalling the example of one plant with 15 lines, four levels of aggregation, and five rework stations, many standard Level 3 solutions would try to manage this at a controller by controller level, putting them right back at the 65X complexity and heightened risk for undesirable configuration issues. Security and access rights become another burden: Changes in controller hardware, new operator accounts, etc., all create costly challenges and add points of potential failure.

A complete Level 3 solution would include robust interface options to Level 4 systems, providing centralized access and control of work orders, delivery orders, product data, customer data, serial number exchanges, EPCIS events and XML files. This would provide a wealth of information to Level 2 systems with a zero-touch approach at the line. Changes or additions to types of integration to Level 4 applications would be streamlined, organized and easily governable in a secure fashion.

3. REPORTING

When it comes to reporting, serialization systems, by their very nature, generate a new level of granularity of information created at the line level and site level. Clearly, the idea of having all reportable information data residing on Level 2 systems spread throughout a plant can hardly be called functional, let alone useful. Data is only useful if it's relevant, and this approach inundates various points of the process with information overload. Context is key.

A complete Level 3 solution would provide an extensive and extendable set of insightful reports. This approach entails the ability to export data, including supporting customized SQL statements to extract the precise data desired in applicable contexts. This affords the ability to extract meaningful serialization data and merge it with corresponding data from other systems.

4. CHANGE MANAGEMENT SUPPORT

A significant cost and challenge to cGMP regulated organizations is controlling and managing changes to systems.

A complete Level 3 solution would provide a full and rich set of features and capabilities that support a robust change management program. A centralized configuration management model ensures unwarranted changes are not possible at the line level by operators or supervisors, even by innocent mistake.

With this approach, all configuration data is stored in the SQL database and, in addition to scheduled backups, can be backed up on demand at any time. This yields the ability to use those data files (or exports of those data files) as versions by themselves, or imported into any number of commercially available Configuration Management tools for versioning purposes.

This high level of control provides a lower risk when implementing changes for new regulations and equipment upgrades and, in turn, directly impacts validation plans and drastically reduces requirements for maintaining compliance.

5. VALIDATION SUPPORT

FDA regulated pharmaceutical companies budget, on average, 30 percent of a project's cost for validation — a figure that reflects less-then-ideal serialization operations efficiency. With this figure in mind, let's recall once more the example of one plant with 15 lines, four levels of aggregation, and five rework stations.

Here, the testing and validation process is compounded by the documentation process, including the exponential impact of configuration specifications requiring the same 65 to 130 changes. In addition, solutions that provide Class 5 or bespoken (custom) software solutions at the line level create a significant burden for the initial implementation and every resulting change for the entire lifecycle of the solution. It's all unnecessarily complicated.

A complete Level 3 solution would have centralized configuration with standardized line level application that provides the least impactful, easiest to access and document, lowest risk application architecture from a validation perspective.

6. IT GOVERNANCE

IT systems and their management have matured a great deal in recent years, and standards such as ITIL and PRINCE have helped add structure and discipline to the support and management of mission-critical IT systems.

See us at Interphex booth #3765
See us at BIO booth #6239

thats nice
A Science Agency

That's Nice is moving into its 22nd year in 2016, so our approach reflects more than two decades of accumulated experience and knowledge in life sciences.

Research. Strategy. Results.

For more information, call +1 212 366 4455 or visit www.thatsnice.com

For production systems, there are two metrics that headline the worry list. They are RTO (recovery time objective) and RPO (recovery point objective); these basically refer to how long it takes to recover from a disaster, and to what point in time, data-wise, one needs to restart from.

A complete Level 3 solution would provide the lowest RTO and highest RPO, and have a centralized SQL database with a multitude of recovery options that can be implemented. This means zero configuration needed to roll out a new replacement Level 2 controller, combined with "no specific knowledge needed" in regards to any line level application configuration.

In the global pharmaceutical marketplace, serialization has been an unsettled buzzword for the better part of a decade. Differing mandates, legislative delays and a variety of other factors have coalesced to create confusion and uncertainty as to precisely what is expected of pharmaceutical manufacturers in terms of securing their supply chains and sharing data both within their own sphere of jurisdiction and beyond.

The best approach to uncertainty lies in flexibility and comprehensive capabilities. Today's serialization solutions must be outfitted to meet tomorrow's demands — a rolling set of new rules that, though unspecific in their totality, will certainly require more exacting track-and-trace practices, documentation and data sharing capabilities. A Level 3 serialization solution that leaves room for these inevitable, near-future must-haves is the keystone to being prepared to meet track-and-trace challenges for decades to come.

ABOUT THE AUTHORS

David Carpentier is Founder & Chief Technology Officer for Adents, and James Cumming is VP Americas for Adents. Headquartered in Massy, France, Adents is a software specialist of unique product identification and traceability helping manufacturers from all sectors to adapt to market changes and comply with regulations on traceability. Adents' innovative solutions enable manufacturers and brands to protect themselves from counterfeiting and grey markets, better control their distribution channels and create a personalized link with their customers. For more information, visit www.adents.com.

Smartindustry 2016

SEPTEMBER 26-28, 2016 • THE DRAKE HOTEL • CHICAGO, IL

ACCELERATE YOUR DIGITAL TRANSFORMATION

Gain insights from leading industry technologists, early manufacturer adopters and solution providers who are creating and implementing new technology and standards for the journey ahead

TOP REASONS TO ATTEND

- Learn about industrial applications, IT/OT convergence, cloud & mobility, and emerging technologies
- Hear digital transformation strategies from influential keynoters and manufacturers further along on their transformation journey
- Discover the up-and-coming technologies during our start-up competition
- Connect with experts during roundtables and networking receptions
- See the latest technologies being demonstrated

98% satisfaction rate

9 out of 10 attendees recommend this event to their colleagues

98% of 2015 attendees plan to attend in 2016

REGISTER TODAY TO SAVE $200!

event.smartindustry.com

SOLVING SOLUBILITY WOES

Capsugel's customized solutions advance challenging compounds

By Karen Langhauser, Chief Content Director

CAPSUGEL'S INVESTMENT in the expansion of its pharmaceutical spray-dried dispersion commercial manufacturing capability at its Bend Research site is helping its clients tackle bioavailabilty challenges.

A 2015 Kline market research analysis estimated that more than 80 percent of drug candidates in the R&D pipeline are poorly soluble in water. Poor solubility is one of the most frequent culprits of poor bioavailability and limited drug absorption. As drug manufacturers square off against these challenging drug development problems, they are looking for novel solutions to advance their difficult compounds to market. This is creating a growing market opportunity for solubilization enhancement technologies, with spray-dried dispersions (SDD) being a prime technology solution.

Developing a deep scientific understanding of client drug development problems and matching that with the right technology is critical. Just ask Bend Research, a division of Capsugel Dosage Form Solutions. Bend Research has more than two decades of proven experience formulating more than 1,000 compounds using spray-dried dispersion technology.

"We find that the majority of pharmaceutical product pipelines need science and engineering support to meet performance, stability and manufacturability challenges," explains Tanya Hayden, vice president at Bend Research and director of clinical and commercial manufacturing, Capsugel Dosage Form Solutions.

Above: Capsugel has invested $25 million to expand its commercial SDD capabilities in Bend, Oregon.

Capsugel, a global leader in providing high-quality hard capsules to the healthcare industry, launched its Dosage Form Solutions business unit in 2013 to significantly broaden its capabilities with a comprehensive suite of technologies and integrated solutions for designing, developing and manufacturing a wide range of finished dosage forms. In October 2013, Capsugel acquired Bend Research to provide the new business unit with an industry-leading position in bioavailability enhancement with access to a premiere suite of technologies to address customers' most pressing formulation challenges for oral delivery.

EXPANDED COMMERCIAL-SCALE OPS

The recent completion of construction of Bend Research's new pharmaceutical SDD commercial manufacturing facility in Bend, Oregon, includes approxi-

mately 6,000 square feet of highly optimized processing space that is already packing a big punch when it comes to tackling poorly soluble compounds. The new facility builds on Bend Research's core R&D competencies in SDD technology, as well as its initial foray into SDD commercial manufacture.

Bend Research broke ground on the $25 million SDD commercial facility in late 2013 and completed construction in June 2015. The new facility, built alongside Bend Research's existing GMP development and manufacturing facility, represented the company's continued focus on developing and expanding its commercial-scale operations for SDD technology. With the facility's completion, Bend Research has the largest integrated pharmaceutical SDD technology capability in North America.

The expansion enables Bend Research to leverage its expertise to support a growing pipeline of customer projects from early-stage development all the way through late-stage clinical and commercial manufacture.

This development spray dryer is used to scale up to the same size commercial dryer in the manufacturing facility.

WHY SPRAY DRYING?

Bend Research has developed solubilization bioavailability enhancement technologies with applicability at all stages of drug development, using a model-based approach to select the best technology for its clients' compounds.

"Spray-dried dispersions can solve a number of different formulations and/or stability or scale challenges, the most common of which is bioavailability enhancement," explains Hayden.

According to Hayden, spray-dried dispersion technology as a bioavailability enhancement solution is often favored. "SDD technology has a broad applicability across a wide range of API characteristics. It is a very robust and well understood technology and is very scalable," says Hayden.

Essentially, the spray-drying process involves dissolving an API, and in this case a polymer excipient, into a solvent. The resulting solution is sprayed with a drying gas such that each droplet becomes a particle of drug uniformly dispersed in a polymer matrix — a homogenous amorphous dispersion. The resulting product is a powder that can then be utilized downstream in either capsule or tablet dosage forms.

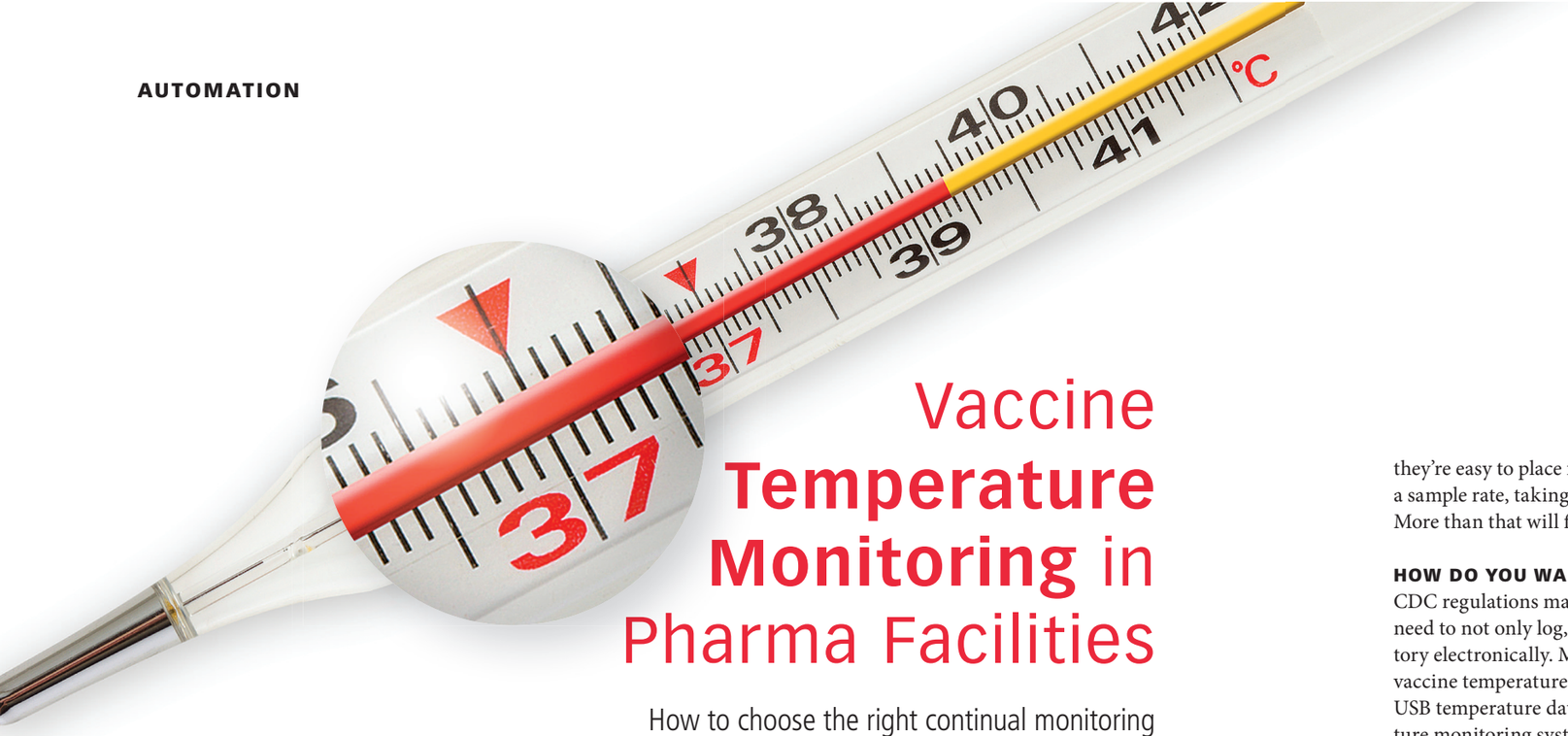
BUILDING A LEADER IN SPRAY-DRIED DISPERSION

With the completion of the new facility, Bend Research now has three commercial scale spray dryers, not to mention mini, lab and pilot scale dryers on-site. One commercial scale spray dryer is dedicated to supporting development activities for clients. The other two, which are designed for cGMP commercial production, use innovative dryer design and manufacturing plant technology to offer a significantly improved product throughput that minimizes cycle times and maximizes productivity. The newest spray-drying unit is designed to accommodate high-potency compounds.

"As part of our quality-driven design, we wanted to make sure that the facility expansion considered design and engineering features that would allow us to manufacture higher-potency compounds with reduced risk," says Hayden.

Producing high quality products was the primary driver behind facility design. "When we were designing the new facility, we wanted to make sure that we included ways to integrate automation technology. We put in new systems that allow our operators to monitor and control the process as well as provide real-time data feedback early to our clients to ensure that we're getting the desired product quality as designed throughout the process."

With its completed integrated SDD capability, and with the new facility already manufacturing commercial product, Bend Research — and parent company Capsugel — has solidified its place as a leader in offering spray-dried dispersion services to drug makers. Says Hayden, "We now have more technologies and capacity to bring the right solution to the right problem. It's all about patient outcomes. And this facility expansion allows us to support that."



Vaccine **Temperature Monitoring** in Pharma Facilities

How to choose the right continual monitoring system for your vaccine monitoring application

By Stew Thompson, CAS DataLoggers

IMPROPER TEMPERATURE control is a leading cause of lost vaccine supplies. When vaccines aren't maintained at the proper temperature (typically 2-8 degrees Celsius/35-46 degrees Fahrenheit), they quickly lose potency. The CDC's 2014 Vaccine Storage and Handling Toolkit, which provides vaccine storage and handling best practices, recommends using a temperature monitoring system for every medical storage unit to best avoid losing valuable vaccine supplies.

Continual monitoring systems provide an automated solution for temperature monitoring and alarming needs for pharmacy manufacturing facilities. These systems feature internal temperature sensors (or connect with external sensors) to record the ambient temperature of the manufacturing environment and can also log temperature data of storage unit interiors where vaccines are kept. These systems store data in a variety of ways with a view to satisfying regulatory requirements regarding vaccine safety.

A continual monitoring system can handle temperature monitoring, alarming and data storage — all with a view to protecting products and proving best practices. Data can be stored to internal memory, flash drive or even uploaded to a cloud storage web service. For example, a wireless system can remotely monitor any healthcare environment using medical storage units.

Many businesses and facilities are still new to this technology and are initially unsure of which of the many systems and manufacturers on the market to choose for their application. If you're considering a monitoring system to help keep you in compliance, your search can be made easier by considering the following short list of questions:

WHAT SENSOR TYPE DO YOU WANT TO USE?

Temperature data loggers are a cost-effective way to monitor temperature in vaccine storage units or the ambient temperature in storage areas. Environmental monitoring is also a useful way to ensure you get an alarm when HVAC systems fail.

Most temperature data loggers have inputs for specific sensor types. If you already know the temperature sensor type you plan to use, this will help narrow down your search. Many systems use the different types of sensors including RTDs, thermistors or thermocouples (by type). Specific systems such as these are typically lower cost than those which take data from several sensor types.

If you don't know which sensor types you'd like to use, there are many universal systems flexible enough to log data from many different sensor types.

You can also use a glycol buffer vial to stabilize your temperature readings. Many temperature probes are small enough to fit inside medical fridges and freezers, so they're easy to place for reliable readings. When selecting a sample rate, taking a reading every 15-30 minutes is fine. More than that will fill up the logger's memory too fast.

HOW DO YOU WANT TO STORE/RETRIEVE DATA?

CDC regulations mandate that those storing vaccines need to not only log, but also store the temperature history electronically. Many kinds of data loggers can store vaccine temperature data, ranging from a single-channel USB temperature data logger to multi-channel temperature monitoring systems with sophisticated alarming and offsite, secure cloud-based data storage.

Cloud storage is convenient as it enables users to download measurement data for offline analysis, and view it in reports, charts and graphs. Administrators can modify the system configuration online from any Internet-enabled location. Data online can easily be downloaded as a CSV file and loaded into most database applications.

Cloud storage services typically charge on a monthly or yearly basis, although a few manufacturers offer a limited amount of free space.

WIRED OR WIRELESS?

Given your building's particular network or lack thereof, you may want either a wired or a wireless system to give you access to your data. Ethernet and WiFi are two popular choices, respectively. Your facility's physical layout and resultant wireless range may be a factor. Consider where the datalogger and/or wireless gateway would need to be installed. Many models of datalogger can operate on either battery or AC power.

The systems come in both WiFi and LAN-wired versions allowing you to continually monitor temperature in a refrigerator or freezer and also providing customized alarming and data storage.

Wireless dataloggers can take the form of standalone pods or wireless repeaters transmitting data to a nearby wireless gateway which sends it out to the Web. When specifying your system, be sure that its indoor wireless range is wide enough to cover the area under monitoring. Some pods can act as repeaters to boost the wireless signal.

Temperature data loggers record vaccine temperature and also send alarms to email or auto-transmit all data to a cloud server.

WHAT LEVEL OF ALARM CAPABILITY IS NEEDED?

When considering a system to monitor vaccine supplies, automated alarming is the most important feature to weigh. Nowadays there's no excuse for missing an alarm when you can receive alarms and view data online from your mobile device.

First, decide what you need — local or remote alarm capability? If you need visual alarms, diagnostic LEDs show the room's current environmental status. Some monitoring systems are audible/visual only, some can even go out to emails or even place phone calls to designated personnel.

A few alarm systems automatically send email, SMS text message, pager or phone sequentially dialed voice messages. Many can also send alarm notifications in case of power or Internet outages, which is a godsend when your medical storage units fail at 3 a.m.! In case of outages, make sure that the logger has a data buffer so it'll keep recording if your power or Internet goes out, or at least an alarm to indicate this.

Continual monitoring systems are an ideal way to monitor medical storage units and help protect your vaccine supplies, meet regulatory requirements and ensure patient safety. Whether you want to go wireless or wired, a single system will record temperature readings, transmit alarms, and store and download data. By reviewing your wish list of features, you'll arrive at the ideal system configuration for your specific vaccine monitoring application.

What's New in Mixers and Blenders?

Improved processing technologies reduce the risk of contamination, increase production times and allow product customization

BY KATIE WEILER, MANAGING EDITOR

HANDLES VOLUMES UP TO 60,000 GALLONS

The Admix RotoMAXX II low-speed agitator complies with cGMP requirements and offers an all-stainless, FDA-approved CIP construction that handles volumes up to 60,000 gallons. The company says its technology, applications expertise and understanding of APIs equate to improved production times. In addition, Admix partners receive access to its pilot lab, so new products move from development to market quickly. Factory Acceptance Testing, QA and validation packages are available.

ADMIX

www.admix.com/biotech • 800-466-2369

DRY BLENDING OF FREE-FLOWING SOLIDS

Charles Ross & Son Company has added 5-, 10- and 25-cubic-foot V-Cone Tumble Blenders to its inventory of stock mixing equipment. Ideal for dry blending of free flowing solids, V-Blenders are rated for 125 lbs./cu.ft. product bulk density and feature stainless-steel 316 wetted parts. Other standard features include hinged covers, a butterfly discharge valve, TEFC direct drive gear motor and a safety gate with limit switch. Optional features include vacuum capability, intensifier bar, spray nozzles, heating/cooling jacket and built-in controls.

CHARLES ROSS & SON CO.

www.mixers.com • 800-243-7677

CLOCKWISE/COUNTERCLOCKWISE ROTATION

This mixer offers a powerful 1/10-hp maintenance-free brushless DC motor that provides 142 in-oz. of torque — enough power to mix solutions up to 20,000 cps or up to 6.6 gallons (25 liters). The company says timed cycles eliminate worries and provide repeatable, accurate results. Users can control vortexing and aeration with reversing timed cycles. The mixer features clockwise and counterclockwise rotation for a variety of mixing applications.

COLE-PARMER

ColeParmer.com • 800-323-4340

RETAINING LID OPTION

Meissner QuaDrum rigid outer containers (ROCs) are now available for rehydration and mixing applications. A new accessory retaining lid, stainless-steel dolly and true bottom drain option on the QuaDrum allow the ROC to deliver enhanced recirculation based mixing functionality for process volumes between 50 L and 200 L. The new retaining lid option for mixing applications not only provides access to fluid paths located on the top of the biocontainer, but also can positively locate and support a 3" TC port on top of it. This port can be used for powder addition or other operations that require large bore access to the biocontainer.

MEISSNER

www.meissner.com/quadrum • 805-388-9911

DELIVERS REPRODUCIBLE RESULTS

MilliporeSigma's Mobius single-use mixing solution delivers advanced technology for mixing pharmaceutical ingredients from intermediate to final drug products and for the preparation of process solutions, such as buffers and media. These scalable and ready-to-use systems and processing technologies reduce the risk of contamination, improve economic flexibility and deliver reproducible results. The mixing solution includes a powder delivery system; 10-, 50-, 100-, 200-, 500- and 1,000-liter

mixers; and the Mobius FlexReady solution for buffer and media preparation.

MILLIPORESIGMA

www.emdmillipore.com/US • 800-645-5476

MINIMIZED CROSS-CONTAMINATION

The Paul O. Abbe Rota-Cone blender is ideal for thorough and gentle blending of powders or crystalline products. Because this tumble blender has no shaft seals or agitator, cleaning is simplified and cross-contamination minimized. All internal surfaces can be inspected from the single loading hatch. Liquids can be added through the optional spray line, and a pin agitator can be added to facilitate liquid dispersion, granulation or de-agglomeration. Loading can be accomplished with automated drum loading and discharging system. Available sizes range from 0.1- to 500-cubic-foot working capacity.

PAUL O. ABBE

www.pauloabbe.com • 630-350-3012

CUSTOM PROCESSING/BLENDING SYSTEMS

Pope Integrated High-Purity Processing Vessel Systems are utilized in production and pilot plants for processing and blending. Skid-mounted systems are custom designed to meet client requirements. High-quality materials, welding and finishing assure integrity and GMP validation in sanitary and ultra-high purity applications. Vessels meet A.S.M.E. requirements and can be CIP/SIP. Equipment ranges from storage or shipping containers to turnkey controlled feed systems, blenders, reactors, fermenters and nutsche filter/dryers.

POPE SCIENTIFIC INC.

www.popeinc.com • 262-268-9300

CUSTOM MIXING EQUIPMENT

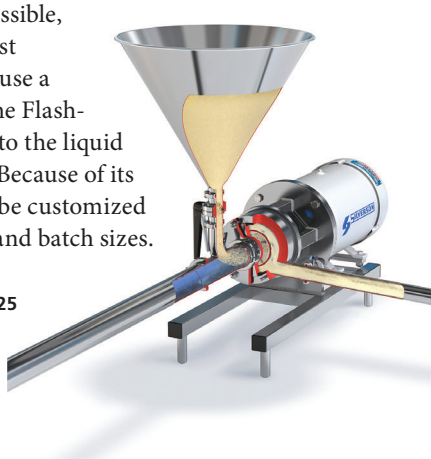
Sharpe Mixers designs and manufactures liquid agitation equipment. Many of the designs for equipment are based on a customer's specific requirements. For example, the PB-Series of mixers is designed for the pharmaceutical/biotech industries and is manufactured using current ASME-BPE standards for materials and finishes. Wetted parts are SS316L or higher alloys and can be polished and electro-polished with surface finishes of 20, 15 or 10 Ra. BPE compliant single dry-running mechanical shaft seals are standard and are rated for 200 psig and 350 F.

SHARPE MIXERS

www.sharpemixers.com • 206-767-5660

NEW MIXER OPERATES TWICE AS FAST

The latest Silverson Flashmix powder/liquid mixer is now two times faster. Large volumes of powder are dispersed and hydrated, agglomerate-free at a rate of up to 500 lbs./min. New technology allows it to bring the benefits of high shear mixing to new applications. The Flashmix can be used at higher temperatures and with higher viscosity mixes than was previously possible, the company says. Unlike most powder/liquid mixers, which use a vacuum to pull in powders, the Flashmix literally forces powder into the liquid stream — without a vacuum. Because of its modular construction, it can be customized to handle many applications and batch sizes.



SILVERSON

www.silverson.com • 413-525-4825

Pharmaceutical MANUFACTURING

CUSTOM REPRINTS

Custom reprint products of articles and features from *Pharmaceutical Manufacturing* create powerful marketing tools that serve as instantly credible endorsements.

LET YOUR POSITIVE EXPOSURE STAND OUT.

Reprints are a simple way to put information directly into the hands of your target audience. Having been featured in a well-respected publication adds the credibility of a third-party endorsement to your message.

REPRINTS ARE IDEAL FOR:

- New Product Announcements
- Sales Aid For Your Field Force
- PR Materials & Media Kits
- Direct Mail Enclosures
- Customer & Prospect Communications/Presentations
- Trade Shows/Promotional Events
- Conferences & Speaking Engagements
- Recruitment & Training Packages

For additional information, please contact Foster Printing Service, the official reprint provider for *Pharmaceutical Manufacturing*.

Call 866.879.9144 or sales@fosterprinting.com

FOSTER PRINTING SERVICE

FOR ADVERTISING SALES OR PRODUCTION INFORMATION, CONTACT THE FOLLOWING

FOR SUBSCRIPTION INFORMATION CALL
888-644-1803 or 847-559-7360

SALES

MARK WIEBUSCH — **PUBLISHER**
mwiebusch@putman.net

JIM BAKER — **SENIOR ACCOUNT MANAGER, EASTERN REGION**
jbaker@putman.net

GREG ZAMIN — **REGIONAL SALES MANAGER**
gzamin@putman.net

POLLY DICKSON — **CLASSIFIED SALES/ ACCOUNT MANAGER**
pdickson@putman.net

HILLARY FREELEY — **CLIENT SUCCESS MANAGER**
hfreeley@putman.net

CARMELA KAPPEL — **ADVERTISING COORDINATOR**
ckappel@putman.net

JILL KALETHA — **REPRINT MARKETING MANAGER, FOSTER REPRINTS**
jillk@fosterprinting.com
866-879-9144 ext. 168

PRODUCTION

RITA FITZGERALD — **PRODUCTION MANAGER**
rfitzgerald@putman.net
630-467-1300, ext. 468

ADMINISTRATION

CARMELA KAPPEL — **ASSISTANT TO THE PUBLISHER**
ckappel@putman.net
630-467-1300, ext. 314

ADVERTISER INDEX

As a service to our readers, *Pharmaceutical Manufacturing* publishes an advertiser directory. Every effort has been made to be accurate in this listing. However, the publisher assumes no responsibility or liability for errors or omissions in the ad index.

EQUIPMENT & CUSTOM SERVIVES

What's New in Dosage Form Analysis?

Or, what have we forgotten?

BY EMIL W. CIURCZAK, CONTRIBUTING EDITOR

WHEN I was teaching, one of the questions that used to drive me crazy was, "We learned this last year; do we still need to know it?" I assured students that science lives on "remembering" what the current ideas were based upon. Hopefully this column will help answer that question.

For some time, I have been talking about continuous manufacturing (CM) as the "next great step" in solid dosage form production. But there are other tools that make the CM process more effective. Some of the ideas were covered previously (re: the work at Rutgers to characterize raw materials), but some other techniques are either new, updated, or have merely been forgotten in the rush to perform process QbD.

One tool is an NIR imaging system by Middleton Labs that "sees" through the base of a blender (as it spins), qualifying a mixture in real time. The system produces images (hyperspectral picture), calculating the homogeneity and agglomeration in real time. They offer the sisuCHEMA as a NIR Chemical Imager, using a short wave IR camera (384 pixels x 288 spectral bands). At 400 frames/s, it is mounted on a scanner with a line illumination system. It is a tool for formulators and OOS investigators to scan a tablet, determining API and/or excipient distribution or to scan blister packs for continuity, production or clinical tablets.

Another (Middleton) tool for lab work is in fluorescence: the macroPhor combines (pushbroom) hyperspectral and fluorescence imaging. The software generates a spectrum at any pixel in the 2D image while the optics are optimized for macro-sized samples. Using an excitation of 488nm, the instrument captures fluorescence spectra from 500-800nm. The sample stage holds petri dishes, well plates or solid samples, placed on the stage, allowing API and excipients to be determined.

TeraHertz has grown from a curiosity to a nice tool in recent years. It is applied in monitoring roller-compacted ribbons (density, thickness, API distribution), following tablet coating, and a diagnostic tool for coating integrity (adherence, cracking). In-process is good, but don't forget the scale up and diagnostic applications. With LASERs and computers, these "new" techniques are becoming workhorses. The technology is used to measure physical parameters; it may be used where NIR or Raman is now utilized in RMID.

This revolution carries over into Raman, demonstrated by Timegate instruments. Timegate's pulsed LASER, followed by a gated detector, allows the investigator to use a shorter (visible) wavelength LASER while blocking the resultant fluorescence, which normally could swamp a Raman signal. Quite good for biopharma applications (since Raman is not bothered by water), it is also a nice tool for powder blends and tablets (and capsules).

LET'S NOT RETURN TO THE "GOOD OLD DAYS," BUT RATHER INCLUDE THE NEWER **STAND-ALONE TECHNOLOGIES.**

A rapid way of gleaning information of a tablet's interior is via a nice, new Raman-based device that can generate a 3-D picture of a solid dosage form (H2Optix). It slices layers from a tablet, scans the new surface, images it, and proceeds slicing and scanning the entire dose. This generates an internal structure of the tablet, showing the distribution of APIs and excipients. Named the "Pillerator," it can provide automated sectioning of 5–1000 µm layers of solid dosage formulations and generate hyperspectral scans of each layer, building a computer model, or 3-D chemical map and structural analysis of a tablet or other solid analyte.

It may be used to characterize solid dosage formulations for API distribution uniformity and/or aggregation and quantify the API and/or other individual component concentrations down to 0.001% by weight. It can also estimate the particle size distribution by component, as well as perform a nearest-neighbor, long-scale correlation, and coverage percentage analysis. It is also a decent tool for prediction of dissolution profile from the solid form.

In short, what I am espousing is not returning to the "good old days," but rather including the newer stand-alone technologies ("stand-alone" meaning not included as "in-process" monitors). I am excited about process monitors and continuous processing, but it is equally important to continue looking for new lab/pilot plant technologies that add to our knowledge of the materials that go into the process stream.

What's old is new again.

EXPERIENCE SCIENCE THROUGH COMMERCIALIZATION

Courtesy of Fette Compacting

> INTERPHEX gave us an opportunity to meet with many of our pharmaceutical clients in one location, saving us four weeks of travel time. INTERPHEX continues to be the best and most important conference in North America for pharmaceutical manufacturing.
>
> *- Sterling Kline, Vice President, IPS Integrated Project Services*

INTERPHEX

April 26-28, 2016
Javits Center | New York City

MORE Innovation & Technologies State-Of-The Art Technologies Launches
MORE Free Full Product Life Cycle Technical Education led by PDA

- Learn It, Experience It with PDA Education @INTERPHEX
- INTERPHEX Live: Valuable Insight from Industry Experts
- Keynote Series @INTERPHEX
- SKAN Engineering Olympics
- CRB Tech Tank
- DME Facility Focus
- IPS Technologies Tours

FREE CONCERT:
RIGHT TURN AT 40

ALL OF THE SOLUTIONS YOU NEED TO COST EFFECTIVELY DEVELOP & MANUFACTURE PRODUCT

Register for your FREE Technical Conference and Exhibit Hall Pass at: www.interphex.com/PUTMAN

Collaboration.

Reliability.

ANGUS LIFE SCIENCES

Dedicated to what matters.

Traceability.

Quality.

The work we do together at ANGUS Life Sciences stems from a 70-year legacy as your primary source of specialized chemistries, like our TRIS AMINO®. We are also your reliable provider of quality buffers, biomolecules and biochemicals.

ANGUS Life Sciences brings a strong commitment to meeting your pharmaceutical and biotechnology needs. Our dedication to providing the best products for R&D, scale-up and production is more than just an ongoing commitment at ANGUS Life Sciences.

It's what we do.

WE MAKE THE BEST PERFORM BETTER.

angus.com