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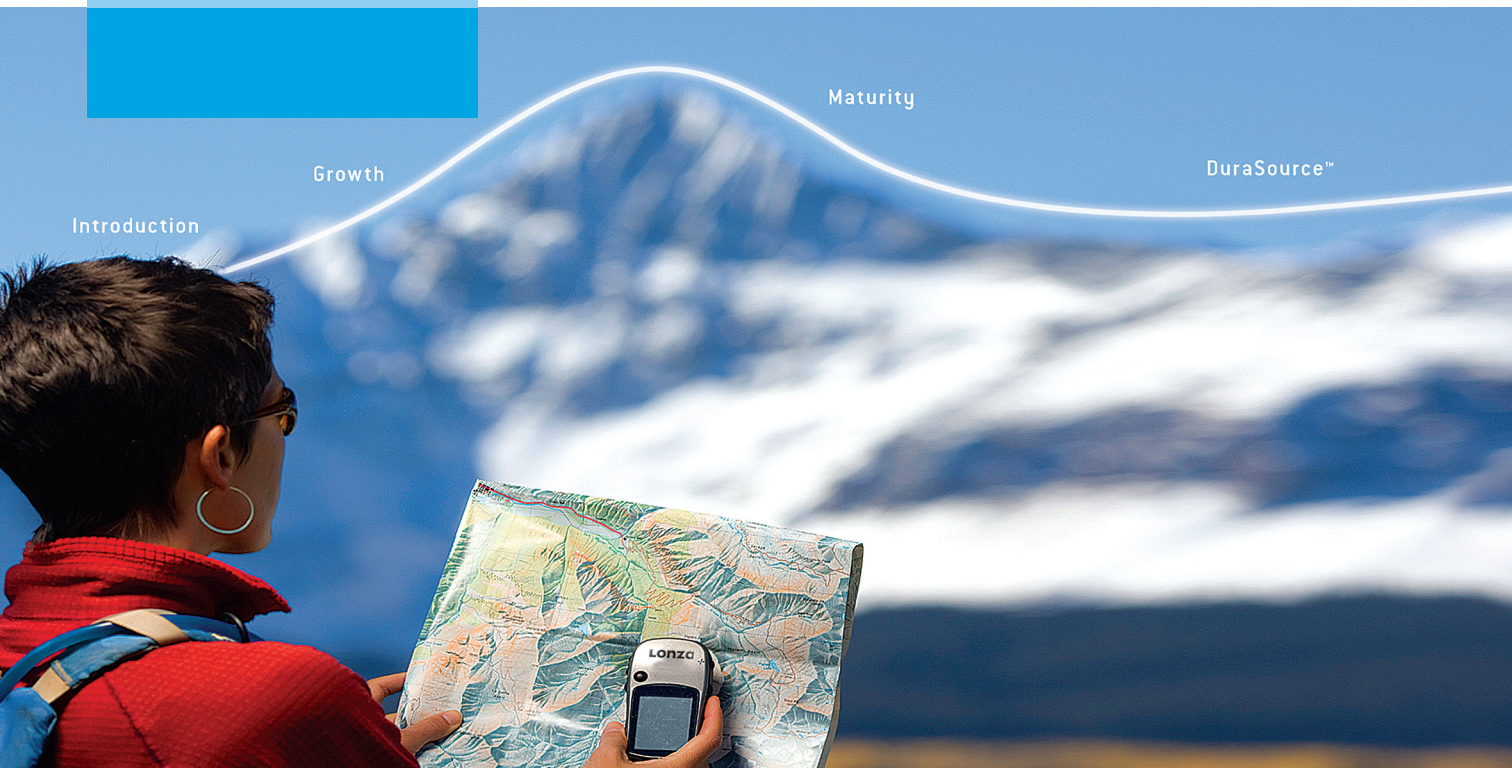

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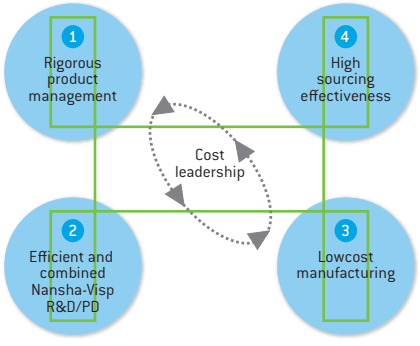

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A Gift Indeed

Thank you Pharma for making the holiday season brighter for everyone

OVER THE Thanksgiving holiday my family had an encounter with a new (to us) pharmaceutical. You see, my mother has COPD, complicated by emphysema, bronchitis and asthma — the result of years of smoking. After about two years of witnessing less-than-promised symptomatic relief from the other most commonly prescribed inhalable COPD therapy, I convinced my Mom to ask her doctor about switching to one of the newer alternatives — something that wasn't as straightforward as it might seem. My Mom comes from an era where the physician's medical opinion is sacrosanct, not to be questioned. However, after much prompting from me, she finally asked the doctor if she could try something different: "One of the new one's my son keeps talking about," is basically what she said. The doctor nonchalantly agreed and provided her with a prescription to Symbicort, AstraZeneca's well-known, but not-so-new, budesonide/formoteral COPD/asthma treatment.

Long story short, my mother took her first two-puff dose off a very familiar pressurized metered dose inhaler (pMDI) and within about five minutes (as advertised I might add) began experiencing real symptomatic relief for the first time in years. Soon, we were all, literally, breathing easier. The affect was dramatic and within days Mom started feeling better. With increasing confidence, she resumed her normal routines without having to stop every 10 feet to catch her breath. After thanking a higher power I started thinking about who else I might thank for the truly transcendent boost to my mother's quality of life. Naturally, my thoughts turned to the pharmaceutical industry.

So I started doing a little digging. AstraZeneca, of course, deserves great credit, responsible for investing the hundreds of millions of dollars to develop the budesonide/formoteral combo and then winning its regulatory approval in Europe for it in 2000. Eventually (2006) the U.S. Food and Drug Administration approved the pMDI version for Americans. Given that the compounds' efficacy was so overwhelmingly well demonstrated I pondered the significant lag time, but didn't dwell on it for long because I think we all know why. Regardless, knowing the complexities of drug development, supply chain resources and subsequent commercial manufacture, I knew there were many more people to thank for the Kuehn family's holiday "miracle."

But where does one start? AstraZeneca has 65,000 employees, many of whom work at the company's 26 or so manufacturing sites. Granted not all of them make Symbicort, but I thank them nonetheless. Then there's Minakem Group, who acquired AstraZeneca's Dunkirk, France API facility in 2009, bolstering global supply with their operational acumen. In its press announcement Minakem mentioned the long-term contract it signed to manufacture budesonide for AstraZeneca. According to an industry report, a few years prior AstraZeneca invested a bunch of capital ($25 million) to develop the facility's production infrastructure and accomplish the apparently tricky fill and finish processes for Symbicort's pMDIs. Jacobs Engineering was responsible for that project, which also included a clean room environment delivered by Carmetec. Apparently Werum was active in bringing contemporary manufacturing data and operational informatics technologies into the mix as well. More digging revealed that at the heart of it are Pamasol's HCA pMDI filling systems and 3M Drug Delivery's dose counter enabled pMDI devices. I'm not sure who supplied the Turbuhaler devices AstraZeneca innovated with the original approval, but that technology was instrumental to Symbicort's overall popularity and effectiveness. According to AstraZeneca's 2011 Annual report, after FDA approval Symbicort garnered $3.1 billion in sales worldwide, of which $846 million came from the U.S. alone.

ALL OF PHARMA PUT THIS THERAPY INTO MY MOM'S HANDS, AS WELL AS **INTO MILLIONS OF OTHERS.**

Alas, my "Nice" list is likely not complete, but my point is this: Yes, there are plenty of individuals who contributed specifically to bring Symbicort to market and deliver its therapeutic and market success, but in the end, it's all of Pharma who put this therapy into my Mom's hands, as well as into the hands of millions of others struggling just to breath during the holiday season. That is a gift indeed and I'll be forever grateful. Thank you.

STEVEN E. KUEHN, EDITOR IN CHIEF
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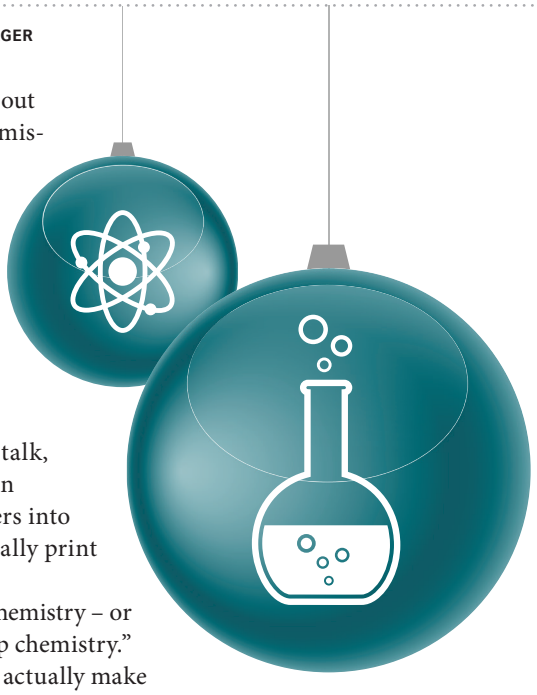
Science Takes Chemistry Sets to the Next Level

BY KAREN LANGHAUSER, DIGITAL CONTENT MANAGER



IN THE mid-1900s (before kids figured out how to use cold meds to make meth) chemistry sets for Christmas were all the rage. Beyond the allure of mixing potentially explosive chemicals in test tubes, these kits inspired generations of kids to get excited about chemistry and perhaps even pursue a future in scientific fields.

As we approach the start of 2015, 3-D printing has collided with drug manufacturing and challenged the idea of traditional chemistry. In a 2012 TED talk, Glasgow University professor Lee Cronin discussed the idea of turning 3-D printers into universal chemistry sets that could actually print their own drugs.

Essentially, Cronin seeks to automate chemistry – or as he has stated in several interviews "app chemistry." Downloadable software could be used to actually make molecules in 3-D printers.

Considering the struggles that come with getting an ordinary office printer to function ("why does it say paper jam when there is no paper jam?") combined with the (probably more important) implications this could have on drug manufacturing as a whole, Cronin's "chemputer" system is intimidating, to say the least…and yet, undeniably cool.

While the far-future end result of the chemputer system could very well be individuals being able to print personalized pharmaceuticals at home, the shorter-term benefits would first involve using the system on a research level, followed by the next step, which would be using the system in local pharmacies. Clearly not without obstacles, but nonetheless a revolutionary idea that could drastically improve collaboration between scientists and drug distribution in many areas of the world.

Along those lines, a team of Louisiana Tech University researchers have developed a way to create an edible capsule using a 3D printer. The capsule could then be loaded with antibiotics or other medicinal compounds and sealed. The long-term implications of such technology would be that pharmacists could tailor the contents or dosage of a drug to meet individual needs.

Much like walking down the stairs on Christmas morning and seeing a tree surrounded by gifts, new technology offers the thrill of endless potential. As 3D printing continues to evolve and its potential role in research and drug manufacturing unwraps itself before our eyes, the bar on traditional chemistry has definitely been raised.

Actavis to Buy Allergan Inc. for $66B

The acquisition will make Actavis among the Top 10 Pharma companies in the world

BY STEVEN E. KUEHN, EDITOR IN CHIEF, AND KATIE WEILER, MANAGING EDITOR

ACTAVIS AND Allergan Inc. have entered into an agreement under which Actavis will acquire Allergan for a combination of $129.22 in cash and 0.3683 Actavis shares for each share of Allergan common stock. Based on the closing price of Actavis shares on Nov. 14, 2014, the transaction was valued at approximately $66 billion.

The combination will create one of the top 10 global pharmaceutical companies by sales revenue, according to an Actavis press release, with combined annual revenues of more than $23 billion anticipated in 2015. The transaction has been approved by the Boards of Directors of Actavis and Allergan, and is supported by the management teams of both companies.

"This acquisition creates the fastest growing and most dynamic growth pharmaceutical company in global healthcare, making us one of the world's top 10 pharmaceutical companies," said Brent Saunders, CEO and president of Actavis. "We will establish an unrivaled foundation for long-term growth, anchored by leading, world-class blockbuster franchises and a premier late-stage pipeline that will accelerate our commitment to build an exceptional, sustainable portfolio. With pro forma revenues in excess of $23 billion anticipated in 2015, this combination doubles the revenue generated by our brands business and doubles the international revenue of the combined company."

"Today's transaction provides Allergan stockholders with substantial and immediate value, as well as the opportunity to participate in the significant upside potential of the combined company," said David E. I. Pyott, chairman and CEO of Allergan. "We are combining with a partner that is ideally suited to realize the full potential inherent in our franchise. Together with Actavis, we are poised to extend the Allergan growth story as part of a larger organization with a broad and balanced portfolio, a meaningful commitment to research and development, a strong pipeline and an unwavering focus on exceeding the expectations of patients and the medical specialists who treat them."

The combined company will be led by Brent Saunders, CEO and president of Actavis, and Paul Bisaro will remain Executive Chairman of the Board. The integration of the two companies will be led by the senior management teams of both companies, with integration planning to begin immediately. Additionally, two members of the Allergan Board of Directors will be invited to join the Actavis Board of Directors following the completion of the transaction.

The growth profile of the combined pharmaceutical business will be unparalleled in the industry with the ability for double-digit revenue and earnings growth while maintaining investments to grow and develop our product portfolios and pipeline, the release said. The addition of Allergan's portfolio, including multiple blockbuster therapeutic franchises, doubles the revenues of Actavis' North American Specialty Brands business.

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COST TO BRING A NEW DRUG TO MARKET IS NOW $2.6B

According to a new study by the Tufts Center for the Study of Drug Development, the estimated cost of developing a new prescription medicine that gains marketing approval is now $2.6 billion. The estimated cost is based on an average out-of-pocket cost of $1.4 billion and time costs of $1.2 billion.

In a study published in 2003, Tufts CSDD estimated the cost per approved new drug to be $802 million (which equates to about 1 billion 2013 dollars), based on average out-of-pocket costs of $403 million and capital costs of $401 million.

"Drug development remains a costly undertaking despite ongoing efforts across the full spectrum of pharmaceutical and biotech companies to rein in growing R&D costs," said Joseph A. DiMasi, director of economic analysis at Tufts CSDD and principal investigator for the study. "Because the R&D process is marked by substantial technical risks, with expenditures incurred for many development projects that fail to result in a marketed product, our estimate links the costs of unsuccessful projects to those that are successful in obtaining marketing approval from regulatory authorities."

According to DiMasi, rising drug development costs have been driven mainly by increases in out-of-pocket costs for individual drugs and higher failure rates for drugs tested in human subjects. Factors that likely have boosted out-of-pocket clinical costs include increased clinical trial complexity, larger clinical trial sizes, higher cost of inputs from the medical sector used for development, greater focus on targeting chronic and degenerative diseases, changes in protocol design to include efforts to gather health technology assessment information, and testing on comparator drugs to accommodate payer demands for comparative effectiveness data.

RESEARCH FIRM ANNOUNCES 100 BEST-SELLING DRUGS

According to an article in Medscape, the cholesterol-lowering drug rosuvastatin (Crestor, AstraZeneca) narrowly beat out the hypothyroid drug levothyroxine (Synthroid, AbbVie) as the most prescribed drug in the United States; and the antipsychotic medication aripiprazole (Abilify, Otsuka Pharmaceutical) remains the best-selling drug, according to a recent report from research firm IMS.

Rosuvastatin reportedly had about 22.3 million prescriptions, followed by levothyroxine, at about 22.3 million prescriptions; proton pump inhibitor esomeprazole (Nexium, AstraZeneca), at about 17.8 million prescriptions; and the asthma medications albuterol (Ventolin HFA, GlaxoSmithKline), at about 17.8 million prescriptions; and fluticasone propionate/salmeterol (Advair Diskus, GlaxoSmithKline), at about 14.5 million prescriptions.

The remaining top 10 most prescribed drugs were the insulin glargine injection (Lantus Solostar, sanofi-aventis), the attention-deficit drug lisdexamfetamine dimesylate (Vyvanse, Shire), the antiepileptic drug pregabalin (Lyrica, Pfizer), the chronic obstructive pulmonary disease medication tiotropium bromide (Spiriva Handihaler, Boehringer Ingelheim Pharmaceuticals), and the antihypertensive drug valsartan (Diovan, Novartis). Read the full article on www.medscape.com.

FUNNY PHARM

"I hear you're looking to hire someone to help with the layoffs."

— Vincent Coca

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

Four Pivotal Steps in Early Stage MDI Formulation

Metered dose inhalers are complex devices; 3M advises a total system approach to optimize its design

BY ALEX SLOWEY, FORMULATION SPECIALIST, 3M DRUG DELIVERY SYSTEMS

PRESSURIZED METERED Dose Inhalers (pMDIs) are complex systems and understood to be technically challenging to develop. In order to successfully formulate a pMDI system, there are many factors that need to be assessed and brought together. The formulator must ensure that the finished product is safe and efficacious for the duration of its shelf life.

A pMDI system is made up of a number of sub-systems, all of which are required to operate with one another to ensure that the finished pMDI product works correctly. To broadly summarize, these sub-systems include the formulation, container closure system, actuator and secondary packaging (Figure 1). The development of pMDIs requires a total system approach to fully design and optimize the production in order for it to meet its stated design requirements.

During critical early-stage development, formulation options are assessed and developed based on a defined, scientific approach. The aim is to repeatedly demonstrate, with meaningful analytical methods, that the formulation is capable of meeting the required product performance criteria. In light of the range of components within a pMDI system that can, and should be optimized and understood (see sidebar, page 14), the following offers an overview of some of the generic activities required to perform early phase formulation and optimization of a robust pharmaceutical pMDI system.

STAGE ONE

Project Preparation and Scoping: During this initial stage, all supplied and public domain information is reviewed. An assessment of project risks is also initiated. This should ensure that all prioritized factors are included in the work plan.

In scoping a project, it is vital that all factors within the plan are considered, even if only a subset may require further investigation. A record of this decision should be kept to help inform any future investigation requirements.

STAGE TWO

Pre-Formulation: During this stage, the API should be characterized. This will involve understanding the key solid-state and physical properties that influence pMDIs. These factors may include polymorphic form, amorphous content, purity and hygroscopicity.

In the first instance, the above factors should be assessed thoroughly at the onset of the project and re-assessed at key times as the project progresses — for example, following particle engineering. Alternatively, specific studies could be performed to investigate the effect of different factors on the above.

Similarly, excipient characterization should be performed on potential excipient options, although it is generally assumed that data may be transferred between projects for common excipients. If a study is required, then tests similar to those performed during Active Pharmaceutical Ingredient (API) characterization should be investigated.

PARTICLE SIZE REDUCTION

Particle size reduction should be undertaken for systems that are likely to necessitate formulation as a suspension product. Note that engineering trials will not be required if a solution formulation route is indicated by an initial theoretical assessment of solubility or solubility study. The aim of a particle engineering study is to identify a suitable process and optimize critical controls for producing size-reduced material. Once a suitable method of particle size reduction has been identified theoretically, a study will typically be performed to establish an operating window and will be based on a Design of Experiment (DoE) type approach. The purpose of this initial study is to generate early data and to allow initial lots to be manufactured.

For the purpose of this article, let us assume that particle engineering is based on jet micronization or spray drying. If adopting a jet micronization process, experimental factors may include product feed rate, ring pressure and Vecturi pressure. If adopting a spray drying process, experimental factors may include product feed rate, aspirator speed and inlet temperature. In each case, parameters will be optimized for Particle Size Distribution (PSD) and yield.

An experimental design, based on a full-factorial design with center points may be utilized. Responses may include:

- PSD by laser diffraction
- Polymorph assessment
- Assessment of change from Input Raw Material (IRM)

The experimental output should identify a suitable process to produce particle size reduced material in the

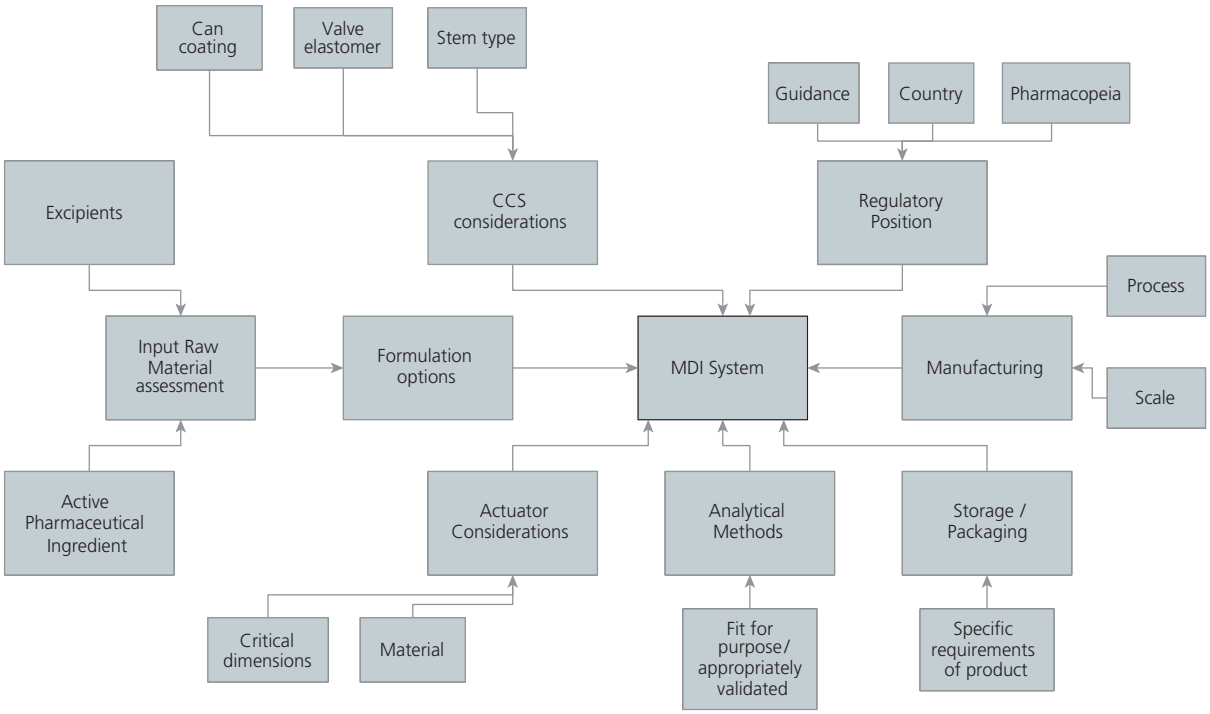

Figure 1: Overview of pMDI input factors.

appropriate PSD. It may be desirable to take two or more options forward into further experimental testing; for example, to allow optimization of the Aerodynamic Particle Size Distribution (APSD) to be performed.

SOLUBILITY, GROSS CHEMICAL COMPATIBILITY

Pre-formulation activities will be completed by performing a study to determine the solubility of the API in potential HFA-based systems and to assess the potential for formulation of a suspension or solution-based system. Dependant on the API, it may also be necessary to assess the level of solubility in co-solvent only. Additionally, this study should provide an early indication of solubility-related effects for suspensions, such as Ostwald ripening. This assessment will typically include all propellant options (e.g., Propellant 134a and Propellant 227).

Solubility should be determined at a range of expected operating temperatures of the formulation. For example, cold fill temperature (-60°C), room temperature and 40°C, to understand whether there is potential for manufacturing issues, or else potential for solubility-related issues during storage. In addition, further units may be prepared and stored under stressed conditions (typically 40°C/75% RH) for a minimum of four weeks. The aim of this is to determine any gross drops in content assay, or increase in impurities (if a suitable imps method is available at this initial stage), indicating degradation effects. Ideally, this solubility study should identify a lead propellant on which to base the next stages of the feasibility program.

In summary, the aims of the solubility and initial compatibility study are to identify the solubility of the API in a range of solvent or propellant systems, determine whether a solution or suspension approach is most applicable, and assess the gross formulation compatibility.

STAGE THREE

Formulation (Compatibility System DoE): The majority of formulation activities, including the justification of potential formulations for progressing to later development stages, will be assessed by performing a limited compatibility DoE. This will also include additional systems being tested at centerpoints of the study design with the aim of reducing testing requirements to a manageable level.

With the aim of determining a suitable pMDI system, a limited half to full factorial DoE may be performed focusing mainly on the numeric formulation variables. These variables can include, but are not limited to, co-solvent level, additional excipient level (e.g., surfactant). If

SPECIFIC AREAS FOR OPTIMIZATION DURING A DEVELOPMENT PROGRAM

RAW MATERIAL – ACTIVE PHARMACEUTICAL INGREDIENT (API)

- Solid-state and other key physical properties
- Polymorphic nature of the API and changes of morphology on storage
- Particle size reduction of the API and method of size reduction (if required)
- The physical stability of the API
- This will necessitate assessment when stored as a raw material and when formulated in propellant
- Solid-state changes
- Understanding API particle size changes in the formulation during storage
- Understanding material chemistry

RAW MATERIAL – EXCIPIENT

- Propellant level / mix (density / hygroscopicity)
- Excipient grade / quality (age, moisture content, solubility)
- Levels of excipients (co-solvents or surfactants) required to produce a robust pMDI formulation
- Impurity / compatibility profiles
- Chemical / physical interactions with API

CONTAINER CLOSURE SYSTEM (CCS) – CAN

- Physical performance characteristics of the can, for example, the propensity for deposition of the API onto the can surface
- Understanding potential beneficial effects of can coatings on API degradation and in relation to impurities, extractables and leachables

required, other factors such as API size reduced material may also be included. At this stage, categorical variables, such as valve type or can coating, may also be included. Testing will include all factors as previously discussed.

As a result of structuring the experiment this way, a test such as APSD, which is labor intensive, could be included on one or both legs of the study, allowing an assessment to be made with respect to the propensity for Ostwald Ripening, without losing the power of the experiment by testing all points. In addition, further system options, which in theory should have a lesser effect on the pharmaceutical performance, would be manufactured to correspond with the DoE centerpoints. Factors could include, for example, elastomer type, valve stem construction and secondary packaging.

This approach would then allow a response surface to be estimated in terms of the main DoE factors, with the possibility to compare the other factors to the DoE centerpoints via use of statistical tools such as an ANOVA or T-test. Further units could be manufactured to allow additional testing to be performed if required.

The advantage of this approach is that it will be possible to perform a robust experiment with limited testing, particularly where tests are labor intensive (e.g., APSD), yet at the same time keep the power of the DoE sections of the study. The study, therefore, aims to allow understanding of potential excipient combinations to progress to later development stages based on the Product Definition. Specific areas of understanding include:

1. Interactions: chemical interactions with API, physical interactions with API and physical interactions with CCS
2. The potential design space window
3. Identification of suitable systems to progress to an informal (short-term) stability

In terms of structure, a compatibility DoE may be based on a full factorial with centerpoints. Experimental factors may include:

- Co-solvent level – x to y% (levels to be defined after solubility testing around solubility co-solvent level)
- Surfactant level a to b% (levels to be defined)
- The effect of different can coating as categorical factor

Additionally, other excipients and propellants may be included, as can additional factors to be investigated at the centerpoint of the DoE only. For example, additional valve options, additional coatings or the effect of foil overwrap and desiccation.

Manufactured units are to be tested initially and following a period of accelerated storage, for example, 40°C/75% RH for six weeks. Testing should include critical performance indicators. These are likely to include APSD of the emitted plume, drug content and impurities. Other responses can be assessed as required. The DoE is designed to provide as output a response surface model of potential system parameters. This will give an early understanding of the system design space with the identification of three to five potential systems to manufacture for a short-term stability assessment of up to six months.

STAGE FOUR

Short Term Stability: Once this stage has been reached, three to five potential systems should have been identified. Batches of approximately 500 units can then be manufactured at a suitable small manufacturing scale, and placed in stability storage chambers for a period of

CCS – VALVE

- Materials of construction, for example plastic versus metal valve, stem or elastomer seal type
- Physical valve dimensions
- Processing parameters during manufacture, for example, crimp dimensions
- Confirmation of the need for, and the optimal type of coating
- Interaction of the formulation on the valve

ACTUATOR

- Jet length
- Orifice size
- Droplet size
- Coatings

SECONDARY PACKAGING

- The requirement for secondary packaging will vary from product to product, although consideration should be built into all new projects at the start. Areas for understanding and optimization include:
- Prevention of known hygroscopicity issues of a particular formulation type
- Prevention of moisture induced physical and chemical degradation of sensitive APIs

MANUFACTURING

- The manufacturing process should be optimized for each product to ensure that product quality is maintained. Generally speaking, this should be based on the commercial scale filling lines on which the final product is to be manufactured

time. The aim of this study is to understand how the three to five systems identified during previous stages perform pharmaceutically on short-term stability and to allow further understanding and definition of the product performance to be assessed.

Stability storage will allow the generation of stability indicating data. The overall aim of this study is to identify two to three suitable systems that may be progressed into further development, including toxicological and human studies. As this study leg is designed to provide stability indicating data with respect to the pharmaceutical performance of a system, the following responses should be investigated:

- APSD
- Content assay
- Impurity level
- Dose content uniformity (DCU)
- Moisture content
- Laser diffraction of emitted plume
- Monitoring of physical properties of API on stability (e.g. polymorphic form)
- Other appropriate testing

Following manufacture and suitable release testing, units will be placed on stability for up to six months. The primary test conditions will be 40°C/75% RH and 25°C/60% RH. Additional units will be placed at appropriate backup conditions. These backup conditions will be based on ICH guidelines and relate to the likely marketing territories. Units may also be placed at a cycling storage condition (i.e. 4°C/40°C at 4 cycles per 24 hours) if deemed appropriate to assess the propensity for solubility related physical incompatibility effects such as Ostwald Ripening.

Consideration should be given to whether a sample or all samples should be foil pouched to further limit moisture ingress on stability. If required, the use of a desiccant within the foil pouch should be included at this point.

The output from this study will provide an understanding of product performance on stability, which will give an initial indication of the potential product shelf life. Assuming the systems perform acceptably during this stage, the aim is to identify two to three lead systems that may be progressed into later development.

Once formulation options have been developed, the product is ready to progress through several more steps. First, the selection of the best product configuration(s) for Phase One and Proof-of-Concept clinical activities, should be based on a thorough understanding of the product performance versus requirements. This involves defining and optimizing the design space, understanding critical parameters and establishing acceptable working ranges. In parallel, methods should be appropriately validated and specifications determined in preparation for a regulatory submission. Secondly, clinical & stability data is generated to further define the product design space in preparation for later development and product registration. And finally, the development of a robust product and manufacturing process, performing Development Pharmaceutics studies and the supply of Ph II / III clinical material.

pMDIs are complex systems and development of a suitable commercialized product remains a technical challenge. However, with a structured approach, the development of a robust, pMDI-based system that meets requirements from a CMC regulatory standpoint is attainable.

SOLID DOSE REALITIES: Reaching

Real-time characterization of Oral Solid Dose formulation in process and nearly prescient control are doing great things for both batch and continuous drug manufacturing

By Steven E. Kuehn, Editor in Chief

WHILE BIOPHARMA'S parenterals may be the belle of the ball lately, Oral Solid Dose's (OSD) dance card remains booked — the form of choice for thousands of medicines and billions of patients. Far from the dowdy, aging wall flower one might expect from such a mature segment, in reality some of the most exciting technological advancements in Pharma processing are occurring right now as Branded, Generic and CMO players reach out for more speed, more capacity and quality in solid dose cGMP operations.

It's always worth a moment to take a quick look at the category as a whole, just to calibrate on how important the OSD form is to the Pharma universe. With the exception of one product (Lantus), OSDs represent most prescribed medications. According to IMS Health, Synthroid (levothyroxine), with 22.6 million prescriptions, remains the nation's most-prescribed drug; the antipsychotic Abilify (aripiprazole) at $7.2 billion, has the highest sales (see Table 1). Of the top 10 highest-sales drugs, OSDs lead, garnering $28.5 billion in sales versus $23 billion for liquid injectables.

There's no doubt that contract manufacturing organizations (CMOs) are capitalizing on the continued expansion of the OSD market. In 2014, says Kate Hammeke, director of marketing intelligence at That's Nice, the contract manufacturing market for solid dosage forms is projected to be $19.6 billion, representing 58 percent of the total CMO market, valued at $33.7 billion.

Table 1

Top 10 Prescribed and Highest Sales Pharmaceuticals 2014

The top 10 drugs by number of monthly prescriptions:

1. Synthroid, $22.6 million
2. Crestor, $22.5 million
3. Nexium, $18.6 million
4. Ventolin HFA, $17.5 million
5. Advair Diskus, $15.0 million
6. Diovan, $11.4 million
7. Lantus Solostar, $10.1 million
8. Cymbalta, $10.0 million
9. Vyvanse, $10.0 million
10. Lyrica, $9.6 million

The top 10 drugs by sales are:

1. Abilify, $7.2 billion
2. Humira, $6.3 billion*
3. Nexium, $6.3 billion
4. Crestor, $5.6 billion
5. Enbrel, $5.0 billion*
6. Advair Diskus, $5.0 billion
7. Sovaldi, $4.4 billion
8. Remicade, $4.3 billion*
9. Lantus Solostar, $3.8 billion*
10. Neulasta, $3.6 billion*

*Liquid, parenteral

Source: IMS. The data reflect a rolling 12 months of history (July 2013 - June 2014) on the top 100 drugs by total sales and total prescriptions in the U.S.

for More

"While the market value percentage for solid dose has been drifting downward," says Hammeke, "and likely related to the shift towards biologics — which are more expensive to develop and manufacture — the propensity to outsource oral solid dosage forms continues to grow modestly." Nice Insight's annual survey results indicated that solid dose manufacturing will be outsourced with the greatest frequency (55 percent) followed by injectables (50 percent), semi-solids (44 percent), then specialty dosage forms (42 percent).

Who's outsourcing solid dosage forms? According to Nice Insights, Big Pharma is (60 percent) followed by Biologics (50 percent), Emerging Biotech (70 percent), Emerging Pharma (49 percent) and lastly Specialty Pharma (51 percent). Who's getting the business? Some of the biggest names head the list (See Table 2), many offering margin-enhancing efficiency and expertise to those Big Pharma players looking to get the most bang for their buck out of patent-expired formulations.

Hammeke says those responding reported they would outsource finished dosage forms with a greater frequency than API manufacturing (for both large and small molecule APIs).

"When it comes to outsourcing behaviors," explains Hammeke, "respondents who will contract solid dose manufacturing in 2014 showed a greater likelihood for considering emerging market providers than the general population, with nearly nine out of 10 stating they include CMOs in emerging markets on their shortlists."

She noted that, among cautions expressed by respondents to the Nice Insight study, intellectual property (IP) concerns were a top reason for not considering emerging market providers because this issue corresponds much more strongly to primary manufacturing/API production than secondary manufacturing of dosage forms.

Among the product types, controlled release tablets were of most interest to Nice Insight survey respondents (62 percent), followed by oral disintegrating tablets (56 percent), immediate release filled capsules (55 percent), and immediate release tablets (54 percent). Other types like controlled release capsules, powder-filled capsules and resin or bead-filled capsules followed at 49, 44 and 33 percent, respectively. Study respondents indicated that timed-release technologies, either rapid or delayed were of significant interest, but of most interest were technologies that protected formulations from stomach acids.

"Both outsourcing and offshoring have shown their efficacy in cutting costs for pharma companies when it comes to solid dose manufacturing," says Hammeke. Another potential development to emerge from reducing capital outlay on in-house manufacturing equipment and technologies, says Hammeke, is the shift from tactical relationships for OSD projects toward more strategic, long-term agreements with manufacturers.

REACHING FOR MORE

Everyday, the economics of drug manufacture are growing more complex to manage effectively. If there is one thing for certain, the future health of the industry is resting squarely on the shoulders of its manufacturing operations, and clearly drug makers are striving to get the most out of their production capacity. Drug safety, supply, access, compliance and shareholder return all hinge on getting manufacturing and process operations right for both drug maker and drug owner. Industry behavior reflects how important manufacturing excellence is to business success and is reflected in recent merger and acquisition activity, the development of strategic and long-term manufacturing related partnerships, and strategic investment in new-era manufacturing technologies.

Without being too remedial, the traditional manufacturing oral solid dosage forms is a primarily a physical (not chemical) multi-stage process. This well-established process involves dispensing, milling or sizing particles and blending the formulation's primary ingredients (APIs, excipients). Granulation is another primary step, and both wet granulation and dry granulation are used by manufacturers to prepare the formulation for direct compression into tablets or to fill capsules. Because a variety of processes can be applied to manufacture OSDs, including drying, compaction and coating, there are a number of factors associated with these fundamentals processes that can significantly impact the chosen form's uniformity, stability and bioavailability.

Table 2

Major Oral Solid Dose CMO Players

- AAI/CML
- Aenova
- Aesica
- Catalent
- Corden
- DPT/Confab
- Fareva
- Famar
- Patheon
- Pfizer CentreSource
- Recipharm

REACHING FOR BETTER DATA

Benoit Igne, of Duquesne University (Pittsburgh), discussed in a recent PharmaManufacturing.com spectroscopy webinar, how closer control of the tableting process demands a better understanding of critical process parameters and critical quality attributes. For example, research conducted with Daichi Sankyo Co. at the university determined that one of the critical process parameters included pan rotation speed (the wrong speed could lead to erosion, breakage or winning), batch size, inlet and exhaust air temperature, inlet air volume, spray rate and time. Researchers monitored the coating and drying endpoint temperature, and applied Near Infrared Spectroscopy (NIR) in situ within the pan coater to estimate weight gain, moisture and tablet coater temperature.

Possibly the most common reason that companies fail at generating a Quality by Design (QbD)-based NDA or ANDA for OSDs is that the wrong measurements are "taken at the wrong place at the wrong time," notes contributor Emil Ciurzak, Doramaxx Consulting. "All too often, a given Pharma producer's 'QbD team' depends on classic techniques to build a Design Space," says Ciurzak. "That means those folks may try to determine blend uniformity by stopping the blender and using a sample thief to gather samples or checking content uniformity by assaying 20 tablets with a HPLC." To design good tablet-based drug-delivery systems, notes Ciurzak, manufacturers need to gain a better understanding of what happens in the making of tablets not after-the-fact assays. Says Ciurzak: "Quality by Testing is not QbD."

Because the process of making a tablet is, as mentioned, a physical exercise and not a chemical one, after-the-fact tests like HPLC, hardness, friability and dissolution tell Pharma processors little about how the powder blends, flows, granulates, compresses and is coated. To obtain these data, says Ciurzak, in-process monitors are required to provide real insight into the "living process" of solid dosage form manufacture. "This is where PAT comes into

the picture," explains Ciurzak, "before a product goes into production, PAT gives us knowledge and a tool to control the process/product."

Blend uniformity is a legal requirement, and Generic Pharma must, by law, test every batch for uniformity. Ciurzak notes the industry has slowly accepted NIR as a "reasonable" test of uniformity. More than a decade ago Pfizer and Zeiss presented the industry with the first wireless, portable NIR instrument. Now several companies offer these devices and the technology has been accepted by the FDA in NDAs and ANDAs. "The development of blend uniformity by wireless NIR was performed on product with 5-50 percent API content," says Ciurzak, noting, "these levels are also quite within the wheelhouse of Raman instruments and have been the standard range of APIs for decades."

LIF FOR LOW LEVEL API

With more potent drugs being developed and tested, the API level in the mix is often below 1 percent, making NIR or Raman detection (in a moving bed) problematic. A better technology for low-level API concentrations is Light-Induced Fluorescence (LIF). Until recently, LIF units had only a single wavelength operational range and induced most organic molecules fluoresce (to varying degrees). There were some specificity questions that slowed its acceptance. Tunable, multiple wavelengths and wireless operation are now available with newer units. These developments allow the formulator/operator to tune the incident light to the excitation wavelength of a low-level API, a lubricant or other organic ingredients in the mix. "Because not all ingredients mix at the same speed, notes Ciurzak, "this specificity allows any or all components to be monitored for completeness of blend."

Powder Rheometers provide another way to measuring powder characteristics after mixing. The Pharma industry has been testing liquid viscosities for decades with similar devices, but now the technology exists where line managers can test the interactions between particles in a powder mixture. There are systems available now that combine shear, bulk, dynamic and axial powder testing methodologies for comprehensive powder characterization. Such information can deliver insight into parameters including flowability, compressibility and correlated to dissolution characteristics.

TO THE CORE

For some OSD manufacturers, testing tablet cores prior to coating may be prudent to explore and understand the characteristics of a number of critical parameters including: hardness, friability and tensile strength for example. Ultrasonic devices are now available to non-destructively measure parameters like the tensile strength of a finished tablet. The speed with which the sound travels through the tablet is measured and correlated with standard (destructive) testing technologies and the curve generated can be used to analyze process samples more rapidly. These data can be used to quickly predict physical parameters and allow formulators to understand what component ratio changes or compression changes are doing to the finished dosage form.

According to Ciurzak, unless direct compression, ribbon compaction, or extrusion techniques are employed, the most likely method of preparing the powder blend for compression is wet granulation. "Despite what some may think," Ciurzak says, "wet granulation is not just a matter of pouring a given amount of liquid into a vat of pre-blended powders. Liquid needs to be added in a specific manner, at a specific rate, and usually from a specific position in the blender. Knowing what the manner, rate and positions are is the trick to a successful granulation."

Wet granulation is not just a matter of pouring a given amount of liquid into a vat of pre-blended powders.

One way of measuring how a liquid disperses through a medium (powdered or another liquid) is tomography. A series of transducers is placed around a mixing chamber (glass or metal); by measuring such things as dielectric constant changes (varying permittivity), the differences throughout a mix can be visualized in real time. The multiple transducers deployed by these systems allow a 3-D picture to be displayed in real time. Using these data, mixing speeds, fill levels, blade type, addition speeds and points of addition may be optimized.

Coatings provide a number of positive attributes including stability, swallowability and cosmetic branding and identity. Coatings are also more technical in nature — now used to protect APIs and the physical make-up of the core, affect or control dissolution times and contain an active ingredient outside the core — thus they need to be accurately measured and controlled. The industry's been using NIR in the coating pan for years to measure the amount of coatings and loss of solvents. In recent years, Pharma has seen Raman probes added to the

coating control toolbox. The data generated from NIR and Raman probes has been used to determine a number of things including spray radius, solution addition speed, drying times, pan rotation speeds and exhaust functionality.

For understanding individual coating integrity, TeraHertz spectroscopy technology is a method worth exploring. Formerly known as "far infrared," TeraHertz has been available for years and Ciurzak notes it may be used as simple spectroscopy but, in his opinion, its strength is in measuring interfaces between layers.

Of course there are numerous tools for fine-tuning dosage forms as part of a successful QbD program for OSDs. These and other technologies are maturing and becoming even more competitively priced and worth careful appraisal.

If you ask Sarang Oka and Fernando Muzzio, from the Department of Chemical and Biochemical Engineering at Rutgers University, the advantages of continuous manufacturing over batch manufacturing are well established. When properly implemented, they say, continuous processes are almost completely steady, can be designed at scale, and can be used reliably to minimize segregation and agglomeration of ingredients. Oka and Muzzio also maintain that continuous process is also the perfect platform for implementing PAT methods because the technology is necessary to ensure closed-loop control of continuous processes.

Continuous manufacturing's business case is equally strong. In development, continuous manufacturing systems allow OSD manufacturers to perform complex DOE matrices in a few days using a tiny fraction of the material normally required to perform comparable studies in batch mode, enabling significant savings in labor, analytical costs and capital outlays. In his company blog, Emerson's Jonathan Lustri explains that in light of all the market and competitive forces at work, in order for the industry to maintain profitability it has to increase its manufacturing excellence. For many OSD manufacturers, the best route to Pharma's manufacturing renaissance is on the continuous manufacturing road. "The financial

driver for the move to continuous manufacturing," says Lustri, "is the significant reduction in capital and operating costs." Rule of thumb metrics put typical batch process capacity utilization at about 35 percent. On the other hand, says Lustri, continuous process can achieve a capacity utilization rate of more than 80 percent. One study by the University of Cambridge illuminated other benefits for OSD manufacturers adopting CM for high capacity production:

- Plant footprint reduction by 70 percent;
- CapEx reduction by 25 percent;
- Operating cost reduction by 30 percent;
- Yield improvement by 10 percent;
- More consistent quality; more controllable, repeatable processes.

For sustainability fans, Cambridge's researchers also noted that adopting CM can reduce carbon emissions by 50 percent.

However, most of what is in the public record does not seem to point to the industry moving en-masse in any hurry toward CM process for OSD manufacture. However the industry's technology suppliers are increasingly confident that the shift is occurring and that its general adoption is inevitable.

GEA Pharma Systems Kris Schoeters noted that continuous processing techniques are not as uncommon in the pharmaceutical industry as everyone seems to think. Schoeter believes there are a number of reasons why the industry has been quite slow to adopt the technology:

- General concerns about start-up and shutdown and waste related to these phases.
- Perception on limited use, for example, that it is only suitable for large volumes.
- Regulatory concerns.
- Installed base of existing (older) equipment in many companies, causing them to question why they should change.

He asserted, though, that the abovementioned concerns are not an issue with certain continuous processing technologies and that switching from traditional processes in general does not lead to a big regulatory impact.

In a recent Pharmaceutical Engineering contribution, Hector T. Davila, director Process/Specialty Engineering, Fluor Engineering explained that firms that act as an integrator of owners' requirements, production constraints, business and capital objectives, find that a stochastic view of the implementation of a continuous process is an effective approach. He said these companies, including Fluor, have a distinct opportunity to look both at the micro and macro of the Integration process. In his article he offered some general observations on the state of development of continuous oral solid dosage manufacture:

- Integration of PAT at critical unit operations is critical to maintain quality and avoid product loss.
- Supplying a continuous process with a large volume of excipients requires more careful logistics planning and control at the warehouse level.
- Use of bulk bags requires modifications to standard warehouse design and planning.
- The overall Continuous Process response to individual unit operations hysteresis is a concern since the available equipment may not deliver proper response and turndown ratios.
- To support quick changeover, it is necessary to determine the application of CIP or dedicated change parts and components.
- Disparity in OSD Continuous Processing can often be traced to Equipment throughput and turndown.
- Equipment processing duration during a production run varies from step to step. The longest duration limits the overall line capacity.
- Pay attention to Transient operations and response to changes.

If recent investments in **developing continuous processes for manufacture of OSD forms** are any indicators, then we are likely to **see rapid change** in this arena.

Rutgers' Oka and Muzzio also are sensing the inevitability of it all as well: "If recent investments by large Pharmaceutical companies in researching and developing continuous processes for manufacture of solid oral dosage forms are any indicators, then we are very likely to see rapid change in this arena, taking much less than 25 years."

Interestingly, say Oka and Muzzio, some of the unit operations that are involved in the process of making tablets and capsules today are intrinsically continuous in nature, namely, milling, spray drying, roller compaction, extrusion, capsule filling tableting and packaging. "This implies that an existing batch process can be transformed into a continuous process with relatively minimal change in most processing steps."

By Mark Hoffman, PE, SSOE Group

CRITICAL SUCCESS FACTORS IN Raw Material Storage & Conveyance

Correct design basis requires deep understanding of raw material characteristics and facility conditions

A WELL-DESIGNED, reliable raw material storage and conveyance environment can make or break a pharmaceutical manufacturing environment. Raw material storage and conveyance is fundamental to quality assurance and profitability. Increasingly, this environment also has become integral to the rigorous regulatory requirements for tracking and tracing products throughout the supply chain. To meet quality and standardization objectives, a design solution must be based on an overview of the entire process from delivery of raw materials to the manufacturing site to delivery of product ingredients to the manufacturing line. The correct design basis is predicated, particularly, on an understanding of raw material characteristics and facility conditions.

DUE DILIGENCE: STARTING A DIALOGUE

The correct design approach is practicing due diligence. Owners and their internal process engineers contribute to a solid basis of design with information about their overall objectives, constraints and future potential changes, as well as knowledge of specific issues associated with raw materials and the facility itself.

Manufacturers and vendors often have detailed information about the properties of the raw materials they supply in material safety data sheets. However, when in doubt about the properties of a raw material, the prudent engineering team always sends out samples for independent testing and verification.

Operations, quality assurance, maintenance and procurement personnel often have valuable insights about their issues, challenges and past experience with raw materials storage and conveyance systems. Experienced engineering teams communicate with them when developing and reviewing the basis of design. In fact, when an engineering team initiates dialogue with all stakeholders, they often gain unique and valuable insights that cannot be obtained in any other way.

For example, talking with operations and maintenance personnel often yields information about subtle operational parameters that can positively influence design, such as how the product is used, handling methods or storage times in intermediate bins or conveyors. There may be variations in environmental conditions that affect the material, or there can be

material properties that affect handling, which may not be included with the supplier's information.

Pragmatic engineering teams ask questions that reveal issues that might not be readily apparent, even to a design engineer. For example, O&M personnel might have noticed bridging or plugging problems that have created unanticipated maintenance or cleaning issues. As a result of this insight, the engineering team would select equipment and design the system to mitigate these issues.

They might have noticed that seals or bearings on rotary airlocks wear out because of the physical environment, causing leakage. As a result of this insight, the engineering team might include an air purge or airlocks in the bearing housing. Or they might report product clogging of the conveying line due to heat build-up in the material storage and conveyance process. In this situation, the engineering team employs air cooling in the conveyance system.

GET TO THE HEART

To get to the heart of these issues, it is essential to uncover memories about issues from months or years in the past. To facilitate the concentration required for this, engineers should interview operations personnel away from their day-to-day activities in a place without distractions, such as a conference room, for an hour or two at a time.

Recounting various design scenarios, the team starts by asking questions about the fundamentals: Quantities of raw material used today, future projections, current supply sources, current conveyance rates and their adequacy, problems in receiving materials, and so forth. Once personnel have answered these fundamental types of questions, the engineering team can go into some of the more obscure issues and problems.

Often, the engineering team can draw out the most valuable insights by asking the conceptual question, "What would you change about this system to make it better?" This question gets at some of the operational problems that are the result of overlooking a key parameter in the original design.

The dialogue should not end with the initial interview process. The engineering team provides and reviews a description of operations so that stakeholders understand how the system is going to work when it is installed and have an opportunity to offer feedback. Their feedback, especially about specific points in the operator-system interface, contributes to refinements in the final design.

This communication process is a wise investment that ultimately saves the owner time, effort and expense because it enables the engineering team to design a system that meets functional objectives with minimal operational and maintenance downtime.

LACTOSE DUMPING
Supersack handling system for bulk dry ingredients.

STORAGE: GOOD DESIGN IS IN THE DETAILS

Understanding raw material characteristics is fundamental to good design in every component of the environment, yet even some experts fail to consider important details. Storage is a crucial aspect of the design.

Sizing and shelf life. The optimal storage container must be large enough to achieve economies of scale, allow easy emptying and refilling, and have surfaces compatible with the characteristics of the raw material. Process design engineers typically account for the basic physical properties of raw materials and the effect on container size, and major equipment, such as blower horsepower, lines and so forth. However, even some experts overlook the impact of a raw material's shelf life on the design of the receiving and storage components. Why design and specify a silo that can handle two truckloads of raw materials if the manufacturing operations will take three months to use it all and the shelf life is only 60 days?

Perhaps a system that is designed for sacks and super-totes would be a better alternative.

Similarly, particle size may be important in the product formulation or final product. In fact, it can be critical where filling or tableting operations require certain particle size ranges for optimal performance in batches. Failing to account for shelf life has an adverse impact on GMP, quality assurance and profitability. This can be problematic if storage time exceeds the supplier's warranty period for product viability. Purchasing large quantities of a material may provide a cost benefit. However, if the batch sizes are small or if the material is a minor ingredient, the material may exceed its shelf life prior to being used.

Material-surface interface. Equally important is the interface between the container's surface and the material inside. Given a corrosive material such as urea, for example, stainless steel would unquestionably make a more durable and cleanable containment surface than fiberglass. Furthermore, using stainless steel may be the most cost-effective choice in the long run. It is far less likely to require replacement if the process will involve a corrosive raw material in the future.

CIP
Product Dryer with CIP

Climate control. The container must be designed around the susceptibility of the raw material to humidity, airborne microbes and extreme temperatures. To prevent a hygroscopic material such as a sugar from absorbing water and clumping or degrading, humidity must be kept low. Temperature control is important for heat-sensitive materials such as glucose, and for materials that are vulnerable to microbes. For example, for storage of soy meal, engineers can use HEPA filtration or UV treatment of the air in the top of the container.

Bin activation and fluidization. Bin activation systems must be configured to match the material's angle of repose, its hygroscopic parameters, and particle size, all of which are related to flow. While some raw materials flow easily out of a cone bottom, others tend to bridge and obstruct free flow. With a hygroscopic material, for example, the storage container can be designed with an envelope dehumidification system and air pads on the container bottom to facilitate flow. Some materials require bin activation using a vibratory or a screw conveyor. However, if the system is hard to clean, the raw material may build up, especially at transition points. In that case, fluidizing may be a better solution, and a fluidizing disk that is compact, self-cleaning and economical is the best choice.

Conveyance in and out of the container. The conveyance of the raw material into and out of the storage is another crucial step. Pneumatic conveyance is a common solution; however, it can be problematic if the raw material is subject to molecular decomposition or other damaging transformation because it can abrade or heat the material. In these cases, the design solution must ensure that conveyor velocity is not too high, and that appropriate piping components are used, including correct tube size and material, and that cooling heat exchangers are employed in the conveying air stream.

Construction materials and accessibility for cleaning. The materials of construction and access are major design factors in assuring a clean storage and handling system. A clean system is critically important in pharmaceutical manufacturing to assure product quality and safety. A clean system also protects the flow of material against clumping or dredging, reducing maintenance downtime. A clean system reduces the need for extra processing steps, such as sterilization, which lowers operating costs

PROJECT: DESIGN FOR HEAT-SENSITIVE, HYGROSCOPIC MATERIALS

SSOE Group designed a raw material storage and conveyance system for a sugar that was heat sensitive, hygroscopic, and created a dust that was explosive under certain conditions. The design addressed these characteristics using dehumidification, conveyance air cooling and explosion suppression. In the wake of its implementation, the following challenges and design insights were revealed:

- **Greatest challenge regarding sugar:** To account for all those parameters and put in the required cooling, explosion suppression, etc., and still make a system that is cleanable and safe for the product.
- **Solution process:** A combination of selecting the right components and designing and specifying the right construction methods.
- **How:** due diligence, especially obtaining the detailed info from the vendors offering the components.
- **Selection criteria:** If there is cooling, is it a heat exchanger; details of fin spacing, depth of coil, and access for cleaning; construction methods and materials of construction. On heat exchangers, for example, there may be components that are not readily accessible for cleaning. Operators might spend a lot of time taking them apart in order to clean them. They are fine in some applications, but not in a GMP application.
- **Potentially overlooked detail:** There are many components that work in other industries, other applications, but might not be the best choices for a pharmaceutical client.
- **Critical success factors:** The materials of construction and access for cleaning were the two main factors.

and ensures quality. For example, many manufacturers will heat a slurry to sterilize it before adding it to their fermenter as a hedge against contamination in unreliable storage conditions.

With cleaning issues in mind, the prudent engineering team typically specifies stainless-steel materials with an 80-grit or better surface finish without crevices or corners where the product could collect. An effective design solution streamlines the container and conveyance system to eliminate or limit transition points and designs remaining transition points with maximum bending radii to allow a free flow of material. The construction methods should also allow operators to take apart and reassemble components as quickly as possible — with minimal tools — to reduce operational downtime. The subtleties of the operation cannot be overlooked in the design, such as the amount of time the material is stored in intermediate bins or conveyors.

FACILITY CONDITIONS: EVERY PLANT UNIQUE

Specific facility conditions affect the design of a raw material and handling system significantly. A facility assessment and dialogue with stakeholders are essential to develop this understanding. Key parameters include the following:

Level of automation. One of the critical success factors in the design is matching the plant's level of automation. It may be desirable to totally automate a process to reduce operating expenses; however, it is capital intensive. Also, the plant maintenance personnel would have to be trained to troubleshoot and repair the system when required.

Material availability. Another factor is the availability of material, including lead time and quantity. Some materials may be available in only small containers, so bulk material handling systems are not an option. Systems need to be designed to handle tote, bulk bags, drums of small bags that are ergonomic, sanitary and cleanable.

A well-designed, reliable raw material storage and conveyance environment is a critical success factor for pharmaceutical manufacturing operations' regulatory compliance, quality assurance and profitability in this highly competitive age. A well-designed, reliable system saves time, effort and expense because it meets performance criteria and functional objectives over its expected lifecycle at the lowest cost.

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INTEGRATED CONTINU

Novel technologies open a new avenue for developing the future of pharmaceutical manufacturing

PHARMACEUTICAL MANUFACTURING has been performed using batch technologies for more than a century. While most other manufacturing industries use continuous operations combined with advanced process control and automation, the pharmaceutical industry has mostly relied on fixed recipes to produce batches. This practice results in very long and expensive processes that have been supported by high gross margins. In contrast, the development of novel manufacturing technologies has the potential to transform the current "batch manufacturing" process into a "novel" integrated continuous manufacturing (ICM) process.

This vision for the future of pharmaceutical manufacturing employs the concepts of continuous flow, end-to-end integration, a systems approach, and an integrated control strategy. The vision was initially validated by a team of researchers at the Novartis-MIT Center for Continuous Manufacturing, who designed and constructed a small-scale prototype system to demonstrate that pharmaceuticals can be produced continuously in a fully integrated manner with automated control. In this way, raw materials can be transformed into finished tablets without interruption (24 hours a day), with the active ingredient being synthesized in situ without isolation. This approach opens a new manufacturing paradigm for the pharmaceutical industry with drugs being delivered to patients much quicker, at significantly reduced cost, and with consistently high quality.

BATCH IS INEFFICIENT

Significant advances in science and technology have opened new avenues toward a first-principles understanding of the pharmaceutical manufacturing processes, whose efficiencies lag behind those of many other industries. A decade ago, pharma companies were challenged by U.S. Food and Drug Administration (FDA) Commissioner Mark McClellan who referred to the science of drug manufacturing as being "behind that of potato chips and soap makers."[1] Unfortunately, there has not been a great deal of improvement so far: The pharmaceutical industry endures losses of ~$50 billion/year in manufacturing costs from inefficient processes.[2] In many cases, pharmaceutical processes lack advanced on-line quality control systems and rely only on numerous off-line material tests. For this reason, regulators have encouraged the industry to embrace concepts such as Quality by Design (QbD) and the use of advanced process analytical technology (PAT) to produce pharmaceuticals with a higher assurance of acceptable quality at the time and place of manufacture.[3]

Many of the issues related to the current inefficiency in drug manufacturing originate from the disconnected nature of the processes the industry employs. Current manufacturing practice consists of a series of lengthy and segmented batch process steps often performed in different facilities around the world including isolation, testing, storage and transportation of the various chemical intermediates, as well as the final active pharmaceutical ingredient (API). The API is then transported elsewhere to be formulated into the final dosage form, packaged and shipped to distributors. Because of this disconnect between API and drug product, there is often limited feedback from downstream operators on the desired API's physico-chemical properties to facilitate its downstream processing. This practice typically leads to a number of "correction steps" that need to be applied to formulate the API into an acceptable dosage form, such as the many APIs that are crystallized as poorly flowable compounds and require micronization and/or granulation before being made into tablets. Also, these series of disconnected

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OUS MANUFACTURING

steps result in large and expensive inventories.[4] Trends in inventory turns are often used as key indicators of improved performance in manufacturing processes and lean management and, unfortunately, in the last decade there have been no significant changes in inventory turns among the top drug companies.[5]

Batch manufacturing introduces a significant lag-time between technical operations such that the cycle time from the start of manufacture to delivery to patients can be as long as 12 months.[6] This practice limits the ability of a manufacturing process to react quickly to changes in demand of a newly launched product or when a large volume of medicine is needed in a relatively short amount of time (such as for flu medicaments). In addition, a recent analysis conducted by the U.S. Government Accountability Office found that the number of critical drug shortages has more than tripled since 2006, especially among cancer drugs and nutritional products, and that these shortages were mainly caused by manufacturing problems, sometimes causing manufacturing shutdowns.[7] A recent example of a manufacturing-limited shortage is doxorubicin (Adriamycin), a cancer drug for children; availability of this drug dropped due to manufacturing lacking the capacity to satisfy increased demand.[8]

The complexity and inefficiency of existing drug manufacturing processes find their roots in the early stages of drug manufacturing process development, where extensive scale-up batches and complex validation procedures are necessary before a new molecular entity can be commercialized, with four major scale-up exercises often being involved (bench, kilo, pilot and commercial). Consequently, clinical trial batches may not be representative of final commercial batches such as for the small molecule drug gabapentin, an anticonvulsant and analgesic, which has been subject to several recalls due to new impurities that appeared after scale-up.[9]

In such cases when the commercial product does not meet specifications, the entire batch must be rejected, which creates a supply problem. Furthermore, the current scenario for quality control during production, which establishes safety and efficacy of a medicament, is not ideal. Drug makers continue to rely mostly on a 'Quality by Testing' (QbT) approach, which involves running a large number of post-processing tests to demonstrate that products meet specifications. Although somewhat reliable, this testing protocol leaves significant opportunities for improvement, as demonstrated by the number of post-approval recalls due to quality issues. This number has not decreased in the last five years (≈ 500/year), 10 with the FDA recording an increase of more than 54% compared to average between second and third quarter of 2011.[11]

NOVEL MANUFACTURING VISION

Although the inefficiency of batch pharmaceutical processes has been well known for decades, the pharmaceutical industry could afford to ignore this inefficiency by focusing their resources on high margin blockbuster drugs. However, the negative forces affecting the pharmaceutical industry today (such as increasing R&D costs, declining new drug approval success rates, major blockbuster drugs going off patent with consequent generic competition, pricing pressure, and introduction of new reimbursement models) make the current manufacturing scenario unsustainable. A transformation of the pharmaceutical development and manufacturing landscape is necessary, and good examples can be found in the oil, gas and food industries that often run their processes in a substantially different way.

While the pharmaceutical industry primarily uses "batch manufacturing," the oil, gas and food industries generally use 'Integrated Continuous Manufacturing' (ICM).[12] In the last five years, the pharmaceutical industry has made some progress in implementing stepwise continuous processes either into their primary manufacturing (APIs only),[13] or secondary manufacturing (final dosage forms),[14] without any efforts to integrate the two.[15] However, recently a team of researchers at Novartis-MIT Center for Continuous Manufacturing demonstrated the concept of ICM for

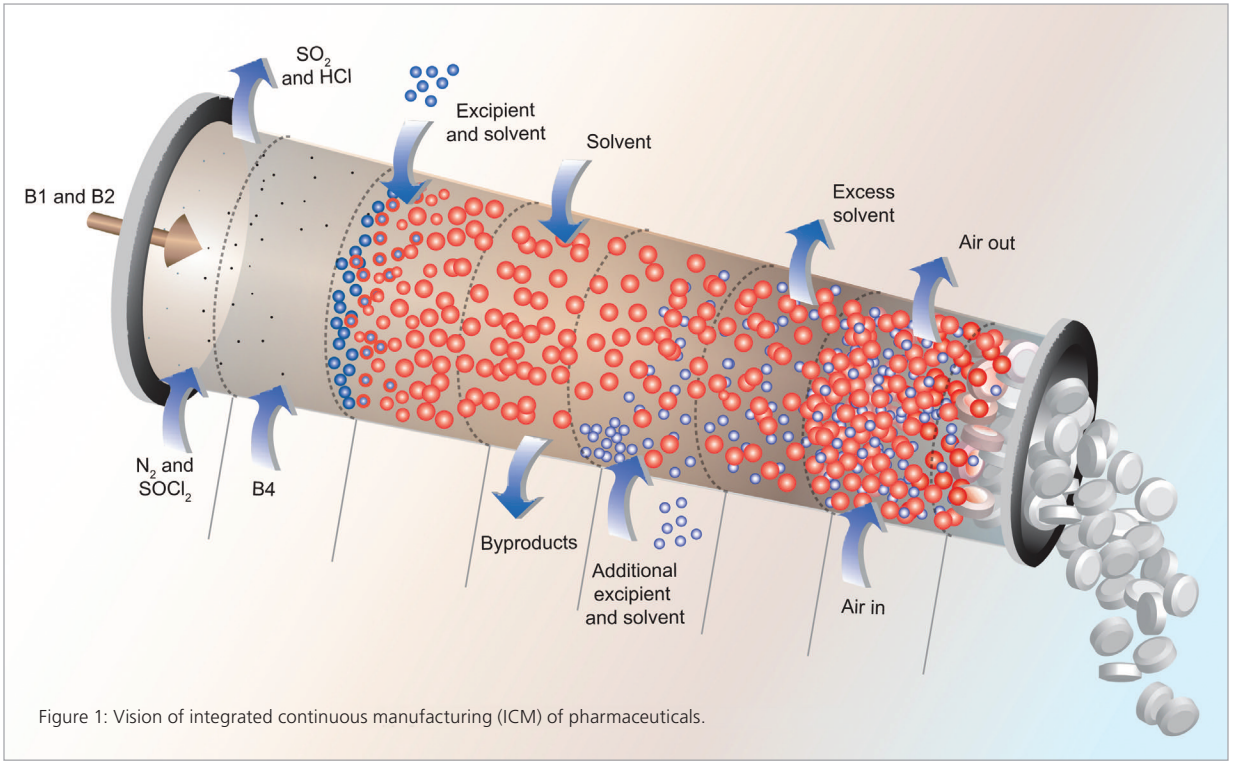

Figure 1: Vision of integrated continuous manufacturing (ICM) of pharmaceuticals.

pharmaceuticals by developing a process that goes from synthesis to pills without pauses.[16] The system consists of developing well-understood, smaller-scale process technologies that can be integrated into a seamless end-to-end manufacturing process for pharmaceuticals. In this way, raw materials can be transformed into finished tablets without interruption (24 hours a day), enhancing the performance of the entire process. This vision of ICM of pharmaceuticals presented in Figure 1 builds on the concepts of continuous flow, end-to-end integration, a systems approach, and an integrated control strategy.

The continuous operation of a particular ICM installation, which can be easily reconfigured, can improve the effective asset utilization (EAU) of pharmaceutical manufacturing processes from the current 30-50%[17] to >85% for a dedicated production line.[18] Furthermore, the opportunity to avoid isolation of intermediates and active ingredients,[19] due to the integrated nature of the plant, translates to minimal work-in-progress inventories and material testing (including testing of the active ingredient), which would only be necessary for the final dosage form.

In addition, ICM can enable drug manufacturing in smaller facilities with integrated development and manufacturing functions[20] and reduced or eliminated product variability associated with scale-up.[9] An FDA approved, 20 m^2 footprint ICM plant could supply approximately 1.5 tons of drug product per year, which would cover the demand for all clinical trial stages in addition to the launch and early commercialization of a small to medium market medicine. Depending on the overall product demand and related economies of scale, pharmaceutical processes could in some cases be simply scaled-out rather than scaled-up. The new ICM plants will be more flexible and able to react more quickly to market changes due to their compact and small-scale characteristics alongside shorter lead time and on-demand production capability. This approach also has important implications during the launch of a new compound where prediction of the actual demand is rarely good.

Economic analyses reported by Schaberet al.[21] on the impact of ICM on the cost of goods sold (COGS) suggest that a small-scale ICM plant will have lower capital and operational expenses by about 30% for the studied case,[21] which can be a conservative estimation given that the analysis was based on a bench-scale demonstration unit that was never optimized for commercial manufacturing. Even with this conservative estimate, the global pharmaceutical market has reached approximately $1 trillion by 2013, meaning that roughly $200 billion/year will be spent in the manufacturing of small molecule drugs;[22] a 30% savings

on the manufacturing of small molecules means that the pharmaceutical industry could potentially reduce its manufacturing costs by about $60 billion/year from transforming their batch operations into ICM.

Finally, the environmental and social impact should be taken into consideration when transformational technologies are introduced into industries with broad societal impact such as pharmaceuticals. We anticipate that integrated continuous manufacturing of pharmaceuticals can reduce waste generation, as reported in many examples of continuous manufacturing,[15] and make pharmaceutical processes safer through confined handing of dangerous chemical reactions and high potency materials. Benyahiaet al.[23] reported a process environmental factor (E-factor) of 15 for an optimized ICM process with use of recycle, which is at the low end for typical batch manufacturing processes (25–100).[24]

There are a number of challenges that need to be addressed before ICM can be adopted within the pharmaceutical industry, which can be mainly categorized in terms of three aspects:

1. Organizational/mind set[25]
2. Regulation
3. Technology

The work published by the MIT researchers addresses the technology aspect in detail, and also provides a novel approach towards control and modeling, which represents important criteria for regulatory approval of ICM processes. Indeed, the transition towards ICM poses new challenges for the control of pharmaceutical processes, and mathematical models can play a crucial role from process development to manufacturing in advancing the different operations and reducing costs.[26] One key is the design of an effective control strategy that improves the performance of the plant as a whole instead of individual unit operations. An ICM process is characterized by a number of connected unit operations, which pose challenges on deciding where in the process to intervene to improve the critical quality attributes of the final product.

An integrated control strategy is used to address such questions when developing ICM processes.[27] In addition, a dynamic model can be used systematically to develop and test a control structure with feed forward and feedback actions to mitigate the impact of any disturbances to the process in real time, therefore ensuring a consistent high product quality[28]. Although ICM is mainly characterized by a state of control in its operations, dynamic behavior is observed, including start-up and shut-down, where a model can help to determine optimal conditions to maintain the process in the "acceptable operating range" and therefore minimize waste generation.[23, 28]

CONCLUSIONS

The pharmaceutical industry is moving into a new era of targeted therapies, where medications need to be developed with specific features and delivered to patients faster. The current batch-to-batch development and manufacturing process, based on the blockbuster model, is costly and inefficient and does not provide the flexibility and quality control necessary for future manufacturing plants. The development of novel manufacturing technologies based on continuous flow can overcome many of these limitations, with Integrated Continuous Manufacturing (ICM)[16] being the ultimate goal for this industry.

Derived from a QbD philosophy and based on a first-principles understanding of the process and the application of concepts as continuous flow, end-to-end integration, systems approach, and integrated control strategy, ICM opens a new avenue for developing and manufacturing pharmaceuticals, where active ingredient and drug product manufacturing are integrated into a seamless process. ICM can produce high quality, low cost pharmaceuticals in a few days compared to current lead times of 12 months,[6] which results from the segmented nature of the batch plant (including materials holding, shipping, and off-line testing of chemical intermediates and API). These shorter ICM lead times should also alleviate manufacturing-limited shortages.

ICM is being implemented by Novartis in Basel, and more recently by CONTINUUS Pharmaceuticals, a spin-off of the Novartis-MIT Center for Continuous Manufacturing. While science is advancing with the development and fundamental understanding of superior drug manufacturing methods, regulatory agencies and pharmaceutical companies would need to initiate important reorganizations for integrated continuous manufacturing of drugs to be adopted largely within the industry.

Editor's Note: For the complete list of references associated with this article visit: www.pharmamanufacturing.com.

ACKNOWLEDGEMENTS

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RISKY BUSINESS: High Potency Products

Manufacturing HP active pharmaceutical ingredient drugs is a challenge best met with a thorough assessment of risk and a robust containment strategy

By Fidelma Callanan, Senior Director, Alkermes Contract Pharma Services

APPROXIMATELY 25 percent of drugs in development worldwide are classified as highly potent, with this percentage expected to grow over the coming years. A compound is generally classed as highly potent if it has an occupational exposure limit (OEL) of ≤10µg/m3, a daily therapeutic dose of ≤10mg/day or if a 1 mg/kg/day dose produces serious toxicity in laboratory animals. While such highly potent compounds can have significant benefits in the treatment of certain medical conditions, they present substantial challenges to the pharmaceutical industry.
These challenges include:

- Can personnel and the environment involved in the manufacture of high potency products be protected;
- Can adequacy of controls preventing contamination of other products by highly potent materials be demonstrated; and
- Can the expectations of clients and/or regulators regarding separation or segregation of manufacturing activities be satisfied?

CLASSIFIED AS HIGHLY POTENT

Many companies are choosing to outsource the manufacture of their highly potent compounds for strategic and/or economic reasons. Approximately 25 percent of drugs currently in development worldwide are classified as highly potent (HP), with forecasts suggesting that their increasing therapeutic use is expected to drive the global market for HP Active Pharmaceutical Ingredients (HPAPIs) by an estimated compound annual growth rate of 9.9 percent from 2012 to 2018[1]. While the majority of HP drugs are anti-cancer compounds (the oncology sector alone is expected to increase in value from $64 billion in 2011 to $104 billion in 2018[2]), other HP products include therapeutics such as hormones, narcotics and retinoids.

HPAPIs DEFINED

The definition[3] of a HPAPI varies depending on the literature, but generally is defined as:

- A pharmacologically active ingredient or intermediate

with biological activity at approximately 150 µg/kg of body weight or below in humans (therapeutic daily dose at or below 10 mg).
- An API or intermediate with an occupational exposure limit (OEL) at or below 10 µg/m3 of air as an 8-hour time-weighted average.
- A pharmacologically active ingredient or intermediate with high selectivity (i.e., ability to bind to specific receptors or inhibit specific enzymes) and/or with the potential to cause cancer, mutations, developmental defects or reproductive toxicity at low doses.
- A novel compound of unknown potency and toxicity.

Before progressing to define required levels of separation or segregation, anyone involved in the manufacture of HP materials must first address the issue of API classification since regulatory guidelines and regulations throughout the world can be inconsistent and often vague.

The International Society of Pharmaceutical Engineering (ISPE) sought in RiskMaPP[4] to engage with regulators and build an approach that would address the impreciseness of the classification approach and replace it with a clearly defined characteristic of active pharmaceutical materials, with the concept being that all manufacturers would demonstrate the adequacy of their controls (used to prevent cross-contamination) referencing the chosen characteristic. Risk-MaPP is defined as providing a scientific risk-based approach, based on ICH Q9 Quality Risk Management, to manage the risk of cross contamination in order to achieve and maintain an appropriate balance between product quality and operator safety.

USE ADE SAYS ISPE

Specifically, the ISPE guideline proposes the use of health-based Acceptable Daily Exposure (ADE) values rather than a tag such as "hormone," "steroid" or "cytotoxic" (with the exception of cephalosporins, which were specifically omitted from the guide). These values would then be used to assess the risk of cross-contamination and ultimately determine the level of controls to be applied along with any facility design and building requirements. Many of what are described as "tagged products" will have very low ADEs and, as a result, any true assessment of their potential risk will place a significant burden on the manufacturer to demonstrate containment and separation.

As a company, Alkermes incorporated RiskMaPP into how it manages and assesses the risk of cross-contamination across all the products it manufactures, including those with very low ADEs (µg/day).

However, while the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA) and others have endorsed risk-based assessments in this area, not all regulators or indeed inspectors share the same view at this point.

To better understand and mitigate the overall risks, a detailed investigation of a company's approach to handling and processing HP compounds should be performed. This analysis should challenge capability and knowledge in potent compound safety (both occupational and environmental), assessing the organization's understanding of cross-contamination risk, of how the product might be affected by other compounds produced at the prospective site, and how current products might be affected by possible introduction of the new product. Key elements to be considered include:
- Compound evaluation and OELs
- Equipment and process containment
- Environmental management
- Procedures and training
- Global compliance
- HPAPI handling experience and expertise

EVALUATING OELs AT ALKERMES

A first step when considering the introduction of any new API is to assess the toxicity and potency of the compound and to categorize it ("control banding"). Alkermes, for example, developed a categorization scheme with input from SafeBridge Consultants. Alkermes considers this an important first step in facilitating the assessment of likely product demands relative to the capability of existing manufacturing equipment technology and/or the ability to enhance its processing approach. Control banding provides a means to group materials by their hazards and risk of exposure so that suitable consistent controls can be defined and applied to ensure safe handling.

There are several limitations associated with banding approaches, so as soon as is practicable Alkermes moves to generate both ADE and OEL values. If Alkermes has a history of dealing with either the sponsor or the organization that's generated the report on their behalf, they will use the data provided by the potential partner, assuming it to be correct, until they can generate their own.

Alkermes typically seeks, as a best practice, to generate combined OEL and ADE reports because similar toxicological data underpins both. Alkermes has established a cross-site review forum for OEL/ADE reports, bringing in-house Environmental Health and Safety (EHS), toxicology and validation experts together to drive consistency and thoroughness in evaluation. Alkermes developed a format for report generation that includes supporting evidence from the toxicologists the company employs. For ADE identification in particular, they demand that formulae and factors applied are

consistent with their template, and that any variation from default values used in calculations is explained. Alkermes' template is based on the process described in the RiskMaPP guidance, and many of the default values the company employs are also based directly on that guidance or on references provided by the ISPE. ADE is a very important element in how Alkermes justifies its assessment of contamination controls — something both U.S. and European regulators that have visited Alkermes' sites or attended presentations have supported with positive feedback.

Developing an OEL and subsequent testing for the presence of that specific material allows us to empirically demonstrate that the working environment is safe. Concurrent with the development of an OEL, Alkermes commissioned Bureau Veritas (American Industrial Hygiene Association (AIHA) accredited) to develop the industrial hygiene sampling and analytical method to allow monitoring of the workplace to occur.

EQUIPMENT AND PROCESS CONTAINMENT

"If an overall manufacturing facility consists of three components — pharmaceutical material, personnel and the environment surrounding them — containment is the isolation of the first of these components from the other two" (ISPE). Containment, how it is achieved, how it is measured, and how it is maintained are key considerations for any provider handling potent or HP materials. The complexity of solutions relating to the contained material (OEL, material form, how much it is diluted by other components, etc.) and the process being employed (material energy, scale, level of operator intervention required, etc.) are key considerations. Where practicable it is best to manage containment at the source.

There is no one solution suitable to all situations. All challenges must be assessed within the context in which they occur and the constraints that apply. Some of these constraints will be of time and cost. Some assessments will reach a conclusion that projects should not be undertaken.

In assessing the containment challenge, Alkermes considers the three levels of protection:

1. Primary containment — equipment targets isolation of the product from the operators and the environment. Equipment is normally equipped with Clean in Place (CIP)/Wash in Place (WIP) and may be supplemented by a flexible single-use element for interventions
2. Secondary containment — includes use of separate processing rooms
3. Tertiary containment — refers to facility design such as dedicated, segregated suite(s), security access controlled, HVAC single pass air (safe change in room), double HEPA exhaust, pressure cascade and fogging shower.

Providers should establish containment performance criteria during commissioning and show that performance is maintained during commercial manufacture. Alkermes bases its approach on the ISPE Good Practice Guide: "Assessing the Particulate Containment Performance of Pharmaceutical Equipment"[5]. As part of commissioning, Alkermes uses a suitable surrogate (less potent) material with very low limits of detection to challenge installations. Alkermes also uses routine Industrial Hygiene monitoring to develop a sufficient level of confidence that we are achieving the OELs and verify ongoing containment performance.

When Alkermes considers cross-contamination potential it does so from two perspectives. First, the company considers the source and the risk (Product Risk) that the product presents, and second, it considers the potential risk of the product contaminating others (Product Vulnerability). Where a product of high "vulnerability" is manufactured on the same equipment or adjacent to a source of high-potential, "product risk" is where adequacy of controls needs to be most thoroughly assessed.

ENVIRONMENTAL MANAGEMENT

HPAPIs typically present greater challenges in environmental management including waste disposal, effluent containment and abatement of air emissions compared to less potent pharmaceuticals.

Best practice suggests all liquid and solid wastes, including wash water from equipment and area cleaning, should be contained until its potential for environmental impact is understood. When it comes to third-party manufacturing relationships, initial project assessment can be greatly helped by a thorough donor/sponsor data package. In this context, the information of interest might include any available eco-toxicity data, respirometry and/or biodegradation data, as well as previous waste-handling methods used, abatement systems utilized, etc.

Clearly, the decision to hold all potentially environmentally damaging materials (in particular wash waters, which would typically be of large volume) has cost implications, so drug owners will need to be confident in their own ability or their CMO partner's ability to reduce wash-water volumes, and by extension, long-term costs.

Certification of a company's systems relating to handling and disposal of liquid/solid waste products and their environmental management system, along with ready availability of associated written procedures, should give anyone whose job is to promote operational excellence, a good initial feel for his or his partner's capability and focus. Additionally, regulatory history and/or licensing of

facilities will provide the donor with further assurance of the company's environmental management capabilities. Alkermes' environmental management system, for instance, is certified against international standard ISO14001 and is assessed against an Integrated Pollution Prevention Control License which is regulated by the Environmental Protection Agency (EPA) in Ireland.

Training and expertise of people involved in the design of facilities, equipment and manufacturing processes as well as those who will handle and manage products in commercial manufacture will be critical to success. Alkermes itself invests significantly in the training of its scientists and engineers to ensure implementation of the best operable design to meet the specified containment performance target. In addition, operators and support staff are trained so they can maintain and operate equipment effectively and understand why containment and controls are in place. It's axiomatic that the discipline and care required from personnel operating and maintaining a facility handling HP compounds, their understanding of how their actions may influence exposure levels, and their understanding of risk are fundamental for the safe and successful operation of the plant.

Any organization seeking a third party to process HPAPIs should pay close attention to the training and expertise of all those who might be involved in process design, transfer, qualification (GMP & safety aspects) and eventual operation.

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Baking a Better Cookie

Continuous collaboration advances Pharma's manufacturing future

By Pamela Bruen-Docherty, Life Sciences,
and Kristin Wagner, Corp. Communications, Siemens

IMAGINE MIXING the ingredients to make a batch of cookies. First, mix the dry ingredients: flour, baking soda and salt. Second, mix the wet ingredients: butter, sugar, vanilla and eggs. Finally, mix the two batches together and then scoop out individual portions to bake. After the timer rings, the cookies are pulled from the oven and begin to cool; they look perfect and delicious. But as soon as you take the first bite, that smile turns into a frown. It's a "bad cookie" and it tastes like a salt lick. The entire batch is ruined. Just think, if one had the ability to make each cookie individually, then the "bad cookie" might have been detected earlier and the "baker" could have fixed the recipe, so the entire batch would not be ruined. Sound familiar? It should, because this is the approach that universities and the pharmaceutical industry are validating for tablet production. Instead of making gigantic batches of medication that require months to process and release, pharmaceutical manufacturers are taking their cues from the food and fine chemical industries, making tablets from a linear process continuum that supports real time release, reducing the production time by more than 90 percent. Known as "Continuous Manufacturing" the method is being recognized for its efficiency and cost and quality control attributes.

INDUSTRY/ACADEMIC PARTNERSHIP

At the forefront of the continuous manufacturing research and development is Rutgers University. Early on, Siemens formed a relationship with Rutgers to help the pharmaceutical industry move forward, to push the envelope and modernize pharmaceutical manufacturing and dosage forms for a more efficient future. The foundation of this relationship is built on Siemens membership in the Center for Structured Organic Particulate Systems (C-SOPS).

Rutgers is C-SOPS' academic leader and is joined by other university participants including Purdue, New Jersey Institute of Technology, and the University of Puerto Rico. Additionally, more than 40 companies are involved in supplying technology, training, mentorship and product testing. The mission for C-SOPS is to develop a structured design, engineering, scaling, optimizing, and control process to manufacture tablets and effectively educate companies on how to adopt and test these efforts.

The ascertainable impact of this effort is to provide a science-based and neutral ground to deliver a proof of concept that will enable and promote the transition from batch processing to continuous manufacturing in the pharmaceutical industry. This test ground is designed to help pharmaceutical companies show proof of concept for continuous manufacturing to the FDA, in order to aid them in acquiring FDA regulation approvals. In February 2013, Rutgers opened a full-scale continuous manufacturing production line on its campus. The research facility allows pharmaceutical producers to conduct performance and feasibility testing for the multiple production paths in continuous manufacturing. At the time of this article, the production line had been running only nine months; nevertheless, a great deal of research and development progress has already been made thanks to advanced process control and automating processes that improve efficiencies.

SIEMENS TECHNOLOGY CONTRIBUTION

Siemens donated its SIPAT data management system, a platform that manages enormous amounts of data, and PCS 7, a distributed control system (DCS) that controls the production line with integrated libraries, preconfigured standard blocks and faceplates. In addition to control, the DCS provides transparency to the process and enables optimization of the manufacturing line's performance to Rutgers University. Additionally, Siemens provided on-site training to get the research team up to speed on how to use the technologies and the research team has access to a full-service support line for ongoing questions. The Associate Director for Industry Relations for C-SOPS at Rutgers, Doug Hausner, shared with Siemens that the benefit of using both of these technologies concurrently is that they "work seamlessly together."

During the continuous manufacturing process, a large amount of data is collected, adding up to 4,000 data points every 1.5 seconds. SIPAT not only gathers this data accurately, it normalizes the data into a common timeline so technicians can make sense of the bombardment of information in order to execute decisions in real time. For example, when testing powder blends, which are eventually molded into tablets, the data management technology understands precisely when a blend is fully mixed, to ensure the medication is made to spec. If an error does occur in the mixing process, the SIPAT

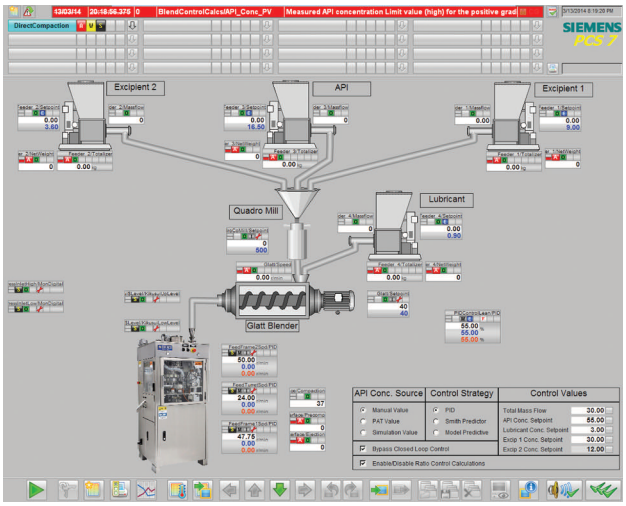
technology alerts the technician and the technology will automatically discard the ruined tablets, without wasting an entire batch. Additionally, if a variable needs to be adjusted to maintain product quality, such as changing the percentage of ingredients to the mix, advanced feedback control is utilized.

Compare it to the task of baking a cake. SIPAT technology ensures that all the sugar doesn't end up in just one piece of the cake and that it's distributed evenly throughout the entire cake. If for some reason a couple of slices were produced without any sugar, the system would place them in the waste basket automatically, in real time.

Ph.D. student, Abhishek Sahay, who interfaces directly with the SIPAT technology, pointed out a number of advantages that the Siemens technology provides him and his team in their continuous manufacturing research. First off, SIPAT enables them flexibility to make agile changes at different stages of the manufacturing process, enabling them to get the system up and running quicker because of the ability to adjust parameters along the line faster. Additionally, without SIPAT, technicians would have to interface with multiple separately operated interfaces which take time and specific training. SIPAT eliminates the time it takes to manage individual interfaces because the technician only has to use one, and that's SIPAT.

Abhishek pointed out that "control is a critical element" and the PCS 7 provides transparency into the operation in order to supervise product quality and monitor performance indicators in order to efficiently optimize the production line with increased production flexibility.

SIPAT and PCS 7 also aid in proving regulatory compliance. The data that the technologies collect support proof of concept for continuous manufacturing in the pharmaceutical industry, which is required for getting FDA regulation approvals.



Control is critical and Siemens' PCS 7 provides transparency to supervise product quality and monitor performance indicators.

Siemens is helping to move the pharmaceutical manufacturing industry forward to improve efficiency and quality-control efforts via continuous manufacturing by donating its leading-edge SIPAT and PCS 7 technologies to Rutgers University, training the staff to use the technologies, and providing support throughout the use of the products. The technologies deliver an easy-to-use interface that save a tremendous amount of time and provide transparency into the manufacturing optimization process.

Rutgers is already identifying major performance improvement metrics in its continuous manufacturing test environment. See Table 1 to compare key performance improvements between continuous manufacturing and batch processing. The operation improvements are impressive.

Benchmark	Measured
Product Testing	80% Reduction Testing Time
Space Footprint	50% Reduction in Space
Waste	30% Reduction in Waste
Capital Investment	50% Reduction in Investment
Manufacturing Cycle Time	>90% Reduction in Cycle Time
Release Time	>80% Reduction in Release Time
Flexibility of Supply	No Longer Need to Scale Production – Produce What's Needed

Table 1: Key Performance Improvements.

In regards to testing the product, three fewer analysts are needed in continuous manufacturing. Additionally, less space is required in continuous manufacturing. The production line is built from the floor up; it's a vertical construction that is about as big as a tractor trailer bed. In comparison, batch processing requires 6 rooms for processing. With a reduction in required space comes a reduction in financial investment. Upfront capital investment reduces dramatically from $24 million to $12 million — major savings right off the bat. One of the most impressive savings relates to the reduction in manufacturing cycle time. Instead of waiting 10-13 days to cycle through batch processing, it takes less than one day to go through the same process in continuous manufacturing. Furthermore, in conjunction with less cycle time, there is a much shorter release time to turn out pharmaceutical tablets, getting them to market quicker. Instead of 30-plus days, the release time is only five days — less than a week. At the same time, with continuous manufacturing, there is no longer a need to scale production in accordance to forecasted demand because companies will be able to produce what is demanded and deliver it to market in a shorter amount of time. All of these findings are contributing to demonstrating the impact of continuous manufacturing in the pharmaceutical industry from a science-based approach. These insights will enable and promote the transition to continuous manufacturing on a neutral ground for development and regulatory consensus.

RESEARCH TODAY AND IN THE FUTURE

As of August 2013, there were six filings for continuous manufacturing with the FDA. Hausner is anticipating a quicker adoption rate for continuous manufacturing in the pharmaceutical industry in the future as more compelling proofs of concepts arise out of the C-SOPS research across the involved universities. Additionally, the FDA is actively promoting continuous manufacturing and supports the research effort.

Interest in continuous manufacturing is prevalent in numerous areas around the pharmaceutical industry. Major pharmaceutical companies are involved in testing concepts in continuous manufacturing, including Johnson and Johnson, Pfizer, GlaxoSmithKline, Novartis, Merck, Bristol-Myers Squibb and Eli Lilly. Furthermore, a generic pharmaceutical company is also involved in testing continuous manufacturing, TevaPharmaceutical Industries. The interest in continuous manufacturing expands globally as China is investigating implementation plans as well. Equipment companies are innovating to stay in the game and are improving product designs to work in conjunction with continuous manufacturing processes and technologies.

The growing interest in continuous manufacturing for the pharmaceutical industry is also creating niche opportunities for students at the university level. The research is a launch pad for nation-wide curriculum in Pharmaceutical Engineering and Science because it is drawing attention to the pharmaceutical engineering field and is providing relevant experience for chemical engineers to better aid them in securing a job after they graduate. The research also opens doors for classes specific to pharmaceutical engineering, so students are not limited to general chemical engineering courses and can gain knowledge specific to their field of interest. This growing advancement will positively impact the pharmaceutical industry going forward as higher skilled and experienced students enter the workforce.

Siemens is invested in helping to modernize the pharma industry, which will result in major economic and quality-control benefits. They are aiding in the effort by donating leading-edge technologies (SIPAT and PCS 7) that facilitate a faster, flexible and controlled research process, providing training and continuous support on how to use the technologies, and donating funds through their C-SOPS membership — an investment for a better future.

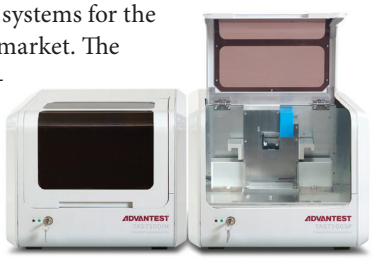
How to Solve Materials Mysteries

Advances in spectrometers, photometers, Raman and other inspection systems provide fast, accurate materials identification

BY KATIE WEILER, MANAGING EDITOR

RAPID, NON-DESTRUCTIVE ANALYSIS

Advantest Corp. has developed new bench top spectroscopy and imaging systems for the pharmaceutical R&D market. The configurable and compact TAS7500 THz Spectroscopy/Imaging Systems use proprietary terahertz wave technology to acquire characteristic spectra based on crystalline structure and 3D images yielding tablet coating thickness and uniformity and the non-destructive detection of cracks and voids in the tablet core. The terahertz spectroscopy is used to measure solid phase transitions and crystalline/amorphous composition, while the terahertz imaging provides information on the strength properties of coatings and multilayer interfaces in tablets.



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RAW MATERIALS ID IN UNOPENED CONTAINERS

Cobalt Light Systems' RapIDsystem identifies raw materials through unopened containers, i.e., with no sampling or controlled environment. RapID uses Spatially Offset Raman Spectroscopy (SORS) technology to see through packaging, and it works with most common containers including layered paper and plastic sacks, plastic bottles and tubs, thick amber glass and super-sacks/FIBCs. RapID is widely compatible with common pharma and biopharma APIs and excipients. Containers such as sacks gain a 10x increase in testing throughput, Cobalt says, which makes 100 percent ID testing feasible with minimal resource impact.

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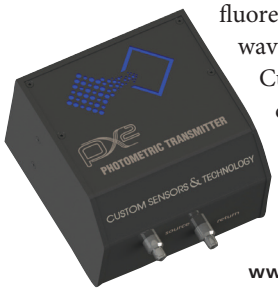

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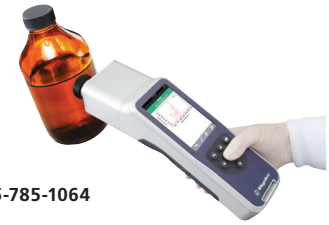
Rigaku Raman Technologies' new generation in handheld Raman technology, Progeny, is easily integratable into pharmaceutical manufacturers' quality control procedures. Progeny identifies non-conforming pharmaceutical materials in seconds, ensuring supply chain security. Pharmaceutical manufacturers' return-on-investment is quickly recognized as they are able to quarantine fewer shipments, send fewer samples to the lab and bring their finished products to market faster, the company says. Progeny delivers error-free operation, repeatability, ease-of-use and analysis of the largest number of materials, all in a handheld form.



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Shimadzu says its IRTracer-100 FTIR Spectrophotometer offers "best-in-class" 60,000:1 S/N ratio, which allows researchers to quickly and easily obtain high-quality data of ultra-small contaminants in raw materials as well as finished products and packaging. Resolution of 0.25 cm-1 provides for highly accurate quantitation and identification while a rapid scan function allows rapid sample acquisitions of 20 spectra per second. It features easy-to-use software, including automated contaminant analysis and identification test programs that provide for easier identification of unknown samples.

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The Thermo Scientific TruScan RM analyzer is light, fast and the most portable handheld instrument for rapid authentication of pharmaceutical raw materials and finished products, says the company. Featuring the specificity of Raman, it allows operators with minimal training to perform reliable analysis wherever pharmaceuticals are manufactured or distributed. The analyzer's non-destructive point-and-shoot sampling principle facilitates rapid verification of a broad range of chemical compounds, both solid and liquid, through sealed packaging.

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Five Trends to Watch in 2015

Collaboration in the supply chain will help Pharma stay out in front of the challenges ahead

BY DIANE PALMQUIST, VP OF MANUFACTURING INDUSTRY SOLUTIONS, GT NEXUS

THE PHARMACEUTICAL industry is changing dramatically with new regulations, advances in technology and tighter revenues. As a result, pharma companies are looking for ways to decrease risk and increase efficiency, transparency and collaboration in the supply chain — all in an effort to help them exploit new opportunities and meet the challenges they encounter along the way. Regardless of the niche you may occupy in the industry, here are five pharmaceutical trends to keep in mind that are sure to affect pharma company operations and business success in 2015:

1. **Serialization** – to combat the circulation of counterfeit drugs, regulation is placing strict demands on companies to be able to track and trace and validate the origin of "medicinal products for human use," and the ingredients within them. Pharma companies therefore are looking at their supply chains to facilitate visibility and collaboration from end-to-end.

2. **Patent Expiry** – pharma companies are starting to see patents running out on their "blockbuster" drugs. Companies will need to look at new revenue streams and cost-saving methods. Profit is no longer based on ownership of the molecule, but developing the best strategies to market the right products in new markets and being able to deliver into emerging regions such as Africa.

3. **Increase in Generic Drugs** – more companies will be offering generic drugs due to patent expiry. This creates challenges in competition and margin pressures.

4. **Big Data** – pharma companies are increasingly in need of supply chain big data to give them complete traceability of where products are, where there may be risk, areas of growth and if there are any hold-ups. It is essential for intelligent forecasting.

5. **Lessons from Retailers** – pharma companies will start looking at retailers' flexible supply chains for lessons. Retailers have lots of suppliers, fragmented markets with very different needs and low margins. They have to channel products to different markets and can't afford to leave things on the shelf.

The most effective mitigation strategy against the supply chain risk these trends may introduce is to develop a robust supply chain management system with processes that allow manufacturers to be agile, transparent and collaborative when working with trading partners and service providers. For example, understanding the processes in one's own plant can be challenging enough, but pharma's manufacturers need to develop a similar understanding of all the processes that their outsourced manufacturers and suppliers deploy if they are to have a predictable, assured supply chain.

PHARMA MANUFACTURERS HAVE TO BE FASTER, MORE AGILE IN THE SUPPLY CHAIN AND **ASSURANCE OF SUPPLY IS ESSENTIAL.**

Most companies fail to look at the full picture to mitigate supply chain risk and assure supply. Instead, multiple departments deal with different aspects of the supplier. Procurement negotiates the price, material handlers place the order, logistics determines how to ship, supply chain tracks the shipment and finance determines when to pay. This fragmented, haphazard approach rarely ends well. A holistic alignment with your suppliers is needed across the enterprise to promote and assure supply chain integrity.

Due to the complexity of global sourcing, everyone has an assurance of supply problem to some extent. Pharma's manufacturers have to be faster and more agile in the supply chain and assurance of supply is essential to competitive agility. The common thread in assurance of supply initiatives is partnering with suppliers by collaborating. Best-in-class companies seamlessly manage all aspects of a supplier relationship.

Diane Palmquist is vice president of Manufacturing Industry Solutions at GT Nexus. The company provides a cloud-based collaboration platform that leaders in nearly every sector rely on to automate hundreds of supply chain processes on a global scale, across entire trade communities. Palmquist's area of interest is creating supply chain technology solutions for global manufacturers.

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