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Update on Continuous Bioprocessing: From the Industry’s Perception to Reality

Although widespread adoption of continuous bioprocessing has been slow, some processes have been an exception.

The biopharmaceutical industry, with annual sales for recombinant biotherapeutics of more than €178 billion (US$200 billion), is maturing its manufacturing. While biopharmaceuticals may be one of the most complex and profitable high-technology products, the fundamental aspects of manufacturing have not changed in decades. This contrasts with other manufacturing industries, such as steel or chemical, which have adopted continuous manufacturing. Continuous manufacturing can be more efficient and cost-effective than current methods of manufacturing. But until recently, the technologies to accomplish commercial-scale continuous manufacturing have been works in progress. In fact, in a BioPlan Associates’ survey (1), 222 industry respondents indicated that the penultimate critical operational area where the industry must focus its efforts was in the development of continuous bioprocessing technologies for downstream production.

Traditionally, biopharmaceuticals are manufactured using batch processing, in which unit operations are performed and completed before the process stream moves to the next step. In continuous processing, the processed products are moved to the next step as each unit process is completed. This process can provide considerable benefit to the manufacturers by being more cost-effective, requiring less infrastructure, less space, less investment, less staff, all while manufacturing products in the same or perhaps less time than traditional batch methods. Although widespread adoption of continuous bioprocessing has been slow, some processes in the industry, such as perfusion, have been an exception.

Perception issues with continuous bioprocessing

Despite the benefits of continuous processing, which include reduced cost, increased productivity, improved quality, and increased flexibility, adoption has been slow. Batch processing works well and is familiar, while continuous processing is seen as more complex and susceptible to problems. As a litmus test for how the industry views continuous vs. batch processing, BioPlan Associates asked biopharmaceutical manufacturing professionals about their concerns with regards to perfusion (a continuous process) as compared to batch processing. Of the 19 areas specified, their top concerns were contamination risks, process development control challenges, and process operational complexity. Although these results are similar to previous years’ data, perfusion and other continuous bioprocessing are becoming significantly less complex, less prone to contamination, more regulatory-friendly, and more easily scalable than fed-batch methods. Therefore, some of the concerns today are the result of the perceptions of continuous bioprocessing as being overly complex and contamination-prone. These perceptions are increasingly not matching the advances taking place in the industry (see Figure 1).

While there are many benefits to continuous processing, there are some substantial reasons why its adoption has been slow. Basic changes in biomanufacturing paradigms take decades, partially because the industry is so highly regulated. The regulatory agencies must be convinced that the changes do not compromise drug quality or patient safety. The United States Food and Drug Administration (FDA) and other regulatory agencies, however, are generally quite open to continuous bioprocessing because they see it provides improved process control, product quality, and allows simpler application of process analytical technology. Even though the regulatory agencies are welcoming of continuous bioprocessing, few manufacturers want to act as the test case when they can use the old standby of batch-fed technology. Other difficulties in adopting continuous bioprocessing include lack of practical know-how, precedents, and cost-effective equipment.

Where the industry stands now

Adoption of continuous bioprocessing at any substantial scale has been restricted to a few unit processes at a minority of facilities. For the most part, continuous bioprocessing is dominated by smaller-scale perfusion, increasingly single-use, bioreactors. In BioPlan’s annual report, respondents were asked about their plans to evaluate or consider continuous
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Outsourcing Review

Looking at the regulatory concerns, FDA recently approved, for the first time, a manufacturer’s change in their production method from batch to continuous manufacturing (3). This approval was for Janssen Products, LP’s, treatment of HIV-1 called Prezista (darunavir). FDA encourages continued efforts by other manufacturers to move in the direction of continuous bioprocessing.

Continuous bioprocessing and capacity

Capacity constraints are perceived as an issue within the biopharmaceutical industry. Analysis in BioPlan’s report shows that 29.9% (vs. 27.2% in 2016) of respondents are experiencing “severe” or “significant” constraints at the commercial manufacturing level, up again from 2015 (26.8%). When evaluating future concerns of capacity constraints, the largest percentage of concern for commercial-scale production were “significant” (34.5% in 2017, vs 29.0% in 2016) in severity, while early-stage clinical systems report 20.3% with “significant” or “severe” expected constraints (vs 15% in 2016).

This trend toward increasing severity of capacity constraints suggests any competent platform capable of addressing capacity issues will be of interest and relevance to the industry. The number-one factor identified as likely creating biopharmaceutical production capacity constraints over the next five years was overall facility constraints. This factor was followed by analytical testing and drug product release, and the inability to hire experienced technical staff. However, the factors identified as key areas to address to avoid future capacity constraints included developing better continuous bioprocessing downstream technologies, which was listed as the third highest factor.

Ongoing technology developments and the new products becoming available have not been enough to spur adoption of continuous bioprocessing in purification and other downstream processing operations. Despite the view within the industry that continuous bioprocessing downstream is a necessity for maintaining and increasing capacity going forward,
few have begun the transition. And this is taking into account some of the new available technologies, such as simulated moving bed and cell retention and periodic countercurrent chromatography that are projected to provide a 20–30% cost savings compared to current methods. Even these substantial savings and benefits have not been enough to motivate the majority of the industry to adopt these systems, with the one obvious exception discussed previously from Pall.

The future of continuous bioprocessing
While it is clear the industry has been slow to adopt continuous manufacturing, unlike many other mature manufacturing industries, changes are happening. Gradual adoption of continuous bioprocessing will occur as products are initially developed using these methods, such as Vertex’s cystic fibrosis drug Orkambi, which has been using continuous manufacturing processes since its approval in 2015. The drivers of cost-savings, flexibility, and product quality will push the industry to explore and adopt continuous processing. Once some of this adoption has occurred, as it must to a certain extent already in the case of perfusion, the industry’s knowledge base and experience will grow and ease the adoption of major changes in manufacturing platforms.

Ongoing technology developments and the new products becoming available have not been enough to spur adoption of continuous bioprocessing in purification and other downstream processing operations.

The adoption of continuous bioprocessing will likely follow a trajectory similar to that of single-use systems. While continuous bioprocessing will eventually become the dominant approach over time, the widespread adoption of single-use systems may have reduced the critical needs for cost-savings, flexibility, and other benefits derived from continuous bioprocessing. It is clear, however, that those within the industry recognize the need for continuous bioprocessing, particularly in downstream processes, and so the lumbering biomanufacturing industry will adapt.

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2. https://novartis-mit.mit.edu/

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EMA Faces Brexit Challenges

The impact of Brexit on the European drug approval regulatory framework presents challenges for EMA.

A big worry for the European pharmaceutical industry about Brexit is the impact it will have—at least temporarily—on the efficiency of the operations of the European Medicines Agency (EMA). As a result of the United Kingdom’s departure from the European Union following a referendum on the issue of its membership in June 2016, EMA is having to move its headquarters from London to a location, yet to be decided, in one of the 27 remaining EU member states. EMA, which has been based in London since its foundation in 1995, runs the EU’s centralized system for the approval of new medicines and its pharmacovigilance system, as well as coordinating the European Union’s regulatory network of national competence authorities (NCA) responsible for licensing and regulating drugs in each member state.

There have been hopes that the effects of the agency’s move would be minimized by the transfer taking place over a phased transition period of a few years in line with a gradual withdrawal by the UK from the EU starting in March 2019. This approach would enable the UK to continue to assist in the agency’s operations to help avoid delays in approvals of medicines and licence variations, as well as in the publication of key documents such as guidelines. However, it is now possible that the relocation may have to take place relatively quickly. The agency revealed in late April 2017 that it is starting to draw up contingency plans for a complete break between the EU and the UK in March 2019.

“Although negotiations on the terms of the UK’s departure have not yet officially commenced and one cannot prejudge their outcome, work will now start on the basis of the scenario that foresees that the UK will no longer participate in the work of EMA and the European medicines regulatory system as of 30 March 2019,” the agency said in a press release (1).

The UK and the EU are due to start negotiations in June 2017 on a withdrawal deal, which is increasingly expected to amount to what is dubbed as a “hard Brexit” without an agreement on trade and regulatory issues, covering matters such as an extended timetable for EMA’s transfer to a new location.

Minimizing disruptions and delays

“We don’t want any disruption of EMA’s operation leading to delays causing the build-up of a backlog of work,” says a spokesman for the Brussels-based European Federation of Pharmaceutical Industries and Associations (EFPIA). “It is essential that we have regulatory continuity across Europe,” he told Pharmaceutical Technology Europe.

EFPIA published in April 2017 an open letter (2) signed by heads of R&D in 19 multinational drug companies expressing anxieties about the “stark and alarming reality that [EMA’s] fundamental activities would undoubtedly be impeded were the operations of the agency to be disrupted as a result of the United Kingdom’s exit from the EU.” It added that “in the event of obstruction or failure, Europe possesses no backup option.”

A disorderly departure by EMA is of particular concern to UK pharmaceutical manufacturers, which include leading international drug companies GlaxoSmithKline (GSK) and AstraZeneca. The country needs a smooth transition to what is likely to be a stand-alone medicines regulatory system operating separately from the EU’s regulatory network.

“Moving an agency like EMA is a huge task,” Virginia Acha, executive research director at the Association of the British Pharmaceutical Industry, told Pharmaceutical Technology Europe. “We have made clear that we would like the EMA and all 28 national competent authorities to work closely to ensure that we avoid delays to the important work of regulating and ensuring supply of medicines for patients across the EU.”

A big challenge for EMA is filling the post-Brexit gap being left by the loss of the expertise of the UK’s drugs regulator—Medicines and Healthcare products Regulatory Agency (MHRA). Its experts have been contributing 30–40% of assessments of new medicines and other items, according to an MHRA official. EMA says that in 2016, the agency acted as a rapporteur for 14% and co-rapporteur for 16% of the products approved by EMA’s Committee for Medicinal Products for Human Use (CHMP). Now EMA has started work on sharing out contributions from experts in national agencies much more evenly. “The expertise available across the network is impressive and [Brexit] is an opportunity to streamline the way we work, increase our capacity, and work even more efficiently,” said EMA’s Executive Director Guido Rasi (1).

Changes in the EU regulatory framework

The agency started discussions in April 2017 on changes to the system for evaluating and monitoring medicines. The changes will be based on the principles of “ensuring business continuity; maintaining the same high standards of the scientific assessment; continuing compliance with legal timelines; and ensuring knowledge retention, either by building on existing knowledge, or through knowledge transfer,” an EMA spokesperson told Pharmaceutical Technology Europe.

A number of EU member states are already preparing to increase their capacity for assessment and monitoring work so what has been done by 28 member states will be able to be carried out as efficiently by 27. Furthermore, the work will be carried out by more mixed teams of experts from different EU countries rather than, as previously, by teams from single states.

“EMA has found an effective response to the challenge [of Brexit],” the spokesperson said. “We have put in place multinational assessment teams. Traditionally, the assessment of medicines was carried out by teams from individual member states. This shows that science works best without borders.”

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“This multilateral approach benefits the EU system as a whole but it also benefits the individual member states as it raises standards and increases participation,” she continued. “This approach will become even more crucial as EMA faces a loss of expertise through Brexit. Increasing skills across Europe and promoting participation in EMA’s activities will allow us to keep our complex machinery working and delivering for patients in the EU.”

EMA claims that the EU regulatory network, the largest of its kind in the world, is strong and flexible enough to adapt to changes such as Brexit without putting at risk the quality of its work. “Using a timely and inter-connected process, it brings together the best experts from across the EU to do the right job at the right time with the right people,” the spokesperson said. “EMA and the patients in Europe cannot afford that this well-oiled machinery starts to stutter.”

In its efforts to maintain continuity, the agency also faces the challenge of keeping as many of its 890 staff as possible, particularly employees who provide expertise and experience. “We have seen a decrease in the number of [job] applications received by the agency,” the spokesperson said. “We are looking at this closely to understand if it could have any implication for the agency’s work and to keep possible disruptions to a minimum.”

**EMA’s new headquarters**

The choice of a new location for EMA, a decision that is due to taken by the governments of the 27 EU member states in 2017, is seen as being crucial to the need to attract adequately qualified staff as not all existing employees are expected to stay with the agency. More than 20 countries are reported to have expressed an interest in hosting the new EMA headquarters with the favourites being countries that have relatively large domestic pharmaceutical industries, such as France, Germany, Italy, Spain, Ireland, and Denmark.

Among the essential requirements for the location listed by the R&D heads in their open letter are a capability to accommodate approximately 36,000 visits of experts annually, excellent transport links, and an adequate number of hotel rooms. Also, there must be “sufficient and decent housing and access to international schools for staff with children,” they say.

Another cloud hanging over the transfer of EMA’s headquarters is a lease agreement that commits it to paying rent on its offices in London until 2039. With business rates and services charges, the total debt could be approximately €400 million. A European Parliament report on the agency’s finances published in April (3) reveals that the total payable rent for the period from 2017 until 2039 amounts to €347.6 million because of the absence of a break clause in the rental agreement signed in 2011 when “the potential exit of the UK from the Union was not foreseeable.”

The report expresses concern about the “risk of budgetary volatility faced by the agency” as a result of the need to move its offices. It suggests that “in the spirit of sound financial management,” EMA should be authorized to maintain a budgetary reverse to cover unforeseen costs due to the transfer.

Some EU politicians are arguing that the UK should pay the outstanding rental and the costs of the move of offices because it voted to leave the Union rather than being made subject to an involuntary exit. This issue should be a matter to be sorted out in the withdrawal negotiations. But with the agreement having to be finalized by March 2019, there may not be time to resolve issues relating to the costs associated with the EMA’s new location.

**References**

As branded drug patents run their course, biosimilar manufacturers are gaining market share. Pharma is increasingly being pushed to find new ways to maintain market advantage for products that are not first-in-class biologics. One route to combat competition is the “Amgen approach;” Amgen has chosen to fiercely defend its intellectual property through a series of high-stakes lawsuits that deal with the interpretation of the information exchange requirements of the Biologics Price Competition and Innovation Act (BPCIA). This approach can be seen in the cases *Amgen v. Apotex* and *Amgen v. Sandoz*. In fact, Amgen’s aggressive legal tactics prompted Sanofi and Regeneron to file a “declaratory judgement of non-infringement” for their investigational atopic dermatitis monoclonal antibody (mAb) Dupixent (dupilumab) in March 2017 (1). Sanofi and Regeneron made this move in advance of any action by Amgen, as Dupixent is an IL-4 inhibitor, and the companies were aware that Amgen has attempted in the past to gain approval for a drug with this specific mechanism of action. Some could say that Amgen is using aggressive legal tactics as a tool to protect its legacy products and consequently, its revenue stream.

Other tactics that reference-product sponsors use to extend the commercial value of their legacy products include filing patents that cover new formulations of a drug (a practice known as evergreening), but these new formulations have to either prove to have an improved therapeutic outcome, an improved safety profile, or a positive effect on patient adherence (2). In addition, pharma companies can bundle their medications with others in combination to preserve some patent juice. While the aforementioned strategies are well known in the industry, it could benefit manufacturers to revisit how their drugs are made—not necessarily how they are patented—to determine ways to maintain the profitability of older products. One of these new industry approaches centers on improving manufacturing efficiency of legacy products.

**FDA’s take on manufacturing efficiency**

Because manufacturing processes are embedded in the product approval process, significant post-approval manufacturing changes must be approved by the United States Food and Drug Administration (FDA). A recent example of such a change is Janssen’s HIV drug Prezista, which was the first candidate to be handled by the FDA’s Center for Drug Evaluation and Research’s (CDER’s) Emerging Technology Team (ETT), a group that was formed to handle inquiries regarding emerging technology in pharmaceutical and biotechnology manufacturing. The manufacture of Prezista (a small-molecule drug) was converted from a batch process to a fully continuous method in April 2016 following the approval of the conversion by FDA.

According to N. Sarah Arden, PhD, from the Office of Biotechnology Products within CDER’s Office of Pharmaceutical Quality (OPQ), who spoke at the BioNJ Manufacturing Breakfast on March 30, 2017, the Prezista conversion process reduced the manufacturing footprint for the drug from seven to two rooms, and reduced the production from two weeks to one day. Doug Hausner, PhD, associate director in the Department of Chemical and Biochemical Engineering at Rutgers University, said at the BioNJ meeting that the changeover only took three
biologics, then, may help reference-solutions for the manufacture of performance.
and drive improved operational help speed up overall production control and coordination due to The improvements in manufacturing continuous (i.e., perfusion upstream).
be the golden ticket for legacy improvements in automation—may efforts to optimize the manufacture of scientific and engineering principles
are a few of the key improvements [of automation] to biologics manufacturing,” notes Mike Smith, US sales manager at Zenith Technologies. It does not appear that incorporating increased automation would warrant a post-approval change application to FDA, as the products themselves would not likely change per batch, but the data collection techniques informing engineers about their manufacture would change. But a change that effectively increases process robustness—including one that influences drug production rate—may, however, constitute a change that would need to be submitted to FDA for approval. It should be noted that while some changes require approval by FDA, others that don’t necessarily require a formal approval should still be reported to the agency. Manufacturers have to prove, with validation data, that procedural changes do not influence the potency, sensitivity, specificity, or purity of a drug, according to an FDA guidance covering changes to an approved application for certain biotechnology and synthetic biological products (5). Although batch data (and other data) are not considered an “established condition” that could require notification to FDA, alterations to established conditions—which could include changes to process parameters and their ranges—usually require manufacturers to alert the agency (6). Thus, if a production rate is improved as a result of increased automation and the inclusion of sensors, would contact with agency officials be warranted? FDA was careful not to say too much about which technological innovations would or would not be eligible for agency review: “The criteria for determining an emerging technology are based on the type of CMC [chemistry, manufacturing, and controls] change the company requests and/or the company’s proposal to the ETT,” FDA’s Sau (Larry) Lee, PhD, deputy director and ETT chair in the Office of Testing and Research/OPQ, told this publication on behalf of the ETT team. “There are rapidly evolving technological areas, so decisions are made on a case-specific basis after evaluating the information regarding the proposed technology.” Notes Smith, “Automation has been a part of pharmaceutical/biotechnology manufacturing for many years; CMC documentation can be leveraged in many cases.” He says that most automation improvements are reserved for new equipment, new facilities, or expansions, not conversions. He points out that FDA validation is already a part of these initiatives. Automation could also be crucial to facilitate end-to-end continuous manufacturing configurations for biologics. When this publication asked FDA specific questions on how to best implement continuous manufacturing principles, FDA’s Lee said, “Prespecifying approaches or providing prescriptive recommendations to manufacturers, or appearing to, may not be helpful in this evolving technological area where the actual practitioners bring extensive expertise. Regardless of participation in the [ETT] programme, it is ultimately the role of the manufacturer to develop technology based on scientific and engineering principles and practices.”

Vendors recognize the benefits of better process control
Many vendors in the bioprocessing space have been working to inject more automation into their processes, either by partnering with companies that specialize in automation or by purchasing these companies outright. The following are a few examples of recent deals in this space. Thermo Fisher Scientific. Players in the bioprocessing space have been
investing in improved automation solutions, data integration, and manufacturing execution systems (MES) to optimize and shorten production cycles. In February 2017, Thermo Fisher Life Science’s Solutions Segment acquired Finesse Solutions, which develops scalable control automation systems and software for the manufacture of biologics. Finesse had been Thermo’s “technology partner” since 2013 (7).

The acquisition is especially beneficial for Thermo because of a patent that Finesse owns covering an aseptic peripheral sensor carrier and methods for installing a sterilized peripheral in a bioprocessing vessel or component. Currently, many types of sensors can’t be used in single-use bioreactors because they are incompatible with sterilization procedures (such as gamma exposure). The setup described by Finesse in its patent application allows the packaged sensors and carriers to be sterilized together, rather than separately (8).

According to the patent, Finesse’s invention helps prevent “many of the negative effects that sensors endure during gamma sterilization” and will allow the insertion of more sensors upstream (7). Finesse wrote in the patent, “To date, one major issue has been the lack of robust, single-use sensors that can be readily and reliably integrated into the single-use bioprocess vessel (e.g., including but not limited to a bioreactor or mixer). By robust, we mean accurate; gamma, beta, or x-ray radiation stable; and capable of being used for real-time sensing (real time within the speeds or time responses required for bioprocessing), e.g., providing samples at 1 Hz (or fractions of a Hz to a few Hz) for biological process monitoring and/or control for at least 21 days without significant drift in any 24-hour period” (8).

Finesse also wrote that use of their aseptic carrier ports/sensors will drive more thorough data collection for each batch produced, and “will increase the number [of] measurement points to enable better process control as well as more detailed batch records with automated software- (rather than operator-) driven process alarming, loop correcting, and deviation reporting in the manufacturing execution system layer, and subsequently, in automatically generated electronic batch records” (8).

**GE Healthcare.** GE Healthcare invested a “meaningful stake” into Zentrix Technologies in 2017. GE had prior experience with Zentrix; the companies have been considered partners in automation integration since 2016. As Ian Makela, general manager, bioprocess, GE Healthcare Life Sciences told BioPharm International, “Automation enables fewer manual operations in the biomanufacturing process and provides real-time data to customers to evaluate their operations more quickly, including batch data and investigations … This greater efficiency can help reduce the non-productive time between production” (9). GE plans to further develop the breadth of Zentrix’s automation and connectivity capabilities, and will incorporate the automation into some of its existing client’s systems via upgrades, as well as offer Zentrix’s support to future clients.

“There is a need to increase automation in order to reduce manufacturing costs and increase time to market,” asserts Zentrix’s Smith. “There is a manufacturing need for facilities to operate equipment for multi-product campaign runs, which involves flexible code design solutions. MES solutions, also, allow for electronic batch record implementation, decreases in batch release timing, reductions in manufacturing errors, reductions in deviations, and improvements in multi-batch and continuous manufacturing.” Smith notes that the use of single-use manufacturing technology also facilitates pre-engineered automation solutions.

**Sartorius Stedim Biotech.** Sartorius just launched a “revamp” of its BIOSTAT STR bioreactors, adding upgraded hardware and software to the bioreactors. The improved design features advanced single-use sensors that were incorporated into the brand’s Flexsafe STR disposable bioreactor bags. The bags are optimized to save time in terms of cleaning, sterilization, and set-up, and they are designed to reduce instances of cross-contamination. According to a company press release, “The new bioreactor range provides greater flexibility in bioprocess control and data acquisition as software connectivity has been upgraded to allow integrated control by either BioPAT MFCS software or commonly used third-party industrial distributed control systems, such as Emerson DeltaV or Siemens SIMATIC PCS7” (10).

The geometry of the BIOSTAT STR bioreactors is the same as that of the company’s ambr 250 mini-bioreactor, so time required for process transfer and scale-up is reduced from months to weeks. The company says that this “direct linear scalability” helps lower costs.

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By combining polymer science, engineering and formulation know-how, we are creating breakthroughs in capsule and encapsulation technologies that are changing the functional role of capsules in medical research, drug formulation and drug delivery. Capsugel provides leading-edge solutions that protect high value compounds, optimize delivery to targeted sites in the body, and ensure the best operational performance in capsule filling. With solutions for rapid product development, solubility enhancement, enteric protection, inhalation, pediatrics and colonic delivery, Capsugel provides the broadest product range and unparalleled service for clinical development and commercial supplies.
Advances in micronization for handling batch sizes of less than five grams make it easier to determine the feasibility and benefits of particle size reduction for new chemical entities (NCEs). At the initial discovery phase, screening of investigational new drugs is challenging, often because of the limited quantities of active pharmaceutical ingredients (APIs) available for analytical and performance testing. With typically 5000–10,000 compounds at the drug-discovery phase, reliable screening technologies are crucial for selecting which compounds should move on to the preclinical phase. Quite often, a mortar and pestle is used for particle size reduction when screening an NCE for in-vitro testing with cell-culture studies, and in-vivo testing using animal studies. While a mortar and pestle is convenient and usually readily available, it is a mechanical process that can generate heat, and it cannot reliably achieve the uniform particle size distribution that is possible with other methods, such as air jet milling.

Accelerating the development of NCEs
Drug development times have increased significantly, and the time taken to bring new drugs to market has increased from approximately three years 50 years ago, to 12 years at the start of the new millennium. The United States Food and Drug Administration approved 45 novel drugs in 2015 and 22 novel drugs in 2016 (1). From 2006 to 2014, the average number of novel drug approvals was approximately 28 per year.

Creating new drugs is no easy process, it usually takes years, and some estimates of the cost per drug are more than two billion US dollars (2). With the number of NCEs entering company development pipelines, there is an increasing pressure for a more thorough, earlier review of an NCE’s potential and how to address pitfalls without further expenditure on the ongoing development of a drug. For example, not using the right technology for the preformulation development of the compound could result in failure during preclinical or even clinical testing due to poor bioavailability of the compound and not seeing the desired therapeutic effect during the preclinical or clinical study. One challenge right now, especially at the R&D and preclinical stages, is that a lot of money and time are invested to find compounds that are efficacious and have a positive therapeutic effect, but further development of these compounds is often unexpectedly challenging. The size of a drug particulate may be crucial to its bioavailability; smaller particles have larger surface area and consequently, a higher dissolution rate. Particle size engineering (i.e., increasing surface area by creating micro- or nano-crystals using techniques such as jet or ball milling) may be an attractive approach because of its simplicity.

Particle size reduction for oral-dosage forms
More than 90% of small-molecule NCEs designed to be taken orally display solubility issues (3). Poor solubility makes absorption of the drug from the gastrointestinal tract into the bloodstream a challenge, and the resulting low bioavailability may require enabling technologies to achieve a therapeutic effect. Today, pharmaceutical scientists working to create new drugs need to have a good working knowledge of the technologies available to develop oral formulations that can be used to improve the bioavailability of novel compounds. Along with salt form, lipid drug-delivery systems, and solid dispersions, particle size reduction is a standard platform technology for enhancing the bioavailability and optimizing the formulation of poorly soluble APIs—especially those falling into the Developability Classification System (DCS) category IIA, where rate of dissolution may be the biggest challenge.

Most APIs in current development fall into DCS quadrant II, in that they have poor solubility but adequate permeability. Quadrant II may be further subdivided into sub-categories for which molecules are either dissolution rate-limited in the gastrointestinal tract (DCS IIa), or solubility-limited (DCS IIb), as delineated by the Solubility-Limited Absorbable Dose (SLAD) rule (see diagonal line in Figure 1). For molecules falling in the DCS IIA category, the dose is expected to dissolve completely during the
approximately three-hour transit through the small intestine, provided that more of the undissolved molecule is available in a form to quickly replace it.

Particle size reduction does not affect a drug’s equilibrium solubility. Instead, it helps by increasing the surface area of drug that is exposed to fluids in the gastrointestinal tract, hence increasing the dissolution rate of the drug. Drugs that dissolve slowly may miss their “window of absorption.” The oral bioavailability of numerous poorly soluble compounds has been improved by micronizing or wet-milling (nanosizing). These compounds include DCS category Ila drugs (nitrendipine, carvedilol) and category Iib drugs that lie close to the SLAD line, where presumably the final bioavailability was satisfactory (perhaps due to having good permeability beyond the small intestine).

Tricor (a brand name of AbbVie) is an example for which particle size engineering provided product differentiation and follow-on approvals. Tricor-1, the non-micronized form of the drug fenofibrate, was approved in 2001 for lowering triglycerides, but had a substantial food effect. This was followed by FDA’s approval in 2003 of Tricor-2, a micronized, lower-dose formulation also with a food effect, for the broader indication of lowering low-density lipoprotein. The third iteration of this drug, the nano-milled Tricor-3, which was approved by FDA in 2004, did not show a food effect. Its label was expanded as a category IIb/IV - solubility limited drug (fenofibrate), which is not as flowable as lactose. With lactose, a wider range of air pressure was achievable within the mill. The mill was able to greatly reduce the particle size of fenofibrate from a D90 of 431 microns to less than 30 microns. With lactose, it was possible to overcome flow problems and mill material at different air pressures and sublot sizes as shown in Figure 2. The optimal yield of 68% was observed at an air pressure of 4 barg. The maximum sublot size of 200 mg was able to achieve optimal yield of 70%. There were challenges in processing fenofibrate at lower mill pressures as shown in Figure 3. The material could not fluidize and flow at pressures below 4 barg. Based on these results, the processing conditions to use with the lab-scale air jet mill are expected to be API dependent. The scanning electron microscope images (see Figure 4) showed that the particle size reduction of the fenofibrate did not have a tight and uniform distribution as observed with large particulates in the micronized product. Despite some limitations, the lab-scale mill is useful for feasibility testing of APIs with small batch sizes of less than 5 g.

**Particle size reduction for inhalation formulations**

Formulation development, particularly particle size engineering through sizing and size distribution, is often crucial in tailoring a drug product to treat specific diseases. Inhalation formulations have long been available to treat lung diseases, for example asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis.

Drugs delivered orally must undergo absorption before they enter the bloodstream, but unfavourable systemic side effects are common. Dosage forms targeting localized diseases have the advantage of delivering drug to the precise disease location, thereby allowing lower doses and reducing systemic exposure (4). Inhaled drugs must be produced within precise size regimes in order to reach specific regions of the lung, for example, the bronchial tract (5). Moreover, particle sizes must be relatively uniform, typically within 2-5 μm in diameter to ensure that they consistently reach the right target region. Particles of greater than 5 μm are absorbed in the larynx and pharynx and into systemic circulation; particles smaller than 1 μm are exhaled from the lung. Micronization using air jet milling is the most common technology of particle size reduction for inhalation drugs.

**Lab-scale case study: Particle size reduction of less than 5 g**

Preformulation development and testing can be challenging due to the resources available. Quite often, the quantity of API available is limited during the early drug discovery phase—at times, as little as 400 mg. Most commercial mills available are limited to processing sublot sizes greater than 5 g. However, there are specialized lab-scale air jet mills available now that can process sublot batch sizes as small as 50–200 mg.

Lab-scale air jet milling of small samples was tested using a free-flowing material (lactose) and a model drug (fenofibrate), which is not as flowable as lactose. With lactose, a wider range of air pressure was achievable within the mill. The mill was able to greatly reduce the particle size of fenofibrate from a D90 of 431 microns to less than 30 microns. With lactose, it was possible to overcome flow problems and mill material at different air pressures and sublot sizes as shown in Figure 2. The optimal yield of 68% was observed at an air pressure of 4 barg. The maximum sublot size of 200 mg was able to achieve optimal yield of 70%. There were challenges in processing fenofibrate at lower mill pressures as shown in Figure 3. The material could not fluidize and flow at pressures below 4 barg. Based on these results, the processing conditions to use with the lab-scale air jet mill are expected to be API dependent. The scanning electron microscope images (see Figure 4) showed that the particle size reduction of the fenofibrate did not have a tight and uniform distribution as observed with large particulates in the micronized product. Despite some limitations, the lab-scale mill is useful for feasibility testing of APIs with small batch sizes of less than 5 g.
The lab-scale air jet mill opens up the preformulation market in particle size reduction with less than 5 g of API. Currently, mechanical approaches using a mortar and pestle cannot achieve the particle size distribution and the crystallinity stability that is possible with micronization. While the design of the lab-scale air jet mill is not the same as the design of larger commercial air jet mill used in the pharmaceutical industry, the lab-scale mill would be a better choice for feasibility testing with API batch sizes of less than 5 g.

References

Figure 2: Throughput (% yield) of lactose at varying air pressure and subplot sizes.

Figure 3: Yields at different air pressures (4 and 6 barg) and subplot sizes (50 and 100 mg).

Figure 4: Scanning electron microscopy (SEM) images of micronized fenofibrate.
Cannabinoids have great potential to treat a wide variety of diseases, leading to tremendous interest among pharmaceutical companies in accessing pharmaceutically pure cannabinoids for the development of novel therapies. Several companies are developing cannabinoid-based treatments, including Vitality Biopharma, GW Pharmaceuticals, Zynerba Pharmaceuticals, INSYS Therapeutics, Teewinot Life Sciences Corporation, and Nemus Bioscience.

Some cannabinoids bind to the same receptors that are bound by endocannabinoids, which are naturally produced in human cells. The human endocannabinoid system (ECS) is a group of endogenous cannabinoid receptors located in the mammalian brain and throughout the central and peripheral nervous systems that are controlled by neuromodulatory lipids, according to Richard Peet, executive vice-president and research director at Teewinot Life Sciences Corporation. “The ECS is involved in a variety of physiological processes, including pain sensation, appetite, memory, and mood. It is for this reason that cannabinoids frequently influence various physiological functions when administered to humans,” he notes.

Cannabinoids such as delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), cannabichromene (CBC), tetrahydrocannabinvarin (THCV), and cannabidivarin (CBDV) have many potential uses, such as the treatment of nausea associated with chemotherapy, epilepsy, appetite control, diabetes, and inflammation, among many others.

Why biocatalysis for cannabinoid synthesis?
Cannabinoids are synthesized in the Cannabis plant via biosynthetic pathways consisting of several enzyme-catalyzed steps. The Cannabis plant produces only small quantities of many of these cannabinoids including the varin series of cannabinoids (THCV, CBDV, and cannabinomerevarin (CBCV)), and cost-effective chemical synthesis of these molecules is not available, according to Peet.

“Traditional chemical manufacture of these complex, chiral molecules typically requires several steps and elaborate purification from impurities,” observes James Lalonde, senior vice-president of research and development for Codexis. Chemical synthesis of cannabinoids such as THC also generates copious amounts of organic waste, takes many weeks to complete at the kilogram scale, and is very expensive, adds Peet. “Practical methods for chemical synthesis for many of the 111 known cannabinoids have not been developed,” he states. Enzymes that have been evolved in nature, in contrast, can synthesize these molecules cleanly with the exclusion of impurity-generating side reactions, according to Lalonde.

Extraction of targeted cannabinoids from the Cannabis plant is also not practical for production of large quantities of pharmaceutically pure cannabinoids. Extraction of targeted cannabinoids from the more than 100 related compounds in the plant is labourious and time consuming, according to Lalonde. “The Cannabis plant must be grown for three to four months and requires large quantities of water and energy inputs. Then obtaining pharmaceutically pure cannabinoids from plant tissue is very expensive, because many cannabinoids are produced in very small quantities in the Cannabis plant,” notes Peet.

The use of enzymes ex vivo allows the synthesis of targeted single distinct compounds, rather than a complex mixture. “Production of these compounds can be controlled for purity and regulatory controls in the same manner as any active pharmaceutical. In addition, the biocatalytic process is independent from the plant growth cycle and the constraints of marijuana cultivation. Scale up of the synthesis of rarer, but desirable compounds would also be made possible in an enzymatic, ex vivo process in which enzymes that catalyze formation only of the desired compounds could be cloned and purified in high yield,” Lalonde explains.
New biosynthetic processes

Teewinot has developed biosynthetic processes for the production of large quantities of cannabinoids including the varin series of cannabinoids. "Compared to chemical syntheses, these processes are less expensive, more efficient, and produce minimal amounts of chemical waste. As a result, biosynthetic processes make possible the production of pharmaceutically pure cannabinoids in much larger quantities than is practical through plant cultivation and cannabinoid extraction," Peet asserts.

The company uses bioinformatics and metabolomics to facilitate the development of synthetic biology and biocatalytic routes to cannabinoids. Genes in the Cannabis plant, as well as chemical compounds in plant tissues, are identified, characterized, and quantified if relevant. "By cloning specific gene sequences from the plant and incorporating them into microorganisms, we are able to develop new expression systems and processes for the production of naturally-occurring and specific cannabinoids," Peet explains. Specifically, Teewinot has cloned genes from the Cannabis plant that code for cannabinoid biosynthetic enzymes and incorporated them into yeast and other microorganisms.

Teewinot refers to its cannabinoid biosynthetic processes as CannSynthesis. Using its synthetic biology and biocatalytic processes, the company can now biosynthetically produce 18 different cannabinoids that have the identical chemical structures to those produced in the plant, including tetrahydrocannabinolic acid (THCA), THC, tetrahydrocannabivaric acid (THCVA), THCV, cannabidiolic acid (CBD), CBD, cannabidivaric acid (CBDVA), CBDA, cannabichromenic acid (CBCA), CBC, cannabichromenevaric acid (CBCVA), cannabichromevarin (CBCV), cannabigerolic acid (CBGA), cannabigerol (CBG), cannabigerovarinic acid (CBGVA), cannabigerovarin (CBGV), cannabinol (CBN), and cannabicyclol (CBL), according to Peet.

For example, Teewinot produces the Cannabis enzymes THCA synthase and CBD synthase in a microorganism. THCA synthase converts the substrate CBGA into THCA and/or CBDA, while CBD synthase converts the substrate CBGA into CBDA and/or CBCA. During biocatalysis, both reactions proceed in a pH-dependent manner in a bioreactor. The CBGA used in this biocatalytic process can be produced in any number of ways, including synthetic biology or chemical synthesis. Alternatively, the entire process can be done in a microorganism by means of synthetic biology.

Purification of cannabinoids from the Cannabis plant is also not practical for production of large quantities of pharmaceutically pure cannabinoids.

Teewinot can also produce next-generation, proprietary cannabinoid pro-drugs and cannabinoid analogs, many of which are novel and have never been produced in large quantities in pharmaceutically pure form. "Some of these compounds have improved efficacy and bioavailability and other beneficial characteristics that improve therapeutic outcomes," Peet notes. He adds that it is now possible to test the efficacy of these compounds in the treatment of a wide variety of diseases, including inflammatory bowel disease, Crohn’s, epilepsy, cancer, migraine, fibromyalgia, and many others, according to Peet. For instance, in 2016, Teewinot licensed its patent-protected biosynthetic processes to Nemus Biosciences for use in the manufacture of its THC pro-drug for treatment of glaucoma.

The company expects to undertake GMP production of cannabinoids using biocatalysis within the next three to six months, and is in conversations with a large number of pharmaceutical companies seeking to purchase cannabinoids produced by its biosynthetic processes for use in pre-clinical and clinical trials.

In March 2017, Teewinot signed a letter of intent with Noramco, a producer of controlled-substance APIs, to commercially produce cannabinoids using its CannSynthesis technology. The agreement provides Noramco access to Teewinot’s patent-protected processes for the production of pure cannabinoids using biocatalysis and the company’s assistance with rapid implementation of the technology.

Noramco will create 10–15 cannabinoid reference standards and evaluate the feasibility of using the technology to produce Dronabinol on a commercial scale. Dronabinol is known for its effectiveness in pain management, as an antiemetic, in the control of vomiting, as an appetite stimulant in the treatment of AIDS and for reducing the side effects of chemotherapy.

Education is important

Although biosynthetic processes like those developed by Teewinot are new and improved methods of production that reduce cost and production time, increases purity, and allow for the synthesis of a much greater diversity of molecules that can be incorporated into drug formulations, the approach is different from traditional extraction or chemical synthesis. As a result, Teewinot has found that bringing this new technology to market has created the need to educate researchers and others in the pharmaceutical cannabinoid field. "Educating researchers includes describing the broad array of cannabinoids that can now reliably be manufactured, tested, and put into clinical trials for development of potential new therapies," Peet comments.

He does note, however, that because synthetic biology and biocatalysis are common pharmaceutical manufacturing processes, pharmaceutical companies and regulators are generally familiar with the technical aspects of these methods. PTE
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Our clients bring us their one-of-a-kind breakthroughs. Our experience gives them a reliable and efficient journey into viable products. We offer complete drug substance and drug product services for small molecules. Plus, a comprehensive range of dosage forms. Let us apply our expertise to help you overcome your toughest solubility challenges and accelerate your path from concept to proof of concept to commercial launch.
Extractables and Leachables Testing for Inhaled Medicines

Follow guidelines for E&L studies of an orally inhaled and nasal drug product formulation in its delivery device.

O
rally inhaled and nasal drug product (OINDP) formulations, which are primarily a propellant including an organic solvent, have a high potential for the leaching of substances from the delivery device components. In this context, a device such as a dry powder inhaler (DPI) or pressurized metered dose inhaler (pMDI) is considered a primary packaging material or a container closure system (CCS). An extractables and leachables (E&L) investigation should be conducted to guarantee that the pharmaceutical packaging system is safe and does not negatively influence the drug product.

Extractables are compounds that are released from a CCS into an extraction solution, which is typically a simulation solvent that mimics the drug formulation, during forced extraction experiments. Leachables are compounds that leach from a CCS into the drug formulation under normal storage conditions, such as those applied during a formal stability study.

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In particular, three new USP Chapters (USP <1663>, USP <1664>, and USP <1664.1>) generically describe how to carry out E&L studies.

In all guidelines, an initial risk estimation is performed with consideration of data obtained from solvent extraction E&L screening. For toxicological risk evaluation of inhalation product extractables data, PQRI recommendations can be applied (9). These PQRI documents focus on orally-inhaled and nasal products, as well as parenteral and ophthalmic drug products. The recommendations were developed in collaboration with FDA, and they provide clear direction and technical considerations for carrying out E&L studies with guidance on how to evaluate data, as well as how to use toxicological relevant limits in E&L data.

Strategies for an extractables and leachables study
An E&L study should be able to provide a complete overview about potentially harmful substances that could leach from the packaging. Several steps must be considered to ensure that the study is in alignment with the current guidelines and tailored to the specific drug products and packaging properties. A well-designed E&L study can be divided into the following major steps:

- Critical assessment: a critical evaluation of the packaging system and the properties of the pharmaceutical formulation, as well as an evaluation of the guidelines
- Extractables study: a set of forced laboratory experiments to extract as much as possible out of the packaging material (under “realistic worst-case conditions” [15])
- Migration or leachables check experiment: includes the use of a drug formulation or placebo in original packaging under worst-case conditions and long-term storage at accelerated temperatures
- Data evaluation: evaluation of the extractable study data, including a toxicological assessment, for the selection of critical leachables
- GMP-leachables study: the final stage, performed as part of the stability study for the drug product after appropriate method optimization and validation for the selected leachables.

The highest risk is typically considered for inhalation or injectable products because they are directly delivered into a target organ.

Step 1: critical assessment.
In the first step, the different materials of construction of the packaging must be evaluated. Each type of polymer matrix (e.g., polypropylene, polyethylene, cyclic olefin copolymer, Teflon, elastomer) contains small molecules that are used as additives (e.g., antioxidants, light stabilizers, modifiers); process chemicals, printing inks, or adhesives may also be present. A typical pMDI, for example, is made of several types of polymers, rubbers, and metals, as described in Table I. Similarly, several materials are used in a nasal spray device (see Table II) and a dry powder inhaler (see Table III).

For a critical assessment of the formulation properties, the interaction potential has to be considered in relation to the administration route for the drug. In the PQRI (9) and FDA/EMA guidelines (3–8), tables and flow schemes are given to guide this step. Depending on the final risk, an E&L study is required. The highest risk is typically considered for inhalation or injectable products because they are directly delivered into a target organ (e.g., lung, blood) without any dilution; ophthalmic and nasal solutions are considered as medium risk.

The interaction potential for the formulation depends on the physical properties. Liquid samples with solvents are related to a high risk of interaction, but solid dosage forms are supposed to have lower risk.

Analytical screening methods that are capable of finding low concentrations of unknown extractables should be used. In the guidelines, thresholds such as the safety concern threshold (SCT) are detailed (9, 16, 17). The SCT varies depending on the route of administration of the drug and the related risk for the patient. Inhaled products are known to be more critical than other delivery routes because they typically exhibit SCTs of 150 ng/day (9). Below this threshold, the intake of an extractable compound can be considered as less risky for the patient independent from its chemical structure.

For extractables with a concentration above the SCT, a full characterization and quantification must be performed. Since the SCT is given in ng per day, the analytical evaluation threshold (AET) has to be calculated with consideration of the volume of the packaging and the maximum daily dose of the drug product. The extraction experiment should be designed in a way that unknown compounds, with

### Table I: Component parts and construction materials of a typical pressurized metered dose inhaler.

<table>
<thead>
<tr>
<th>Component</th>
<th>Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Housing</td>
<td>Polycetal (POM)</td>
</tr>
<tr>
<td>Metering chamber</td>
<td>POM</td>
</tr>
<tr>
<td>Valve top body</td>
<td>POM</td>
</tr>
<tr>
<td>Upper stem</td>
<td>POM</td>
</tr>
<tr>
<td>Lower stem</td>
<td>POM</td>
</tr>
<tr>
<td>Seat gasket</td>
<td>EPDM rubber</td>
</tr>
<tr>
<td>Outer O-ring</td>
<td>Nitrile</td>
</tr>
<tr>
<td>Spring</td>
<td>Stainless steel</td>
</tr>
<tr>
<td>End cap</td>
<td>Anodized aluminum</td>
</tr>
</tbody>
</table>
Inhalation Drug Manufacturing

Table II: Component parts and construction materials of a typical nasal spray device.

<table>
<thead>
<tr>
<th>Component</th>
<th>Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actuator</td>
<td>Polypropylene (PP)</td>
</tr>
<tr>
<td>Dip tube</td>
<td>PP</td>
</tr>
<tr>
<td>Chaplet</td>
<td>PP/Ethylene-vinyl acetate</td>
</tr>
<tr>
<td>Long spring</td>
<td>Stainless steel</td>
</tr>
<tr>
<td>Stem gasket</td>
<td>Silicone</td>
</tr>
<tr>
<td>Neck gasket</td>
<td>Silicone</td>
</tr>
<tr>
<td>Stem</td>
<td>High-density polyethylene</td>
</tr>
<tr>
<td>Piston</td>
<td>Linear low-density polyethylene</td>
</tr>
<tr>
<td>Dust cap</td>
<td>Linear low-density polyethylene</td>
</tr>
<tr>
<td>Housing</td>
<td>PP</td>
</tr>
<tr>
<td>Cap</td>
<td>Aluminium</td>
</tr>
</tbody>
</table>

Table III: Component parts and construction materials of a typical dry powder inhaler (DPI).

<table>
<thead>
<tr>
<th>Component</th>
<th>Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Housing top</td>
<td>Acrylonitrile butadiene styrene (ABS)</td>
</tr>
<tr>
<td>Housing bottom</td>
<td>ABS</td>
</tr>
<tr>
<td>Top cover</td>
<td>ABS</td>
</tr>
<tr>
<td>Cam strap</td>
<td>Polycetal (POM)</td>
</tr>
<tr>
<td>Cartridge</td>
<td>Polyolefin</td>
</tr>
<tr>
<td>Spike</td>
<td>POM</td>
</tr>
<tr>
<td>Lower drive gear</td>
<td>POM</td>
</tr>
<tr>
<td>Dose counter</td>
<td>ABS</td>
</tr>
<tr>
<td>Top drive gear</td>
<td>POM</td>
</tr>
<tr>
<td>Transfer gear</td>
<td>POM</td>
</tr>
<tr>
<td>Detent</td>
<td>POM</td>
</tr>
<tr>
<td>Dust cap</td>
<td>High-density polyethylene (HDPE)</td>
</tr>
<tr>
<td>Mouthpiece</td>
<td>Polypropylene</td>
</tr>
<tr>
<td>Actuator</td>
<td>HDPE</td>
</tr>
<tr>
<td>Screen</td>
<td>ABS</td>
</tr>
</tbody>
</table>

- 150 ng/day / 0.3 mL/day = 500 ng/mL (i.e., concentration of extractables)
- 500 ng/mL x 15 mL = 7500 ng = 7.5 mg (i.e., total released amount of an extractable)
- Assuming a part has a weight of 1 g, 7.5 mg/g (ppm) of an extractable must be analyzable with the applied method.
- Quantitation limit for extractables must be better than 7.5 ppm (i.e., typical value in extractable studies).

Example 2: impact of route of administration on AET. Compare a 2.0 mL unit dose vial used for two different applications: an ophthalmic drug product and an inhalation drug product in a nebulizer.

- Lowest acceptable daily dose for an extractable (SCT) is:
  - 150 ng/day for OINDPs (based on PQRI)
  - 1.5μg/day for parenteral and ophthalmic drug products.
- Application scenario is:
  - 0.5 mL for the ophthalmic application
  - Two ampules/day for the inhalation drug product
- AET is:
  - For the ophthalmic solution: 1.5 μg/day/0.5mL/day = 3μg/mL
  - For the inhalation product: 0.15 μg/day/4 mL/day = 375 ng/mL.

Step 2: extractables experiments. The extraction conditions and solvents have to be adapted to realistic conditions that may occur during the storage of the drug product. In general, the extraction experiments should reflect the worst-case scenario. The extraction conditions should include thermal stress without deteriorating the polymeric matrices, and the chosen solvents should mimic the drug formulation and have similar properties (e.g., with respect to solvent properties, polarity, pH) while slightly exaggerating its extraction strength. Typically, pure organic solvents or mixtures of water and organic solvents are used for this purpose; the content of organic solvent in such mixtures should slightly exceed the content of organic components in the drug formulation to ensure worst-case conditions. It must be ensured,

Example 1: AET calculation for an MDI.
- Lowest acceptable daily dose for an E&L compound (SCT) = 150 ng/ day (based on PQRI [9])
- A typical volume of an MDI is 15 mL
- The application scenario is 0.1 mL in 3 doses per day = 0.3 mL/day depending on application scenario and size of the packaging system.

The following examples illustrate that the AET calculation is essential for proper design of subsequent extraction studies, because the analytical detection limit varies a concentration in the range less than the AET, are still detectable; the analytical screening method applied to the extract should be sensitive enough to cover the calculated AET.

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Table IV: Different types of drug product container closure systems and the corresponding extraction study conditions.

<table>
<thead>
<tr>
<th>Device</th>
<th>Container contents</th>
<th>Extraction study type</th>
<th>Extraction solvent type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressurized metered dose inhaler (pMDI)</td>
<td>API plus excipients - pH-buffer - Ethanol (10%) - Propellant (40% fluorinated HC)</td>
<td>Only with single parts</td>
<td>Strong organic and aqueous solvents with pH adjustment due to the high solvent strength of the organic propellant</td>
</tr>
<tr>
<td>Nasal spray application</td>
<td>- API plus excipients - pH-buffer - &gt;90% water for injection</td>
<td>With single parts or assembled device</td>
<td>Aqueous alcohol and pH adjustment to simulate the pH range covered by the buffer</td>
</tr>
<tr>
<td>Typical dry powder inhaler (DPI)</td>
<td>- API plus some excipients, stationary phase - No solvent and no water</td>
<td>With single parts or assembled device (mainly the blister)</td>
<td>Organic solvents or sorbent</td>
</tr>
</tbody>
</table>

however, that the chosen solvents do not degrade the drug formulation or dissolve the polymer matrix of the packaging.

Table IV lists typical simulation solvents and extraction set-ups for typical drug products and application cases. Inhaler devices or containers for nasal applications consist of many different assembled parts, which are sometimes only partially in contact with the drug formulation or not accessible for the simulation solvent due to the specific construction. In this case, it makes sense to perform the extractables study with the disassembled parts of the device. The different rubber and plastic materials are extracted and analyzed individually or the individual extracts are pooled and analyzed once. For the pooling approach, the mass or surface contribution of each individual part defines its percentage in the final extract sample. The individual screening of each part has the advantage that identified extractables may be assigned to a specific part of the inhaler. If the pooling of the extracts is performed, it could be helpful to carry out an additional analysis using thermodesorption coupled to gas-chromatography-mass spectrometry (TDS–GC/MS) on the single parts to get a qualitative comprehensive overview of most of the contained, generally volatile and semi-volatile, extractables that will simplify the later assignment of specific extractables to specific parts.

In some cases, the devices can be incubated with the simulation solvent as assembled devices. For spray products, for example, the assembled device can be filled with the extraction solvent and the pump released a few times to bring all internal parts in contact with the solvent, which would simulate the application.

### The extraction conditions and solvents must be adapted to realistic conditions that may occur during the storage of the drug product.

For a dry powder inhaler, instead of organic extraction, a solid adsorbent (e.g., TENAX organic sorbent) can be used for simulation of the solid drug product. In the case of a solid drug product, most of the extractables will be volatiles, which may be adsorbed on the solid surface of the powder. The solid adsorbent is then extracted with organic solvents, which are analyzed with comprehensive techniques or TDS–GC/MS.

After extraction of the device or container closure system with different solvents, the screening analysis is conducted and different analytical techniques can be applied. Sometimes it will be possible to directly inject the extract solution into the analytical instrument. In most cases, however, a back extraction with solvents suitable for specific analytical techniques is required. Typical screening techniques are GC/MS with and without derivatization, headspace GC/MS, high-performance liquid chromatography (HPLC)-MS and inductively coupled plasma (ICP)-MS or optical emission spectroscopy (OES) for elemental impurities coming from catalyst residues or filling material.

#### Step 3: migration or leachables check experiment. In addition to the extractions with simulation solvents, a leachables check experiment should be performed in which the sample is incubated with the pure drug formulation or placebo to capture potential reaction products formed from extractables and formulation components. Moreover, volatile compounds tend to migrate through polymeric layers or seals if the barrier properties are not good enough. Well-known sources for migrating substances include labels, adhesives, inks, or even secondary packaging components, such as cardboard boxes, often made from recycled paper, which potentially contain inks or volatile photoinitiator residues. Those compounds are only detectable if the sample is incubated for a longer period at accelerated thermal conditions or if aged samples are analyzed.

#### Step 4: evaluation and assessment of the E&L data. After the analytical work of the E&L study is finalized, all the results obtained must be evaluated. A list of all relevant extractables and potential leachables is generated. All components above the AET limit have to be identified, and these compounds must be checked frequently as potential drug impurities during a GMP leachables monitoring study, such as a formal stability study. Sometimes, a toxicological assessment may be performed for dedicated extractables to replace the AET and monitoring specifications with a new limit that is based on existing or derived toxicity data.
Step 5: GMP leachables study.
The leachable study is performed as part of the stability study for the drug product and conducted after appropriate method development and validation is complete for the selected leachables. The monitoring is compound-specific and fully quantitative. Moreover, the validation has to be performed according to International Council for Harmonization (ICH) Q2A/Q2B, which includes experiments to ensure sufficient linearity, specificity, accuracy, precision, reproducibility, limit of detection, and limit of quantification. From this stage, the monitored leachables are considered as potential drug impurities. The monitoring study has to be carried out under full quality control. In contrast to the extractables screening, after finalization of the validation, there is no experimental freedom for adaptation of the methods as was the case during the initial screening steps.

Potential issues during E&L studies
Choosing the correct solvent strength is crucial. In Figure 1, a typical GC/MS-chromatogram obtained after organic extraction of polyethylene (PE) is shown. Clearly visible is a series of PE homologues that are dissolved by the organic solvent. In this case, the solvent may be too strong, because more critical extractables, such as stabilizer additives and their degradation products, are hidden in the baseline noise. If the concentration of these extractables exceeds the AET level, they must be considered in subsequent leachables monitoring.

Another example of non-realistic or excessively harsh extraction conditions is a water-extraction of a polyether material performed at 95 °C. As a result, a very complex liquid chromatography (LC)/MS spectrum was observed that showed multiple distributions of homologue series. In a subsequent detailed evaluation, a general increase of the high molar weight components was found (see Figure 2), but the low molar mass components (measured with GC/MS) showed a decay after 15 min of extraction time (see Figure 3), indicating continuous degradation of the matrix polymer caused by the accelerated extraction conditions. The low molar mass extractables will be fully leached out of the material after a certain period, making them difficult to detect.

In complex chromatograms, it’s possible that some compounds are potentially invisible. The extraction of a rubber material, for example, produces a chromatogram with an overcrowded baseline with many peaks. Organic back extraction and pH variation were used to identify extractable components (see Figure 4).

Only after the pH variation step was it possible to clearly detect the presence of mercaptobenzothiazole (MBT), which is known to be pH-sensitive (18). MBT and other benzothiazoles are common vulcanization accelerators for rubber materials that are used in pharmaceutical container/systems, such as the gaskets in a pMDI. MBTs are considered a potential carcinogen and have been shown to migrate into drug formulations.
Due to the toxicological concern and leachability of MBT and other benzothiazoles, analytical methods have been developed to study these types of compounds (18). These examples illustrate the importance of a realistic study design customized for the type of packaging, the drug formulation, and its route of administration, particularly for OINDP products.

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For more articles on developing and manufacturing inhalation drug products, visit www.PharmTech.com/inhalation.
The United States Pharmacopeia (USP) states that ophthalmic solutions should be free of visible particulates upon inspection and meet the subvisible particulate matter requirements specified in USP Chapter <789>. In this study, the authors describe a forensic microscopy approach to characterize particles that were visually observed during stressed stability testing of an ophthalmic solution formulation. The particulate present in the formulation was chemically identified at low parts per million levels.

This report describes a microscopic investigative approach to characterize particles that were visually observed during stressed stability testing of an ophthalmic solution formulation. Topical ophthalmic solutions should be “essentially free” of visible particulates upon inspection as specified in the United States Pharmacopeia (USP). Ophthalmic solutions are also required to meet subvisible particulate matter requirements per USP Chapter <789> at the time of product release and during stability testing to verify manufacturing cleanliness and support shelf life of the finished product (1). The analytical characterization work needed in cases where USP <789> failures occur is considered trace or ultra-trace analysis. For example, the USP <789> limit for particles between 10–25 μm is 50 particles/mL. In cases where the limit is exceeded due to a 20 micron needle-shaped particulate with a density of 1.5 g/cm³, the particulate level would correspond to approximately 2 parts per billion (ppb) on a concentration basis for a 5-mL fill size. Particle isolation and enrichment practices coupled with direct sample analysis using micro-analytical techniques are essential to productive problem-solving during particulate matter failure investigations due to the inherent trace concentration levels.

Forensic microscopy uses a progressive problem-solving approach to yield the maximum amount of information from consumption of a minimal amount of sample in an efficient manner (2). The investigation follows a careful, stepwise approach to limit contamination or loss of trace materials along the analysis pathway. Maintaining an “eye to sample” connection during sample handling is also essential. The testing progression typically follows this pathway:

- Visual and low-power stereomicroscopic inspection of the sample to understand the context of the defect/failure
- Isolation and enrichment of the offending particulates or defects; negative control sample is essential
- Low- to high-power polarized light microscopy examination, including thermal analysis
- Selected spectroscopic techniques such as infrared microspectroscopy for organic and scanning electron microscopy–energy dispersive spectroscopy (SEM–EDS) for inorganic materials
- Confirmation of identity with authentic material if available. The chemical information from each step builds a body of evidence for the assignment of identity to the unknown. Mass spectral information of particles can be obtained using atmospheric solids analysis probe.
Materials and methods

Samples. The formulation of interest was an isotonic, buffered, and preserved solution of travoprost (0.04 mg/mL). Travoprost is a synthetic prostaglandin F analogue indicated for the reduction of elevated intra-ocular pressure. The formulation ingredients are listed in Table I.

A laboratory formulation of travoprost ophthalmic solution was prepared at pH 6.5 using commercially available ingredients. Aliquots of the formulation were placed in capped glass vials and stored in a 60 °C stability cabinet (Fisher Scientific, Isotemp Incubator, Model 650D). The samples were visually examined at regular intervals.

Particle isolation and enrichment. A visible precipitate was observed in laboratory prepared samples after storage in glass at 60 °C for six weeks. Particles were isolated either through centrifugation or by filtration through gold-coated polycarbonate filters (Whatman, Nuclepore, track etched, 13 mm, 0.8 μm porosity). Samples were centrifuged for approximately 15 mins at 2000 rpm using a bench top centrifuge (Fisher Scientific, accuSpin 1R). Filtration was conducted in a Class 100 clean hood using pre-cleaned glassware. Isolated particles were washed extensively with 0.2-μm filtered water prior to analysis to remove residual formulation components.

Polarized light and hot stage microscopy. The use of polarized light microscopy by a seasoned microscopist is a powerful identification method with many common environmental particle types such as fibers, skin flakes, and cellulosic materials capable of recognition by sight.

Particles from the formulation were dispersed in 1.66 refractive index (RI) oil (Cargille Labs, certified grade) and observed microscopically with and without polarized light (Nikon LV100 POL 100-400X) using transmitted illumination. Hot stage microscopy (100x) was conducted from ambient temperature to approximately 250 °C with heating at 10 °C/min using a Linkham hot stage (TMS 94, controlled microfurnace). Microscopic observation during heating was used to identify changes in crystallinity and melt events.

Infrared microspectroscopy. Infrared microspectroscopy can be used for identification of single particulates down to approximately 20 μm through comparison of the unknown particle’s infrared spectrum to spectral library databases. For particles smaller than 20 μm, diffraction effects become problematic and a Raman microscope is more appropriate for spectroscopic analysis. In this study, infrared spectra were collected using a Nicolet 6700 Fourier transform infrared (FTIR) spectrometer (Thermo Scientific) equipped with Nicolet Continuum infrared microscope set in reflectance mode when using gold-coated polycarbonate filters or transmission when using 13-mm sodium chloride windows. The Continuum uses a 32x objective and condenser along with a mercury-cadmium-telluride (MCT)-A detector and a motorized x-y

---

Table I: Formulation composition. USP is United States Pharmacopeia, NF is National Formulary. PEG is polyethylene glycol.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Source or grade</th>
<th>Each mL contains (mg)</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travoprost</td>
<td>Industriale Chimica/USP</td>
<td>0.040</td>
<td>Drug active</td>
</tr>
<tr>
<td>PEG-40 hydrogenated castor oil</td>
<td>BASF Chemicals/USP–NF</td>
<td>5.00</td>
<td>Drug solubilizer</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>NF grade</td>
<td>2.50</td>
<td>Tonicity</td>
</tr>
<tr>
<td>Boric acid</td>
<td>NF grade</td>
<td>10.00</td>
<td>Preservative/buffer</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>NF grade</td>
<td>7.50</td>
<td>Preservative; toxicity</td>
</tr>
<tr>
<td>Zinc chloride (ZnCl)</td>
<td>EMD Chemicals/USP</td>
<td>0.025</td>
<td>Preservative</td>
</tr>
<tr>
<td>Hydrochloric acid (HCl) and/or sodium hydroxide (NaOH)</td>
<td>q.s. to pH</td>
<td></td>
<td>pH adjustment</td>
</tr>
<tr>
<td>Purified water</td>
<td>q.s. to 1 mL</td>
<td></td>
<td>Vehicle</td>
</tr>
</tbody>
</table>

---

Figure 1: Forensic microscopy sequential problem-solving approach. SEM–EDS is scanning electron microscopy–energy dispersive spectroscopy; IR is infrared; MS is mass spectrometry.
stage. The following scan settings were used:

- wavenumber range (cm⁻¹): 4000–600 nominal
- display mode: reflectance or transmission
- number of scans: 64 or 256
- resolution (cm⁻¹): 4
- sample aperture/iris: ~ 50 μm x 25 μm.

A background spectrum was collected immediately after the sample was analyzed. The sample single-beam spectrum was then normalized to the appropriate background scan to yield absorbance spectra. Spectra were collected and searched using OMNIC 7.4.127 (Thermo Fisher Scientific, Inc.) software.

**Elemental analysis by SEM–EDS.**

Particles were mounted onto an aluminum SEM stub using a carbon adhesive tab. Prior to analysis, the sample was sputter coated with ~2 nm of Au/Pd for charge control. SEM micrographs and energy dispersive spectra were collected under standard (high) vacuum conditions using the FEI Quanta 400 scanning electron microscope and Oxford INCA X-sight energy dispersive spectrometer (EDS). The sample analysis configuration was set to 20KV accelerating voltage for imaging and EDS with a 10-mm working distance. A focused electron beam was rastered across the surface of the sample. The electron beam generates X-rays in the beam-specimen interaction volume beneath the sample surface; depth is approximately 1 μm. Elemental analysis is performed by measuring the energy and intensity of the X-ray signals exiting the sample generated by the electron beam. The EDS detector converts the energy of each characteristic X-ray into a voltage signal of proportional size.

**Results and discussion**

A visible precipitate formed in laboratory prepared samples of 0.04 mg/mL travoprost solutions at pH 6.5 after storage in glass vials at 60 °C for six weeks. The formation of particulate matter under stressed conditions indicates a critical product quality issue that affects the potential development, safety, and longevity of the product formulation. Identification of the chemical composition of the particles was essential to understand the mechanism of formation and to mitigate the problem. Figure 1 illustrates the steps of a forensic microscopy investigation.

**Particle characterization by polarized light and hot stage microscopies.** Particles were isolated by two methods. Centrifugation of the sample was a simple way to concentrate particles and wash them of residual formulation components. In some cases, particles were also isolated by filtration through a gold-coated polycarbonate filter. The gold-coated filter membrane made possible direct infrared analysis of particles via specular reflectance.
A sample of the precipitate was dispersed in 1.66 RI oil onto a clean microscope slide. Microscopic examination (Nikon LV100 POL 100–400X) revealed fine needle crystals having weak birefringence. Most of the needle-shaped particles were 5–20 μm long and approximately 1 μm in diameter (see Figure 2). Occasionally, needles as long as approximately 200 μm were observed. Thermal analysis by hot stage microscopy revealed the needles melted between 155–160 °C suggesting a crystalline state. Based on the needle morphology and an assumed density of 1.5 g/cm³, it was estimated that ~ 0.6 ng of material per particle was present (Figure 3).

**Infrared microspectroscopy.** Individual needle particles isolated onto a gold-coated polycarbonate filter were analyzed by infrared microspectroscopy using specular reflectance off of the gold coating. A representative spectrum is shown in Figure 4. The particle spectrum was searched against infrared spectral libraries and revealed good correlation to a salt of a long alkyl chain fatty acid as shown in Figure 5. The needle particle spectrum had the following spectral features consistent with a carboxylic acid salt: strong band at 1540 cm⁻¹ due to the asymmetric stretching of the CO₂⁻ group, bands at 1470, 1415, and 1400 cm⁻¹ due to the symmetric stretching vibration of the CO₂⁻ group. Strong peaks at approximately 2900 cm⁻¹ and at approximately 2850 cm⁻¹ were due to the asymmetric and symmetric C–H stretching vibrations of a long-chain alkane. The broad peak at approximately 3300 cm⁻¹ was consistent with O–H stretching.

**Elemental analysis by SEM–EDS.** A precipitated fatty acid salt was the suspected cause of particulate formation; thus, elemental composition was investigated using SEM–EDS to identify a potential counter ion. Care was taken to copiously rinse particle isolates of formulation components prior to analysis. A representative SEM–EDS spectrum of the needle particles is shown in Figure 6. A strong and consistent response for zinc (Zn) was observed in the needle particle spectrum in addition to carbon and oxygen. The travoprost formulation is preserved with 0.025 mg/mL zinc chloride (ZnCl₂), which is the likely source of Zn²⁺ for the fatty acid salt.

**Particle formation from solutions of ZnCl₂ and 12-hydroxystearic acid to confirm identity of needle particles.** The particle characterization data indicated that the precipitate isolated from stability samples was consistent with a zinc salt of a long-chain fatty acid. A logical source of fatty acid is the polyethylene glycol (PEG)-40 hydrogenated castor oil used as a drug solubilizer in the formulation. Ricinoleic acid is the principal fatty acid component in castor oil; its structure is shown in Figure 7.

Ricinoleic acid is converted to 12-hydroxystearic acid during hydrogenation of castor oil. PEG-40 hydrogenated castor oil
is then produced through polyethoxylation of hydrogenated castor oil. The resulting ester groups can be susceptible to hydrolysis and thus release hydroxystearic acid. This hydrolysis is a potential degradation pathway of the excipient and could result in free hydroxystearic acid in the travoprost formulation.

Hydroxystearic acid could also be present in the PEG-40 hydrogenated castor oil as a low-level impurity because castor oil derivatives have acid value specifications for control of the carboxylic acid content of the raw material.

Based on this hypothesis, a simulation experiment was conducted using 12-hydroxystearic acid (12-HSA) purchased from a commercial source (TCI America, Part# H0308). Addition of a few mLs of 12-HSA solution in isopropyl alcohol to a 5 mg/mL aqueous solution of ZnCl$_2$ resulted in rapid formation of visible particulates. The ZnCl$_2$/12-HSA particles were isolated from the solution and dried. The infrared spectra of these particles were compared to the precipitate isolated from the travoprost formulation (Figure 8). The infrared spectra of the simulated precipitate are nearly identical to the unknown and provide strong evidence that the particles that formed in the travoprost formulation are hydroxystearic acid zinc salt.

**Conclusion**

Particulates that formed in an ophthalmic solution during accelerated stability storage at 60 °C were identified as a zinc salt of hydroxystearic acid. The hydroxystearic acid was present in the formulation as a free acid impurity or hydrolysis product of PEG-40 hydrogenated castor oil. Zinc is present in the formulation as part of the preservative system. A forensic microscopy approach was used to chemically identify the offending particulate present in the formulation at low ppm levels. These data were critical to an understanding of a significant issue affecting further development of the formulation.

**Acknowledgement**

The authors are grateful to Steve MacLeod and Brian Rohrs for critically reading this manuscript and for many helpful discussions.

**References**

1. USP General Chapter <789> “Particulate Matter in Ophthalmic Solutions” (US Pharmacopeial Convention, Rockville, MD, 2012).

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Understanding Dissolution Testing

Industry experts discuss best practices for dissolution testing of poorly soluble, immediate-release, and controlled-release formulations and the different analytical approaches used.

Moderated by Adeline Siew, PhD

Dissolution testing provides crucial in-vitro drug release information that is routinely used for quality-control (QC) and quality-assurance (QA) purposes in the pharmaceutical industry. The quality-by-design (QbD) approach places strong emphasis on the role of dissolution testing in optimization of a formulation’s drug release rate and evaluation of critical process parameters (CPPs) in the manufacturing process that may affect performance of the dosage form, notes Bryan Crist, scientific affairs manager, Agilent Technologies. “Data from dissolution studies form an essential component in regulatory submissions and all stages of the approval process,” he says. “Post approval, the dissolution test provides continual assurance of batch-to-batch consistency in product performance as well as the ability to reject sub-performing batches. Additionally, scale-up and post-approval changes (SUPAC) guidance relies heavily on dissolution testing to assure that these routine post-approval activities do not impact product performance.”

According to Marcel Arndt, head of Dissolution Laboratory, Evonik Health Care, a QC dissolution test should be discriminative for critical quality attributes (CQA) of a pharmaceutical product. The dissolution rate can significantly affect bioavailability, he highlights; therefore, the dissolution test and acceptance criteria should distinguish batches with unacceptable bioavailability. “Risk assessments and definition of quality target product profiles are used throughout development and lifecycle management to identify potentially high-risk formulation and process variables. Design of experiment (DOE) procedures, which include dissolution testing, can be used to achieve an improved product and process understanding to develop an appropriate control strategy. A design space can then be defined based on dissolution test results,” he explains.

During product lifecycle management, the dosage form or formulation constitution might change, Andreas Gryczke, global technical marketing manager, Solubilization at BASF, points out. In such cases, it is important that the dissolution test is reviewed critically, he says.

Challenges in dissolution testing

PTE: What are the challenges in dissolution testing?

Gryczke (BASF): Dissolution testing is still a model with constraints. The main challenge lies in establishing a proper in vitro–in vivo correlation due to differences between human beings—for example, pH, drug residence time in the gastrointestinal (GI) tract, and the viscosity caused by food consistency can vary from individual to individual, influencing the drug release and ultimately drug absorption.

Arndt (Evonik): For QC purposes, the challenge is to design a dissolution test method that can distinguish between different product qualities as a surrogate for predicting acceptable or nonacceptable bioavailability. For development purposes, the challenge is to achieve a dissolution test method that is able to sufficiently simulate the GI physiology in order to predict how the formulation will behave in vivo (e.g., for de-risking clinical studies).

There are also several technical challenges to overcome. Just to mention a few: Coning is an issue in dissolution tests, where undissolved material forms a mound in the stagnant zone below the paddle, which inhibits dissolution and can be overcome by either adapting the stirring speed or by using peak vessels. Capsules may require the use of a sinker (a stainless-steel wire helix) to prevent the dosage form from floating to the surface of the dissolution media, which would otherwise result in variable dissolution. Filter clogging can restrain online ultraviolet (UV) measurements or block systems using the United States Pharmacopeia (USP) IV test setup. Undissolved particles forming a turbid suspension limit the use of fiber optic UV dissolution systems.
Dissolution Testing

Additionally, conducting dissolution tests for lipid formulations, which are often filled in soft gelatin capsules, can result in the floating of the low-density lipid matrix and prevent adequate mixing in the USP I and II dissolution test setups.

Crist (Agilent): Manual dissolution testing can introduce technique-dependent variability into the test and for this reason, automation is often sought as a way to standardize the dissolution with less analyst-to-analyst variability.

The five major areas of the dissolution test are typically: setup, executing the test, sampling, sample analysis, and cleaning. Testing, whether manual or automated, still relies heavily upon the analyst’s level of training and attention to detail contained in dissolution standard operating procedures (SOP) and analytical procedures.

Setup challenges begin with media preparation, which must be exactly as dictated in the dissolution method, including deaeration if required. Observational checks must ensure that the apparatus is clean, in proper condition, properly adjusted, and that sources of environmental vibration are absent from the area. Manual or automated sampling equipment must be clean and ready for use with the proper disposable filters.

Challenges for executing the test begin with the media being accurately measured and introduced into the vessels to control the volume within 1% of its total volume through the test period with proper evaporation covers. The timing begins with samples introduced into non-rotating media; the samples must settle to the bottom prior to rotation. Dosage units should be observed to confirm they are present and not floating.

The main sampling challenge involves introducing dosages simultaneously because samples must be withdrawn within 2% of the time they were dropped. For a 30-minute sample, this means you have ± 36 seconds to pull all six samples at the correct midway position and filter all of them into their respective vials or tubes; this is one of the primary reasons the dissolution test may be automated.

Analytical procedures (whether using UV or high-performance liquid chromatography [HPLC]) have their own set of challenges, and the testing concludes by performing a validated cleaning procedure to ensure that all traces of the product and media are removed from the dissolution equipment.

Approaches and techniques

PTE: What are the different approaches and techniques used in dissolution testing? What are the pros and cons of the different approaches and techniques?

Arndt (Evonik): The basket (Type I) and paddle (Type II) USP apparatus are by far the most widely used dissolution test equipment. Both are extensively recommended in the individual USP monographs as QC methods. The basket and
paddle apparatus can cover a wide range of oral dosage forms, with the basket apparatus having particular advantages in the testing of multiparticulate dosage forms. A limitation of both the USP I and USP II apparatus is the inability to use volumes other than in the 500–1000 mL range, which thereby restricts the use of biorelevant volumes under certain GI conditions (e.g., fasted state gastric volume) in contrast to the USP IV flow-through cell apparatus.

When detailed GI transit with multiple test media is required, for example, for pH-sensitive modified-release dosage forms, the USP III reciprocating cylinder is far more appropriate than either the basket or paddle apparatus. Another advantage of the USP III apparatus is that the more disintegration tester like hydrodynamics, keep lipid formulations dispersed in the dissolution media, which may float without any mixing in a USP I or II setup. However, because the operating volume for each vessel of the reciprocating cylinder is comparably low, it may be difficult to generate sink conditions, which may be a crucial factor especially for poorly soluble drugs.

The USP IV apparatus is described mainly for oral modified-release dosage forms testing, but can also be used for suppositories, parenteral depot dosage forms, suspension-type extended-release dosage forms, or microparticles. For this apparatus, however, certain variables including the size of the glass beads and filter material used to maintain the formulation in the sample cell may influence the hydrodynamic behaviour, thereby, making it difficult to interpret the dissolution profile. A detailed review of the different dissolution equipment is given by Kostewicz et al. (1).

**Crist (Agilent)**: Dissolution and drug release apparatus are quite flexible to accommodate numerous dosage forms, and the requirements for testing have continued to evolve well beyond traditional oral medicines requiring only the paddle or basket apparatus. Due to alternative routes of drug administration and delivery modifications, special apparatus have been developed over the years to address products ranging from topical forms (e.g., transdermal systems, ointments, creams, and gels) to implants (e.g., drug eluting stents, pacemaker leads, and mesh); as well as injectable dosage forms incorporating micro- and nanomedicines.

“A quality-control dissolution test should be discriminative for critical quality attributes of a pharmaceutical product.” —Arndt (Evonik)

Many of these injectables or implants rely on targeted drug delivery that contain very small quantities of API. To address these needs, typical apparatus have been miniaturized to allow dissolution in small-volume vessels in 50–200 mL or less, with reciprocating holder apparatus now capable of precise and accurate drug release testing in only 5 mL. In contrast, veterinary bolus dosage forms containing grams of active drug may require 2 L or even larger-volume systems to accommodate sink conditions required to solubilize the drug during the dissolution test.

These alternatives have provided essential product performance testing platforms to the pharmaceutical industry usually through joint collaborations with drug product and dissolution apparatus development teams. Because many of these apparatus modifications are made for new and proprietary drugs, however, the knowledge of these alternative methods of analysis unfortunately remains non-available to the public even though the new apparatus platforms are commercially available.

**Gryczke (BASF)**: Nowadays, many different dissolution test models exist. Some models such as the USP standard methods are well established, while others are complex because they try to replicate in detail in-vitro GI conditions, including the aspect of drug absorption. For QC of controlled- and immediate-release dosage forms, methods such as the USP Dissolution Apparatus 1 and 2 are suitable; whereas methods such as the reciprocating cylinder and the flow-through cell are suitable to reflect the requirements of the major challenges in achieving a sufficient bioavailability, such as in poorly soluble API formulations using polymers as a solubilizer.

At BASF, we collaborate closely with academia (e.g., University of Copenhagen) to implement more sophisticated dissolution test models for poorly soluble drugs. An example is the so-called acceptor-donor-model that includes the aspect of biphasic dissolution, which we use for both polymer-based amorphous solid dispersions and triglyceride-based self-emulsifying drug-delivery systems.

New approaches such as Permeapad, a multiwell plate system from the University Odense, Denmark, help to study the aspect of drug absorption better. For soft-gelatin capsule formulations, we use the same dissolution test model as for amorphous solid dispersions, but with the addition of a lipolysis model. For dermatologic formulations, the ‘Franz Cell’ apparatus is a suitable method.

Beside the apparatus, the media play an important role. In our lab, for example, we have moved away from using simple buffer and hydrochloric acid and now use biorelevant media containing sodium taurocholate, lecithin, and pepsin, which mimic a fasted state or fed state. Lastly, the aspect of enzymatic degradation can be reflected by using a pancreatin-based lipolysis model if the formulation requires this aspect. These complex test media provide the advantage of measuring dissolution in a more biorelevant environment. Using the in-vitro and in-vivo data together with the available performant statistical test methods allow us to build complex and precise computer models that can more accurately predict the drug release performance of a dosage form.

**Analytical practices**

PTE: What would you describe as acceptable analytical practices for dissolution testing of poorly soluble,
immediate-release, and controlled-release formulations?

**Crist (Agilent):** Most solid oral-dosage forms fall into the categories of immediate release and some form of controlled release—extended, modified, or sustained. Immediate-release products are formulated to dissolve the API(s) within 30 minutes, at which time a single time point requiring at least 80%, typically, of the label claim to be in solution is demonstrated. Immediate-release drugs that are designed to release up to an hour will require a second time point to verify a release profile through that period.

Controlled-release testing requirements may vary greatly due to the wide variety of dosage forms that fall into this category. Most require drug release profiles consist of at least three time points: initial, midpoint, and final. The initial point early in the dosing period ensures that there is no dose dumping (i.e., a sudden and uncontrolled release of the drug). The midpoint determination ensures that the profile is controlling the release as expected about halfway through the release period, by concentration with most extended-release products, or by time with most sustained-release products. The final time point, usually near the end of the dosing interval, serves to indicate that typically a minimum of 80% of the drug is in solution and is available for absorption.

Drug solubility plays heavily into the suitability of the drug product formulation to fully release the active component(s) when expected, whether it is an immediate- or controlled-release product. Poor API solubility can be improved by providing salt or amorphous forms to increase its rate. Many poorly soluble drugs, however, require additional dissolution practices to solubilize the drug product, including the addition of surfactants or increased agitation. Higher volumes of dissolution media are occasionally required and used in special 2-L dissolution apparatus that are available for these purposes.

**Gryczke (BASF):** In immediate-release formulations, such as pellets of bitter tasting drugs coated with a polymer for taste-masking and moisture protection (e.g., Kollicoat Smartseal), the polymer dissolution is pH dependent. Therefore, it is necessary to establish a realistic pH-over-time profile.

The challenge of controlled-release formulations containing freely soluble APIs and based on sustained-release polymers is to guarantee that under all circumstances (e.g., low and high alcohol concentrations, fasted and fed state), the dissolution release profile is constant. In this case, the dissolution test needs to reflect not only on media constitution, such as ethanol concentration and bile salt concentration, but also on hydrodynamic influencing parameters, such as paddle speed.

“Manual dissolution testing can introduce technique-dependent variability into the test and for this reason, automation is often sought as a way to standardize the dissolution with less analyst-to-analyst variability.”

—**Crist (Agilent)**

For poorly soluble APIs, the two core aspects of formulation are:

• To bring the API into the saturated solution (e.g., by using vinylpyrrolidone-vinyl acetate copolymers in amorphous solid dispersions)

• To maintain the API in a supersaturated state until it is absorbed (e.g., by using solubilizers).

The challenge for poorly soluble materials is to generate a suitable calibration curve. Because this curve cannot be developed in water, typically an organic solvent-based HPLC method is used to determine the correct API concentration in different resulting phases—for example, aqueous phase, lipid phase if adequate, and pellet phase for crystallites. In summary, we can say that one needs to specify first what the critical parameters for the dissolution test are and then develop the corresponding method.

**Arndt (Evonik):** For development projects with poorly soluble drugs, biorelevant media such as Fasted (FaSSIF) or Fed State Simulated Intestinal Fluid (FeSSIF) should be considered. These media contain solubilizing ingredients such as bile salts and phospholipids at physiological concentrations, and therefore, are more precise in simulating the in-vivo solubility and dissolution rate of poorly soluble compounds than pure buffer media. Also, dissolution volumes used in the in-vitro test can be adapted to better reflect the physiological situation. Dissolution testing for QC purposes may require a non-physiological pH or the addition of solubilizers, such as sodium lauryl sulfate, to enable different product qualities to be differentiated based on the dissolution behaviour.

For dissolution testing of standard immediate-release formulations using either the USP apparatus I or II, the test setup is in general less complex and of shorter duration compared to the test setup for controlled release dosage forms. According to the *European Pharmacopoeia* (Ph.Eur.), one suitable dissolution medium needs to be used for conventional release solid dosage forms. In contrast, a two-stage test is required for delayed release dosage forms. An acid stage of 2 hours, in which the formulation should release less than 10%, is followed by a buffer stage at pH 6.8, in which rapid release is targeted. Controlled-release formulations, which target a release in the colon, could even require another buffer stage at pH 7.2, for example. Dissolution testing with increased change of media can be more convenient using the USP III apparatus. However, there are also controlled-release dosage forms for which the release rates are robust to variations in GI physiology (e.g., many osmotic pump formulations aim for a prolonged release at zero-order, and therefore, do not require a change of dissolution medium).

**Method development and validation**

**PTE:** Can you outline how to develop and validate a discriminating in-vitro dissolution test?
A dissolution test procedure intended to be used as a routine control test for drug products should be robust, reproducible, and discriminatory to ensure consistent product quality. The formulation prototype should, therefore, be tested during development under various conditions in vitro (e.g., media, pH, apparatus, agitation) to identify a suitable method. Preliminary tests, such as API solubility and stability in the respective media, and filter compatibility studies can contribute to the test setup. Testing conditions, including sampling time points and frequency, should be chosen to provide the most suitable discrimination. If a surfactant is used in the dissolution media, the amount needed should be justified. After the identification of an appropriate QC dissolution test which is discriminative for CQAs of the drug product, the validation process can be initiated, it should include the following parameters.

The validation of the dissolution method should involve specificity testing to ensure that there is no interference with other components (e.g., excipients or dissolution media ingredients). Also, accuracy as well as linearity over the calibration range need to be examined and should cover the lowest expected concentration to more than the highest concentration during release testing. Precision testing (by performing replicate measurements of standard solutions) and intermediate precision/ruggedness testing (e.g., by repeating a run by at least two different analysts and different equipment from the same laboratory) also need to be performed as well as stability testing of standards and sample solutions. In later development phases, robustness should be part of the validation as well, which involves deploying deliberate changes to the dissolution conditions to determine an analytical design space.

Crist (Agilent): The complexity of developing a discriminating dissolution test is highest with new innovative products and novel delivery systems that have little or no public information. It is less complex for generic drug products, for which there may be an abundance of public information available.

Development requires information including solubility determinations, intrinsic dissolution, sink condition (which will assist with volume considerations), and selection of the intended biorelevant media similar to fluid at in vivo sites where dissolution occurs. This information will ultimately help with apparatus selection and the required agitation to provide a discriminating dissolution profile.

“Using the in-vitro and in-vivo data together with the available performant statistical test methods allow us to build complex and precise computer models that can more accurately predict the drug release performance of a dosage form.”

—Gryczke (BASF)

Sample filtration ensures that the integrity of the sample obtained during the test is preserved by removing undissolved drug substance and clarifying the sample without binding drug substance for analytical measurement. Additional method development tasks include setting specifications of specific dissolution time points, defining analytical methods of analysis, identifying the need to use sinkers, and justification for alternative test methods or components other than established harmonized pharmacopeial dissolution and drug release procedures.

When the crucial steps have been developed and a method is written, it must be validated to ensure it is accurate and precise and as robust as possible. Validation steps should challenge media preparation and deaeration, filters and cleaning procedures, analytical solution stability, and calculations accounting for analyte and volume loss. The analytical method must demonstrate linearity, range, specificity, accuracy, recovery, and precision. It is crucial that the suitably developed dissolution method will ultimately discriminate between a good batch and a bad one and ensure that batch-to-batch consistency (in terms of drug product performance) is maintained throughout the product’s lifecycle including any changes that may occur to the formulation post approval. The *USP* General Chapter <1092> The Dissolution Procedure has captured many of the steps required for development and validation of dissolution methods and is an excellent resource.

Gryczke (BASF): Firstly, the purpose needs to be determined—whether it is a QC method, one that measures pharmacokinetic performance, or both at the same time. Secondly, it has to be decided if all the different critical test parameters will be assessed in one method or if separate tests for particular aspects needs to be developed.

As an example, for lipid-based formulations of poorly soluble APIs, the specific aspects of enzymatic degradation, supersaturation (high kinetic solubility), and potential precipitation of the API from supersaturated state all need to be considered. One solution to investigate the dissolution and drug release is to use a multi-compartment model (acceptor-phase and donor phase). The sample is retrieved with the complex matrix of free fatty acids, bile salts, and pancreatin, for example. The API is then separated from the matrix by HPLC to determine the API concentration in the different phases of the release process. For daily use in a normal lab, this approach is quite a complex model although still manageable.

Conclusion

As discussed, there are several approaches and techniques used in dissolution testing, but it is important that key considerations such as the API, formulation, and methodology are taken into account when designing a dissolution test.

Reference

Fake pharmaceuticals continue to have an impact on people and economies throughout the world. Legal penalties for counterfeiting prescription drugs remain lax, the cost of entering the market is low, and the profits extremely high. According to one estimate, a criminal investing $US1000 in fake prescription drugs can expect to earn returns of $US30,000, 10-times higher than what he or she might gain from trafficking a comparable investment in heroin (1).

As more criminals enter the business, counterfeit drugs are making a dent in economies, even in regions and countries with strict controls and regulations. In the European Union, for example, a study by the European Patent Office (EPO) and the EU Intellectual Property Office (EUIPO) suggested the impact that counterfeit drugs have on the economy and employment (2).

In 2013, the study found the EU pharmaceutical industry lost more than 4% of direct total sales, some €10.2 billion in revenue, to drug counterfeiting. Countries hardest hit by counterfeiting were said to be Spain, where fakes accounted for nearly 6% of sales, and Italy, where they accounted for 4%. Germany and France each lost approximately €1 billion in direct sales, according to the study.

For the EU as a whole, the study found that lost sales translated into 37,700 lost jobs, with nearly 7000 jobs lost in Germany, and between 3000 and 4000 pharma sector jobs lost in Italy, France, and Spain. Including indirect effects, pharmaceutical counterfeits resulted in approximately €17.3 billion in lost revenue to the EU economy, leading to additional losses of 53,200 jobs.

In the United States, the National Association of Boards of Pharmacy has estimated that counterfeit drugs generated $US 75 billion in revenues in 2010, which translates into $US1 8 billion in lost industry profits (3).

According to the US Office of the United States Trade Representative (USTR) 2017 Special Report (4) issued in May 2017, traffic in counterfeit pharmaceutical and biopharmaceutical products, and active ingredients, continues. In 2016, the USTR reports, 90% of the counterfeit pharmaceuticals seized by the US government were found to have come from China, Hong Kong, India, and Singapore. In 2016, 16% of 31,560 US government seizures of counterfeit goods involved pharmaceuticals, down roughly 3% from 2015, when 5196 fake drug shipments were seized (5).

**Increased reliance on express mail**

Counterfeiters no longer ship most fake drugs as cargo, the USTR report says, but send them in small quantities via legitimate express mail. In 2016, more than 90% of US counterfeit pharmaceuticals seized at the borders were found in express carrier and mail, the USTR report said.

Even counterfeit active ingredients are being shipped via express mail, for processing in “facilities,” in apartments, houses or garages, often using crude, outdated, and unsanitary equipment, according to a report that described scenarios that EU enforcement officials are more frequently seeing (6).

In September 2016, for example, authorities in Poland shut down a large counterfeit pharmaceutical operation that included 48 pieces of equipment including pharmaceutical mixers, tablet presses, and label printers, the report said. This operation sourced partially processed products from China, Greece, Romania, and the United Kingdom, and finished processing them on this equipment to “manufacture” fake erectile dysfunction treatments, anabolic steroids, and other counterfeit pharmaceutical products. This single operation was selling millions of Euros worth of products, and it is only one of many, in a constantly changing environment.

Lack of stiff criminal penalties is a major reason why counterfeit pharmaceuticals remain such a presence on the global market, the report says. Even in the US, attorney Sheldon Bradshaw noted, in a March 2017 legal position paper (7), penalties for counterfeiting remain in a catchall that lumps sales of unapproved drugs (that may be approved in other countries), substandard drugs, and intentionally counterfeit products.

The result, he writes, is an enforcement “whack-a-mole.” When one illegal operation is shut down, others simply take its place.
Decoding Serialization Regulations

Multiple serialization and transaction data collection regulations are coming into effect within the next couple of years, as mandated by the US Drug Supply Chain Security Act (DSCSA) (1), the European Union (EU) Falsified Medicines Directive (FMD) (2), and the EU Delegated Regulation (DR) (3). The DSCSA, FMD, and DR were developed to overcome the escalating issues of counterfeit drugs within an interconnected and evolving supply chain, to ensure safety, quality, and efficacy.

These landmark regulations are ambitious in two ways: their aggressive, international scale and the requirement to track product identifiers with electronic tracking and tracing systems. For biopharma companies looking to remain globally competitive, evaluation of current quality and documentation systems ahead of deadlines for implementation and compliance is crucial. With these directives, it is imperative that companies understand their supply chain and their individual responsibilities within the supply chain as the scope of the FMD/DR and DSCSA widens, and that companies anticipate future needs.

The DSCSA

Signed into law by former US President Barack Obama in 2013, the DSCSA is aimed at increasing supply chain traceability, verifying the legitimacy of drugs, and streamlining recalls. Title II of the DSCSA introduces serialization standards and the recordkeeping requirements for electronic transaction data capture. A multiple phased rollout of the DSCSA began in 2015 and, over an eight-year period, will be fully implemented by 2023.

In 2015, all US trading partners were required to be licensed under the US Food and Drug Administration (FDA). Thereafter, manufacturers, repackagers, and distributors were expected to begin exchanging lot-based documentation. By 17 Nov., 2017, manufacturers must start adding unique serial numbers to each product and must electronically submit transaction documentation.

The FMD and DR refer to verifying received products as commissioning. Commissioning requires checking the anti-tampering elements, uploading the serial numbers, and comparing recorded data to repositories managed by the European Medicines Verification Organization (EMVO).

Comparing the FMD/DR and DSCSA

The FMD, DR, and DSCSA do not require use of a specific serial number system. The DSCSA does allow manufacturers to add a unique serial number to their National Drug Code (NDC) number to form a serialized NDC. This format poses limitations, as it is only applicable within the United States. To export internationally, US companies would need to use a separate product identification system. GS1’s Global Trade Item Numbers (GTIN) and the Electronic Product Event Data (UPCIS) systems come widely recommended because of their wide breadth.

<table>
<thead>
<tr>
<th>Table I: Data required to meet the Falsified Medicines Directive (FMD) and the Drug Supply Chain Safety Act (DSCSA).</th>
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<tbody>
<tr>
<td><strong>FMD/DR</strong></td>
</tr>
<tr>
<td>Product Code</td>
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<tr>
<td>Randomized and Unique Serial Number</td>
</tr>
<tr>
<td>Drug Registration Number (If applicable)</td>
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<tr>
<td>Lot Number</td>
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In order to take advantage of the benefits of GTIN, companies must first register with GS-1.

Each directive requires that manufacturers and repackagers label each lot with unique serial numbers in a barcoded format for event recording, verification, and for data recordkeeping. Mandated information for collection is shown in Table I.

The FMD and DR refer to verifying received products as “commissioning.” Commissioning requires checking the anti-tampering elements, uploading the serial numbers, and comparing recorded data to repositories managed by the European Medicines Verification Organization (EMVO).

Decommissioning an individually packaged product removes its serial number from the supply chain, and this is only done if a product is lost, destroyed, stolen, or consumed. Per the DSCSA, as a product progresses through the chain and changes hands, additional records are needed. They include:

- **Transaction Information (TI)**, which includes production information about the drug and the transaction
- **Transaction Statement (TS)**, a statement that certifies the accuracy and completeness of the data
- **Transaction History (TH)** a history of previous transactions

Currently, there are no provisions within the DSCSA necessitating the commissioning or decommissioning of individual products. In 2023, following implementation of the Enhanced Drug Distribution Security (EDDS) regulations, this could change.

Companies must also institute a serialization system that provides immediate compliance and is flexible enough to achieve future goals; they should strive to plan, organize, and analyze compliance gaps, and evaluate possible solutions. Each company must identify its priorities, expectations, and timelines with cross-departmental input before exploring the technology best suited to its goals.

References


— Kelly Waters is director of marketing for InstantGMP, Inc.
Can pharma meet new mandates?
Despite these challenges, regulations have been in force for the past few years to help pharmaceutical manufacturers stem the tide of counterfeit drugs reaching the patient.

The US Drug Supply Chain Safety Act (DSCSA) and the EU Falsified Medicines Directive (FMD) aim to ensure the safety of the pharmaceutical supply chain. Complying with these regulations requires different, but overlapping strategies (see Sidebar).

Both DSCSA and FMD require use of serialization and improvements in IT and electronic data management to enable supply chain traceability. Large pharmaceutical companies have been working on the systems required for several years, and most are ready to meet legal requirements.

Some still haven’t serialised or upgraded IT
A number of pharma companies and contract manufacturing organizations may not be ready, however. According to a survey of both these groups by the serialization system provider SEA Vision and the life-sciences IT company Zenith Technology, 36% of respondents were not even working toward meeting serialization requirements (8).

In addition, most pharmaceutical brand protection experts agree that serialization alone will not be enough to secure their supply chains. “It should be combined with other technologies,” says Bob Migliani, chief of business development for Applied DNA Sciences, Inc.

His company offers SigNature DNA, a marker that can be traced at parts-per-trillion levels, is being used in the textile industry, and has been used by global law enforcement departments and six US government agencies.

Instead of focusing on adding the marker directly to pharmaceutical formulations, Applied DNA is now evaluating its use in the inks that are used to print labels and bar codes on pharmaceutical packaging.

Offering complementary technologies is Systech, which provides serialization services to the pharmaceutical industry, as well as its own patented authentication solution, Unisecure, that compares scanned barcodes to an original “fingerprint” from when the label was first printed. This year, a simulation study (9) at St. James Hospital in Ireland involving Systech and Sharp Packaging Services found that both end-to-end scanning and scanning at each transfer point in the supply chain (as required by the DSCSA) still allowed some counterfeit product to reach patients.

In 2013, the EU pharmaceutical industry lost €10.2 billion in revenue and 37,700 jobs to counterfeiting. In the US, counterfeited drugs generated $75 billion in revenues in 2010.

Product authentication: crucial to protecting patients
The additional authentication step prevented counterfeit medicines from reaching patients, the simulation study showed. These results underscore the importance of using serialization, but adding the use of complementary product authentication technologies.

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- Survey Suggests that One-Third of Pharma Companies Aren’t Ready for Serialization
Facility Design Issues for Single-Use Processes

Single-use technology is a proven alternative to traditional stainless-steel vessel and pipe bioprocessing. Available for all stages of processing, from media prep and upstream operations to buffers and downstream processing, single-use systems (also known as disposables) are found in licensed biopharmaceutical manufacturing facilities around the world. The most common applications today are hybrid systems combining both disposable and traditional stainless-steel unit operations. Most importantly, single-use connectors, sampling, and transfer systems provide for truly closed processes.

Cleanroom classification
Being a closed process by itself represents savings over traditional fixed systems. The most obvious is the downgrading that can be achieved in cleanroom classification of the process spaces. An open process that would typically require Grade B space can now be Grade C or perhaps even lower. With each higher grade of classification, a greater number of air changes is required with a corresponding greater operational cost per square foot. As a result, reducing the classification of a space provides operational savings that continues year after year. In addition, downgrading space classifications can reduce or even eliminate the gowning rooms and airlocks that are needed to transition to those higher classifications. Every time gowning and airlocks are removed, savings accrue from a broad range of reductions, including gowning supplies, gowning time and labour, material transfer time and labour, cleaning supplies and labour, and environmental testing. From an operational perspective, these accumulate over time and provide opportunity for greater productivity.

Cleaning requirements
If thoughtfully designed, stainless-steel process trains can also be closed operations. However, non-disposable equipment requires maintenance, especially cleaning between batches. With stainless steel, this is achieved through robust clean-in-place, sanitization-in-place (CIP/SIP) systems. In contrast, single-use technology is simply disposed of. It eliminates the need for CIP/SIP and all that goes with it. The equipment, piping, and space that houses CIP/SIP tanks and pumps are no longer needed. There is a reduced burden on the utilities supporting the system, and the need for purified water, water-for-injection (WFI), or clean steam is eliminated, at least as far as CIP/SIP is concerned. CIP requires a tremendous amount of water. The elimination of its use is environmentally friendly, and there is no need for cleaning chemicals. The elimination of CIP/SIP and its supporting utilities simplifies facility design in many ways, reduces energy use, and has a corresponding reduction in capital and operational costs.

Handling disposables
Although single-use technologies can reduce the amount of cleanroom production space and associated technical support requirements, single-use technologies also increase the amount of consumables that are handled. Single-use bag and tube sets need to be stored before use, and these same items need to be deactivated and staged for disposal after use. Even with sophisticated just-in-time receiving and shipping technologies, the space implications must be addressed. Increased warehousing and space dedicated to deactivating and staging of the used disposables must be accommodated. Although these unique space needs are added requirements, their capital and operational costs are significantly lower than the higher-grade GMP process spaces demanded by stainless steel.

The disposal of single-use technologies raises obvious concerns regarding its environmental impact. The materials are plastic, which the public typically associates with being non-sustainable. This concern, along with the continual waste generated, presents the obvious question regarding sustainability. But sustainability can be a complex question and requires a lifecycle assessment to provide a comprehensive answer. Single-use technology presents pluses and minuses on both sides. The production, distribution, and disposal of components generates potentially significant amounts of waste; however, it also reduces the generation of large quantities of WFI, process water, and steam. In fact, numerous studies have shown some...
environmentally beneficial aspects of single-use (1–3). In a comprehensive lifecycle assessment study reported in BioPharm International, it was found that “single-use process technology can have less impact on the environment than traditional process technology in a broad range of environmental impact categories … in this study, single-use process technology exhibited lower environmental impact compared to traditional process technology in all midpoint and endpoint damage categories that were considered” (4). The conclusion drawn is that compared to stainless steel, single-use systems are sustainable.

Conclusion
The implementation of single-use technology in a facility has important differences from traditional, fixed stainless-steel installations. These changes, however, are not extreme; overall, they are more about the shifting of space and cost from one area to another. There are shifts in the configuration of spaces as well as shifts in capital and operational costs. Expensive classified cleanroom spaces can be reduced, but inexpensive storage space is increased; there is an increased cost for consumables but reduced turnaround time between batches; and there is an overall increase in production time compared to the labour expended. Despite these realignments, a consistent picture emerges that the savings are many, especially with the elimination of CIP/SIP. The consensus has developed that single-use systems save both capital and operational costs over fixed stainless steel. Although a facility with single-use technology in all its unit operations returns the most savings, savings are possible even with hybrid facilities. As companies experience these unit savings it seems natural that pressure will build for more, and more complete implementation of single-use systems.

References

GE Healthcare announced on 25 April 2017 that United BioPharma (UBP) has selected the FlexFactory manufacturing platform, based on integrated single-use technologies, for its new facility focusing on late-stage clinical and commercial production capacity of therapeutic monoclonal antibodies in Hsinchu Industrial Park, Taiwan (1); and on 17 May 2017, GE announced that Dr. Reddy’s Laboratories will be installing the first FlexFactory in India, at its facility in Hyderabad (2).

The UBP project received support from the Taiwanese government to help improve access to biopharmaceuticals and boost the bioprocess market in the region. The new facility will be dedicated to late-stage clinical and commercial production capacity of biopharmaceuticals, especially a monoclonal antibody, UB-421, which will be used for HIV treatment. GE will also continue to work closely with UBP on the establishment of its contract development and manufacturing organization (CDMO) business.

“The completion of this state-of-the-art facility equipped with two of GE’s 2000-L single-use bioreactors and integrated manufacturing process is a much-anticipated achievement for UBP to enter into commercial-scale cGMP-production with international standards. It also resolves the manufacturing bottleneck for UBP’s rich pipeline. With the potential expansion to twelve 2000-L production lines within this eight-story building, UBP is and will continue to be the largest protein drug manufacturer in Taiwan in the foreseeable future,” said Chang Yi Wang, PhD, chairperson of UBP, in a press release (1).

“UBP’s Flex Factory will help deliver increased capacity as well as supporting Taiwan’s growing pharma industry requirements more rapidly. Taiwan’s desire to boost its manufacturing capacity is an industry need we are hearing echoed across the globe,” said Sven Henrichwark, general manager, Global Commercial BioProcess, GE Healthcare Life Sciences, in the press release. “Local production capability is a crucial element in providing national healthcare systems with the vital medicines to address growing patient needs. We are excited to contribute to UBP’s development by delivering a robust and flexible biomanufacturing solution, that includes final qualification and training.”

In India, the new FlexFactory will help Dr. Reddy’s increase its capacity to meet the expected demand for its currently marketed biosimilars and support the launch of a portfolio of new biosimilar products. FlexFactory enables Dr. Reddy’s to transition from stainless steel to single-use technologies.

“We are pleased to partner with Dr. Reddy’s in their efforts to increase the availability and affordability of biopharmaceuticals globally by bringing single-use, flexible manufacturing capacity to its facility in Hyderabad,” said Milind Palsule, country manager, South Asia, GE Healthcare Life Sciences in a statement. “India today has one of the fastest growing biopharma sectors in the world and we are keen to support this development and the production capability of Indian pharma players with the latest biopharma technology and know-how” (2).

References

——The editors of Pharmaceutical Technology Europe
Over the past several months, manufacturers have released a variety of new laboratory equipment and operations to optimize efficiency. Some manufacturers have made updates to products already on the market, as is the case with Novartis’ Breezehaler and Copley Scientific’s Sample Preparation Unit. New technologies, such as the Nexis GC-2030 gas chromatograph from Shimadzu Scientific Instruments and MilliporeSigma’s Poloxamer 188 Emprove Expert polymer, have also been announced. The following is a sample of some of the new laboratory equipment that has been released over the past several months.

**Updates to inhalation drug delivery technology**

Copley Scientific’s Sample Preparation Unit (SPU) Model 2000 for inhaler testing has been updated to include a modified induction port fixture with a view (1). The upgraded SPU 2000 now accommodates a fluticasone propionate/salmeterol xinafoate (FP/SX) induction port, in addition to the standard Andersen cascade impactor (ACI) and next-generation impactor (NGI) induction ports.

Conducting well-controlled, highly reproducible cascade impaction tests is crucial for obtaining reliable data, for product development, and quality control. Cascade impaction is used to measure the aerodynamic particle size distribution of inhaler generated aerosols and is a critically important procedure. Although not a technically complex task, recovering the active drug sample from the ACI and NGI induction ports, and NGI pre-separator (for which another fixture is available), is repetitive and susceptible to human error. Copley’s modified induction port fixture accommodates the new FP/SX induction port, semi-automating the process and reducing the potential for error associated with manual drug recovery.

Novartis recently entered a collaboration with Propeller Health to connect its Breezehaler device to Propeller’s digital health platform (2). Novartis’ Breezehaler inhaler is a patented capsule-based dry powder inhaler for treatment of chronic obstructive pulmonary disease (COPD). The company entered into a collaboration with Propeller Health to develop a custom add-on sensor for the Breezehaler device that will passively record and transmit compliance data, better informing patients and their physicians of adherence and other treatment factors through the Propeller platform. The Novartis-Propeller partnership is focused on COPD in Europe.

**Gas chromatograph incorporates remote connectivity**

The Nexis GC-2030 gas chromatograph from Shimadzu Scientific Instruments includes an interface with graphic icons (3). The Ethernet-based communication allows the user to remotely connect to the gas chromatograph via computer or mobile device. This allows the operator to monitor run status or launch a new batch of analyses from a remote location. The chromatograph also includes tool-free column installation and inlet maintenance, and a built-in oven light.

The GC-2030 allows for up to three analytical lines for greater productivity or for the versatility of more analyses to be packaged into one gas chromatograph. A choice of four inlets, six detectors, and specialized valve accessories enables configurations tailored to fit the needs of laboratories. The
The chromatograph has an eco mode to optimize the use of carrier gas such as helium and reduce electricity use when idle. The Nexis GC-2030 also includes day and time programming, a system self-check feature, and automatic notification of when to replace consumables. The GC-2030 has an optional, built-in sensor to monitor real-time levels of hydrogen in the oven. The chromatograph will respond to elevated levels by shutting down the hydrogen flow maintaining a safe working environment.

**Polymer improves cell viability**
The Poloxamer 188 Emprove Expert polymer from MilliporeSigma is a surface-active nonionic polymer used in cell-culture media as a shear protectant and has become a standard component to cell-culture media for production processes (4). The new polymer increases viability of cells in the bioreactor. The Emprove Expert polymer aims to provide lot-to-lot consistency and reliable performance. The product has been cell culture tested and comes with Emprove Expert polymer dossiers to help manufacturers meet regulatory requirements for risk assessment.

**Modular standalone vision systems**
The In-Sight 7000 series, from Cognex Corporation, is a suite of highly modular standalone vision systems (5). This new system performs inspections and keeps pace with increasing line speeds. The In-Sight 7000 series is compact and fits into space-constrained production lines. The suite’s modular design offers more than 400 different field configurations, increasing flexibility.

The In-Sight 7000 is IP67-rated and includes Flexible Image Technology. This vision system features a patent-pending LED ring light that produces even, diffused illumination across the entire image, eliminating the need for external lighting. A variety of light colours, optical filters, and polarizers can be swapped in to meet specific application requirements. The In-Sight 7000 uses In-Sight Explorer to set up and monitor machine vision inspections. This software includes the EasyBuilder interface for step-by-step application setup and the In-Sight spreadsheet view for greater control. The system also includes a full set of powerful In-Sight vision tools, including PatMax RedLine pattern matching technology, OCRMax optical character recognition, and SurfaceFX feature extraction technology.

**Conducting well-controlled, highly reproducible cascade impaction tests is crucial for obtaining reliable data, for product development, and quality control.**

**Mass detector for flash purification**
The Isolera Dalton 2000 mass detector for flash purification from Biotage (6) expands functionality through a wider detection range of ion masses, up to m/z 2000, and new analysis features. Isolera Dalton 2000 is integrated with Isolera Spectra flash purification system via the Isolera Dalton Nanolink unit, a sampling device that handles all fluids and synchronization between the two instruments. Compounds are identified in real time during purification and this informs the flash fractionation process, enabling the correct product to be collected. Isolera Dalton 2000 fits inside a standard fume hood and is capable of both normal and reverse-phase separations, so it is compatible with the diverse purification needs.

**Conclusion**
The editors of Pharmaceutical Technology Europe are looking for newly released laboratory equipment and operations to include in upcoming issues of the magazine. If you have a new product you would like to share, please submit it for consideration to ptpress@ubm.com.

**References**

Do You Listen to What Your Data are Telling You?

This column presents a data case study of a laboratory refrigerator and its qualification performance over five days, with important lessons for using average and individual results, as well as user requirements.

Some years ago, the analytical laboratory in a small pharmaceutical company used a domestic refrigerator to store standard solutions for high-performance liquid chromatography (HPLC) analyses. The laboratory head decided that the temperature of the refrigerator was to be recorded manually twice a day using a mercury in glass thermometer positioned on the middle shelf. As this refrigerator lacked formal qualification documentation as required by United States Pharmacopeia (USP) General Chapter <1058>, however, the laboratory head requested that it be temperature mapped over a working week. The acceptance criteria to be adopted was that the mean temperature was to comply with the USP requirements of 2 °C to 8 °C. Recognizing that twice-a-day monitoring was probably insufficient for qualification, the laboratory head decided that the average temperature over two hourly intervals on the middle shelf would be used to generate the data over 60 hours of routine operation.

Average temperature over two hourly intervals
To capture the data, certified and calibrated data loggers were used with an accuracy of better
than ±0.3 °C, which was considered sufficient for the qualification. The average temperature over two hourly intervals on the middle shelf from the qualification run is shown in Figure 1.

Noting that the acceptance criteria were 2 °C to 8 °C, the data logger two-hourly means were rounded to a single significant figure. However, 10 of the 30 averages were identified as failures and an investigation was undertaken.

Fortunately, there were also data loggers on the top and bottom shelves in order to map the operational volume of the refrigerator. When these data were reviewed in the same manner as the middle shelf, a more interesting picture emerged as shown in Figure 2.

All the points on the top shelf except two meet the acceptance criteria and all the points on the bottom shelf except two fail the acceptance criteria. At this point, the laboratory head mentioned that they did sometimes find solutions that had frozen.

The data loggers used had the data storage capacity to record the temperature every 4.8 minutes and Figure 2 could be updated to include the maximum and minimum temperatures for each of the two hourly means (Figure 3). The temperature range over the five days was a high of 12.6 °C and a low of -6.0 °C. Hence, there is demonstrable lack of control.

Even more instructive is to simply trend the 1500 individual readings (Figure 4). The thermostatic control is so poor that cycles of 10 °C are not uncommon, which is more than the USP specification range. In addition, the lack of air circulation creates a large temperature difference between the top and bottom shelves.

**Conclusion**

This example gives rise to some important learning points:

- Always carefully consider whether individual readings or means are appropriate for setting acceptance criteria. Note that on many occasions both are appropriate.
- Always plot the trend of individual readings to see evidence of time-related phenomena.
- Always consider the frequency of measurement of data loggers in the context of actual use.
- Always consider the positioning of data loggers in the context of actual use.
- Never purchase a piece of equipment that was not designed to perform to specific user requirements.

Remember that a domestic refrigerator is not designed to control an environment to meet USP standards of 2 °C to 8 °C. PTE
Ensure Quality in a Contract Test Laboratory

Q: I am a quality control (QC) manager of a contract test laboratory. I am going to be upgrading the laboratory and would like to know if you have any advice on how I should approach this activity?

A: Upgrading a laboratory is an exciting activity but it needs to be approached with a thoughtful, well-constructed plan that does not interrupt the business needs of your clients. You mentioned that you are a contract test laboratory, which would imply the products you test could include clinical trial material, final product dosage forms, and potentially APIs. In addition, you might be performing final product release as well as stability testing. Regardless of the testing you are performing, the first step of this process should be to notify your clients of your intention to upgrade. This is important because some clients may not wish you to perform their analyses on new equipment. You will need to work with these clients closely to make sure you understand their concerns and that you address them before decommissioning any equipment used to analyze their materials.

The next step in the process is to take inventory of the equipment you have and start making some risk-based decisions on a project plan that will define what should be replaced, in what order, and what the requirements are for each. Regardless of which piece of equipment you decide to tackle first, there are several issues you must address with every replacement. If you are simply upgrading to a new piece of equipment to replace an aging piece of equipment (i.e., like for like), your requirements will be straightforward. If you are replacing an existing technology with a significant upgrade or different technology, a more comprehensive approach will be necessary. In all cases, you will need to make sure the current equipment is performing adequately and is still capable of generating reliable results.

Like-for-like equipment or new technology?
For a simple like-for-like replacement you should perform installation qualifications (IQ) and operational qualifications (OQ) on the new equipment. The next step in the process would be to execute a performance qualification (PQ) and a comparison protocol to show the results obtained with the new equipment are the same as the results obtained with the old equipment. In many cases, the PQ and comparison may be combined into one document. If the results from the protocol match up, you can decommission the old equipment and start using the new equipment.

When changing from one type of technology to a different, more sensitive technology, there are more decisions that need to be considered. You need to work closely with your client on the specifics of their product so you can perform the transition with minimal disruption to their and your product flow. These more complex upgrades require a lot of upfront planning. As with the like-for-like replacement, you need to make sure the current equipment is operating appropriately. As before, you need to perform the IQ and PQ on the new equipment. It is in the PQ and comparison protocol where attention to detail will be crucial to execution. For instance, when changing from high-performance liquid chromatography (HPLC) to the more sensitive ultra-high pressure liquid chromatography (UHPLC), you need to be prepared to address the possibility that you could see some unknown peaks during the analysis. These peaks need to be identified and characterized before you can continue with the transfer. While this investigation is underway, you need to determine the suitability of the product for release and the potential impact these unknown peaks might have on the stability of the item being analyzed. If the method being converted is a US Pharmacopeial Convention (USP) method, you need to be sure that the new methodology generates results that are equivalent or better than the results obtained using the compendial method. The comparability protocol details will help you address the unforeseen circumstances should they occur during the execution of the protocol. The issues arising from the conversion of one method to a more sensitive method need to be fully addressed and explained before decommissioning the obsolete equipment.

There may be situations where you will need to maintain both the new and the old equipment operational at the same time. For instance, you may want to continue to monitor the stability of a product on the equipment the analysis was started on and not change to the new equipment until the last stability time point has been analyzed. In this case, you will want to maintain the old equipment while utilizing the new equipment for release and future stability monitoring. These situations need to be discussed with your client and included in the laboratory timeline for transitioning the laboratory.

The importance of training
Another important element of transitioning a laboratory is making sure your analysts are properly trained on the new equipment while maintaining expertise on the old equipment until the transition is complete. Many companies selling analytical equipment have experts to perform the necessary
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training and to help address issues that may come up as the analysts become more familiar with the equipment. It is important for the laboratory and your clients that analysts are properly trained so they can deal more effectively with problems that occur during the transition period. The more training and familiarity the analysts have in running the new equipment, the less disruption there will be to operations.

When introducing new equipment and new methodologies to a laboratory, it is important to have a comprehensive implementation plan that discusses what equipment you will introduce, the timeline for the introduction of the equipment, how you will investigate unexpected analytical results during the transition, and how you will make sure your analysts are appropriately trained while causing minimal interruptions to operations and your clients.

Putting your plan down in writing and discussing it with your clients up front will save you a lot of time and minimize delays as you implement your plan. PTE

Your opinion matters.
Have a common regulatory or compliance question? Send it to Susan.Haigney@ubm.com and it may appear in a future column.

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