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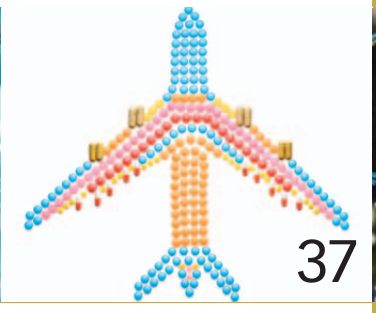

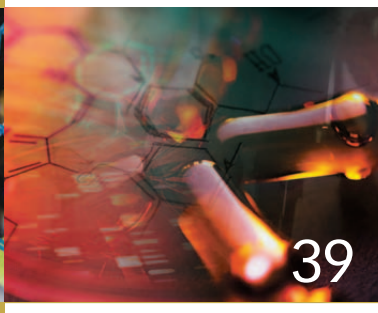

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Pharmaceuticals in the Environment

Publication of proposed new regulations for pharmaceuticals in the environment has been postponed due to challenges in working out solutions and establishing a common framework.

The European Union has been committed for several years to drawing up a strategy on allaying public concerns about contamination of the environment by pharmaceuticals. The strategy on pharmaceuticals in the environment (PIE) would deal in particular with worries among Europeans as well as health professionals and non-governmental organizations (NGOs) about environmental causes of antimicrobial resistance, including untreated waste from plants making antibiotics and their APIs. The objective was that the strategy, due to be published this year by the European Commission (EC), the EU's Brussels-based executive, would include both legislative and non-regulatory proposals, as laid down in a 2013 EU directive (1) on control of water pollution by pharmaceuticals. The directive stipulates that the EC should propose measures with "a view to reducing discharges, emissions, and losses of [polluting pharmaceutical] substances into the aquatic environment."

Delays in PIE legislations

The EC has decided to postpone making proposals for legislative measures, including a decision on whether to go ahead with the controversial option, strongly opposed by the industry, of laying down standards for waste treatment in pharmaceutical plants by extending good manufacturing practice (GMP) to cover environmental controls. After a series of studies by outside consultancies, workshops, and consultations with the public and stakeholders, the last of which was completed in February 2018, the commission was expected at last to fulfil its commitment by publishing a full strategy, including coverage of regulations, and then pressing ahead with its implementation.

"When we met commission officials in early July [2018], it was clear that they were delaying the publication of any proposals on regulations, including any planned legislation on applying GMP to waste management in pharmaceutical plants," Adela Maghear, pharmaceuticals officer at Health Care Without Harm (HCWH), told Pharmaceutical Technology Europe. "This could mean even more delays in the introduction of legislation on PIE," commented Maghear, who was in a delegation of NGO representatives visiting the EC.

The splitting of the PIE strategy into two stages, the first without regulations and the second with, will result in the existing EC passing to a new Commission the responsibility of proposing legislation. The new executive, with commissioners appointed by the governments of the EU member states, is due to take over in 2019. The slow pace at which the EC is adopting a PIE strategy is likely to work in favour of the pharmaceutical industry, which has been pushing forward with its own voluntary solutions to environmental problems with pharmaceuticals, especially those related to antimicrobial resistance. It gives the industry the opportunity to demonstrate that the voluntary approach is a viable alternative to regulation.

One priority behind EPS activities is the compilation of best industry practices in the management of pharmaceutical manufacturing effluents.

Combating antimicrobial resistance

An Antimicrobial Resistance (AMR) Industry Alliance, a global life-sciences coalition of more than 100 biotech, diagnostics, generic-drug, and research-based biopharmaceutical companies, has been combating AMR through work on the environment, as well as research, easing access to appropriate medicines and appropriate use of pharmaceuticals. In Europe, the three main pharmaceutical associations—European Federation of Pharmaceutical Industries and Associations (EFPIA), Medicines for Europe, and the Association of the European Self-Medication Industry (AESGP)—have set up the Inter-Association Task Force on Pharmaceuticals in the Environment. They have also cofounded the Eco-Pharmaco-Stewardship (EPS), which deals with the entire lifecycles of medicines, taking into account the responsibilities of public services, the pharmaceutical industry itself, environmental experts, health professionals, and patients.

One priority behind EPS activities is the compilation of best industry practices in the management of pharmaceutical manufacturing effluents so that drug producers can minimize the risks to the environment and the spread of AMR. The assumption is that because the production processes for many medicinal producers are broadly similar to each other, potentially dangerous discharges into the environment should be equally controllable, as long as the knowledge about how to limit emissions is uniformly available.

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Thirteen members of the AMR Industry Alliance including leading pharmaceutical multinationals such as AstraZeneca, GlaxoSmithKline, Johnson & Johnson, Merck & Co, Pfizer, and Novartis have signed up to a roadmap committing themselves to a number of aims for clean antibiotics production. These aims include establishing a "common framework" for managing antibiotic manufacturing emissions based on "science-driven, risk-based targets for discharge concentrations for antibiotics."

The work being done by EPS and AMR Alliance will help demonstrate that international good environmental practice standards can be created, which make the use of GMP in the environmental area unnecessary. "We are strongly opposed to the use of GMP in environmental matters because we believe it should remain entirely focused on product quality," Bengt Mattson, co-chair of the Inter-Association Task Force on PIE, told *Pharmaceutical Technology Europe*. "The environmental management standard would be entirely different," he added. "It would be an alternative standard that could ultimately become the basis for a uniform global regulatory initiative."

Harmonization of legal emission standards

By the time the EC draws up proposals for tighter regulatory controls on emissions from pharmaceutical plants, it is likely to need the data on best practices and concentration thresholds collected by the industry. Because the vast majority of APIs in antibiotics marketed in Europe are produced in India and China, the EU will require harmonized legal emissions standards that can be applied to imported pharmaceuticals in the same way that uniform GMP standards are currently applied to them.

What the EU has achieved by raising product quality through GMP requirements for API imports, India is now looking to the EU to do the same with environment waste controls in Indian pharmaceutical plants. Indian NGOs, health professional groups, and community rights activists sent a joint letter in early July 2018 (2) to the EC claiming that EU action was needed to deal with "the grave environmental and human health crisis" in India linked to the lack of regulatory controls on effluent from the country's API plants. This issue was causing "rampant" pollution around the country's pharmaceutical manufacturing hubs such as Hyderabad, which has led to a "huge" AMR problem in India, according to the letter (2). It argued that the only way to tackle the crisis was by the EU extending GMP to include environmental criteria.

Efforts from the industry

Partly as a result of the growing evidence from academic studies connecting AMR to manufacturing waste and the industry's own collective initiatives on the issue, individual pharmaceutical companies have established their own "clean" or "green" supply chains extending, if necessary, from starting materials and API production to distribution. DSM Sinochem Pharmaceuticals (DSP), a joint Dutch-Chinese venture, has introduced in its plants in China, India, Mexico, and Spain a green fermentative and enzymatic process for antibiotic intermediates (3). In addition to eliminating solvents and achieving low-carbon footprints, the company is also committed to minimizing the release of antimicrobial active ingredients into the environment.

Mylan, one of the world's largest producers of antibacterial APIs, has switched its plants in Hyderabad to a system of zero-liquid-discharge (ZLD) so that antimicrobial compounds can be kept out of the environment. The technology is being extended to Mylan's other plants in India. These pharmaceutical multinationals with audited green APIs supply chains are not only gaining business from international producers of finished medicines. They have also attracted the attention of a number of Scandinavian and other European governments that operate green procurement policies for drugs, particularly antibiotics. However, government buyers of antibiotics and other medicines in bulk as well as pharmaceutical companies purchasing APIs are using different criteria to judge whether the products are adequately green. There is, therefore, a pressing need for harmonization. But this uniformity is unlikely to be achieved until more evidence is available on the biological and chemical mechanisms that create AMR within pharmaceutical plant effluent.

Signatories of the AMR Alliance Roadmap do not expect to be able to determine resistance-based limits on discharge volumes until 2020 at the earliest. These limits will then be used to devise good practice methods. Before it even considers PIE regulations, particularly in relation to AMR, the EU is likely to fund research projects to fill knowledge gaps on the hazards of AMR in the environment, including in manufacturing effluent.

The pharmaceutical industry wants to be able to influence the direction of this research, as well as being closely involved in the deliberations of the new Commission on possible regulations. "There could be a lot of non-legislative initiatives following the [current] Commission's publication of its strategy document and research will be a big part of these," noted Mattson. "We can help to define what research is needed. We will also have a lot of information to share with the new Commission—not just on research issues but particularly when it comes to discussing possible regulations."

Once regulations are in place, the next stage will be efforts to extend the principles behind them to outside Europe so that they fit into a harmonized global approach to problems with pharmaceutical plant waste.

"We've still got a long way to go," Mattson said. "The length of time it has taken for the EU to draw up a PIE strategy shows the difficulties of working out solutions. There will have to be a lot of discussion before a common framework can be established."

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The Challenge of Building Better Biologic Drugs

Development costs and time to market continue to put pressure on the biopharma industry, driving the need for innovation in methods and technologies.

Feliza Mirasol

As the pipeline of biologics matures, the pharmaceutical industry is expected to see new biotherapeutics that offer improved efficacy. Pressure from the current healthcare environment, however, is pushing the pharmaceutical industry toward lower-cost therapies and faster times to market.

The CHO standard

Biologic drug development has traditionally depended on the use of Chinese hamster ovary (CHO) cells. Over the past three decades, the CHO cell line has become the automatic choice of expression system for biomanufacturers, notes Mark Emalfarb, CEO of Dyadic International, a biotechnology company focused on developing biologic vaccines and biologic drugs.

Emalfarb notes that the pharmaceutical industry is nonetheless experiencing the limitations that CHO expression yields present, which is complicated by pressures to develop affordable drugs quickly. "These [limitations] are particularly evident for the next wave of biologics, bi-specific, and tri-specific antibodies. The relatively low yields and relatively high costs of producing biologics with CHO appear to make it less sustainable and less commercially affordable for producing these more complex molecules," Emalfarb says. "In a way, using CHO cells to develop and manufacture biologics is a bit like driving a 1900s model car in a 2020 Tesla world."

Using CHO cells as the industry standard for biologic drug development has several major drawbacks, adds Mario DiPaola, PhD, senior scientific director at Charles River Laboratories, a contract research organization. The most significant drawback is product yield, which is typically less than one gram per liter, followed by costs related to the extensive cell-line development and limited cell viability for production.

"CHO expression systems work reasonably well for expression of less complex glycoproteins, but not well for new product modalities. For instance, in the case of AAV [adeno-associated virus]-like particle-based products, many developers are relying on HEK293 cell lines. Aside from yield and cost issues, the CHO cell-based expression system has other limitations related to glycosylation," DiPaola explains. "The introduction of the immunogenic Galactose- alpha 1,3–Galactose linkage or N-glycolylneuraminic acid into glycan moieties of glycoproteins lacks certain transferases such as alpha 2,6 sialyltransferase, and it fails to produce any glycan with alpha 2,6 sialic acid."

Driving innovation behind better biologic drug development is decreasing the cost of these therapies, which is quite high for most biologic drugs, DiPaola comments. "It is important to drive the costs down through innovations in order to lower both the costs of development and costs of production. It is interesting to note that over the course of the past two decades the time from patent filing to market has increased from an average of 130 months to about 150 months, and the cost of getting a biologic approved has gone from approximately €557 million (US$650 million) in 1996 to more than €1.7 billion (US$2 billion) in 2018," DiPaola says. "Clearly, these trends must be reversed so that more patients can benefit from these drugs at reasonable costs."

In addition, there is a separate need for more complex drugs, including more effective antibody drug conjugates (ADCs), multi-valent antibodies, and gene/cell therapies, "all of which will require innovation across the industry to ensure success," according to DiPaolo.

Emalfarb further comments to say that "'better, faster, more affordable' is a mantra we should all take to heart as we pursue the knowledge that could—at least potentially—make it easier to make

the drugs that could save lives more affordably."

"It is the responsibility of those working in the industry to enhance pharma companies' ability to develop and make drugs efficiently and more cost-effectively. A large part of this entails encouraging pharmaceutical companies to study the potential of viable alternatives to CHO and to *Escherichia coli (E. coli)*. Working together, government, regulatory agencies, academia, and pharma and biotech companies can indeed change things for the better," Emalfarb says.

Exploring a new expression system

A cell source being explored as the basis of a new expression system for biologic building blocks is the fungus *Myceliophthora thermophila*, nicknamed C1, which Dyadic has been developing for the past two decades. C1 technology is a fungal expression system for gene discovery, development, and production of enzymes and other proteins.

Known as the C1 Expression System, Dyadic's technology turns genes into a broad range of products and helps to overcome some of the inadequacies inherent in existing expression technologies used for gene discovery, product development, and commercialization.

"C1 scales up the rate at which enzymes and other proteins can be produced and was initially used to produce biofuel and other enzymes in greater amounts and in less time than was possible before. To develop C1, our scientists exposed the cells of the *Myceliophthora thermophila* species of fungus to ultraviolet light. They expanded and reinforced beneficial mutations to change the shape of C1 from long, spaghetti-like strands to short, grain-sized sections. Since C1 fungal cells secrete enzymes from the ends of the filaments, there were more secreting ends, multiplying the potential total yield of proteins," says Emalfarb.

"Furthermore, due to its new shape, C1 became easier to grow in large tanks. It offers a much shorter production time for monoclonal antibodies (mAbs) than CHO, requires smaller production facilities, and does not require expensive production media nor viral purification. When C1-expressed proteins are secreted from the cells, they come out in a purer form than CHO-produced mAbs," he adds.

For those reasons and others, C1 is said to represent an "innovation" in biologic drug development. "We hope one day C1 will be a safe and efficient expression system that can help speed up the development, lower the production costs, and improve the performance of biologic vaccines and drugs at flexible commercial scales. We believe it may also potentially enable the development and commercialization of genes that are difficult to express at reasonable yields in CHO, *E. coli*, and other cell lines and might also be able to produce larger amounts

of protein to enable drug discovery and development to move forward faster," Emalfarb states.

Research results to date support the use of the C1 expression platform on an industrial scale in the biopharmaceutical industry. "In January 2018, for example, the maximum mAb yield from C1 stood at 1.34 grams per liter per day (G/L/d). Two months later, we had raised that to 1.71 G/L/d," Emalfarb explained, then continued, "As of May 2018, this figure had been raised again to 2.46 G/L/d—representing an 84% improvement in productivity in only four months. This progress is accompanied by a corresponding 67% drop in the cost of the already low-cost, chemically defined medium required to produce the mAbs" (1,2).

The most pressing challenges that the biopharma industry faces are development cost and time … which are becoming unsustainable for the industry.

Charles River, which worked on approximately 80% of the drugs approved by US Food and Drug Administration last year, has many technologies and methodologies that can be applied throughout the development cycle of a biologic drug, according to DiPaola. The company specifically develops a wide spectrum of animal models for testing products against specific diseases to screen, confirm, or validate a product's functionality and biological activity *in vivo* in the early stages of development.

"Charles River also possesses a variety of *in vitro* screening assays to assist in identifying the most potent drug candidates. To help drug developers weed out toxic drug candidates early in development, Charles River offers toxicological studies based on robust protocols utilizing multiple species," DiPaola says. The company also offers capabilities that support production cell-line characterization, cell banking, and viral clearance for purification-process validation.

Improving the system

The C1 expression platform offers the biopharmaceutical industry potentially significant time and cost savings at each stage of cell development and biomanufacturing process development when compared to CHO cells, Emalfarb remarks.

For one, C1 creates a stable cell line in a shortened timeline. "Dyadic has estimated a reduction of 50% in the time from gene fragment to stable cell line; C1 stable cell lines can be developed in just over three months versus six-plus months typically needed for CHO," he says.

Other "savings" benefits of the C1 expression system, according to Emalfarb, include:

- Significant upstream bioprocessing savings: C1's doubling time (rate of cell growth is two hours versus 20 hours for CHO cells), leading to an estimated 10-day savings in time for the cell growth phase to charging the production fermenter with the required cell densities needed for commercial biologics production.
- Greater savings once commercial fermentation starts: The production time for C1 is significantly shorter—four to seven days versus CHO, which is typically a 12- to 14-day process, offering a 50% or even greater time savings.
- Saving on cell media costs: Based on the large difference of media needed for production using CHO, C1 achieves higher productivity using low-cost-defined synthetic media, estimated to offer a cost savings of five to 10 times over CHO media.
- Additional downstream processing savings: These are expected when using C1 versus CHO including the elimination of two viral inactivation steps that are typical in CHO biomanufacturing.

"As indicated earlier, C1 shaves off 50% or even greater time savings in the commercial fermenters, but most importantly, C1's productivity is higher despite the much shorter time needed for production of biologics," says Emalfarb.

Dyadic recently reported that the company was able to produce a full-length mAb with productivity of nine grams per liter in 90 hours, or in less than four days (1). This represents a greater-than-twice the industry average productivity for CHO, which is reported to be approximately 4 G/L, in one-third the time. "Putting this in perspective, C1's mAb productivity equates to 2.4 G/L/d versus .30 G/L/d for CHO using much lower-cost media and the elimination of two viral purification steps typical for CHO," Emalfarb notes.

Industry challenges

The most pressing challenges that the biopharmaceutical industry faces are development cost and time, both of which are becoming unsustainable for the industry, DiPaolo states. Another significant challenge is the lack of internal innovation and research capabilities across many of the medium-to-large size biopharmaceutical companies. "As a result, they must rely primarily on collaboration, in-licensing, or acquisition of new start-ups for innovation and new product leads," DiPaolo says.

"Some significant re-engineering is needed within the industry to bring about new strategies and approaches, possibly through greater use of automation, robotics, and artificial intelligence to allow for faster transition of biologic drug candidates from lab bench to clinic and then from clinic to market. These changes are necessary in order to address unmet medical needs, such as treatment of types of cancers, Alzheimer's disease, and certain autoimmune diseases in a quicker and financially efficient manner," DiPaola asserts.

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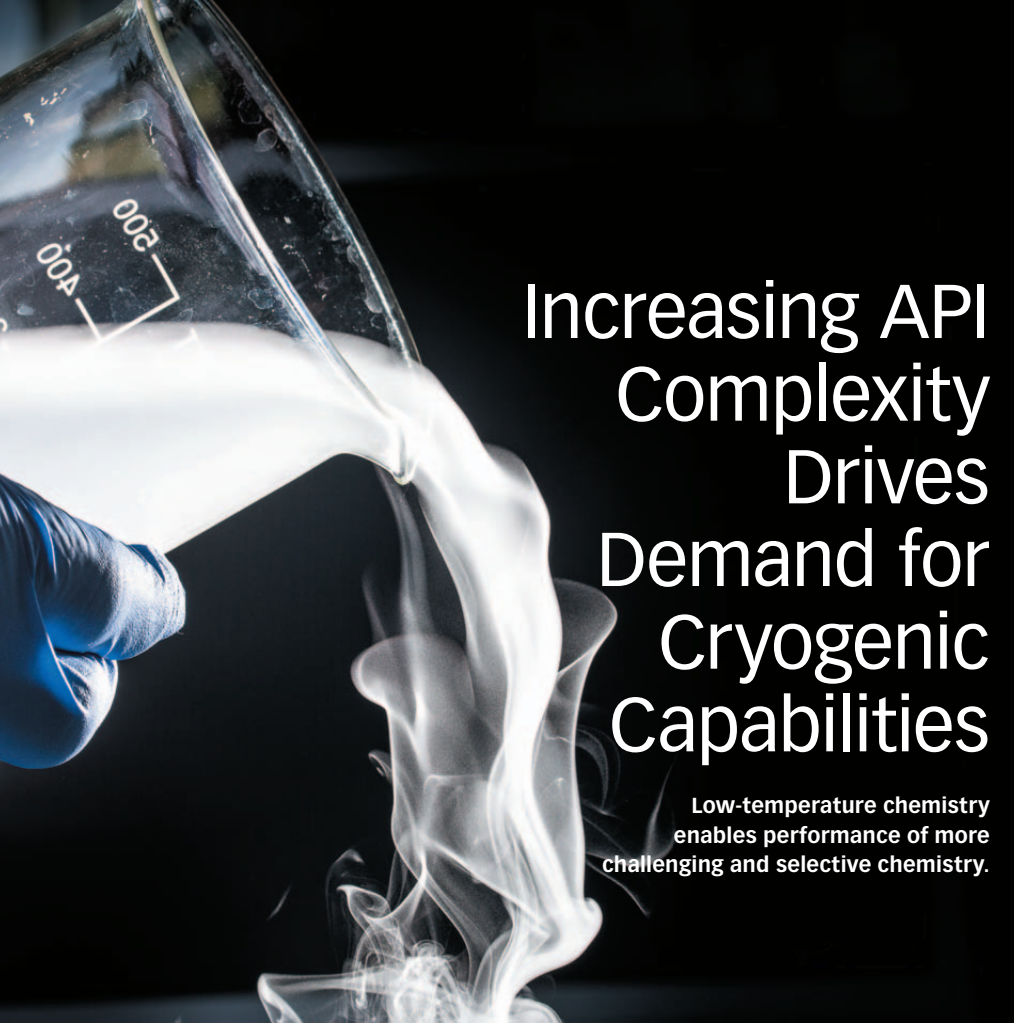

Increasing API Complexity Drives Demand for Cryogenic Capabilities

Low-temperature chemistry enables performance of more challenging and selective chemistry.

Cynthia A. Challener
is a contributing editor to *Pharmaceutical Technology Europe*.

As the pharmaceutical industry matures, the complexity of new drug candidates is increasing. More complex molecules are more challenging to synthesize, often requiring advanced chemistry techniques to ensure both high yields and high selectivity. Sophisticated chemistry such as exotic catalytic transformations are used more widely as a result. Many of these reactions are highly sensitive to temperature and pressure, with control of one or both of these reaction conditions improving the selectivity and yields of desired products, particularly in cases where undesired impurities have similar structures and physical characteristics. Low-temperature chemistry, and in particular cryogenic chemistry at temperatures down to -80 °C, can facilitate transformations that cannot be achieved at higher temperatures.

Enabling technology

In the past few years, there has been an increase in the number of new API projects being brought to contract development and manufacturing organizations that require low-temperature chemistry. New routes to existing products that are designed to improve efficiency and productivity also more often involve cryogenic processes, according to Jean-Pierre Pilleux, site director at Novasep's Chasse-sur-Rhône facility in France. "As novel APIs become more and more complex, cryogenic conditions are often mandatory to obtain the required selectivity. For example, processes employing organometallic chemistry can be critical in API synthesis," adds Jean-Baptiste Guillermin, head of process development at the Chasse-sur-Rhône plant.

Use of low temperature can influence the reaction pathway, particularly for reactions in which desired and undesired products differ only slightly from an energetic standpoint, whether with respect to stereo-, regio-, or chemoselectivity. Reactions involving unstable intermediates, notably organometallic reagents, that cannot be conducted at or near room temperature are often possible at much lower temperatures. In addition, processing involving gaseous reagents can be easier to implement at low temperature.

"Cryogenic chemistry is an enabling technology that can allow the limiting of impurities, performance of processes with highly reactive compounds, improvement of reaction selectivity, elimination or reduction of unwanted side reactions, prevention of ice crystal formation, and reduction of the volatility of compounds for greater safety," notes Ed Price, president and CEO of PCI Synthesis.

Sophisticated equipment

Running large-scale cryogenic processes is an entirely different proposition than performing low-temperature chemistry in the lab, according to Price. "In the lab, glassware can be placed in an acetone/dry ice bath. For commercial production, heat transfer fluids must be pumped through jacketed vessels using sophisticated pump technology (costing five to six times that of conventional pumps) and complex control systems," he explains.

In addition, specialized analytical tools are required; measuring cryogenic temperatures cannot be achieved with normal mercury or alcohol thermometers because they freeze. Platinum resistance thermometers that exhibit well-defined electrical resistance behaviour as a function of temperature must be employed instead.

Many challenges

"The need for specific and expensive equipment means that the capex [capital expenditure] for newcomers can be significant," observes Pilleux. He adds that greater energy consumption and handling of unstable intermediates also must be considered. In addition, while there are always challenges going from small to large scale, scaling cryogenic chemistry and processing is significantly more complicated because extreme temperatures must be delivered and maintained, according to Price.

"Running processes under such cold conditions is as much an art as a science. These reactions are very touchy and sensitive. They have to be

run very specifically, which involves controlling an entire system of pumps and heat exchangers to reach, maintain, and control the temperature as the reaction progresses," he notes. For that reason and based on 40 years of experience running cGMP cryogenic processes, Pilleux considers process robustness to be key. "Understanding the impact of reaction parameters using a quality-by-design approach during development, coupled with close interactions between chemists and chemical engineers using thermal modeling allows the efficient prediction of scale-up parameters for such highly demanding processes," he states.

The need for strict control of the reaction temperature throughout the entire reaction mixture can pose challenges as well. The addition of reactive reagents to such processes may lead to the generation of local exotherms that must be removed via efficient mixing and good heat exchange properties of the reactors, according to Pilleux.

In addition, the low surface area-to-volume ratio of batch reactors restrains the size of vessels for production. In fact, it is not just the need to achieve and maintain low temperatures that is challenging. It is the fact that batch processing has not changed dramatically from a technology standpoint for decades, according to Price. "Pharmaceutical plants today look similar to those in operation 20–30 years ago," he says.

Managing the economics

For certain chemistries, there is no other option than to perform them at low temperature. "It goes back to the perennial organic chemistry battle between yield, cycle time, and impurities. Achieving the required purity levels is always the first priority. In early development phases, the goal is to deliver high-purity products, and the economics of the process are not as important. That comes into play if a candidate progresses to later clinical stages. If the process cannot be performed economically at low temperature, another route will need to be identified," Price comments.

It is important during development, he notes, to gain an extensive understanding of the process and determine the warmest reaction temperature that won't cause significant problems and the potential benefits that can be gained if the reaction is performed at the lowest possible temperature.

In many cases, gains in yield and selectivity can overcome the additional costs of running a process at cryogenic temperatures. For instance, Prices notes that a product that is produced in multiple small batches can cost significantly more and take more time to manufacture than if that product is produced in one or two large-scale cryogenic runs.

Moving to flow chemistry

As drug candidates continue to become more sophisticated, demand for processing under extreme conditions, including cryogenic temperatures, will continue to grow. "The question then becomes, how do we incorporate novel engineering/processing solutions that really move the needle for drug manufacturing?" according to Price. Manufacturing on a smaller scale in a continuous manner to obtain the same yields and throughputs of larger equipment could be one answer, he notes.

Guillermin agrees. "Reactors having a higher surface-to-volume ratio and more efficient mixing can be used to increase the productivity of low-temperature processes and avoid the potential for high-temperature hot spots," he says. "Continuous flow reactors are a breakthrough solution."

Recent investments

Novasep is, in fact, focusing on the development of flow-chemistry solutions at production scale in order to offer alternatives to batch processes. "This technology generally enables the use of less extreme temperature conditions and control of very short reaction times, even at production scale, allowing the production of unstable intermediates that cannot be obtained under batch conditions—and with a reduced energy cost. These technologies are rapidly expending and Novasep has built a strong expertise in this domain," says Guillermin.

Late in 2017, Novasep also initiated a €4-million ($4.7-million) investment to expand its low temperature capability at its Chasse-sur-Rhône facility and address the increasing market demand for cryogenic processes. The company now has a total low-temperature capacity of 35 m^3. The investment includes the installation of a new cGMP cryogenic production line capable of operating at temperatures as low as -80 °C and is equipped with a 4000L Hastelloy reactor, filter drier, and cleanroom. The cGMP pilot-plant capabilities were also expanded with the addition of a new stream comprising a 400L Hastelloy reactor, filter drier, and cleanroom.

PCI Synthesis, meanwhile, added a 1000L jacketed reactor specifically designed for cryogenic chemistry to meet the needs of two recent projects including a new chemical entity moving from Phase I to Phase II and a generic API for which its client wished to de-risk the supply chain by adding PCI as an approved alternate supplier with in-house cryogenic capacity.

In addition to the 1000-gallon Hastelloy C reaction vessel, the system comprises three separate heat exchangers for liquid nitrogen, steam, and glycol; a specially designed pump; and control valves and control logic. The reactor is housed in a special suite and is paired with a 50-gallon glass-lined reactor for workups and additional processing and a 3-m^2 Hastelloy pressure drier. **PTE**

Several applications for cryogenic chemistry

Some reactions that are most often performed under extreme low temperature conditions, according to Ed Price, president and CEO of PCI Synthesis, include:

- Halogen-metal exchange (e.g., lithium)
- Lithium and sodium metal reductions
- Selective deprotonation and subsequent stereoselective, regioselective, and chemoselective reactions
- Stereoselective, regioselective, and chemoselective reductions of ketones, imines, and esters
- Asymmetric reactions such as Michael additions
- Selective Friedel-Crafts acylation (e.g., with oxalyl chloride)
- Swern oxidations.

The Case for Extended Dwell Flat Tooling

Increasing dwell time can improve tablet production.

Rob Blanchard is Research, Development, and Quality Systems manager at I Holland.

The requirement for quality tablets to be produced quickly and cheaply have led to advancements in tooling. To achieve problem-free tablet production, many processes must be investigated, and one of the main considerations to examine is the dwell time.

Dwell time is defined as the amount of time each individual punch head flat is in contact with the compression roller of a rotary tablet press when the compression force applied to form the tablet is above 90% of its peak value.

How formulation characteristics affect dwell time

Many issues can be traced to the characteristics of certain ingredients in a formulation that display differing plastic or elastic properties. These plastic or elastic properties can lead to tabletting issues such as sticking and capping. Particles that exhibit elastic form will change shape during applied stress; however, this effect is not completely permanent, with the particle returning to its original shape when the applied stress is alleviated. Those ingredients displaying plastic properties are permanently deformed when stress is applied above their elastic limit. The force employed and the length of time in compression can affect the way the formulation reacts, where the behaviour of a particle under compression can either stay deformed or "spring back" to its original shape. In cases of formulations with more time dependent consolidation behaviour, a long dwell time is important to create strong bonds between the particles.

Punch displacement velocity (i.e., strain rate) and dwell time are two factors that can significantly affect the compression behaviour of powders (1). As a rule of thumb, slower compression and decompression speeds and longer dwell times will improve the mechanical properties of a tablet (1). When certain elastic particles are subjected to a compression force for a longer period, further plastic behaviour is demonstrated; less "spring back" happens, which results in a more stable compacted tablet.

The effect of dwell time on friability

There may also be the problem of tablet friability with the tendency to crack, chip, or break during compression because of the formulation. It is important to get the compression force right—too high and it can adversely affect the tablet, but if the formulation is not cohesive and does not bind together sufficiently, then friability will occur.

Many tablet formulations are dwell-sensitive and require more time under compression to guarantee that they come out of the press without any faults. Some granules are difficult to compress effectively and require extended time under peak compression to ensure they receive the required hardness to shape into the fully formed tablet.

Trapped air and its negative effect

At pre-compression, a long dwell time at low to medium compression force is essential to expel air from the powder bed and for uniform distribution of granules in the die bore prior to final compaction under the main compression. Air must be expelled in order for the particles to stick together and form the tablet.

Air in the formulation can cause severe problems during manufacture. If the air is insufficiently squeezed out and/or density variations occur in the tablet volume, the tablet tensile strength is negatively affected, and the risk of tablet capping (when the top of tablet separates horizontally when ejected from the press) or delamination (when the tablet splits apart) increases. This problem used to be predominantly solved through the method of slowing the press down to expel air, but with today's requirement for faster tablet production, this approach is no longer a viable option and new, effective methods of increased dwell time to reduce air entrapment are required.

Other techniques

The crucial importance of extended dwell time can be illustrated by the frequent application of other

Key considerations in multilayer tabletting—a Q&A with Jean-Yves Balfin, product manager at Korsch AG

Multilayer tablets deliver a combination of therapeutic payloads in a single dosage form. An added advantage is that the API contained in each layer of the tablet can be designed to have different release profiles. The manufacturing of multilayer tablets is, however, more challenging compared with single-layer tablets, observes Jean-Yves Balfin, product manager at Korsch AG. "At first glance, it seems to be simple duplications of the classical single-layer compression cycle, one after the other in the same tablet press, but in reality, only the beginning of the process is classical, up to the dosing of the first layer," he explains. "From that point onwards, the differences become more obvious."

According to Balfin, the addition of further layers in a tablet creates several complexities. "For example, the previous layer has to be prepared in such a way that it allows bonding with the next layer while having a perfect separation line between the layers. Filling of the next layer has to be done without pulling down the lower punch during this step as is the case in a classical compression cycle using a filling cam," he says. "In addition, the product dosed out of the feeder must not be recirculated, otherwise cross-contamination would occur between layers. The individual weight in each layer must be regulated, while having several layers in the die." Balfin spoke to *Pharmaceutical Technology Europe* about the ins and outs of multilayer tabletting.

PTE: What are the key considerations in the production of multilayer tablets?

Balfin: There are several key considerations in the manufacturing process of multilayer tablets.

- **Filling.** The filling of the first layer is classically done using a fill cam that pulls the lower punch down, but for the second and subsequent layers, it is only the upper punch penetration at the tamping stage of the previous layer that creates space inside the die. This space is then used to fill the next layer. It is not possible to use a fill cam after the first layer, because the tamped first layer may remain in place in the die due to radial die-wall forces. For this reason, the upper punch penetration is required to make space in the die and to push the tamped first layer deeper in the die to facilitate the next layer fill.
- **Tamping.** A low tamping force, between 100 N and 1000 N, is typically applied to the intermediate layers with a minimum densification effect, so that a flat surface is created for the next layer filling space. The tamping force is then used for the weight regulation of the corresponding layer.
- **Layer separation.** There are different ways to keep each layer from passing into the next layer feeder. The best way is to contain the material in each feeder and to incorporate an integrated dust extraction nozzle to capture any fines or residue that may escape each feeder.
- **Weight control.** Final tablet weight is controlled by the main compression force. Single-layer weight control is based on the same principle, but it is adapted to the tamping forces and single-layer sampling. Due to lower forces applied when tamping multilayer tablets, the force measurement transducers may need to have increased sensitivity.
- **Layer sampling.** How can we sample a single layer if it is only tamped (not tabletted) and the compression cycle has not finished? Intermediate layer sampling can be achieved by increasing the tamping force during sampling to produce a sample that is hard enough to permit a weight measurement. Some tablet presses can eject every single layer through an additional outlet channel located just after tamping. Others are equipped with retractable feeders, and the layer is ejected through the general discharge chute. In this case, the layer hardening is executed at the final compression station, and the tamping force remains under automatic control during layer sampling.

PTE: What are the critical process parameters, and how do these affect the critical quality attributes of multilayer tablets?

Balfin: The following process parameters are crucial in multilayer tabletting:

- **Turret speed.** The multi-layer compression cycle is more complex than that for single-layer tablets and, thus, requires a very precise setup. Turret speed and the related dwell times for filling and pressing are, therefore, critical parameters for achieving the targeted layer weight and hardness.
- **Filling.** The time and space dedicated to the filling of the successive layers are more limited than when manufacturing single tablets, and there is limited fill space for the second and subsequent layers. All parameters related to the filling of the different layers are, therefore, critical for achieving weight uniformity of the layers and final tablets. The feeder paddle configurations and speeds of the successive feeders, as well as the settings of the upper punch penetrations, will greatly influence the ability to achieve target parameters (weight uniformity and hardness).
- **Tamping force.** A tamping force study is generally recommended to establish the maximum force at which delamination (i.e., layer separation after tabletting) will occur. The maximum force is balanced on the low end by the force necessary to create a clear and horizontal dividing line between the layers. Due to lower forces applied when tamping, the force measurement transducers may need to have increased sensitivity.
- **Vacuum for layer separation.** Effective layer separation is crucial for multilayer tablets, not only for aesthetic reasons, but also for chemical and pharmacological purposes (such as incompatibilities between the APIs, the different release profiles, etc.). The vacuum should, therefore, be high enough to avoid any cross-contamination between the layers but not high enough to adversely impact the production yields. Excessive dust extraction may also impact layer weight uniformity.

PTE: What are the solutions available for addressing the typical challenges in the production of multilayer tablets?

Balfin: The important thing is to achieve enough upper punch penetration to produce the required layer weight. There are upper punches adapted to multilayer compression (i.e., the upper punch tip has to be longer than the maximum insertion depth, while the lower punch and the die are the same as for single-layer tabletting). There are also some tablet presses with a 'deep fill' option.

There's also the need to achieve the right flow of the different layers with less space and time to fill the die. For this requirement, there are several configurations of feeders available.

Low tamping forces have to be measured with high accuracy. In this case, special compression rollers with strain gauges adapted to low force range are available.

Manufacturers also have to address delamination risk. The formulation and lubrication with excipients especially adapted to multilayer applications play a key role in avoiding delamination risk. The right setting of tamping force and the possibilities to increase the dwell time will further help.

And lastly, steps should be taken to avoid cross-contamination between two or more different products handled at the same time in the same machine. This can be prevented by special execution of the feeders with a sealing of the gap between feeder plate and die table, optimized die table scraping, and dust extraction before each feeder.

—Adeline Siew, PhD

techniques to increase the time that the punch is in contact with the compression roller, for example:

- Reduction of the tablet press speed in case of capping or insufficient hardness
- Installation of larger compression rollers to increase the total compression time
- Use of punches with a larger head to increase the size of the dwell flat.

These options are not always viable with the strict time and monetary constraints put on tablet manufacturers. This dwell time issue and customer demand led I Holland to investigate a method to increase the dwell time without slowing the press so that production could run sufficiently.

I Holland designed an elliptical head form, the eXtended dwell flat (XDF), to increase dwell time on existing presses without the need for expensive modifications. XDF can run on standard cams, giving users higher press speeds with challenging products and formulations. It also enhances tablet compaction/cohesion and can increase dwell time by up to 50% over a standard punch head, allowing more dwell than a D-type punch on a B-type tool. This increase helps to solve compression problems without upsizing punches or investing in a new press.

The following case study illustrates the benefits of XDF tooling in a production environment when tested by a leading pharmaceutical manufacturer.

Case study

The challenge. A specialty pharmaceutical company agreed to assess the XDF tooling. The goal was to create an operating environment where tablet quality was increased and waste reduction was improved on the production of a cold and flu tablet. The formulation would regularly stick to upper and lower punch faces. To minimize the problem, several methods were used to increase the compaction force, such as run the press to rejects to clear the sticking and manually scrape the tooling or remove the tooling for a polish, which resulted in downtime during manufacture.

Equipment. A Fette 2090i high-speed compressing machine with industry standard B type tooling was used in the trial during the manufacture of a tablet measuring 10.5 mm round and weighing 3.46–3.66 g. I Holland provided a full set of punches including the new XDF tooling.

Results. The maximum press output of 150,000 tablet per hour (tph) was regularly reduced to prevent sticking as the formulation was found to have low hardness and friability issues. XDF tooling stopped the problem of sticking, while increasing output from 150,000 to 225,000 tph. The use of XDF improved compaction force dwell time by 44% and an output of 225,000 tph was achieved, an improvement of 50%.

Overall it has been demonstrated through rigorous trials that the use of XDF tooling helps to prevent sticking, friability, capping, and tablet hardness. XDF also enhances tablet compaction and cohesion and can increase dwell time on a standard punch type. This increase helps to solve compression problems without upsizing punches or investing in expensive modifications or new presses.

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CPhI Pharma Awards to Celebrate Industry Innovations

Companies developing innovative new technologies, materials, and services will be recognized for their contributions to the bio/pharma industry with the presentation of the 2018 CPhI Pharma Awards at a dinner and ceremony on 9 Oct. 2018 during the CPhI Worldwide trade show.

The awards recognize pharma industry innovation across 17 categories of bio/pharmaceutical development, manufacturing, and management, including APIs, excipients, formulations, drug-delivery technologies, packaging, patient-centricity, contract services, and business performance.

The awards programme, now in its 15th year, honours companies and individuals advancing the pharma industry by developing advanced innovations, technologies, and strategies. An independent jury of bio/pharma industry experts reviews applications; and finalists will be announced on 28 Aug. 2018.

Winners will be announced at the CPhI Pharma Awards Gala Dinner at the Eurostars Madrid Tower on 9 Oct. 2018 during the CPhI Worldwide trade show in Madrid. UBM (part of Informa PLC), is the organizer of CPhI Worldwide and the awards programme.

More than 200 entries were submitted in 2017, more than double the number submitted in the previous year. Organizers expect an increase in applications for the Bioprocessing and Manufacturing category in 2018 as CPhI expands its coverage of bioprocessing technologies with the bioLIVE event, which will be co-located with CPhI Worldwide.

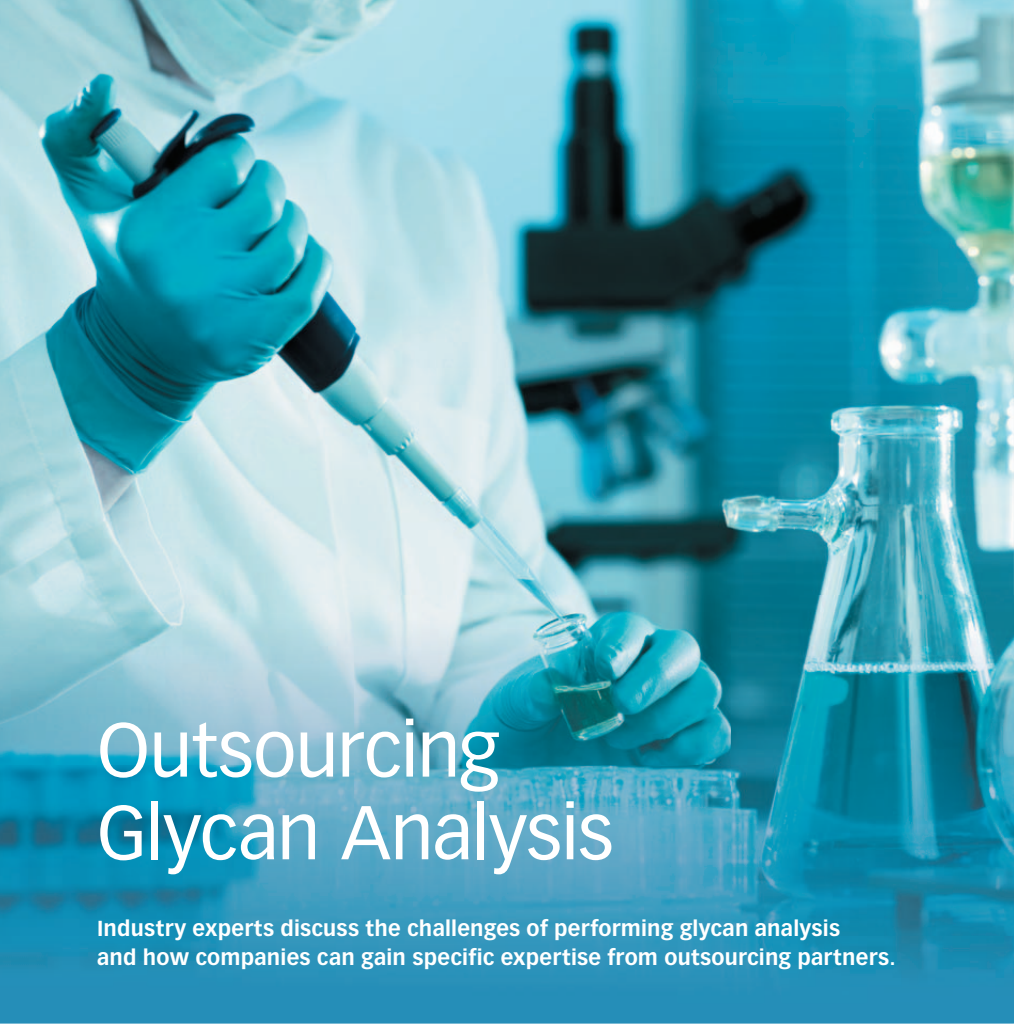
The categories for 2018 are as follows:

- Excellence in Pharma: API Development
- Excellence in Pharma: Formulation
- Excellence in Pharma: Excipients
- Excellence in Pharma: Manufacturing Technology and Equipment
- Excellence in Pharma: Bioprocessing and Manufacturing
- Excellence in Pharma: Analysis, Testing, and Quality Control
- Excellence in Pharma: Drug Delivery Devices
- Excellence in Pharma: Packaging
- Excellence in Pharma: Supply Chain, Logistics, and Distribution
- Excellence in Pharma: Contract Services and Outsourcing
- Excellence in Pharma: Regulatory Procedures and Compliance
- Excellence in Pharma: Corporate Social Responsibility
- Excellence in Pharma: CEO of the Year
- Excellence in Pharma: Pharma Company of the Year
- Excellence in Pharma: OTC
- Excellence in Pharma: Patient Centricity
- Excellence in Pharma: IT, mHealth & Digitalization

Additional information can be found at http://awards.cphi.com/.

CPhI Worldwide and *Pharmaceutical Technology Europe* are UBM (part of Informa PLC) brands.

Source: CPhI Worldwide



Outsourcing Glycan Analysis

Industry experts discuss the challenges of performing glycan analysis and how companies can gain specific expertise from outsourcing partners.

Susan Haigney

Pharmaceutical Technology Europe spoke with Aled Jones, senior product and applications manager at ProZyme; Philip Widdowson, European Application Development Scientist at Thermo Fisher Scientific; and Daryl Fernandes, chief executive at Ludger Ltd about the challenges of performing glycan analysis and how outsourcing companies can offer specific expertise.

The complex nature of glycan analysis

PTE: What are the specific challenges associated with glycan analysis?

Fernandes (Ludger): Thorough drug glycosylation analysis would involve full structural characterization of the oligosaccharides of each unique glycoform as well their absolute quantitation. However, this is not straightforward and getting even close to this still requires significant time, resources, and skill. To achieve this ideal you would, in principle, need to isolate each glycoform (including non-glycosylated drug variants), determine its relative abundance, then elucidate the glycan structures at each glycosylation site. However, it's generally very difficult to separate out all of a drug's glycoforms with complete resolution, and even if you have isolated a single glycoform, you need to deal with the glycans.

At first glance, glycans look like they should be simple to analyze because they're small molecules with a relatively small number of constituent monomers. However, unlike polymerization of monomers in linear macromolecules, there are many ways to link monosaccharides together to form glycan moieties. So, for each glycosidic linkage, you need to determine the identities of the connected monosaccharides, the anomericity (i.e., the spacial configuration) of that bond, and which of the hydroxyl groups around the monosaccharide rings are involved in the linkage.

Also, most drug glycans are not linear structures but are branched. This means you can find glycans with identical masses and monosaccharide constituents but different topologies, and these topological isomers can confer different physico-chemical and biological properties to the drug.

Another problem is skewing of glycoform profiles. This can be caused by degradation of glycans or either selective losses or enrichment of glycan species during sample preparation.

A further issue is that underivatized glycans can be difficult to visualize at analytical scale. They don't have natural fluorophores or strong chromophores for HPCL [high-performance liquid chromatography], and their ionization on MS [mass spectrometry] can be challenging as the glycan signals are readily attenuated by other chemicals such as salts and peptides.

Jones (ProZyme): As glycan analysis is still somewhat of a niche, it's perhaps less accessible than genomics or proteomics. Glycans display a broad structural diversity based on monosaccharide composition, linkage type, and branching. Added to this complexity is the site of glycan attachment; there is usually just one N-glycan site in the case of most IgG-based therapeutics but there can be more in Fc fusion proteins and other glycosylated biotherapeutics, and O-glycans may also be present in these.

Widdowson (Thermo Fisher Scientific): Due to the nature of their production, glycoproteins are highly heterogeneous molecules with numerous different glycan structures present at a single glycosylation site (1). Glycans are commonly released from the protein prior to analysis; however, the chemical properties of glycans make them difficult to analyze in their native form. Therefore, glycans are required to be derivatized in order to make them amendable for traditional analytical methodologies (2). O-glycans are much more difficult to analyze in the released form due to the lack of a universal release enzyme (3). In addition, glycans can be isomeric in composition, which complicates the accurate determination of structure, particularly

when using methods such as mass spectrometry (4).

Methods of analysis

PTE: What are the various methods for glycan analysis? Is there a preferred method?

Jones (ProZyme): Glycan analysis can be approached on a few different levels, from intact protein through to glycopeptides, released glycans, right down to individual monosaccharide components. Each of these techniques have their advantages and drawbacks. The route taken may depend on the molecule and the data required, but in general, relative quantitation of released glycans labelled with a fluorophore and separated by liquid chromatography is one of the most common approaches for analysis of mAb [monoclonal antibody] N-glycosylation.

Widdowson (Thermo Fisher Scientific): Depending on the specific information required, glycosylation analysis can be performed on different levels. Intact glycoprotein analysis allows for a quick overview of glycan distribution to be carried out. Analysis at the glycopeptide level makes site-specific glycosylation profiling possible by assigning specific glycan structures to distinct glycosylation sites. Analysis of released glycans analysis is currently the preferred strategy due to the high amount of information regarding the total glycan population, which can be elucidated (2). For released and fluorescently labeled glycans, HILIC [hydrophilic interaction liquid] chromatography is commonly applied either in isolation for relative quantification through fluorescent detection or coupled to mass spectrometry for characterization. More recently, there is a drive in the direction of analysis at the glycopeptide level, specifically when assessed as part of a multi-attribute method (MAM) workflow (5).

Fernandes (Ludger): The key is to develop a glycoanalysis toolset composed of orthogonal techniques that reliably measure the glycosylation critical quality attributes (GCQAs) for your therapeutic. You need several methods because there isn't a single technique that can cover all glycan analysis needs. In particular, you must have reliable methods for characterizing and quantifying potentially immunogenic glycans (such as those bearing Gal-alpha–1,3Gal motifs), as well as those for glycans that confer high therapeutic activity for your drug. So, selection of glycan analysis methods must be driven by a thorough understanding of the glycan structure-protein activity relationships for your therapeutic.

Also, your toolbox must furnish the breadth, structural detail, and sensitivity needed for every stage of your drug's lifecycle—and at suitable cost and throughput. This allows you to tune the methods according to the task. For example, glycan analysis for selection of clones to match your quality target product profile (QTPP) or in QbD [quality-by-design] studies to determine design space (DS) will typically require a very different performance profile from those needed for batch release.

Benefits of outsourcing

PTE: What are the benefits of outsourcing glycan analysis for sponsor companies?

Widdowson (Thermo Fisher Scientific): There is no single method that permits complete glycan analysis, and therefore, a panel of methodologies is often required not only to fully characterize the glycans, but also to meet regulatory requirements. Meeting these requirements in full demands the use of numerous types of instrumentation and analytical platforms. Sponsor companies regularly do not have direct access to all of these platforms, and it is not often economically or logistically viable to bring them on-site. Dedicated outsourcing companies for glycan analysis, therefore, play a key role in filling any potential gaps which may exist with respect to instrumentation and necessary expertise required to perform these methods (6).

Jones (ProZyme): Smaller or early-stage companies may not have the personnel to perform glycan analysis, or the instrumentation required such as liquid chromatography with fluorescence detection, capillary electrophoresis, and mass spectrometry. The existing instrumentation they have may not provide the data quality or capabilities of the 'latest and greatest'. Or there simply may not be time to implement or run an analytical method for glycans within the constraints of a project timeline. In these cases, it can make sense for sponsors to seek an outsourcing partner that has experience with glycan analysis and can turn data around in a timely manner.

Fernandes (Ludger): Outsourcing glycan analysis can allow sponsors to significantly extend their capabilities for drug realization. However, for success, it needs to be well-planned with a carefully chosen outsourcing partner. When poorly done, outsourcing can result in you losing time, money, and control of a critical part of your drug's development and give you data that's less than useful. Good outsourcing with an accomplished partner does the opposite, allowing you to overcome regulatory hurdles more smoothly and get your product to market faster than if you relied solely on your own resources.

The first step to successful outsourcing is choosing a reliable partner with the expertise and services that match your needs. They need to demonstrate their ability and experience with therapeutics of similar or greater complexity to your drug. Other key considerations include the quality of communication between you and your outsourcing partner, whether or not they will share their detailed methods with you and what follow-on services they could provide. Not that reliable glycan analysis will typically be much more complex and therefore more costly than, for example, routine peptide analyses. However, with a suitable outsourcing partner and carefully considered and well-executed plan, you should benefit from a significant return on your investment.

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Evaluation of Physical Characteristics of Dexlansoprazole Orally Disintegrating Tablets

Haiyan Grady, Michael J. Kukulka, Takako Ono, and Sai V. Nudurupati

Dexlansoprazole orally disintegrating tablet (ODT) is a proton-pump inhibitor (PPI) in a delayed-release formulation. The ODT presentation facilitates medication intake for patients with swallowing issues, whereas the delayed-release formulation enables intragastric acidity control for 24 hours. The microgranules used to prevent immediate drug release, however, could confer an unpleasant, gritty texture in the mouth. This article describes the approaches used during the development of a dexlansoprazole delayed-release ODT to evaluate tablet size and texture as they relate to disintegration rate and patient experience; in addition, the resistance to alcohol was also characterized. *In-vitro* and *in-vivo* disintegration studies, dissolution studies, and bioavailability studies were conducted. The experimental data presented in this article demonstrate the acceptable product physical characteristics of an ODT with a dual delayed-release mechanism.

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Orally disintegrating tablets (ODTs) have been widely accepted as a convenient dosage form, especially for geriatric and pediatric patient populations, because they can be taken easily without the need to swallow a whole tablet (1–3). The United States Food and Drug Administration (FDA) *Guidance for Industry: Orally Disintegrating Tablets* has provided basic requirements for the characteristics of an ODT product (4).

Most ODT products on the market are immediate-release tablets (5, 6). Formulation development for these immediate-release ODT products is commonly focused on achieving rapid oral disintegration in the mouth. After this disintegration, the residuals are either dissolved in the oral cavity or become a wet mixture of fine particles that is easy to swallow without water (7).

Dexlansoprazole ODT is a proton-pump inhibitor (PPI) in a delayed-release ODT formulation. Dexlansoprazole ODT contains two types of active microgranules that do not disintegrate or dissolve in the mouth. These microgranules are coated with different enteric-coated polymers to protect acid-unstable dexlansoprazole from stomach fluid and to release the drug in different intestinal regions via dissolution at different pH levels.

The microgranule size is significantly less than 500 µm to avoid a gritty feeling in the mouth after the ODT disintegrates into microgranules. Sucralose is used as a sweetener (8) and strawberry Durarome as a flavouring agent to create an acceptable taste.

Although the tablet disintegrates quickly in the mouth without water, the microgranules are protected by the enteric coating and remain intact until they enter the intestine and begin dissolving and releasing the drug. As a result, the pulsatile (or dual-delayed) drug-release profile provides prolonged plasma exposure.

The physical integrity of the enteric coating for the two types of microgranules must be preserved throughout the tablet compression process. An appropriate combination of inactive ex-

cipients is required to provide sufficient protection from the mechanical compression applied to the microgranules. The excipients must be highly water soluble and the quantity minimized to meet the requirements for a rapidly disintegrating tablet. After incorporation of these elements, the final form of dexlansoprazole ODT was a 700-mg round tablet.

PPIs are the first recommended therapy for patients with gastroesophageal reflux disease, one of the most common ailments treated by gastroenterologists (9); however, swallowing a capsule or a conventional tablet can be challenging for some patients, such as children, and this can impact adherence to medication regimens. Gastroesophageal reflux disease is common among people with difficulty swallowing, and dysphagic patients have reported a preference for ODT preparations over conventional tablets because of the reduced effort required to swallow them (10).

To the best of the authors' knowledge, there are only two approved ODT PPIs: lansoprazole ODT (Prevacid SoluTab; Takeda Pharmaceuticals America, Inc.; Deerfield, IL) and dexlansoprazole ODT. Prevacid SoluTab is a conventional delayed-release ODT product, whereas dexlansoprazole ODT is the only ODT product with a formulation that has a dual delayed-release mechanism. This formulation is efficacious regardless of food intake and time of administration and enables control of intragastric acidity for 24 hours (11–13). Therefore, the development of this product has widened the field of ODT technology (11, 14).

Several challenges arose in designing a dual delayed-release formulation ODT, including controlling tablet size, disintegration rate, and resistance to alcohol. Tablet size must be balanced with ease of administration and a disintegration rate rapid enough for patients to take it without water. Although tablet weight is not a direct measure of ODT product performance in patients, generally a large tablet (by size or weight) cannot be ingested easily without biting, chewing, or taking with water. Because many factors can affect ease of ingestion, tablet weight must be evaluated within the context of overall product performance (4). Finally, because enteric-coated polymers are soluble in common solvents (15), it is important to ensure that drug release is not significantly affected by alcohol in gastric fluid (16). This is necessary to avoid faster (or earlier) release of excessive drug levels ("dose dumping") mediated by ethanol.

This article describes the approaches used to address these challenges in the development of dexlansoprazole ODT. The authors focus on the process of evaluating product acceptability and the integrated approaches used, which incorporated *in-vitro* testing and clinical study data.

Materials and methods

Materials. The drug product (dexlansoprazole ODT 30 mg) was manufactured by Takeda Pharmaceutical Company, Osaka, Japan. Common pharmaceutical manufacturing technologies, such as wet granulation, fluid bed enteric coating, and tablet compression, were used. The tablet consists of dexlansoprazole (active ingredient) and the following inactive ingredients: lactose monohydrate-microcrystalline cellulose spheres, magnesium carbonate, low-substituted hydroxypropyl cellulose, hydroxypropyl cellulose, hypromellose, talc, titanium dioxide, mannitol, methacrylic acid copolymer, ethyl acrylate–methyl methacrylate copolymer, polysorbate 80, glyceryl monostearate, triethyl citrate, anhydrous citric acid, ferric oxide (red), ferric oxide (yellow), polyethylene glycol 8000, methylacrylate methylmethacrylate methacrylic acid copolymer, microcrystalline cellulose, crospovidone, sucralose, strawberry Durarome, and magnesium stearate.

Enteric polymers were purchased from Evonik Industries (Essen, Germany). The other excipients used are commonly used in pharmaceutical products and were purchased from commercial sources.

***In-vitro* disintegration test.** The disintegration test was performed per the procedure outlined in *United States Pharmacopeia (USP)* <701>, using a *USP* standard disintegration apparatus (17). Briefly, a basket rack assembly was used with 1000-mL low-form beakers (138–160 mm in height; inside diameter of 97–115 mm). This assembly contained six baskets, and each test tablet was placed in each basket. The baskets were lowered and raised in water as medium (37 °C) at a consistent speed. Tablet disintegration was observed and recorded.

***In-vivo* disintegration study.** The *in-vivo* disintegration of dexlansoprazole ODT was evaluated in a Phase I study conducted at Senopsys LLC (Woburn, MA). In this open-label study, eight healthy subjects (25–80 years of age) performed an oral disintegration test in triplicates. These men and women were trained to detect, identify, recognize, and describe different taste elements and flavour combinations and to measure oral disintegration times.

Each subject sipped and swallowed 20 mL of water. The time recording started. After 30 seconds, each subject placed a single 30-mg dexlansoprazole ODT on the tongue and gently rolled it against the roof of the mouth until it disintegrated into small granules. At the point when they would normally swallow the granules, the subjects recorded the time to disintegration and then expectorated the disintegrated tablet mass. Disintegration time was reported as the total elapsed time minus 30 seconds. This process was repeated on three separate days.

Subjects were contacted by phone one week after the testing to inquire about any adverse events.

Relative bioavailability study 1. The methodology for the clinical study to assess the effect of concomitant administration of a high-fat meal on the bioavailability of dexlansoprazole from the ODT has been reported previously (1). As an exploratory assessment, a taste questionnaire was given to subjects after dosing to assess reactions to the taste of the ODT. Participants evaluated the flavour, texture, and overall taste on a scale of 1–5 (from 1 = "disliked it very much" to 5 ="liked it very much") and rated the ease with which this formulation can be taken once daily without water for four to eight weeks on a scale of 1–5 (with 5 being the easiest). The results of the taste questionnaire were tabulated and descriptive statistics computed.

Relative bioavailability study 2. The methodology for the clinical study to assess the effect of mixing the ODT with water and administering the mixture *via* an oral syringe or nasogastric tube on the bioavailability of dexlansoprazole from the ODT has been reported previously (1). A questionnaire assessing the subject's reaction to the tablet residue and the need for a water rinse was used as an exploratory assessment. The questionnaire was administered after the delayed-release ODT had been placed in the subject's mouth, allowed to disintegrate on the tongue, and swallowed without water. The following questions were posed:

1. Following administration of the ODT without water, did you feel that there was tablet residue remaining in your mouth? (Yes or No)
2. If yes, please estimate the amount of water you think would be needed to clear the residue from your mouth by selecting 1 of the 3 choices below:
   a) No water rinse would be needed.
   b) A sip of water would be needed.
   c) Would need one-half of a glass of water or more.

The results of the questionnaire were tabulated and descriptive statistics computed.

Dissolution test. The dissolution test was performed per the procedure for delayed-release product in *USP* <711> (18), using *USP* basket apparatus 1. *In-vitro* dissolution was performed in two stages (acid and buffer stages). Tablets were first exposed to 0.1 N hydrochloric acid (HCl) for 120 minutes. After acid-stage testing, the resulting granule sample was transferred to the corresponding buffer-stage medium. Buffer-stage testing was continued per the procedure, and the assay was conducted by UV spectrometry.

For evaluation of dexlansoprazole ODT resistance to alcohol, ethanol concentrations of 0, 5, 10, 20, and 40% (vol/vol) were mixed in acid- and buffer-stage dissolution media. The pH of the buffer media was adjusted after ethanol was added.

Results

Disintegration by *in-vitro* and *in-vivo* methods. *In-vitro* disintegration data from three lots in a long-term and accelerated stability study are summarized in **Table I**. Disintegration time ranged from 29–37 seconds for tablets stored at 25 °C/60% relative humidity between 0 and 24 months and from 29–36 seconds for samples stored at 40 °C/75% relative humidity for six months.

To determine whether dexlansoprazole ODT exhibited the same properties in a more physiological environment, a

Table I: Mean *in-vitro* disintegration time for dexlansoprazole orally disintegrating tablet (ODT) stability study. RH is relative humidity.

		Disintegration time (s)		
Storage condition	**Testing interval (months)**	**Lot A**	**Lot B**	**Lot C**
25 °C/60% RH	0	32	31	29
	12	32	30	31
	18	30	32	33
	24	37	33	34
40 °C/75% RH	6	35	36	34

Table II: Descriptive statistics of taste questionnaire for dexlansoprazole orally disintegrating tablet (ODT) 30 mg administered without water. SD is standard deviation.

	Flavour	Texture	Overall taste	Ease of administration*
N	68	68	68	68
Mean ± SD	4.4 ± 0.62	3.9 ± 0.87	4.3 ± 0.64	4.4 ± 0.72
Range	3-5	2-5	3-5	3-5

*The question was, "On a scale of 1 to 5 (with 5 being the easiest), please rate how easy it would be to take this formulation daily without water for 4 to 8 weeks."

human *in-vivo* disintegration study was conducted with four men and four women. Disintegration time is inherently variable because of differences in salivation rate and oral cavity size geometry between subjects. Individual disintegration times for each trial ranged from 29–43 seconds. The mean and median *in-vivo* disintegration time was 36 seconds.

Dexlansoprazole ODT disintegrates in less than one minute in both *in-vitro* and *in-vivo* tests. Similar to what was described in other studies, there was good correlation between the *in-vivo* human oral disintegration test data and the compendia *in-vitro* disintegration data for dexlansoprazole ODT (19, 20).

Tablet weight. To assess the size acceptability of dexlansoprazole ODT, a survey was conducted in conjunction with a Phase I food effect study. Responses are summarized in **Table II**.

Overall, healthy subjects in this study found the product flavour, texture, and overall taste agreeable, with the highest mean scores for flavour and overall taste. Subjects also indicated that dexlansoprazole ODT could be easily taken daily without water for four to eight weeks.

Another survey was conducted during a different Phase I study to assess reaction to tablet residue and the need for a water rinse after administration of dexlansoprazole ODT. After allowing oral disintegration and then swallowing, 60% of subjects reported tablet residue; most (73%) could use a sip of water to clear the residue (**Table III**).

The active enteric-coated microgranules are designed to remain intact in the mouth, but optimal design should prevent them from imparting a gritty feeling in the mouth. The authors found that 40% of subjects did not sense any residue, whereas of the remaining 60% who felt some residue, 93% thought no water was needed or a sip of water was sufficient to rinse the residue.

Table III: Residue questionnaire response for dexlansoprazole orally disintegrating tablet (ODT) 30 mg administered without water.

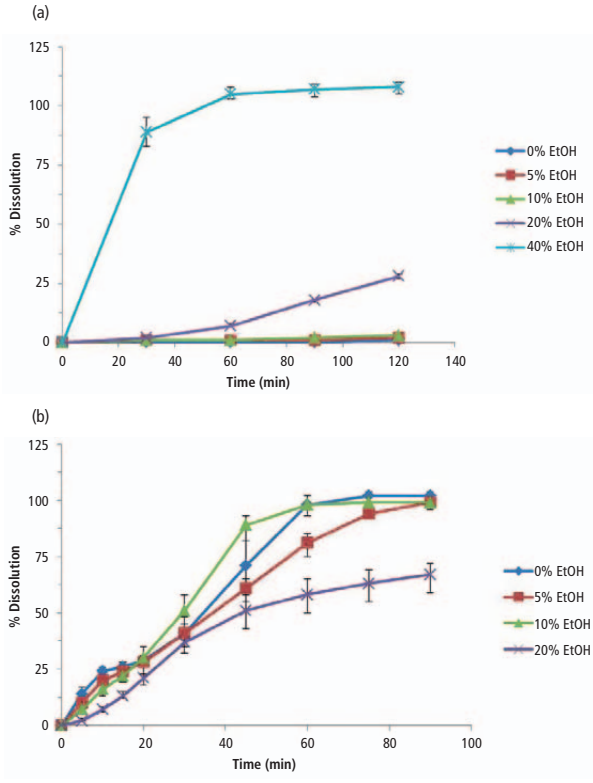
Question	Response, n (%)
Was there tablet residue? (N=75)	
Yes	45 (60)
No	30 (40)
If residue remained, amount of water needed to rinse (N=45 who answered "Yes" previously)	
No water	9 (20)
A sip of water	33 (73)
1/2 glass of water	3 (7)

Effect of alcohol on dexlansoprazole ODT drug release. Dissolution experiments were performed to evaluate the effect of alcohol on dexlansoprazole ODT drug release. The mean dissolution results of the acid and buffer stages in the presence of ethanol are shown in **Figures 1A** and **1B**, respectively.

During the acid-stage dissolution test, if the ethanol content was not more than 10%, the prespecified acid resistance criteria were met, with no more than 10% dissolution occurring during a maximum of 120 minutes, and the enteric coating left intact. At 20% ethanol content, the enteric coating was dissolved gradually and reached 28% release by 120 minutes. When 40% ethanol was used, the enteric coating was entirely dissolved within 60 minutes.

At alcohol contents up to 10%, the drug-release profiles in the buffer stage were similar to those seen without alcohol. In 20% alcohol medium, drug release was less than 70% of

Figure 1: Dissolution profiles of (A) acid-stage media by ethanol concentration and (B) buffer-stage media by ethanol (EtOH) concentration.



the starting amount because 28% of the drug had already been released in the acid stage. The buffer-stage medium containing 40% ethanol was not tested because all of the drug was released in the acid-stage medium containing 40% ethanol (18). At 40% alcohol concentration in acid-stage medium, drug release was quite high because of the solubility of the enteric-coated polymer under these conditions. However, alcohol concentrations of 20% to 40% in gastric fluid are much higher than those likely to be present under physiological conditions.

Discussion

The ODT formulation of dexlansoprazole 30 mg was developed to address challenges in patients who have difficulty swallowing. The FDA *Guidance for Industry on ODTs* considers the following characteristics in defining an ODT: rapid disintegration time and tablet size and weight in relation to the intended use for the drug. The integrated *in-vitro* and clinical approach presented here demonstrates how the authors evaluated three key parameters crucial to an effective ODT design: tablet size, disintegration rate, and resistance to ethanol.

FDA recommends that products labelled as ODTs have an *in-vitro* disintegration time of approximately 30 seconds or less, based on the *USP* disintegration test method (4). Using the *USP* <701> disintegration test, the disintegration time of dexlansoprazole ODT was shown to be consistent in a range from 29–37 seconds, regardless of product storage conditions and length of time stored.

USP test conditions do not necessarily resemble actual conditions in the human mouth. For example, the testing medium volume significantly exceeds the saliva volume in the human mouth. The testing agitation pattern (i.e., baskets moving in and out of medium) is also different from the motion in a human mouth (19, 21).

To better assess disintegration under physiological conditions, the authors also conducted a human *in-vivo* disintegration study. The mean *in-vivo* disintegration time, 36 seconds, was consistent with the results from the *in-vitro* study. Although FDA guidance recommends less than 30 seconds for disintegration for ODT products, they also acknowledge that 30 seconds is a general time period associated with drugs that match the characteristics of ODTs (4). For this reason, agreement between *in-vitro* and *in-vivo* disintegration rates at close to 30 seconds, without water or chewing in the *in-vivo* test, is acceptable for an ODT formulation.

FDA guidance further states that ODTs should not weigh more than 500 mg, unless the product's performance and ability to act as an effective ODT justify the extra weight (4). Because of formulation and manufacturing necessities, each dexlansoprazole ODT weighs approximately 700 mg. The surveys reported here showed that volunteers considered the tablet to be easily taken daily with water from four to eight weeks. The authors also found that 40% of all volunteers taking dexlansoprazole ODT without water did not note any tablet residue remaining in their mouth. Almost all the volunteers (93%) who did note residue found that it could be rinsed away with no more than a sip of water. These results together support the acceptance of a 700-mg tablet in this formulation. The results are consistent with the presence of other ODTs on the market that weigh more than 500 mg that have generally been well accepted (14).

Because patients might consume alcoholic beverages while on medication, the risk of dose dumping caused by an alcohol-induced drug-release rate change has generated several discussions between regulatory agencies and the pharmaceutical industry (16, 22, 23). The results of the *in-vitro* dissolution studies showed that administration of dexlansoprazole ODT with a moderate amount of ethanol did not result in premature or excessive release of the drug (i.e., dose dumping). The enteric coating of the granules maintained its integrity at ethanol concentrations up to 10% for 120 minutes. This concentration of ethanol could be expected in the gastrointestinal tract for patients who consume alcohol immediately before taking the medication. Complete release of the drug in the stomach can only occur at ethanol concentrations of 40% for 60 minutes. This concentration is not likely to occur *in vivo* for a 60-minute period. For

FIGURE COURTESY OF THE AUTHORS

example, a 1.5-ounce (approximately 50 mL) shot would be diluted in the gastric fluid (approximately 240 mL) in the stomach, and the alcohol concentration would be reduced to less than 10% (24,25). Only the rapid intake of a substantial volume of alcohol would increase the concentration over 10%, but it would be very unlikely to reach 40%, which is the ethanol concentration at which the most rapid dissolution occurred in the acid-stage medium.

Conclusion

Dexlansoprazole ODT is a unique ODT product containing two types of enteric-coated microgranules for a delayed-release formulation and extended control of intragastric pH over 4.0. Design of such a tablet presents certain inherent challenges with regard to allowing oral disintegration and a delayed-release pharmacokinetic profile while maintaining convenience and palatability for patients. The authors have described an effective method that combined *in-vitro* and *in-vivo* approaches to evaluate the tablet's weight, disintegration time, mouth feel, and resistance to alcohol. The experimental data presented here demonstrate the acceptable product physical characteristics of an ODT with a dual delayed-release mechanism.

Disclosures

Haiyan Grady is an employee of Takeda Development Center Americas, Inc., Deerfield, IL. Takako Ono is an employee of Takeda Pharmaceutical Company, Japan. Michael Kukulka and Sai Nudurupati were employees of Takeda Development Center Americas, Inc., Deerfield, IL, at the time of this study.

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Exploring a Modern Control Strategy for Wurster Coating

A process control system based on PAT can compensate for variations in particle size, resulting in more consistent coating thickness.

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Drug-layered multiparticulates are a common dosage form for extended or modified-release pharmaceutical formulations. Delivered either in capsules, tablets, or as food additives in paediatric or geriatric applications (1), these formulations typically feature a functional coating designed to delay dissolution of the drug in the body.

Wurster coating, using bottom-spray fluid-bed technology, is commonly used to manufacture these formulations, in a multi-phase process. Manufacturing is typically controlled by spraying a fixed quantity of coating factor on the substrate. For a well-developed coating process, spray efficiencies can be highly consistent. However, variability in product quality can often result from raw material variations in the substrate.

This article discusses research into ways to improve control of the overall process, to minimize substrate raw material and final product variability. In this work, microcrystalline cellulose (MCC) multiparticulates were used as a substitute for a drug-layered substrate and were layered with an aqueous-based enteric coating.

Because coating thickness is the primary critical material attribute influencing dissolution rate (2–4), the goal of this research was to minimize the impact of varying substrate raw material particle size and surface area on the resultant coating thickness. A smart process control system was used in conjunction with process analytical technology (PAT) to monitor and dynamically control key process parameters in order to improve consistency in measured coating thickness at the end of spraying. The automated fluid-bed control system was designed so that the spraying process would stop once a pre-determined coating thickness had been reached that would provide the required dissolution profile.

The approach was demonstrated in application to two different substrate materials, with marginally different particle size characteristics in order to represent real-world raw material variability. Results showed that even a small variation in median diameter can have a significant influence on the total surface area. Experiments documented the differing quantities of coating factor that were required to achieve target growth in each case.

Materials and methods

Materials. Cellets 500 (MCC) (Ingredient Pharm) were used as a substrate material for coating. No API layer was applied for this development study due to processing limitations. A 15% w/w aqueous suspension of 80:20 Surelease:Opadry (Colorcon Inc.) was used to coat the particles. Surelease (aqueous dispersion of ethyl cellulose) was applied as a barrier membrane coating on the Cellets while Opadry (a hypromellose-based coating system) acted as a pore former in the coating formulation.

The Cellets 500 (approximately 500–710 µm) were screened with a 600-µm sieve to create two populations of marginally different sizes (approximately 67-µm difference in Dv50, which is a measure of the volumetric median particle diameter). Both populations fall within the material specification for Cellets 500 and may be considered to represent a batch-to-batch variation for this application.

Three batches of each size were coated to establish the repeatability of results. The three batches of larger size pellets are referred to as L1, L2, and L3, and the three batches of smaller material are referred to as S1, S2, and S3.

Equipment. Wurster coating was conducted in a Glatt GPCG2 lab-scale fluid-bed system with a six-inch, PAT-compatible, bottom-spray product container. A Schlick 0.8-mm nozzle was used to spray the coating solution with a 4.5-mm air-collar spacing. A type-B orifice plate was used for appropriate fluidization, with a Wurster column height of 25 mm.

The Eyecon$_2$ Direct Optical Imaging Particle Analyser (Innopharma Technology) was used for real-time measurement of the particle size distribution inline, through the lowest window of the product container, as shown in **Figure 1**. Direct imaging involves capturing images of the particles in-process through the window/inspection port, and running these through a series of image analysis steps to measure the size and shape of each particle present. Analysis parameters were set to fluid-bed coating defaults, with a results integration period of 120 seconds to optimize data for smooth process control.

Variability in product quality can often result from raw material variations in the substrate.

Control. In-line particle size data and all GPCG2 sensor data were aggregated during processing in real time and used for process control by the SmartFBx (Innopharma Technology) advanced development and manufacturing platform for fluid-bed systems.

Rather than determining the end point of the process' spraying phase based on when a fixed quantity of coating factor has been added, the SmartFBx controller was configured to monitor particle size growth and continue spraying until a target growth had been achieved.

This target was determined by inline, real-time measurement of the Dv50 of the fluidized pellets during the material preheating phase prior to the start of spraying and comparing Dv50s reported throughout the spraying phase with this baseline value to determine growth. For these experiments the target Dv50 growth was 32.5 µm, equating to a coating thickness of 16.25 µm. This value was chosen because it was the approximate growth achieved in prior experiments during which coating factor had been added to reach a predicted 10% weight gain.

Other key equipment parameters of the GPCG2 were also controlled by

Figure 1: Process analytical technology compatible product container with Eyecon2Particle Analyzer (Innopharma Technology).

Figure 2: Automatic process controller flow diagram. PI is a proportional–integral control algorithm.

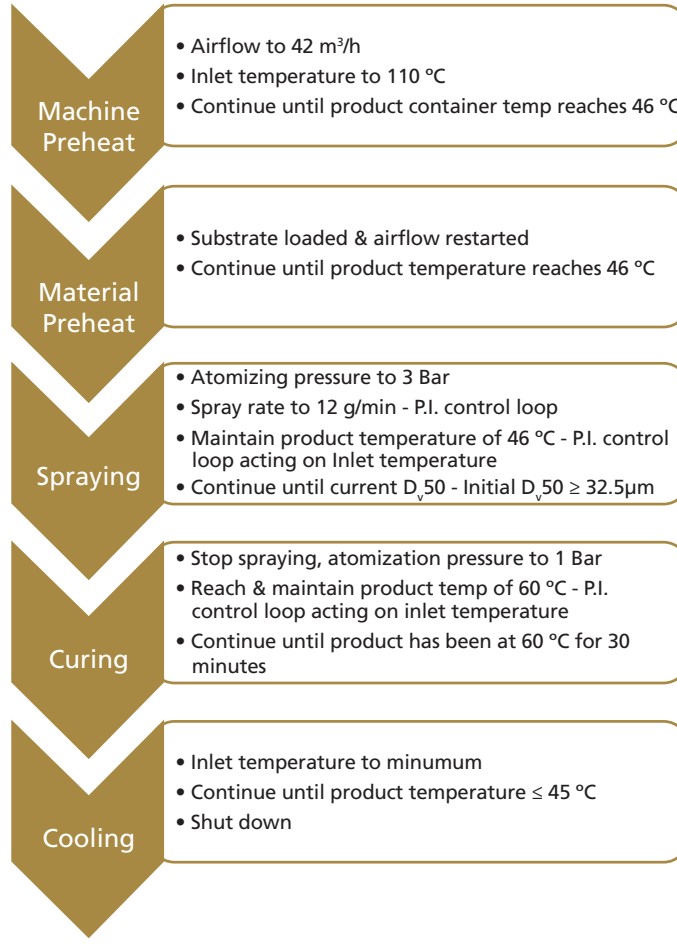

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Figure 3: Eyecon2 Particle Analyzer (Innopharma Technology) particle size data for batch S2. Dv50 is the volumetric median particle diameter; Dv10 and Dv90 define the 10th and 90th percentiles.

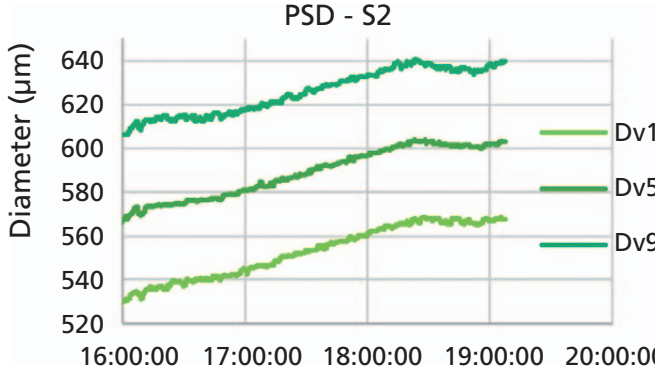
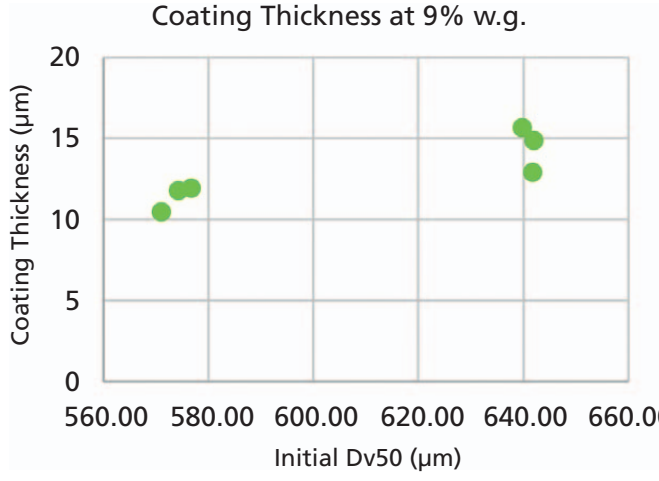


Figure 4: Coating thickness at 9% weight gain (w.g.) vs. substrate starting size (Dv50).



SmartFBx within optimum ranges as determined during an earlier design of experiments study. The controller also automatically stepped through process phases when the appropriate conditions for each had been met. A flow diagram for the process phase logic used is presented in **Figure 2**.

Results and discussion

Two approaches were used to explore the effects of the variation in substrate particle size on the coating process:

1. Measurement of growth in coating thickness for a fixed quantity of coating factor, equivalent to a constant projected weight gain.
2. Control of the total quantity of coating factor sprayed based on Eyecon data to achieve a precise target coating thickness.

Particle size data. Figure 3 aids in visualizing the particle size data used by the process controller by showing an example of the Dv10, Dv50, and Dv90 trends measured by the Eyecon$_2$, in this case from batch S2. Dv50 is the volumetric median particle diameter, while Dv10 and Dv90 define the 10th and 90th percentiles; together these three values provide a simple description of the particle size distribution (PSD). Spraying took place between 16:05 and 18:22 minutes from cycle start, during which time a steady increase in particle size across all three parameters was seen. During the course of each batch, the Eyecon$_2$ made approximately 500,000 particle measurements.

PSD impact on coating thickness. Before examining results from the coating-thickness-driven control strategy, it is important to consider what effect the ~67-µm variation in Dv50 would have had on product quality under a traditional fixed-spray-quantity control regime. To assess this, the measured particle growth for a given spray quantity (1050 g of solution or a predicted weight gain of 9%) was compared across all batches.

A control strategy using real-time particle size distribution measurement to calculate growth has been shown to provide consistent coating thickness results for varying substrate sizes.

In **Figure 4**, two groupings of points can clearly be seen: batches S1, S2, and S3 with initial size of 570–575 µm, and batches L1, L2, and L3 with initial size of approximately 640 µm. The coating thickness value was derived from half the difference in Dv50s between the start of spraying and the point at which 1050 g of coating factor was added. It can be seen from **Figure 4** that the coating thickness for the smaller batches is approximately 3 µm thinner than that of the larger pellets. This result demonstrates that there is a discernible impact on coating thickness due to variation in particle size of substrate under a fixed-spray-quantity control regime.

Impact on dissolution. To assess the influence that coating thickness would have on end-product dissolution (assuming that the process target were 9% weight gain), the authors developed a simple mathematical model (4), correlating

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coating thickness against dissolution for the same Surelease/Opadry coating applied to a chlorpheniramine maleate (CPM) drug-layered particle. The relevant equations from the model (4) are:

$D_{15} = 0.053T_c^2 - 4.524T_c + 98.71$

$D_{30} = 0.007T_c^2 - 2.61T_c + 100.2$

$D_{60} = 0.0005T_c^2 - 1.7416T_c + 101.8$

$D_{120} = -0.017T_c^2 - 0.455T_c + 100.3$

$D_{240} = 0.008T_c^2 - 0.163T_c + 99.74$

where D_T indicates dissolution percentage after the given time in the water bath, and T_c is the measured thickness of the coating at the time the sample was extracted from the process.

Making control decisions based on real-time process measurements to track true particle growth eliminates the need for complex, formulation dependent empirical models.

Figure 5 shows the variability that would be expected for these functional coating thicknesses applied over a CPM-coated bead.

Due to the relatively thin coatings and function of Opadry as a pore former in this formulation, these dissolution rates are representative of a relatively fast extended/modified-release product, such as one targeting a specific area of the gastrointestinal tract. For a slower release coating, however, similar variations in dissolution but over longer timeframes would be expected. Variation in this case is >10% at the 30-minute dissolution time point and 9% at 1 hour.

Variation in required coating quantities. Using the control strategy of spraying until a target particle growth is reached resulted, as expected, in consistent coating thicknesses with a variation in the total amount of coating solution required for each batch. This result can be linked to the variation in the particle size of the substrate, and may also be influenced by other parameters, such as fluidization patterns, surface porosities, and spray efficiencies (5,6).

Figure 5: Predicted chlorpheniramine maleate dissolution profiles for each batch at 9% weight gain (w.g.).

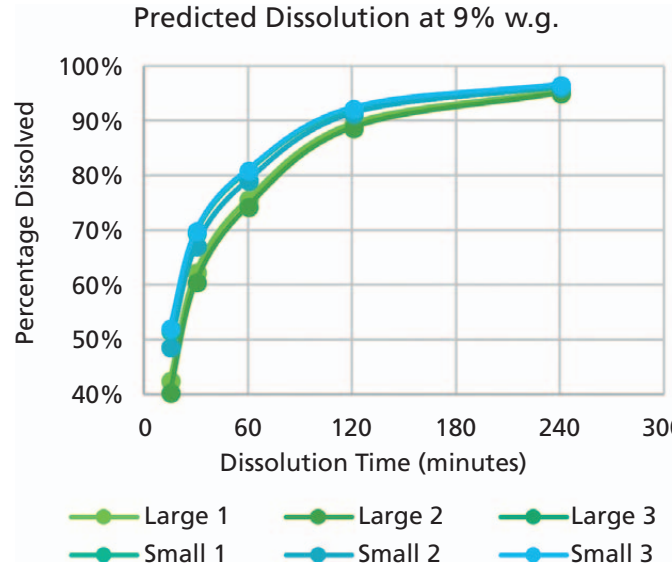


Figure 6: Total coating solution required per batch to reach coating thickness target. Dv50 is the volumetric median particle diameter.

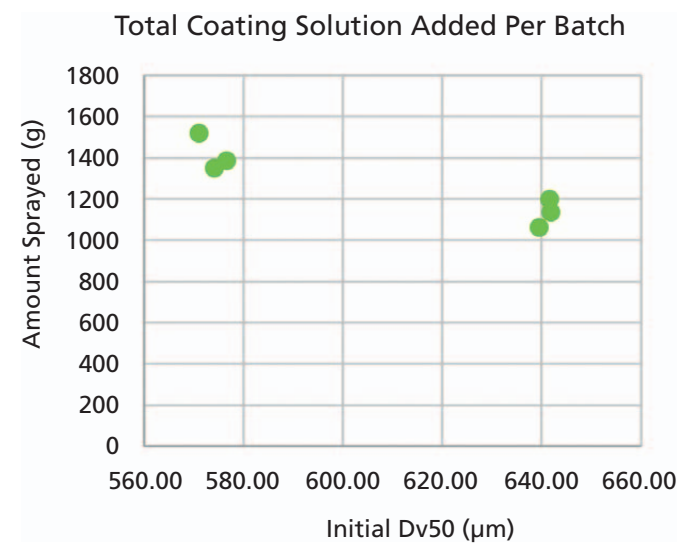
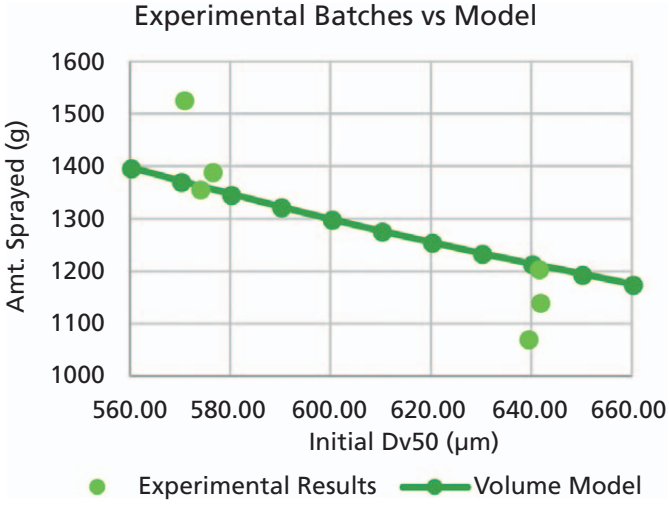


Figure 6 demonstrates a clear downward trend in coating solution requirement from the "small" runs (left-hand cluster) to the "large" runs (right). This behaviour is as expected due to the greater total surface area present in the smaller particle size batches. The behaviour demonstrates the control strategy's ability to effectively compensate for these variations without the need for formulation-specific empirical models.

Predictive model results. The benefit of basing these control decisions on PAT measurements can be demonstrated by examining the results of a simple prediction model relating coating factor requirements

Figure 7: Coating factor required vs starting Dv50 (the volumetric median particle diameter), for experimental batches and a simple prediction model.



to initial substrate particle size. **Figure 7** displays the experimental results compared to the predicted quantities for a range of starting Dv50s based on a calculation of the ratio of final coating layer volume to substrate volume.

Figure 7 shows an agreement in overall trend between the experimental and predicted results, although there is considerable variation. Because each batch was coated to a constant coating thickness, the variation in quantities sprayed could be attributed to variations in other processing factors such as spray efficiency, substrate porosity, particle mass effects, PSD width, and any agglomeration or attrition present in the process.

Making control decisions based on real-time process measurements to track true particle growth eliminates the need for complex, formulation-dependent empirical models to calculate and compensate for such sources of variability. This traditional approach would be necessary if spray quantities were being controlled solely based on off-line raw material size measurement.

Conclusion

With traditional process control methods, variation in substrate particle size impacts coating thickness on a meaningful scale. Dissolution model results indicate that the tested size difference of ~67 µm in Dv50 would have resulted in more than 10% variability in quality control dissolution test results in which pellets were coated to 9% weight gain.

A control strategy using real-time particle size distribution measurement to calculate growth, however, has been shown to provide consistent coating thickness results for varying substrate sizes. Similar results could not be achieved using offline measurement without the use of complex empirical models and variability due to other process attributes.

Additional work is planned to apply this control methodology to an API-coated substrate and validate the predicted lower variability in quality control dissolution testing.

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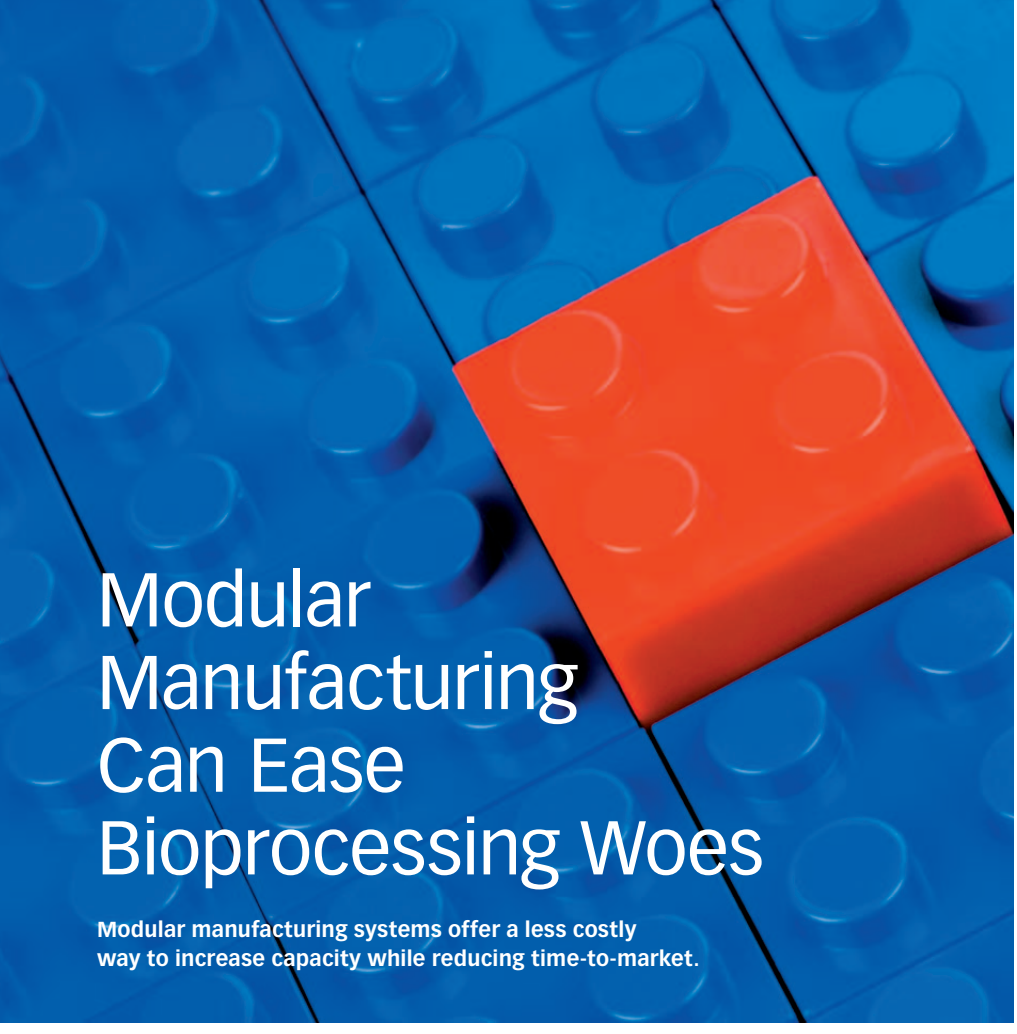

Modular Manufacturing Can Ease Bioprocessing Woes

Modular manufacturing systems offer a less costly way to increase capacity while reducing time-to-market.

Feliza Mirasol

Modular manufacturing is being increasingly used in the biopharmaceutical industry where flexibility and low-cost manufacturing systems are sought out. The design of a modular system in biopharmaceutical and pharmaceutical processing can involve breaking down a manufacturing facility into smaller functional building blocks, also known as modules (1).

The term modular manufacturing is used throughout the biopharmaceutical industry in reference to modular facilities, modular processing equipment, or modular automation platforms, according to Joe Makowiecki, Enterprise Solution architect at GE Healthcare Life Sciences.

"Any of these can fit the definition in that they involve modules as the basis of design or construction. Modular is particularly attractive for its ability to provide flexibility for diverse and evolving technologies," Makowiecki says.

In addition, a major trend in the cleanroom industry is a shift toward using modular construction, such as PODs, which are pre-assembled modules that are typically built offsite and then integrated into a facility onsite. PODs provide self-contained and autonomous cleanrooms (2).

Reduction in lead time, increased flexibility, functionality, and ease-of-cleaning are factors driving the cleanroom industry toward modular systems (2).

A critical point to consider when creating a modular manufacturing system is the biomanufacturing process that will be used with the system. To that end, GE Healthcare designed KUBio, a prefabricated, modular manufacturing facility solution based on single-use technologies, to optimize the process flow in biopharmaceutical production. The facility has been standardized to reduce facility-modelling time and offers a consistent setup in any global location.

One of the challenges in the industry today is that the the large and diverse pipeline of biologics does not largely fit the current manufacturing infrastructure, Makowiecki points out. Higher product titers, biosimilars and new personalized therapies are driving batch sizes, cost reduction, and multiproduct manufacture flexibility.

"KUBio has been created with these drivers in mind, providing flexibility, reduced time to production, defined investment from the beginning of the project and global regulatory compliance," Makowiecki adds.

A major trend in the cleanroom industry is a shift toward using modular construction, such as PODs.

Modular construction

POD cleanroom units differ from traditional, fixed cleanrooms in that they offer ease of scalability, are mobile, and can be repurposed once a production process reaches the end of its lifecycle (3). PODs can be applied to many types of biopharmaceutical product manufacturing, including monoclonal antibodies, vaccines, recombinant proteins, personalized medicines, cell therapies, and gene therapies. In addition, the unit can be used for laboratory work (4).

G-CON Manufacturing, a provider of autonomous cleanroom PODs, works with pharmaceutical and biotechnology companies to design POD cleanrooms that fit the specific applications required by these companies.

Following construction of the initial box structure, G-CON would then install internal wall systems and outfit the unit with ductwork, air-handling systems, automation and controls, doors, windows, flooring, and fire alarm systems, depending on the specified design (4).

Once built and outfitted, the PODs are subjected to a factory acceptance test (FAT) to confirm that predetermined specifications are met. From there, PODs are wrapped and shipped to the onsite location, where they will be interconnected, according to G-CON. The process of constructing PODs differs from the traditional method of constructing cleanrooms because PODS require less crew member and less time to construct (4).

Modular manufacturing… helps engineers maintain timelines and cost certainty while allowing them to adhere to design specifications.

Integrating modular systems

Because modular systems can also be integrated into already existing facilities, it offers a less capital-intensive means to adopt modular manufacturing than having to build a new facility. As an example, GE Healthcare's FlexFactory, a configurable, integrated, single-use biomanufacturing platform, is designed to fit a new or an existing manufacturing plant.

"The FlexFactory is a flexible, multiproduct biomanufacturing solution that can incorporate existing, qualified technologies as well as integrate new technologies that improve costs and process efficiencies," says Makowiecki.

The KUBio facility consists of 50–80 prefabricated modules, each module manufactured and fitted out with building services infrastructure, including heating, ventilation, and air conditioning (HVAC), electrical, and plumbing prior to shipping.

"Parallel production pathways save time; while the modules are being manufactured, the customer site is prepared, and the manufacturing equipment is secured," according to Makowiecki.

Furthermore, a prefabricated facility like KUBio can be added to an existing site to increase manufacturing capacity or to increase production in a segregated manufacturing environment for sensitive products such as viral vectors that require an enhanced biosafety level of production.

Adding capacity is particular challenging for pharmaceutical facility planners because it involves many strategic engineering and logistical factors. Modular manufacturing is an optimal platform to address these challenges by helping facility engineers maintain timelines and cost certainty while allowing them to adhere to design specifications (5).

Modular pharmaceutical manufacturing helps mitigate the problems in older, traditional biomanufacturing buildings, many of which were designed prior to the most current cGMP regulations. These traditional facilities often have energy-inefficient heating, ventilation, and air conditioning (HVAC) systems that may not be properly isolated from other operations, according to Germfree Laboratories, a provider of custom-built biosafetly equipment.

Modular manufacturing systems offer solutions to problems such as these by providing self-contained, energy-efficient HVAC and air filtration systems. They also give engineers a new range of options and allow engineers to focus on changing product requirements, capacity demands, and new R&D initiatives during the planning and design phase (5).

"We see that there is an increasing need for flexible, multiproduct, prefabricated biomanufacturing solutions for commercial production. Today there are three KUBios and over 50 FlexFactories globally. Most of these facilities are used for clinical production, but there are also commercial sites, and the number is expected to increase in the coming years," says Makowiecki.

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Risk-Based Predictive Stability for Pharmaceutical Development–A Proposed Regulatory Template

A published regulatory template sharing best practices for filing RBPS data would benefit the industry and regulatory reviewers by enabling a consistent presentation of predictive data and conclusions.

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The science of stability has significantly evolved since the advent of International Council for Harmonization (ICH) Q1A(R2) (1). Improved modelling tools coupled with appropriately tailored protocols have enabled similar or better stability predictions within accelerated timeframes, when compared to a more traditional ICH approach (2–4). These tools provide increased understanding of attributes that influence drug substance and product stability instead of following the traditional ICH approach, which simply demonstrates stability in an empirical manner. These contemporary tools and approaches are well aligned with the science and risk-based approaches detailed in ICH Q8–Q11 (5–8) and have been termed risk-based predictive stability (RBPS). Companies are utilizing these RBPS tools to better enable development of medicines (9).

In 2015, the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) launched a working group to focus on the use of RBPS tools to optimize pharmaceutical development. The working group has approximately 50 members from 18 companies across the pharmaceutical industry. The working group conducted a survey of the industry to understand sponsor companies' experiences using RBPS tools (10). The survey was highly informative and indicated that RBPS tools were being utilized in a variety of applications across the development continuum. A key learning was that of all of the companies utilizing RBPS tools, approximately 55% of them were leveraging the data in a regulatory capacity. Over the course of working group discussions, it was determined that utilization of RBPS data was used in excess of 100 submissions by the working group companies. A selection of case studies that discuss the regulatory feedback on these submissions will be published in the near future.

During the course of discussions within the RBPS working group, it was concluded that a published regulatory template sharing best practices for filing RBPS data would benefit the industry and regulatory reviewers by enabling a consistent presentation of predictive data and conclusions. The majority (85%) of survey respondents confirmed that a template would benefit the industry. This template could help companies standardize on key elements that should be included when filing RBPS data in Module 3 stability sections (i.e., S.7 and P.8) of regulatory submissions. The recommendations within this manuscript for presenting RBPS data in a regulatory submission are based on industry early adopter experience and are intended to be used in setting shelf-life for drug substance or drug product that is used to support clinical development. The term 'shelf-life' is used throughout this manuscript, but the terminology will vary for drug substance (re-test) and from company to company (e.g., clinical use period).

This manuscript consists of two sections. Section I is a high-level outline of the key elements for a RBPS filing section. Section II provides a specific example of how a RBPS filing may look.

Section I–RBPS filing high-level outline

The following elements (**Table I**) should be considered when filing a RBPS data package to support an initial shelf-life for drug substance or drug product. The sponsor should also describe the assumptions as context for its modelling approach and assess the impact of these assumptions on the study results and interpretation.

Each section is described further as follows.

Introduction. A discussion of the stability risk assessment, along with a justification of the chosen potential shelf-life limiting attributes (SLLA[s]), should be included in this section. All potential SLLAs should be considered, including both physical and chemical attributes. Utilization of RBPS leverages advanced modelling approaches of data that have been generated under a variety of stress conditions. Typically, there are a few key quality attributes that are shelf-life limiting, such as a degradation product. Based on the stability risk assessment, the rationale for the choice of which attributes were modelled as shelf-life limiting attributes should be discussed and justified.

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Table I: Key elements of a risk-based predictive stability (RBPS) filing.

Introduction (Intention of Predictive Study)
Description of the Model Used
Discussion of Experimental Design
Discussion of Results
Confirmatory Stability Programme
Conclusion

Description of the model used. Provide a description of the model used, along with appropriate literature references, as applicable. A description of the software that is used should also be included. Additionally, any assumptions regarding packaging (e.g., material type, moisture permeability, or moisture vapour transmission rate) should be detailed if they are used to support modelling.

Discussion of experimental design. Provide the experimental conditions (e.g., temperature/relative humidity and time points) that were used for the study in tabular format. A discussion may be included on how the storage conditions were selected, especially if they were driven by particular physiochemical properties of the drug substance and/or drug product formulation components. In some cases, the samples assessed may be a different formulation than the clinical formulation, where the excipient-to-active ratio may be worst case. In this case, include a discussion of why the samples used for the study were 'worst case' to maximize possible degradation. Also discuss why the studied container closure was selected (e.g., open containers allowing for better correlation with the impact of humidity).

Provide a summary of what shelf-life limiting attributes were evaluated after storage (e.g., degradation product X, appearance). Address any differences in analytical procedures used from those provided in the Analytical Procedures sections of the regulatory filing, if applicable.

Discussion of results. Provide a detailed discussion and interpretation of the results. Specifically discuss the shelf-life limiting attribute(s) (e.g., degradation product x) and how this was modelled to set a shelf life for the drug. A discussion/explanation of any other changes (e.g., appearance) would be appropriate as well.

Long-term stability programme. The planned long-term stability commitment should be discussed. The study design may be supported by RBPS results. Based on the understanding of the modelling, this could encompass a variety of approaches. These approaches could include ICH-like testing, reduced time points, reduced conditions, and/or contingency storage.

Conclusion. Provide a conclusion to indicate the shelf-life that is supported by the modelling data. Where applicable, outline how extensions to the initial shelf-life will be assigned.

Section II–RBPS filing specific example

The purpose of this section is to provide an example of a RBPS filing for a first-in-human (FIH) study. The example given below is for a small-molecule, solid oral dosage form and could be included as part of P.8.1 within the clinical application. It may be adapted for other small-molecule formulation types and drug substances as relevant. This example is based on the Accelerated Stability Assessment Programme (ASAP) model. Other models or software packages may be used as appropriate.

Introduction. Based on a stability risk assessment, it was concluded that drug product Degradant A is expected to be the SLLA. The drug product is designed as an immediate-release capsule. Dissolution was not modelled, because it is not expected to be a SLLA. This is based on the fact that drug product, when exposed to accelerated conditions, did not show any meaningful changes in dissolution profiles. Drug product assay is also not expected to be a SLLA because the drug product degradant limits (i.e., not more than 0.5%) are set such that they would fail before a significant change in assay would be observed.

The ASAP approach was used to develop an in-depth understanding of the chemical stability performance of the drug product as a function of temperature and relative humidity. This understanding was used to determine appropriate packaging (as described in Section P.7 of the regulatory filing) and storage conditions, to predict an initial shelf life for the clinical drug product, and to determine the SLLAs to be included in the confirmatory long-term stability protocol on a representative batch of drug product.

The RBPS will be supplemented by a confirmatory study that includes long-term storage conditions and traditional accelerated storage conditions (40°C/75%RH); this confirmatory stability study has been initiated for a representative batch. [Include specific information such as lot number, manufacturing scale, etc. Also include a justification as to why it is considered to be representative.] The accelerated and long-term data from this batch, when available, will be used to confirm the predictions of the model and to support further shelf-life extensions.

Description of the model used. The ASAP approach was used. This is a statistically designed RBPS programme based on the modified Arrhenius equation. The design of the predictive study is based on literature that demonstrates the modelling of observed degradation of solid oral-dosage forms (2,3). Short studies were conducted on open-dish samples of the representative batch of drug product at elevated temperatures over a range of humidity conditions with the goal of reaching the specification limit for the identified SLLA at each condition as detailed as follows. Humidity determines water activity in the drug product and, therefore, can have a significant effect on reaction rates in solid drug products, even for reactions which themselves do not involve water. The humidity-corrected Arrhenius equation (**Equation 1**) reflects both the influence of the temperature and the influence of moisture on the kinetics of the degradation product formation. The resulting open-dish data were fit to a humidity-corrected Arrhenius equation using ASAPprime Version 5.0 [alternative commercial or in-house software may be used]:

$$\ln k = \ln A - Ea/RT + B(RH) \quad \text{[Eq. 1]}$$

Where k is the degradation rate, A is the Arrhenius collision frequency,

Ea is the activation energy for the chemical reaction, R is the gas constant, T is the temperature in Kelvin, B is a humidity sensitivity constant, and RH is relative humidity.

The moisture sorption isotherm for the drug product was determined, and the moisture permeability of the primary package was determined based on literature data. This information was used to estimate the dynamic water activity in the packaged drug product as a function of time at the proposed storage condition.

The model derived from fitting the data to **Equation 1** was then used to calculate the expected value and the upper and lower 95% confidence limits for the SLLA as a function of time in the selected package at the long-term storage condition.

Discussion of experimental conditions. A representative drug product lot for compound X was stored in an open dish configuration at the temperatures and humidity conditions outlined in **Table II**. The exposed samples were then tested for degradants by the high-performance liquid chromatography (HPLC) procedure that is described in P.5.2 of the regulatory filing. Other potential SLLAs were also tested over the conditions studied. These included physical appearance and dissolution. [If the analytical methodology used differs from that provided in P.5.2, provide further explanation.]

Discussion of results. The data collected indicate that Degradant A will be the SLLA at long-term storage conditions of 25 °C/60%RH. Levels of Degradant A ranged from 0.00% to 1.00% (**Table II**).

These data were fit to the modified Arrhenius equation (**Equation 1**).

All stability attributes are expected to remain within specification limits for at least 12 months. Modelling predictions for the shelf-life limiting attribute, Degradant A, are included in **Table III**.

The results are plotted in **Figure 1** and shown in **Table IV**.

The modelled data presented in **Figure 1** are based on an assumption that the degradation kinetics to the specification limit is occurring in a linear fashion. For this degradation pathway—and based on the ASAP study data—this assumption is consistent with the chemistry and stability knowledge of the drug substance, stability knowledge of the drug product at this stage of development, purposeful degradation, and literature. The data may also be based on drug substance and drug product knowledge gained to date.

Other non-SLLA drug product attributes were tested following exposure to the conditions studied. This included physical appearance and dissolution. None of the data showed a meaningful change in those attributes.

[If no degradation is observed during an ASAP study with conditions such as 70 °C at both high and low humidity for at least three weeks, an initial shelf life of a minimum of 12 months is deemed to be appropriate (11).]

Long-term (confirmatory) stability programme. The initial shelf life is based on the ASAP study. Subsequent shelf-life extensions will be supported using a long-term stability study. The identified SLLA will be studied as well as assay, physical appearance, impurities, and dissolution. The protocol for the long-term stability study is provided in section P.8.1 of the regulatory filing. As additional long-term stability data become available, they will be assessed against the same acceptance criteria and reviewed against the modelling predictions. The shelf life may be extended as these additional long-term data become available. The shelf life will not be extended beyond the last time point as outlined in the long-term stability protocol.

Table II: Growth of Degradant A in Drug Product X under open dish storage at various temperature humidity conditions. RH is relative humidity.

Condition			
T (°C)	%RH	Duration (days)	Amounts (%) of shelf-life limiting Degradant A
		0	0.00
70	75	3	0.70
60	50	14	0.50
60	50	21	0.70
70	20	14	0.50
70	20	21	0.60
50	75	21	0.30
80	50	3	1.00

Figure 1: Predicted growth of Degradant A at 25°C/60%RH when packaged in a 60 cc induction sealed high density polyethylene bottle.

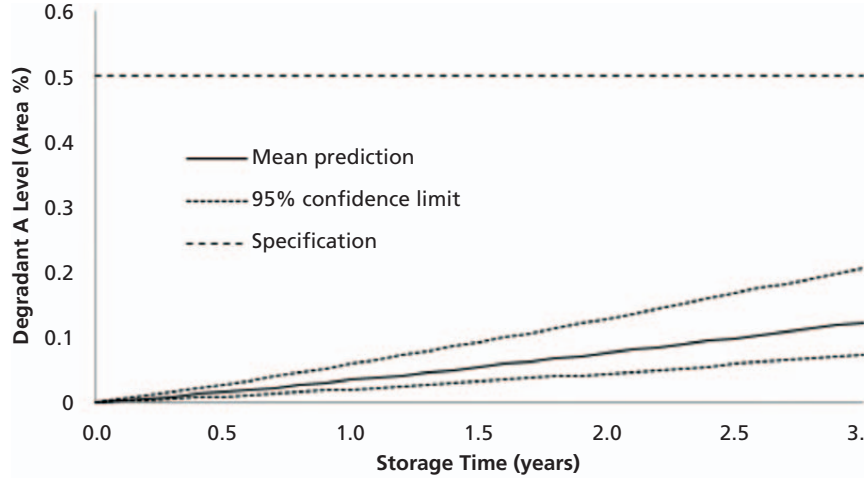

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Table III: Shelf-life limiting attribute (SLLA).

SLLA	Specification	Packaging configuration	Minimum shelf-life predicted by the model (upper 95% confidence limit)
Degradant A	0.5	30 capsules in a 60 cc induction sealed HDPE bottle	> 3* Years

* Companies may manage this differently depending on the circumstances. Some companies may choose to use a shorter shelf-life (e.g., > 12M).

Table IV: Predicted stability data.

Predicted stability data at 25 °C/60% RH	Storage time (months)					
	0	6	12	18	24	36
Degradant A Level (Area %) *	ND	< 0.05	0.06	0.09	0.13	0.21

* Data based on upper 95% confidence limit

Following each long-term stability time point, the results are reviewed to confirm that the acceptance criteria are met and to monitor for trends and unexpected test results. Trending is conducted to confirm the extrapolation of the shelf-life remains appropriate. An amendment will be submitted if there is any change in the storage condition or packaging configuration of the investigational medicinal product during the clinical trial.

On the basis of additional long-term stability data for the representative batch, the shelf life will be extended without submitting a substantial amendment, unless stated otherwise in applicable regulations. The specifications and recommended storage conditions will remain the same.

Conclusion. An initial shelf life of 12 months when stored at or below 30 °C has been established.

Discussion and conclusion

The industry survey on use of RBPS tools indicated that more than half of the companies surveyed use the data from RBPS studies in their regulatory submissions. As outlined within this article, an effective application of RBPS within regulatory submissions is to support an initial shelf-life for an early development formulation. Companies have been using this science-based approach for several years.

The stability understanding gained from a well-designed RBPS study generally exceeds knowledge gained from a three-month time point data at the long-term storage and traditional accelerated conditions (40 °C/75% RH). Therefore, shelf-life predictions supported by RBPS studies are considered conservative, because typically, the predicted shelf-life limiting attribute will not breach the acceptance limit until well beyond the assigned shelf-life. Per current clinical guidelines published by the European Medicines Agency (EMA) (12), three months of long-term data may be used to set a 12-month clinical shelf-life. Given the increased knowledge obtained on potential degradation from predictive tools, a similar initial clinical shelf-life may be justified if the RBPS data support it. Additionally, companies are maintaining a conservative approach past the 12-month initial clinical shelf-life by basing further extensions on long-term data.

Use of this approach can reduce clinical start timelines by months, resulting in potentially life-saving therapies entering the clinic faster. The template outline provided within should provide others wishing to implement a similar strategy with a good starting point. A publication of industry case studies with regulatory feedback is currently under preparation. Industry continues to seek collaborative interaction and is open to consultation with regulatory agencies to jointly integrate RBPS tools to support shelf-life assignments.

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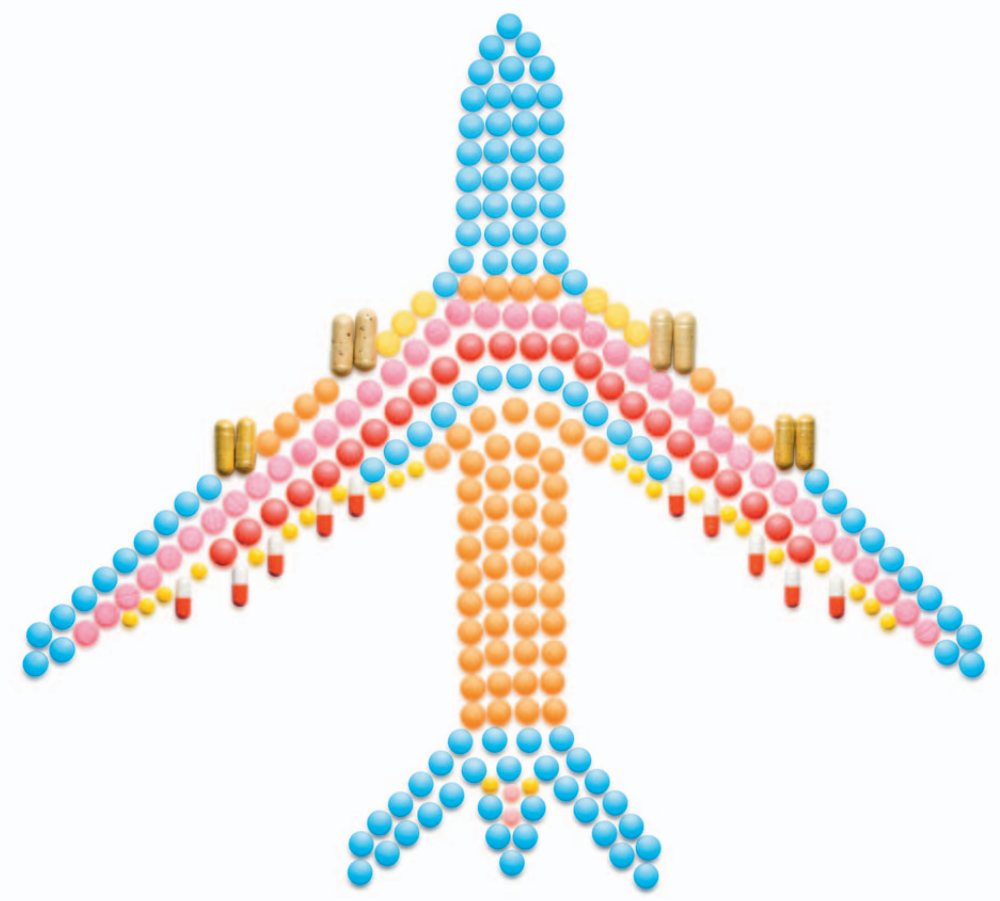

Reducing the Risk of Pharma Air Shipment

Air transport continues to be the most secure way to ship valuable therapies, but it is also the riskiest. Standards are helping to improve service quality.

Agnes Shanley

Several years ago, groundbreaking studies revealed the losses that pharmaceutical companies incur each year as a result of temperature excursions or transportation delays. In 2014, analysts at IMS Health found that the top 10 pharmaceutical companies lost €13.7 billion (US$16 billion) worth of product each year, 20 times the average pharma company's price-to-earnings ratio, due to transportation problems and resulting temperature excursions and other delays. For the entire pharmaceutical industry, losses exceeded € 30 billion (US$35 billion) (1).

International shipments have proven the riskiest. The product is out of the pharmaceutical manufacturer's control, and manufacturers need to rely more on subcontractors, third-party logistics companies, and other supply chain partners whose primary focus may not be pharma, said Rafael Palma, regional logistics manager for Latin America for AbbVie, during a webcast at the Temperature-Controlled Logistics online conference in March 2018 (2).

More countries are establishing requirements for temperature traceability

Of all the modes of global pharma transportation, air transport has been deemed the most potentially risky, and, according to some estimates, accounts for 80% of all reported temperature excursions (3). Within a plane, turbines can generate heat, leading to potential temperature exposure problems, but the challenges only intensify once the product moves outside the plane. Delays during which pharma cargo is left waiting on the airport tarmac can leave product vulnerable to temperatures that can be 50 °F higher than ambient levels (1). Delays caused by product transfers are also part of the problem. In Brazil, for example, Palma said on the webcast, it can take 10 to 20 days just to get the permits required to move product from the airport to ground transportation. "End-to-end risks and lead times must be considered closely," he said.

Regulators and standard setting groups, notably the European Commission, have promoted current good distribution practice (cGDP) guidelines to ensure that best practices for temperature control and optimal risk assessment and management practices are used (4). More countries have set requirements for temperature traceability, and new regulations have been established, not only in the European Union but in Canada, Israel, Saudi Arabia, and Peru, Palma told attendees at the webcast (2).

Reducing temperature excursions

At the same time, all stakeholders, from pharmaceutical manufacturers to third-party logistics companies, shippers, airlines, airports, freight handlers, and packaging companies, have been working to reduce opportunities for temperature excursions. One of the most significant achievements to date has been the establishment of the International Air Transport Association's (IATA's) Centre of Excellence for Independent Validators (CEIV) Pharma Logistics programme in 2014 (5).

CEIV's goal is to amalgamate local regulations and standards to set global air transportation standards for pharmaceuticals, to certify stakeholders that use best practices, and to encourage collaboration and communication between different stakeholders. The effort was a practical response to the fact that air transportation had lost ground to ocean transportation, and fell from 17% in 2000 to 11% of

all transportation in 2013. According to recent estimates, 3.5 million metric tons (m.t.) of pharmaceuticals were shipped by ocean in 2016, compared with 0.5 million m.t. by air (3). However, IATA saw demand for pharmaceutical air cargo shipments growing 9% in 2017 (6).

Since it was established, CEIV's effort has been making progress in reducing the number of temperature excursions. At the 2018 Temperature Controlled Logistics Conference, Francisco Rizzuto, cargo specialist and manager at IATA, noted that 221 organizations are currently CEIV-certified, and over 75 more companies are in the process of becoming certified. CEIV has also launched a bulletin board, designed to help pharmaceutical and biopharmaceutical companies locate business partners that have been certified (7).

Shippers responsible under GDP

As Rizzuto noted, global GDP regulations assign shippers with the responsibility of securing the transportation chain, from the manufacturing plant to the patient. As the pharma and biopharma markets grow, he said, lane validation based on clear risk assessment is especially important in emerging markets and unknown territories.

It has become imperative that freight forwarders help and support shippers in these efforts. However, Rizzuto said it is crucial for pharmaceutical companies to learn how the air cargo industries, and particularly, how airports work, in order to improve communication. There should be some understanding of capabilities at sourcing airports says Palma. "A lot of truck transportation is used in Europe, but a key question is how much product can be kept waiting in a truck safely? Based on each shipping lane, companies need to understand specific issues," he said at the webcast (2).

Meanwhile, pharma companies should also communicate more clearly with cargo firms, noted Rizzuto. "Air cargo companies need to be made aware of the consequences of temperature excursions," he said.

PIL, not PER!

One important step that more companies must learn, Rizzuto said, is that pharmaceuticals should not be shipped as "perishables" with the PER label, but as pharmaceuticals, with the PIL label, in order to be handled properly. Some companies have attempted to reduce costs by going with the more basic label, and that has often led to service and quality problems.

Better communication is needed between manufacturers and air cargo companies, and standardization efforts such as CEIV are improving results.

Generally, choice of transportation mode will impact cost. Controlled room temperature requirements will raise shipping costs, noted Palma on the webcast (2), with air transport in active or passive shippers leading to a 70–80% cost increase, compared to reefer trucks and containers, which would increase costs by 15–25%. However, air transport offers enhanced security, he said, which can be particularly important for high value products.

As Rizzuto noted, IATA is working to update certification requirements, continuously, to reflect changes in regulations (6). In the meantime, individual airports are reporting significant improvements, such as Brussels Airport's BruCargo arm, which is collaborating with Johnson & Johnson, Pfizer, and Merck, as its strategic pharma advisors.

The airport invested 68% more in its pharma services in 2017, and saw nonconformance drop 45% that year, according to Nathan De Valck, Cargo and Product Development Manager at the Brussels Airport Company, who spoke at IATA's annual meeting in March 2018 (8). Milan Airport, which is CEIV certified, found irregularities decreased 77% between 2016 and 2017 (6).

The CEIV initiative is stimulating the use of new technologies, such as thermal blankets and cabinets designed to keep temperature-sensitive pharmaceuticals at stable temperatures for 26–32 hours on any airport tarmac. However, Rizzuto said, the right packaging is crucial, and manufacturers need to devote time to ensuring that product leaves the facility in the best possible packaging designed for the specific conditions of that particular destination and shipping lane.

While collaborative efforts with CEIV are leading to improved shipping solutions, they may also result in some new technologies. Two CEIV-certified airlines, Air Bridge Cargo in Russia and Cargo Logic in the United Kingdom, are currently working with SITAOnAir to use its Internet of Things technology to allow the two carriers to monitor the movement of pharmaceuticals in real time (9).

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E&L Risk Assessment for Biologic Drug Products

Materials in contact with a drug must be fully characterized to ensure that they do not negatively affect the safety and efficacy of the product.

Adeline Siew, PhD

The primary packaging or container closure system that is meant to protect a pharmaceutical product can be a source of contamination. Comprehensive extractables and leachables (E&L) studies are, therefore, required to identify and quantify harmful impurities that could affect the quality and safety of drug products.

Pharmaceutical Technology Europe spoke with Lester Taylor, Pharma marketing manager, Agilent Technologies; Andrew Blakinger, manager, Extractables and Leachables Testing, Eurofins Lancaster Laboratories; and Fran DeGrazio, vice-president, Global Scientific Affairs and Technical Services, West Pharmaceutical Services, about the ins and outs of extractables and leachables assessments in biologic drug products.

PTE: What are the E&L challenges for biologics compared to small-molecule drugs?

Taylor (Agilent): Compared to small-molecule drugs, biologics face additional challenges. For example, the efficacy of a biologic drug may potentially be reduced through undesirable interactions of leachables with drug molecules through post-translational modification (PTM) biochemical reactions (e.g., oxidation, aggregation, clipped variants, unfolding, adducts formation, and glycosylation). Alternatively, a leachable arising from single-use systems (SUS) or components used for bioprocessing may adversely affect the manufacturing process through cellular toxicity and Chinese hamster ovary (CHO) cell death thereby reducing the productivity of the bioprocess. There are several examples where leachables have been associated with these undesirable effects on biologic manufacturing and drug efficacy, leading to major manufacturing losses and, even worse, dangerous side-effects and loss of drug efficacy.

Blakinger (Eurofins): The evaluation of biologics for leachables presents many unique challenges. The protein itself can interfere with testing, so removal prior to analysis may be warranted. But if care is not taken, this process can unintentionally remove potential leachables, resulting in false negatives, or it may lead to contamination of the sample that may result in the generation of false positives.

Other ingredients in large-molecule formulations, such as polysorbate 80 and other surfactants/stabilizers, can also cause issues. These compounds often interfere with chromatographic analyses in the form of multiple large peaks that display numerous ions by mass spectrometry throughout the retention time window. These large surfactant peaks can easily mask leachables. Furthermore, proteins, surfactants/stabilizers, and other ingredients in large-molecule formulations are difficult to clean from mass spectrometers and, therefore, may carry over from one analytical run to the next if not dealt with properly.

DeGrazio (West): The likelihood of leachables in any drug product will depend on the packaging materials, type of formulation ingredients, and conditions of use. The occurrence and impact of leachables in biologic products can present greater challenges compared to that of small synthetic molecules due to several factors. Biologics are living molecules that can be difficult to solubilize and stabilize, and quality attributes are not easily characterized compared to small molecules. The formulation ingredients for biologics often contain co-solvents or surfactants and will have more propensity to extract chemicals from packaging materials compared to typical small-molecule formulations.

Biologic products are complex and very sensitive to their environments. Extractables or potential leachables that may migrate into a drug product have the potential to interact, and therefore, affect the product quality, safety, or stability. In general, biologic products are formulated to solubilize, stabilize, and optimize pharmacokinetic properties consistent with the route of administration. Anything that migrates from the packaging that could interfere with this optimized environment is of concern. This

includes interactions with active or excipients in a drug product formulation that lead to said quality, safety, or stability issues.

Additionally, large molecules have greater surface areas with sites that have a propensity for interactivity based on polarity and charge. This can lead to conformational modifications and other interactions that may impact product quality.

Primary packaging and container closure systems

PTE: What are the key considerations when selecting primary packaging material for biologic drug products?

DeGrazio (West): With every drug product and especially biologics, the most inert primary package possible must be chosen to minimize the potential for interactions to occur. Potential leachables are not the only interaction of which to be wary. Because of their reactive nature, biologic drug products can adhere to surfaces or absorb into materials. An understanding of possible interfacial interactions must be a consideration. In addition, there are other packaging considerations that must be addressed, such as container closure integrity, particle generation, and other performance concerns.

Blakinger (Eurofins): For any drug product, it is crucial to ensure the packaging does not adulterate the drug product. Any compounds that leach from the packaging could affect the product in a variety of ways, including impacting patient safety if compounds are toxic or interfering with other analytical assays during release testing. There are a number of other potential E&L risks that are unique to large molecules. Leachables may cause conformational changes in the protein or may cause the protein to aggregate. Large-molecule drug products may also chelate inorganic leachables. These types of interactions can increase the toxicity of the drug product, reduce the product's efficacy, or affect the product's stability. It is, therefore, important to fully evaluate the E&L risks to avoid costly delays in getting a product to market.

PTE: What components in a container closure system can pose E&L risks to a biologic drug product?

Taylor (Agilent): Typically, the container and closure components that come into direct contact with the drug product usually have the highest impact in terms of leachables observed. However, there have been many examples of leachables arising from package labels such as the inks or adhesives, as well as from secondary packaging components. These risks should, therefore, be assessed during bioprocess development.

Blakinger (Eurofins): Nearly any component in a container closure system may pose E&L risk to a biologic. Because many biologics are packaged in prefilled syringes, some of the most common components of concern are rubber stoppers. Rubber stoppers are notorious for containing nitrosamines and polynuclear aromatic hydrocarbons (PAHs), both of which are carcinogenic. Glass prefilled syringes are another common example of a component type posing a special risk to biologics. During manufacturing, tungsten pins are used to hold open the fluid path in the syringe barrel. Because manufacturing occurs at extremely high temperatures, the formation of tungsten oxides is possible. The residual tungsten oxide on the glass syringe can then leach into the final biologic drug product and cause protein aggregation or degradation.

DeGrazio (West): The most common primary packaging system for a biologic drug product is a vial system. This system is composed typically of a glass vial with an elastomeric rubber stopper and an aluminum seal with a plastic flip-off button. The other common primary package is a prefilled syringe system, which is typically a glass syringe with an elastomeric plunger and a tip cap or needle shield. Each of these components has the potential to leach substances into a drug product with contact over time. Of course, the extractables of most significant concern from glass materials are metal ions. It is well known that some biologics drugs are sensitive to various metal ions. Although these reactions are drug-product specific, these reactions are a consideration when evaluating packaging components.

Other types of extractables are expected from elastomeric components. Elastomeric components are composed of much more than just the base polymer. Elastomer formulations typically have six to 12 added ingredients that are mixed with the base polymer under heat and pressure. This process causes chemical crosslinking to occur, which result in the formation of reaction products. These reaction products, along with residual compounds of the original raw materials, may interact with the active drug product or environment. Many of these compounds are organic; some may be inorganic, and, therefore, provide an additional source of metal ions.

In the case of a prefilled syringe system, there is the potential for even more extractables. A glass syringe may be formed with the use of a tungsten pin. This can result in tungsten residuals that are known to interact with proteins. Another issue is that syringes typically use silicone oil as a lubricant for easier plunger movement. Silicone oil can migrate into the drug product and silicone oil droplets can act as a nucleus for particle formation/growth and protein aggregation.

Newer packaging components are now being introduced to the industry; for example, engineered polymers are replacing glass. These polymers, such as cyclic polyolefins, are much lower in extractables and have lower surface tension characteristics that make them suitable for biologic drug products.

PTE: Why is it important to fully characterize contact materials and understand the material of construction for the container closure system and their associated E&L?

Blakinger (Eurofins): Fully characterizing contact materials is crucial to ensure the materials chosen do not negatively affect the safety or efficacy of the drug as a result of leachables. Ideally, multiple options for container closure systems should be evaluated during the initial extractables screening. Then the packaging with the lowest risk can be selected. Establishing an extractable compound profile helps to ensure that the observed compounds are not overlooked during

subsequent leachables evaluations. The constituents of large-molecule drug products often interfere with the analytical tests used to evaluate E&Ls. By establishing a material's extractable profile, leachable analysis by mass spectrometry, using extracted ion analysis, can specifically target those compounds to evaluate their presence in the drug product. This technique effectively eliminates any matrix interferences and ensures leachables are not overlooked.

Risk assessments

PTE: What assessments should be performed to evaluate the potential risks of E&Ls from primary packaging that meets the biologic drug product?

DeGrazio (West): It is important to take a risk-based approach to choosing and evaluating the packaging components. It should start with supplier information on the components or system, addressing questions such as:

- What are the basic material characteristics of the components?
- Are there special needs associated with the biologic drug product application, such as the environmental conditions of storage?

Once this information is gathered, basic evaluation by standard compendial methods is needed for compliance and allows one to begin to 'qualify' a component for use. But this is only the first step in proving suitability. Once compendia requirements are passed, material characterization is essential to better understand what may be extracted from the material (at levels critical to the drug product).

The following highlights the best practice recommendation for addressing E&L for a primary package:

- **Material characterization:** Each individual component should be assessed to assure it has broad applicability for the application.
- **Controlled extractables study:** This study is a comprehensive programme to understand what could be extracted from the components under a broader series of solvents, if the material characterization information is found not to be sufficient. It is crucial to perform a risk assessment to decide if this step is needed, and to determine the appropriate next step in the process based on the application. The solvents used should be aqueous-based, with considerations for organic solvents (if needed), pH, extraction conditions (such as time), extraction methods, material-to-solvent extraction ratios, etc.
- **Simulation study:** Depending on the drug product application, it may be appropriate to complete a simulation study, instead of going directly into a leachables study. This study is highly probable when it is especially challenging to reach the analytical evaluation threshold (AET). This may occur in a circumstance such as when evaluating a large-volume parenteral (LVP) application where there is a significant volume of drug solution. If many extractables are found from the controlled extractables study, the simulation study is a way to help identify the probable leachables to target in a formal leachables study.
- **Data assessment:** To determine the targets for a leachables study, it is important to evaluate the risk in the specific drug application.
- **Leachables study:** Method development and validation for specific leachables in the drug product should occur. Leachables testing should be conducted over drug product shelf life, at both room temperature, and accelerated conditions. The leachables should be identified based on the safety concern threshold (SCT). The SCT is the threshold dose below which a leachable would present negligible safety concerns for carcinogenic and noncarcinogenic effects. The recommended SCT for parenteral drug products, per the Product Quality Research Institute (PQRI) Extractables & Leachables Working Group for parenteral and ophthalmic drug product (PODP), is 1.5 ug/day (as described in an April 2018 workshop).
- **Special considerations for biologics include:** biologic activity, efficacy, degradation, oxidation, chemical modification, immune adjuvant activity.

Taylor (Agilent): Typically, the first step is to perform an extractables profiling study on the packaging component of interest to identify the potential list of leachables in the drug formulation. The profiling study results may be used to perform a risk assessment with two goals:

- To identify potential 'bad actors' from the list of extractables through predicting toxicity or performing toxicology experiments
- To select components that have more desirable extractables profiles for the final process and eliminate components found to likely contribute to an undesirable leachable.

PTE: How do you identify and quantify potential E&L from container closure systems?

Blakinger (Eurofins): The first step is to expose the components of the container closure system to several model extraction solvents at exaggerated conditions of time and/or temperature. The resulting solutions are then screened by headspace and direct injection gas chromatography–mass spectrometry (GC/MS) for volatile and semi-volatile organic compounds, liquid chromatography–mass spectrometry time of flight (LC/MS–TOF) for non-volatile organic compounds, and inductively coupled plasma-mass spectrometry (ICP/MS) for elemental impurities. Additional testing methods may be used if appropriate, such as those specific for halide ions, nitrosamines, or PAHs. At Eurofins, we use the Wiley/National Institute of Standards and Technology (NIST) databases to identify compounds detected by GC/MS. For those compounds detected by LC/MS, we have a propriety database, the Eurofins Extractables Index, containing more than 1500 non-volatile organic compounds. If a compound cannot be identified via the database, additional testing may be necessary. Not only does this additional testing require advanced instrumentation (e.g., quadrupole

time of flight [Q-ToF]), but it also requires the expertise of experienced and highly educated analysts.

Taylor (Agilent): Establishing a holistic extractables profile for an article of interest is a complex and intensive process involving the use of a variety of analytical technologies. Gravimetric studies and total organic and inorganic carbon analysis are often performed to gain an understanding of the total extractable content. Fingerprinting of extracts using spectroscopic methods such as ultraviolet–visible spectroscopy (UV–VIS) and Fourier transform infrared spectroscopy (FTIR) resulting in generic information about constituent chemical classes is also common.

These methodologies are typically followed by more specific qualitative studies to identify volatile, semi-volatile, and non-volatile extractables using GC/MS and LC/MS techniques respectively (including high resolution accurate mass [HRAM] determination). Compounds are usually identified above the (AET) that has been determined for the material or article of interest. The AET for an article of interest depends on the target dose and number of doses expected to be stored in the container closure system or component. Analytically, the AET is used to estimate a detector response threshold using a set of reference standards carefully selected to represent the chemicals expected to be extracted. Once a list of extractable peaks above AET is identified, relative quantitation is also performed to better inform risk assessment.

In parallel, it is also important to identify any elemental impurities that result from the extractions. This [assessment] is usually performed through either inductively coupled plasma optical emission spectrometry (ICP–OES) and inductively coupled plasma mass spectrometry (ICP–MS) methods depending on required specificity and sensitivity.

PTE: Which analytical techniques are robust enough to identify potential E&Ls?

DeGrazio (West): There is no one method that will identify all potential E&Ls. Multiple analytical techniques are needed for comprehensive assessment of extractables and leachables. For inorganic species, ICP/MS or OES are typically employed. GC/MS and LC/MS are the most common techniques for detection and identification of organic compounds. There are various LC/MS configurations for robust non-volatile organic analysis. Various additional features/techniques can improve sensitivity. One such example is ion mobility and Q-ToF to enable more precise analyses and identification of unknowns by combining ion mobility and mass-to-charge ratio. **PTE**

Ad Index

Ask the Expert: Submitting Extractables and Leachables Data to Regulators

Susan J. Schniepp, executive vice-president, Post-approval Pharmaceuticals and distinguished fellow at Regulatory Compliance Associates, explains when to submit extractables and leachables (E&L) information for a product in early stages of development.

"There is a lot of information on what extractables and leachables are but there is little information on when this information should be submitted to the regulatory authorities. The best place to start is to define what E&L are and why they are considered important," she explains. "Extractables are defined as chemical compounds that can be pulled from the primary container/closure components into the drug product. Basically, they are generated by the product and the packaging interacting overtime usually in the presence of a solvent under extreme condition of time and temperature. Leachables are slightly different and are defined as compounds that leach or migrate into the product from the interaction between the product and the container/closure system."

Traditionally, E&L data were gathered and submitted in the late stages of the drug development process, observes Schniepp. "Packaging suppliers were often able to provide an extractable/leachable package for their materials to the pharmaceutical manufacturer in a format that could be submitted directly to the agencies," she says. "Lately, regulatory authorities are requesting this type of information for early stage clinical trial material. This change seems to have come about during the past few years. The extractables and leachables profile in clinical trial material has become a growing concern for regulatory authorities, mostly due to advances including unique packaging materials, new and novel formulations, new drug delivery systems, new combination products being introduced, the emergence of biologics and biosimilars, and the increasing use of single-use disposables systems for manufacturing."

"Why we need to submit this information is clear, but when to submit the E&L data depends on the product type, the container and closure system being used, as well as the materials and equipment used in manufacturing," Schniepp highlights.

"If you are developing a generic with the same active and packaging components as the brand drug, the E&L report can be submitted and be available later in the process. If this is a new novel product associated with clinical trials or an old active being reformulated into a new dosage form (e.g., from a tablet to an injection), then you should probably have the E&L report much earlier in the process. If you are updating the manufacturing process of an old product to use single-use disposable systems, you should include the E&L information as early in the filing update as possible. If you are developing a new, novel product using unique packaging components and new manufacturing advancements, this information should be evaluated early in the development of the product and be available to regulators as soon as is feasible," Schniepp says.

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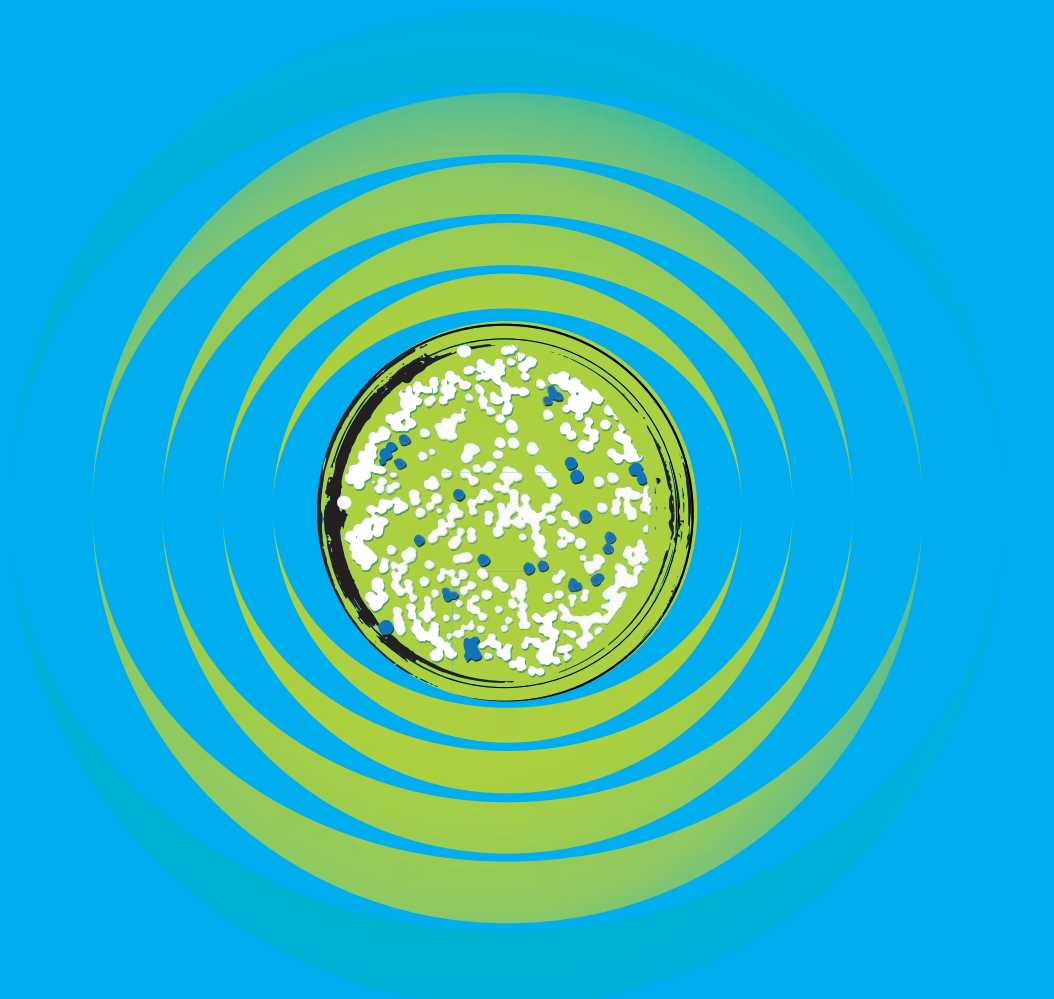

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