Early Development Strategies
Visual Inspection Week

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Interest Group Meeting Visual Inspection | 13 April 2018
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Features

COVER STORY
14 Early Development Formulation Strategies May Deter Late-Stage Failures
Assessing potential formulation and manufacturing issues in early development phases can improve a drug’s chances for success.

API SYNTHESIS & MANUFACTURING
18 Small Volumes, Big Challenges
Highly complex APIs developed to treat rare and orphan diseases present big technical questions for contract developers.

PARTICLE ENGINEERING
20 Dry Particle Coating—A Unique Solution for Pharmaceutical Formulation
Aston Particle Technologies has developed a technology that produces functionalized particles in a one-step, environmentally friendly process.

TOPICAL FORMULATION
24 Formulating Topical Products Containing Live Microorganisms as the Active Ingredient
Case studies compare efficacy testing of preservatives for topical formulations with probiotic actives.

ANALYTICS
34 Stability Testing Determines Proper Drug Storage Parameters
Stability testing on APIs/finished drug product helps define optimal drug packaging for shelf-life storage.

QUALITY
38 Expectations in Quality Agreements
Robert Iser of PAREXEL Consulting answers questions regarding the regulatory expectations of quality agreements and how companies can ensure the quality and safety of their products.

LAB OPERATIONS
42 Improving Operations in the Lab
New and emerging products advance bio/pharma laboratory operations.

COLD CHAIN
44 Poseidon Takes on the Pharma Supply Chain
Lower costs, fewer opportunities for temperature excursions, and a smaller carbon footprint are making ocean transport more attractive for pharmaceuticals.

Columns and Regulars

6 Product Spotlight
8 European Regulatory Watch
Tackling Medicine Shortages in Europe
10 US Regulatory Watch
FDA Heightens Drive for Transparency
12 Outsourcing Review
Current Challenges in Bioprocesses Development
47 Company Profiles
50 Ask the Expert
Computerized Systems Validation
50 Ad Index

Peer-Reviewed

28 A New Method for Risk Assessment of Pharmaceutical Excipients
This article describes a new, combined, quantitative method for assessing excipient risks that has been developed by the authors.

SUPPLEMENT

Be sure to check out this month’s special issue, Outsourcing Resources 2018, for articles on sterile filling operations, translational pharmaceutics, analytics, and more!
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Five-Hundred-Gallon Multi-Shaft Mixer

Ross, Charles & Son has added a 500-gallon option to its line of VersaMix multi-shaft mixers, which are suitable for processing medium to high-viscosity applications up to several hundred thousand centipoise including slurries, pastes, gels, and suspensions.

The new VMC-500 model is equipped with a custom combination of independently driven agitators. The anchor agitator with helical flights and the screw agser agitator work in unison to promote product turnover while bringing air pockets to the surface, as stated by the company. Two saw-tooth, high-speed disperser blades impart shear for improved powder wet-out and thorough deagglomeration.

Additional features include special air casters to promote mobility of the mix vessel, programmable logic controller recipe controls with data acquisition capabilities, and a purged explosion-proof operator station.

Ross, Charles & Son
www.mixers.com

AR/VR Simulator for Plant Personnel Training

Honeywell’s cloud-based simulation tool uses a combination of augmented reality (AR) and virtual reality (VR) to train plant personnel. The tool, Honeywell Connected Plant Skills Insight Immersive Competency, can be used to bring new industrial workers up to speed quickly by enhancing training in a contemporary way.

The training solution combines mixed reality with data analytics to create an interactive environment for on-the-job training. It uses Microsoft’s HoloLens, a self-contained holographic computer, and Windows Mixed Reality headsets to simulate various scenarios for the company’s C300 controller—such as primary failure and switchovers, cable, and power supply failure—that train and test personnel on their skills.

Specific job activities are simulated through virtual environments accessed through the cloud. According to the company, trainees can safely experience the impacts of their decisions similar to a flight simulator. This approach improves skill retention versus traditional training methods by up to 100% and reduces the length of technical training by up to 66%, as stated by the company. Additionally, the employees’ training progress is tracked as part of a formal competency management system.

Honeywell
www.honeywellprocess.com

Twin Screw Extruder System

The ZSE 50 MAXX twin screw extruder system from Leistritz Extrusion is suited for a range of compounding tasks. The system includes a modular design for barrels and screws and an insulated barrels cover. The set also has an extended length that facilitates multiple downstream operations, including multi-stage venting, liquid injection, and up to two of the company’s LSB 50 XX side stuffers for filler/fiber introduction into the melt stream. According to the company, the system can be equipped with a 600-horsepower alternating current motor and produce 1000 kgs+/hr at 1200 screws rpms.

Leistritz Extrusion
www.extruders.leistritz.com

Dissolved Oxygen Sensor

Endress+Hauser’s Memosens COS81D hygienic optical sensor can measure dissolved oxygen in pharmaceutical fermenters and bioreactors. The device can be used in all measuring points ranging from lab fermenters to production processes and has measurement capabilities that also include gaseous oxygen and temperature with accuracy up to ±0.2%, in addition to temperature, partial pressure, and raw measured values, according to the company.

The sensor is suitable for cleaning-in-place (CIP) and sterilizing-in-place (SIP) procedures and works in process temperatures from 15–280 °F and pressures ranging from 0–190 psi. The device also has a low sampling volume, making it suitable for residual oxygen measurement in water treatment and boiler feedwater. The sensor has a compact stainless steel 12-mm design with lengths currently up to 220 mm.

The device connects to a transmitter via a cable that transmits an optical digital signal, which is continuously monitored and analyzed. The transmitter senses unusually high or low measured values, irregular values caused by incorrect measured values, and aging of the sensor cap. When errors are detected, the transmitter displays a warning and produces an error message.

Measured and calibration values in the sensor are sent to the transmitter using a non-contact connection that has reduced potential interference, according to the company. Memosens technology in the transmitter generates an automatic error message if the sensor fails, or if the connection between sensor and transmitter is interrupted.

Additionally, the sensor has integrated electronics that store calibration data and other information, such as total hours of operation and operating hours under extreme measuring conditions. Calibration data are stored in the sensor, enabling the device to be calibrated and adjusted independent of the measuring point.

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Tackling Medicine Shortages in Europe

The upcoming serialization deadline and the United Kingdom’s departure from the European Union could result in supply bottlenecks.

The European pharmaceutical industry and regulators are worried about an imminent worsening of the persistent problem of shortages of medicines in the region. Although both agree that regulations are partly to be blamed for a likely rise in the number of incidents of drug scarcities, they have different views on the issue of how regulations are reducing the availability of medicines. The industry contends that regulations, particularly those relating to pricing policies, are being applied too strictly so that it has become uneconomic to retain low-priced drugs on the market. The regulators reckon that shortages are occurring when regulations are not being used effectively enough to ensure that medicines remain available.

The Falsified Medicines Directive and Brexit

The first half of 2019 could be a crunch time for medicines supplies in Europe as a result of a new packaging regulation coming into effect, which is aimed at combating counterfeit drugs, and the United Kingdom’s official departure from the European Union triggering legal changes that will have a big impact on pharmaceutical supply chains. The implementation of rules on the identification of individual medicine packs under the EU’s Falsified Medicines Directive (FMD) will be followed by Brexit, where the UK will no longer be a member of the EU’s single market. Supply bottlenecks could start to form before the two events through to their aftermath. “Both FMD and Brexit will come into operation within a couple of months,” Adrian van den Hoven, director general of Medicines for Europe, representing generic medicines and biosimilars producers, said at the 17th Regulatory and Scientific Affairs Conference, which took place in London on 25–26 Jan. 2018. “Are we going to risk a total regulatory overload within a six-month period from the end of this year to the spring of 2019 during which the supplies system could become clogged up?” he asked.

A large part of the conference focused on the issue of shortages of medicines and the impact of the FMD packaging legislation and Brexit on their availability. “The evidence that the root causes of medicines shortages are economic, including unsustainable pricing and reference pricing policies, is overwhelming,” Marc-Alexander Mahl, head of the generic-drug business of Fresenius Kabi and president of Medicines for Europe, told the meeting. He noted that claw- and pay-back measures used by governments to limit public sector overspending on pharmaceuticals were also partly to blame. A claw- or pay-back is a tax imposed when there is overspending within a budget so that the total net expenditure is kept within the budget’s limit.

Challenges faced by generic-drug companies

In Romania, 2000 medicines had been withdrawn because of reference pricing and a claw-back tax, while in Portugal, there had been a “drastic reduction” in the number of hospital drug suppliers due to the impact of a pay-back scheme, according to Mahl. He cited the conclusion of a 2016 report (1) by the European Commission on the fiscal sustainability of funding healthcare. “While overspending is recovered via the claw-back tax, it has led to withdrawals of generic medicines from the market,” the report said (1).

Not only have generic-drug companies struggled to cope with the downward pressures on their profits and sales revenues, but they also have to cope with the expense of running complex supply chains in a high-volume, low-margin business, Mahl highlighted at the meeting. He pointed out that a large generic-drug company in Europe may have as many as 25,000 marketing authorizations, with more than 800 supply-chain employees working with more than 2000 partners and shipping products to up to 50,000 locations. At the same time, generic-drug companies have to invest in R&D to launch new products, formularies, and biosimilars to ensure competition and wider pharmaceutical access in the market, he said.

Meanwhile, the regulatory demands on generic-medicine producers at the EU and national levels are increasing, particularly with requirements to keep marketing authorizations up to date. Typically, 75% of the EU regulatory fee budget of a generic-drug company is taken up by the maintenance costs of marketing authorizations. Partly as a result of the number of variation approvals nearly doubling in four years, maintenance fees had risen by an average of 45% annually per marketing authorization in 2011–2014, Mahl said. He explained that one way to prevent medicine shortages would be to improve regulatory efficiency so that the administrative and cost burdens of keeping products on the market can be reduced. There should be a flat fee structure for the approval of variations. He also suggested that there should be a lower authorization and maintenance fees for older molecules that still serve a medical need.

A study in 2017 (2), cited at the conference, showed that national competent authorities (NCAs), which license medicines under the EU decentralized approval procedure, were making more flexible use of regulations to deal with shortages. But the report (2), carried out by the heads of medicines agencies (HMA) representing NCAs, indicated also that often, rules being applied by national authorities were aiming to be even more restrictive.

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Dealing with shortages
Governments have introduced procedures for banning exports of essential medicines at times of acute shortages. Regulatory authorities are also wanting to monitor more closely pharmaceutical plants liable to production disruptions, through measures such as risk-management plans. Finland, for example, has legislation that obliges manufacturers and wholesalers to store additional life-savings medicines for periods of three to 10 months (2). On the other hand, national authorities are being flexible with the enforcement of regulations when dealing with shortages. They are, for example, relaxing language rules on labels and patient leaflets in order to import replacement medicines from other countries. They are also giving emergency authorizations to bring in medicines from abroad.

Within the EU regulatory network for medicines, extending from the European Commission and European Medicines Agency to the HMA and the Co-ordination Group for Mutual Recognition and Decentralized procedures for human medicinal products (CMDh) at the national level, there are moves to adopt more uniform approaches to medicines availability. An HMA/EMA Task Force on medicines availability, which was set up in late 2016, has started meeting regularly since the middle of 2017. It comprises representatives of the HMA, EMA, the European Commission, and the chairs of the CMDh and its veterinary equivalent.

Kristin Raudsepp, co-chair of the task force, told the conference that it would be addressing issues such as the detection of potential supply disruptions and ways of avoiding shortages. Among the actions planned by the task force was the development of a definition of medicine shortage. The task force also wanted to “develop a concept of reportable shortage and agree on a common set of reporting requirements [as well as] develop metrics that could be used to measure a shortage,” Raudsepp said.

Making medicines available
Currently, among the major factors influencing the availability of medicines, is the number of authorized medicines that are either not being marketed or are no longer marketed in the EU. In addition, supply chain disruptions are affecting availability. These disruptions could result from difficulties with failed approvals of GMP-standard manufacturing or other safety or quality problems and the effects of parallel trade. Raudsepp, who is director-general of Estonia’s State Agency of Medicines, said that in her own country’s market, 60% of authorized medicines are not available. With those that are being marketed in Estonia, there are approximately 100 medicines experiencing shortages each year, with an average shortage period of 100 days in 2016. “Every [type] of medicine may be in shortage,” she said. “We have had cases of shortages for vaccines in the national vaccination scheme, for cancer treatment, and life-saving hospital medicines.”

Among the options for dealing with the issue of authorized medicines not being placed on the market was the use of regulations to require companies to make authorized products available, Raudsepp said. The European Commission is planning to send out a questionnaire to stakeholders on the implementation of article 81 of the 2001 EU directive on medicinal products (3). Article 81 stipulates that the holder of a marketing authorization for a medicine and its distributors “shall, within the limits of their responsibilities, ensure appropriate and continued supplies of that medicinal product to pharmacies and persons authorized to supply medicinal products.”

Some participants at the conference pointed out that authorized medicines may not have been put on the market for economic reasons. There may not be the production capacity for manufacturing them. Also, with the FMD packaging regulation and Brexit looming on the horizon, it was not the time for considering the use of regulations to force companies to make products available.

The conference was warned that there was a danger, which due to its cost and complexity, pharmaceutical companies may not be able to meet the deadline for the implementation of the FMD packaging legislation. The regulation introduces pack identification of medicines involving the use of individual pack barcodes and anti-tamper devices within an “end-to-end” system under which the serialization and other data on each pack can be verified by a pharmacist with a scanner at a dispensing point connected to a central data bank. According to Philippe Drechsle, chair of Medicines for Europe’s FMD task force, a recent survey of the readiness of Medicines of Europe members for the legislation found that the most compliant company reached only a 55% state of readiness while other companies are at a level of 30% or even less (4).

Moreover, Brexit could result in a number of medicines no longer being available in the EU because of the need to obtain UK-based authorizations or because the UK was the original reference member state (RMS) under the mutual recognition procedure. These authorizations will have to be transferred to an EU state to remain valid after the UK’s departure. Both the FMD regulation and Brexit look highly likely to divert for awhile efforts to tackle the underlying causes of medicine shortages in the EU.

References
Secrecy and black-box operations are out; public disclosure is the mantra for regulators and manufacturers alike, as the United States Food and Drug Administration (FDA) explores more options for communicating agency policies, approval decisions, and concerns about product quality and safety. The drive for greater transparency in agency decision-making fits a range of health policy goals. More information on drug pricing, discounts, and rebates is considered key to limiting payer and patient outlays for prescription drugs. The Federal Open Payments, or “Sunshine” policy tracks industry payments, gifts, and transactions with healthcare professionals to uncover any industry influence on prescribers. And more timely and complete information on product safety and recalls aims to prevent patient harm, as do efforts to make drug labelling more informative.

A main transparency issue involves public access to clinical study data and results. While industry sponsors of clinical trials are meeting requirements for listing new studies on the ClinicalTrials.gov website, the record is weaker for timely posting of research results for newly approved medical products. The data transparency movement also has prompted biopharma companies to provide scientists and researchers with access to confidential clinical research data and to limit publications to open access journals. Meanwhile, academic researchers have lagged in disclosing clinical research activities, prompting the National Institutes of Health (NIH) to threaten to cancel grants to organizations that fail to meet requirements.

Transparency also is considered important for enhancing drug quality to reduce product recalls and shortages, according to a white paper from the Office of Product Quality (OPQ) in the Center for Drug Evaluation and Research (CDER) (1). As part of efforts to encourage manufacturers to adopt continuous manufacturing and systems to better ensure quality, an OPQ pilot study is exploring strategies with potential to enhance the transparency and consistency of assessments and facilitate team-based review and communication.

Other nations are joining the transparency movement. The China Food and Drug Administration (CFDA) issued draft guidance on policies for disclosing information regarding the acceptance, review, and approval of drug applications. While aiming to keep trade or technical data confidential, CFDA will make public information on active ingredients, dosing, license holder, and patents 60 days following an approval.

Seeking CRLs
Despite expanded information disclosure related to biomedical research, drug marketing, and product safety, stakeholders want to know more about the status of drug applications and FDA’s decision-making process in both rejecting and approving submissions. A main demand—from both consumer activists and free market deregulators—is for access to complete response letters (CRLs) sent to manufacturers that essentially delay or reject an application and outline what additional clinical or manufacturing information is needed to achieve approval. FDA currently posts summaries and reports on newly approved drugs and biologics and has indicated interest in also posting CRLs. But manufacturers strongly oppose such a move as CRLs usually contain trade secrets or confidential information. Current law requires FDA to redact such manufacturing information from public disclosures, and any move to change that policy may require legislative action.

A main demand—from both consumer activists and free market deregulators—is for access to complete response letters.

These issues are not new and reflect decades of reviewing and updating FDA policies on public access to information on agency operations and regulated products. A Transparency Initiative launched in June 2009 under former FDA Commissioner Margaret Hamburg and former Principal Deputy Commissioner Joshua Sharfstein has established FDA online “dashboards” that track agency actions and programmes, including inspections, recalls, imports, and compliance actions. A “Drug Trials Snapshots” initiative posts data from clinical trials on products approved since January 2015. FDA has expanded access to agency enforcement reports and adverse event data and has made its guidance development process more visible and efficient.

Last year, Sharfstein, now affiliated with the Johns Hopkins Bloomberg School of Public Health, organized a group of experts to produce a Blueprint for Transparency at FDA, which was published March 2017 in a special issue.
of the *Journal of Law, Medicine, and Ethics* (2). Among its 18 recommendations for making FDA decisions less opaque, the Blueprint calls for FDA to provide more public information on its evaluation process for new drugs, generics, and biosimilars, including what products are in the review queue and why certain applications are not approved. The rationale is that discussion of unsuccessful R&D would help researchers avoid studies unlikely to succeed, reducing costs and avoiding patient exposure to potential harm. The analysts also seek authority for FDA to correct misleading information issued by manufacturers, such as incomplete factors underlying a CRL, and for the agency to disclose data from clinical trials for approved products when sponsors fail to do so.

Such proposals reflect greatly expanded public access to information on drug testing and production through the Internet, social media, and smart phones—not all of it accurate or unbiased. Consumers and industry competitors can obtain reports of adverse events and enforcement actions, raising questions about the value and impact of limits on what FDA can or cannot disclose about a product or manufacturer.

FDA Commissioner Scott Gottlieb addressed these issues at a January 2018 forum on the Hopkins transparency report. He announced a new pilot to test the impact of FDA posting more data from clinical study reports (CSRs) of approved drugs, asking that sponsors of nine new products voluntarily provide CSR data, protocols, and statistical analysis plans for pivotal studies (3). In addition, FDA aims to better track drug studies from initial Internet posting through FDA approval by adding the ClinicalTrials.gov identifier (NCT) number to all clinical data submitted to the agency.

However, Gottlieb hedged about publishing CRLs, proposing to further explore FDA’s authority to release these documents. While he acknowledged that some information in CRLs might enhance the safe use of already approved products, he noted that redacting proprietary information from these letters is burdensome and questioned the value of disclosing letters that cite manufacturing shortcomings.

Recalls and safety

Gottlieb also mentioned FDA efforts to inform the public more quickly about adverse events and product recalls, which totalled more than 9000 in 2017, including 1200 involving drugs. Up until now, FDA has delayed recall announcements until it determined whether a safety issue raises serious health consequences, as with a defective anaesthesia product, or represents low risk. Now FDA’s Office of Regulatory Affairs (ORA) will include in weekly Enforcement Reports “not-yet-classified” recalls while the months-long classification process continues. FDA issued draft guidance in January 2018 outlining when a manufacturer should issue a public warning about a recall, including timelines and important data to include and what information FDA will post in its reports (4).

Although FDA has authority to require recalls, most drug manufacturers initiate such actions voluntarily, aware that FDA can issue press releases and alerts if companies are slow to act. Recall announcements from companies seem to appear almost weekly, many involving particulates or contamination of sterile injectables. Unfortunately, the failures that lead to drug recalls often create shortages in needed medicines. FDA and manufacturers will be looking to see if the earlier recall listing process generates alarms that turn out to be unnecessary, or if the new policy gets high-risk products off the market more quickly.

References


GOTTLIEB ENCOURAGES BIOSIMILARS AND SAFER OPIOID PACKAGING

In highlighting key US Food and Drug Administration priorities for the coming months, Commissioner Scott Gottlieb told agency advocates in Washington, DC that he will continue to seek ways to curb rampant opioid addiction, to promote competition that curbs high drug prices, and to advise on right-to-try legislation that helps patients. An ongoing challenge is to maintain resources across all FDA operations in an “austere budget environment,” particularly for those programmes without support from user fees.

More access to biosimilars is key to bringing down outlays on prescription drugs, and FDA is preparing a “comprehensive plan” to bolster the market for these products, Gottlieb said at a briefing held during the first week of February 2018 in Washington, DC, sponsored by the Alliance for a Stronger FDA and the Pew Charitable Trusts. He urged health plans, payers, and supply chain entities to support biosimilar coverage and reimbursement, as opposed to established products offering rebates designed to discourage biosimilar reimbursement. FDA also will propose regulatory action to facilitate approval of interchangeability claims for the new alternative therapies.

Current Challenges in Bioprocesses Development

Modern bioprocessing and antibody manufacturing are mature fields; however, challenges remain, and the advances themselves often bring new challenges. This is the nature of progress. The current challenges are exemplified by the ongoing advances and industry adoption of technologies such as continuous processing, the importance of modelling bioprocesses, increasingly seamless downscaling of processes, and other factors that are expected—and even required—by regulatory agencies.

Over the past 15 years, the industry has evolved into a mature, productivity-oriented segment. Of the dozens of trends evaluated in the annual BioPlan Associates survey (1), productivity continues to show the highest focus as an industry objective (see Figure 1). This suggests that other operational aspects must address industry challenges around improving productivity and efficiency.

But to achieve successes, operational challenges must be worked out. As an example, continuous bioprocessing is one of, if not the most, challenging area for process development. Continuous processing—including both upstream perfusion and downstream continuous purification processing—remains rare and elusive despite the fact these technologies have been established for some time. These challenges particularly stand out when continuous and conventional batch processing options are compared. Figure 2 shows survey results when bioprocessing professionals were asked to indicate issues with adoption of upstream perfusion that are much or somewhat bigger.

Upstream continuous processing

Bioprocessing professionals clearly see a number of operational problems remaining with upstream perfusion versus conventional batch processing. In 2017, a number of concerns were cited by more than 50% of respondents to BioPlan’s survey:

- Process operational complexity
- Contamination risks
- Upstream (process) development and characterisation time
- Process development control challenges.

This daunting collection of concerns about perfusion persists despite it being in use and marketed for multiple decades—including for commercial biopharmaceutical manufacture—notably for Factor VIII. In many respects, perfusion may be viewed as a technology adoption model in bioprocessing that demonstrates the slow nature of adoption of rational, effective technologies.

BioPlan market research studies (1) have shown that approximately 5% of bioreactors use perfusion, with many of these being feeder and not production bioreactors. Further, while perfusion is seen by users as highly productive, often better and cheaper versus batch processing, most using it in early manufacturing continue to avoid its use in commercial manufacturing, viewing the challenges as high and the risks significant, in terms of regulatory approvals.

One challenge for perfusion process adoption is that single-use perfusion units only recently became available. This lack of familiarity could be a factor in the reporting of high levels of concerns with—and even fears of—perfusion versus batch bioreactors likely among those not using the technology.

Many challenges remain before the industry gains experience and confidence in this option for continuous upstream processing.

Downstream processing challenges

Downstream continuous operations, particularly chromatography, has more challenges; suitable hardware with built-in data systems are just starting to become available from suppliers. Downstream continuous bioprocessing was cited as the second single-most important bioprocessing trend or operational area on which the industry must focus its efforts. In BioPlan’s study, perceived need for improvements carries over to facility budgets with interviewees reporting an average increase of 8.8% in their 2017 downstream technology budgets vs. 7.7% for upstream; 33.8% cited continuous chromatography as a “top area where suppliers should place their efforts on.”

Adoption of continuous chromatography, generally involving use of multiple interfaced columns with integrated controls, is growing more rapidly than perfusion adoption; however, adoption has only recently started from a near zero baseline and is low. Combined with other downstream advances (e.g., increasing use of membranes in place of resin-filled columns, automated in-line buffer dilution and
column packing, better resins, and more single-use and recyclable columns), downstream processing is in many respects changing and evolving more rapidly than upstream, but the adoption and integration into actual bioprocessing remain slow. When asked to cite the top downstream areas where suppliers should focus their development efforts, disposable purification systems were cited by 35.9% of respondents, followed closely by continuous purification cited by 33.9%. Geographically, European respondents are much more interested in continuous purification compared with those in the United States (44.4% vs. 25.3%).

But basic problems remain with broader adoption of both upstream and downstream continuous bioprocessing, including the inability to integrate related manufacturing systems. Currently, implementation of end-to-end continuous bioprocessing, or even upstream or downstream segments, remains rare or nonexistent, with at best one or a few unit processes implemented as continuous.

Process scalability challenges

Bioprocessing modelling and understanding of implications of changes in scale remains another challenging area. The industry has naturally concentrated on scale-up, as drug product volumetric requirements increase as products advance in development. More is known about scaling up versus scaling down. But the importance of scaling down is rapidly increasing, including the ability to model and predict what happens in research and development by using smaller scales, rather than having to run experimental studies at various scales, including full scale. Having scale-down capabilities and understanding is increasingly expected, if not required, in US Food and Drug Administration and other major market regulatory filings, particularly for product approvals. Being able to scale down and have related models and knowledge are now key parts of process analytical technology, quality by design, and other regulatory/quality initiatives. In addition, validated process down-scaling methods often are required for cost-effective design and refinement of bioprocessing. This is exemplified in the use of down-scaled bioprocesses to validate process biosafety, including reduction in virus titers from virus filtration and chromatography steps. The costs of validating virus removal and inactivation would be too expensive and time-consuming if run for full-scale processes.

Bioprocess system designers also want the ability to conduct computer-based modelling to scale up and scale down a process using bioprocessing equipment from the same product line. This particularly applies to purchases of bioreactors, mixers, chromatography, and other major bioprocessing systems, but also extends to filters and other equipment. Scalability, particularly including scale-down ability, is a top equipment/technology selection factor cited in bioprocessing supplies-related market research studies. Many facilities will not purchase equipment unless reasonable scalability is known and documented among products throughout a product line, particularly for bioreactors and chromatography and filtration systems. Bioprocessing professionals regularly cite an expectation that bioprocessing systems will seamlessly scale up and down. In addition, the users want to model or predict the operation of the systems at scales higher than anticipated use to provide better assurance of actual scalability throughout the range of scales they actually will use, such as from mini/desktop to 2000-L or larger production bioreactors.

Conclusion

To move forward, industry and its investors need to recognize this segment has historically been one of the slowest, but also the most persistent, in terms of adopting the advances that the industry requires. To achieve success, operational challenges must be worked out, but in this regulated, high-stakes environment, the timelines for development and adoption of new technologies create challenges that, sometimes, require years to resolve.

Reference

The submission of a new drug application is a milestone for drug companies, from virtual startups to Big Pharma. Many complex steps and potential pitfalls await, however, on the path to commercial approval. While many drug innovations result from surprises during research phases, a surprise that occurs during development—such as formulation or manufacturing problems—could result in approval delays or failure for a drug product.

To reduce the risk of late-phase surprises, some industry experts recommend that additional screening efforts in early development can smooth the pathway in later development stages. Developers of promising compounds emerging from drug discovery, however, must balance the need to better understand potential formulation challenges and the manufacturability of the drug product with the reality of time and budget constraints.

Prior to first-in-human drug trials, drug owners are expected to provide information about the pharmacological and toxicological effects of a prospective drug product, as well as its physical, chemical, or biological characteristics and stability of the drug substance. Information about formulation and manufacturing processes typically are defined in later stages.

For drug development companies, particularly small startups, the focus is often short-term: get the compound to clinic or get an investor or buyer interested in the potential drug. This type of approach can be short-sighted, some experts say; drug companies would be better served by focusing on getting the drug to market. In recent presentations, consultants and representatives of contract development and manufacturing organizations (CDMOs) shared a similar theme: shifting some formulation steps normally conducted in Phase I or...
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Early Development Strategies

Phase II to the preclinical stage can help identify potential formulation and manufacturability roadblocks earlier in the development process.

A major challenge for drug owners in early development is balancing what they don’t know, what they can afford to investigate, and what they need to know. A longer-term focus involves more detailed assessment of the drug’s properties, formulation, and manufacturing potential in early development phases. A better understanding of an API’s properties, polymorph forms, interactions with excipients, and the overall performance of the formulation can help avoid problems and expensive rework of formulation steps during scale up to commercialization.

For small pharma companies, limited financial resources may restrict their ability to invest upfront in characterization and preformulation screening. The US Food and Drug Administration commissioner has expressed concern that added upfront costs may slow early phase development and increase costs (see Sidebar).

Building a better molecule

While speed is the top priority for most small pharma companies with molecules in discovery phases, drug candidate quality should be the top consideration, said David Elder, principal consultant, David P. Elder Consultancy, in a webcast (1).

If more work is done in medicinal chemistry stages to optimize a molecule, formulation challenges may be easier to solve, said Elder. Historically, formulation scientists were expected to “rescue” molecules that were intrinsically insoluble. To get more drug candidates with fewer solubility issues, drug companies should focus more on the quality of the candidate molecule—its lipophilicity, molecular weight, and ring systems—and not just its potency. And, noted experts in multiple presentations, medicinal chemists and formulation experts need to work in partnership to improve the molecule’s chances of success.

Drug companies that fail to evaluate the physicochemical characteristics and manufacturability of a drug candidate in early development stages will not have adequate risk assessments of challenges that may arise later in development stages. Drug candidates with demonstrated data on solubility, intestinal permeability, dissolution, bioavailability, and dose will be more attractive to potential partnerships or acquisitions by other pharma companies, or investors.

Often, preclinical efforts are geared to achieving a desired pharmacokinetic response in an animal model while minimizing formulation development time and cost. However, in vitro–in vivo relationships are often not straightforward and, therefore, require additional time and cost to establish, experts note. Fast and simple approaches, such as pharmacokinetic studies using the API in a hydroxypropyl methylcellulose suspension may not give accurate results and can result in formulation delays later in the development process (2).

A range of in-silico modelling tools are available to screen drug candidates to predict degradation, metabolism, toxicity, solubility, excipient selection, and other characteristics while conserving valuable API and avoiding laboratory-based trial and error. CDMOs offer screening services that use modelling and medicinal chemistry and formulation tools to evaluate drug candidates and guide formulation strategies. Modelling also is being used to evaluate manufacturing approaches and excipient selection, and for process scale up and design of experiments.

The solubility question

Drugs are frequently cited as fitting into one Biopharmaceutics Classification System (BCS) classification; however, this system is a regulatory tool to identify efficacy and patient safety, said Julien Meissonnier, vice-president, science and technology, Catalent Pharma Solution, in a webcast (1). A better tool for evaluating new drug development issues including permeability, solubility, dose, and dissolution rate is the developability classification system (DCS) (3), he said.

Like the BCS, the DCS tool also categorizes molecules based on solubility, dose, dissolution, and permeability. It further classifies Class II compounds, which have low solubility and high permeability; Class Ila are dissolution-rate limited and Class Iib are solubility-limited. The dissolution of Class Ila molecules can be enhanced by reducing particle size. Knowing where a drug candidate fits on the classification scheme can expedite the formulation process, Meissonnier said.

Catalent works with drug companies to characterize a molecule using high throughput screening to identify physicochemical properties and a DCS classification. Drug metabolism and pharmacokinetics (DMPK) modelling is used to understand formulation parameters. Parallel screening—at a small scale—of different solubility enhancing technologies (e.g., lipids, hot-melt extrusion, spray drying, and micronization) is used to assess stability, drug load, solubility, and concentration increase. Based on the screening results, the best candidate molecule can be selected for animal studies.

In a presentation at the 2017 AAPS workshop (4), Sanjay Konagurthu, a senior director at Patheon, part of Thermo Fisher Scientific, described a solubility enhancement formulation platform that uses algorithms to analyze a drug’s structure against manufacturing methods including solid dispersions, lipids, particle size reduction, crystalline forms, and cyclodextrin complexes. The results indicate the potential of each technology on a scale. The tools can be used to view a drug’s molecular properties, identify potential excipients, and computationally screen excipients and drug loading prior to experimentation. Konagurthu reported accuracy of predictions of more than 80%, based on validation studies with commercially available molecules.

Build for the drug’s lifecycle

In the typical drug discovery/early development scenario, a company may have only a few grams of the compound, and most likely has not attempted to synthesize the
Early Development Strategies

In a series of speeches in the latter half of 2017, US Food and Drug Administration (FDA) Commissioner Scott Gottlieb said that high costs and delays in early development efforts are setting the stage for more expensive drugs—and drug programme failures. The agency is introducing initiatives to improve drug development efforts, but industry also needs to change preclinical, development, and clinical trial efforts.

While researchers have been able to use science to reduce the time from a breakthrough discovery to the creation of patient therapies, the process for developing such opportunities is more costly, uncertain, and prolonged, especially for new drug development, he said. “We’re on an unsustainable path, where the cost of drug development is growing enormously, as well as the costs of the new medicines. We need to do something now, to make the entire process less costly and more efficient. Otherwise, we won’t continue to realize the practical benefits of advances in science, in the form of new and better medicines,” he said (1).

The same policies that the agency pursued to advance the science of drug development and make that process more efficient must be directed toward lowering the cost of developing medicines, he said, and more focused clinical trials can help reduce overall development costs. However, he said, “on a relative basis, in many cases the cost of early-stage drug development has grown at a proportionally faster rate than the cost of late-stage drug development” (1).

“By front-loading the cost of drug discovery, the broader biomedical community is making it harder to advance new ideas. It’s economically harder to capitalize the cost of an early-stage drug programme, relative to funding a later-stage project. So, front-loading the costs are a recipe for reducing the amount of new ideas that can be advanced,” he said (1).

The agency is encouraging early engagement with product developers, especially small biotechnology companies who may not be familiar with the regulatory filing process. Some sponsors sometimes overestimate the amount of information needed to file an investigational new drug application, front-loading the costs of development, he explained. FDA’s review staff may be able to recommend steps to streamline the early development process by eliminating unnecessary preclinical tests or by suggesting optimal preclinical or clinical designs, he said.

“Ideally, it would be easier to get products into development, with more of the costs pushed further out, after some of the initial preclinical work is already done, and there’s a better understanding of whether a new product has clinical promise,” he said.

Reference
The switch in emphasis in the pharmaceutical industry from the development of blockbuster drugs to therapies that treat rare diseases and smaller patient populations has led to the need for small-volume current good manufacturing practice (cGMP) API manufacturing capabilities. These APIs must meet the same regulatory requirements as larger-volume drug substances, except at smaller scale and with less—but much higher value material—available for analytical testing, and often under accelerated timelines. In addition, the APIs used to formulate these products are typically highly complex, requiring multi-step syntheses using unusual reagents. Managing multiple projects can be a challenge for contract development and manufacturing organizations (CDMOs).

CDMOs often manage at any one time numerous small-volume API development projects involving a wide range of chemicals targeting a broad array of therapeutic indications. As a result, they must deal with many different challenges simultaneously. “These molecules tend to be highly complex, and most have never been synthesized before except perhaps at small scale in the laboratory. They also typically require the application of specific, sophisticated technologies, some of which must be engineered for the first time,” says Ed Price, president and CEO of PCI Synthesis.

Practical syntheses must be developed that can be transferred to cGMP processes that consistently meet quality requirements. Even though commercial processes for these APIs involve smaller volumes than those of APIs intended for blockbuster drugs, scale-up issues must still be addressed. Understanding critical process parameters (CPPs) and their impact on critical quality attributes (CQAs) is essential to understanding the process and conducting risk evaluations for unit operations and equipment to ensure “right-first-time” technology transfer, according to Shyam Vispute, general manager of tech transfer at Neuland Labs.

Analytical methods must also be developed and validated, which can be challenging due to the complexity of the molecules. In addition, given the small quantities of high-value material being manufactured even at commercial scale, minimizing the quantity of material consumed in these activities is important. “Alternative protocols may need to be developed in some cases to allow for use of reduced quantities of these costly APIs,” Vispute says.

Don’t forget the technical challenges

The complex molecules being developed as drug candidates today require sophisticated technology for their production, such as advanced chromatography systems and specialized isolation techniques like tangential flow filtration, according to Price. PCI Synthesis has seen the need for low-temperature chemistry grow significantly. “Doing cryogenic chemistry is manageable at the lab scale, but is much more challenging at the 1000-gallon scale,” he says.

Often it is necessary to design suitable hardware for use in the laboratory and then transfer the technology to plant scale, according to Vispute. In some cases, existing equipment can be modified, but in others, new systems must be purchased.

Scale-up and optimization of small-volume processes can be challenging because for many, there is little information available in the literature. “It is essential to consider all of the various process parameters—temperature, pressure, mass transfer, etc.—upfront,” Vispute observes. Risk analyses for each unit operation—reaction and purification (extraction, distillation, crystallization, filtration, etc.), drying, and powder processing—should be conducted to avoid problems at plant scale.

Joshua Hoerner, senior director of research and development at Noramco Athens, notes, however, that solution mixing, pressure, and temperature challenges may actually be reduced on a small-volume basis due to the smaller surface areas involved.

In some cases, the batch scale, which is determined from the dosage strength of the final formulation, will impact the choice of technology used in a synthesis. When developing peptides, for example, researchers must determine whether solid-phase, solution-phase, or hybrid technology is most appropriate, according to Partha Pal, head of custom manufacturing solutions and business development for Neuland Labs.
Because most of these molecules have not been synthesized on any appreciable scale before, it is also necessary to develop practical purification strategies, according to Price. Poorly soluble compounds falling in Biopharmaceutical Classification System (BCS) classes II and IV can be particularly challenging. “Exploring all available techniques to improve solubility and bioavailability, such as employing suitable techniques to modify the physicochemical properties or increase the specific surface area of the API powder particles, is often necessary,” notes Girish Kavishwar, associate vice-president of R&D at Neuland Labs.

Some isolated intermediates and APIs may be oily liquids, which can create handling and stability challenges, according to Hoerner. “Managing active ingredients that are predominately viscous oily liquids is a significant challenge, both from a handling and stability perspective. Noramco is working on dosage form solutions to help improve the processability of such substances while also enhancing their commercial shelf-life,” he notes.

Crystalline powders, on the other hand, may have different polymorphs and crystal habits that can impact drug product manufacturing robustness and the bioavailability of the API, Hoerner adds. “Identifying and stabilizing the appropriate polymorph requires special skills and should be performed early on in the process to avoid problems late in the development cycle,” agrees Pal.

Handling cytotoxic and highly potent compounds is yet another issue. Appropriate facility and equipment design is required for handling such compounds, and appropriate disposal facilities are also required based on their occupational exposure limits. Automation of process operations is also important for reducing the exposure of operators and the environment to hazardous chemicals, according to Pal. “A process hazard analysis (PHA) should always be conducted prior to implementing a small-volume cGMP synthesis to systematically identify and mitigate hazards that arise from innate chemicals or chemical reactions,” Hoerner asserts.

Maximizing process knowledge
One of the key technical and operational challenges associated with cGMP manufacturing of small volumes of intermediates and APIs is difficulty in obtaining reliable reaction yields and consistent quality, according to Hoerner. Noramco tackles this issue with thorough process development efforts to maximize process knowledge and understanding. In-process controls for monitoring reaction completion, crystallization, drying, and other critical steps are also used to ensure completion.

“Overall, we emphasize a company culture that focuses on the patient/customer and ensures our products are of optimal quality and produced in a safe and compliant manner,” Hoerner comments. From a technical perspective, Noramco begins at the R&D stage, selecting and developing a phase-appropriate route and evaluating critical raw material sources, reagents/solvents, equipment, and analytical controls to ensure robust delivery of cGMP material. In addition, Hoerner says that scale changes between development and cGMP supply are modelled with advanced software; process analytical technology (PAT) or advanced offline analytical technologies are applied to synthetic steps that are highly complex or have significant risk to impact product quality.

Neuland uses quality-by-design (QbD) and design-of-experiment (DoE) approaches beginning at the development stage to identify relevant process parameters and identify the design space that will have minimal variations at the plant scale, according to Vispute. Use of simulation software, such as for scale up and mixing behaviour studies, allows the evaluation of equipment performance prior to actual experimentation in the plant, leading to reduced costs and development times for Neuland. PAT tools are used for real-time measurement of CPPs, such as focused-beam reflectance measurement (FBRM) probes for particle size distribution, particle vision and measurement (PVM) probes for particle shape and polymorph determination during crystallization processes, infrared (React IR, Mettler-Toledo) for monitoring the real-time progress of reactions, and near infrared (NIR) probes to perform drying profile studies for determination of desired polymorphic forms of temperature-sensitive products.

The internal protocol at PCI Synthesis places emphasis on doing a good job at building a practical process early on in a project. “Once the chemistry and analytics are locked in, if any changes are needed, a tremendous amount of work will need to be repeated. That is why it is so important to take the time upfront to choose the right raw materials (considering cost and availability), really understand the process, and build into the early stage chemistry what will be required down the road,” Price observes. Process optimization using a DoE approach allows efficient yet thorough exploration of the design space. Method development for in-process and final product testing and confirmation of process robustness and reliability at larger scale are then performed before moving to GMP production.

Tailored solutions for complex problems
Small-volume cGMP chemistry is clearly an area that can pose significant challenges. “The first focus should always be on safety and compliance during manufacturing and ensuring robust production of high-quality intermediates and active ingredients,” Hoerner says. That cannot be achieved if small-volume API manufacturing is treated as a commodity business, according to Price.

“We work with many different small companies, each with its own business model, culture, internal resources, and level of experience. Each project they bring us is unique, involving vastly different raw materials, equipment, and chemistry. Flexibility and the ability to respond to the different needs of our customers and their projects are crucial to success. We must be able to bring a significant number of differing resources to bear to create custom-tailored solutions to complex problems,” Price concludes.
Particle surface modification is becoming a vital strategy in the pharmaceutical industry for “difficult to formulate” APIs. Most surface modification techniques, however, alter innate particle properties either chemically or physically. These surface modification technologies involve the use of elevated temperatures, high pressures, and/or solvents, making these processes highly unsuitable for unstable APIs that are degraded when exposed to such conditions.

Aston Particle Technologies (APT) has developed the world’s first aerosolized dry particle coating technology. This technology is a one-step, ambient temperature process, with controlled processing parameters that can deliver repeatable product performance with commercially available excipients.

The science underpinning this technology requires the use of a high G-force chamber, with a curtain of nitrogen gas to fluidize the powder at the chamber wall, which disperses any agglomerated fine or coarse particles. The co-aerosolization of particles results in coating of all the fine particles onto the surface of the coarse particles and can produce particles with designed functionalities, even with highly sensitive APIs. These functionalized particles enhance the inherent properties of API without degrading them in any way. There is no exposure to heat/solvent, and the particles suffer no attrition during processing, which is a significant advantage compared with other current state-of-the-art dry coating technologies (1–5) (see Table I).

The difference in this technology is that blending occurs through particle–particle interaction in the aerosolized state compared to traditional solid–solid interactions of technologies such as high-shear blending.

Dry coating using the technology can be depicted in three primary stages (Figure 1), which occur simultaneously: firstly, the dispersion of all the agglomerates of both the fine and coarse particles through application of the high G-force generated by revolving the processing chamber at high speed, balanced by the injection of nitrogen gas into the chamber; secondly, the dispersal of the fine particles around the coarse particles; and finally, the attachment/adhesion of the fine particles to the surface of the coarse particles, reaching a uniform spatial distribution of the fine particles.

Coating examples
Powders generated by APT’s dry coater at both laboratory and pilot scale have demonstrated proof of concept for various formulation applications, including blends for dry powder inhalers (DPI), API solubility enhancement, and modification of dissolution rate. Scanning electron microscopy (SEM) images of the coating process show the successful adherence and uniformity of the fine particles to the surface of the coarse particles.
microscopy (SEM) and confocal laser scanning microscopy (CLSM) images of the coarse host particles loaded with the fine guest material are shown in Figure 2.

The SEM micrographs show that the fine de-agglomerated guest material is coating the coarse carrier as individual particles. These images also show that there is no free or unbound fine material and that the host particles appear to have mopped up all the available fines in the field of view.

**Coating occurs because the forces of attraction between fine and coarse are greater than the weight of the fine particle itself.**

Additionally, the CLSM micrographs confirm that the larger particles can be completely dry coated with finer material using APT’s dry coating technology. In the case shown in Figure 2, micronized, fluorescent rhodamine particles have been dry coated onto non-fluorescent microcrystalline cellulose (MCC). The cross-sectional images demonstrate that the microfine rhodamine particles form a coherent coating on the surface of the MCC host.

Blend investigations demonstrate that this dry coating principle can generate highly ordered blends, using different APIs and excipients, with reproducibly tight content uniformities. Even at concentrations as low as 0.5% w/w, the relative standard deviation (RSD) is consistently <2% with good API recovery of typically >98% (see Figure 3A).

### Table I: Common issues associated with the different commercialized dry particle coating techniques compared to Aston Particle Technologies’ processing method.

<table>
<thead>
<tr>
<th>Technology name</th>
<th>No heat generated</th>
<th>No particle attrition</th>
<th>No risk of contamination</th>
<th>No effect on stability of API</th>
<th>Suitable for pharmaceutical applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mehanofusion (Hosokawa Micron, Japan)</td>
<td>x</td>
<td>x</td>
<td>√</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Hybridizer (Nara Machinery, Japan)</td>
<td>x</td>
<td>x</td>
<td>√</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>MAIC Magnetically assisted impaction coating (Aveka, US)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>√</td>
<td>x</td>
</tr>
<tr>
<td>APT dry particle coating technology (APT, UK)</td>
<td>√</td>
<td>√</td>
<td>√</td>
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For consistent dose performance, the industry typically requires blend concentration RSD to be <6% (13). This requirement is particularly crucial for inhaled formulations in which the therapeutic dose is often in the microgram range. Through optimized process development, a platform for the application of the technology to a DPI formulation has been registered as APT-Hale.

The controlled nature of the APT-Hale process for DPIs leads to consistent API delivery, which means that the technology also determines the dosing performance of the formulated blend. The technology produces tight content uniformity and can also be tuned to deliver a particular fine particle fraction (FPF) as demonstrated in Figure 3B, where a single-blend formula processed in a designed set of experiments has been "dialled up" to deliver increasing FPF.

To demonstrate the potential of the technology in respiratory medicine development and manufacture, a series of designed experiments, using a quality-by-design approach, has been completed with two different, commercially sourced lactose carriers. The object of these experiments was to optimize an API/lactose formulation based on key critical quality attributes. Optimizing time and rotation speed...
of the blending process, which were identified as critical process parameters, demonstrated that the carrier influences the processability of the formulation (see Figure 4). The resultant design space enables the formulator to visualize a manufacturing control space for a formulation using either carrier.

**Future work**
Although many of these experiments were carried out at laboratory scale, APT recently collaborated with the automation engineering team at GB Innomech, which has designed and developed a system to scale up the technology 100-fold. The system has been designed so that operators can quickly access and store the required process conditions for specific production batches. Operational qualification at this pilot scale is ongoing but the process is proving to be completely scalable.

**References**
Formulating Topical Products Containing Live Microorganisms as the Active Ingredient

Case studies compare efficacy testing of preservatives for topical formulations with probiotic actives.

In recent years, many topical probiotic personal care products have been launched into the market (1). In an August 2016 review for Dermatology Times (2), dermatologist Patricia Farris concluded, “The studies reviewed suggest that topical prebiotics, probiotics, and bacterial cell lysates do provide demonstrable skin benefits … At this time, it appears that more studies are warranted to determine if these products are really worth the hype.” These scientific reviews are quick to point out that well-crafted, vehicle-controlled clinical trial results are not generally available for topical semisolids containing live microorganisms. One reason that topical probiotic therapies have not advanced beyond the personal care “post-marketing surveillance regulatory environment” into the controlled clinical trial “new drug approval regulatory environment” is the difficulty in reconciling FDA microbiological requirements for a product containing live microorganisms. More specifically, how can a topical suspension containing more than 50,000 colony forming units (CFU) of probiotic active pharmaceutical ingredient (API) pass United States Pharmacopeia (USP) microbial enumeration testing (USP <61>-) (3), tests for specified organisms (USP <62>-) (4), and antimicrobial preservative effectiveness (USP <51>-) (5)?

Two case studies are being presented here to explore the strategy of adequately preserving the formulation, but using a preservative of sufficiently narrow spectrum to maintain viability/potency of the probiotic active. The first case study uses a probiotic strain of Propionibacterium acnes (P. acnes). P. acnes is a lipophilic, gram-positive anaerobic bacillus that resides in the pilosebaceous unit of human skin. Hundreds of different strains of P. acnes exist. The lipases, proteases, and hyaluronidases secreted by certain strains of P. acnes injure the lining of the pilosebaceous unit and activate production of proinflammatory cytokines that in turn lead to acne vulgaris. Other strains of P. acnes produce no inflammatory response and thus do not induce the symptoms of acne vulgaris. One of these non-inflammatory strains of P. acnes has been chosen to be used as an “active ingredient” in a topical formulation product. In the second case study, the microorganism is a bacteriophage (phage), which is a virus that infects and replicates within a bacterium, ultimately causing bacterial death. The phage used in this study was isolated from the follicular casts obtained from volunteers with facial comedones. Bacteriophages were identified and isolated from the comedones and were then propagated using an amplification process and plated against different P. acnes strains to determine breadth of efficacy to assure the selected phage was suitable to infect and eradicate pathogenic (inflammatory) P. acnes strains.

Formulating a living microorganism is fundamentally different from formulating a small-molecule active topical product. Because the P. acnes probiotic or phage products will be dosed as suspensions, active solubility, solvent compatibility, and penetration across the stratum corneum do not factor in to the development of a topical probiotic. In contrast, the aqueous probiotic formulation does require that pH and osmolality be adjusted to values that assure a favourable environment for the microorganisms to remain viable. In these two case studies, eight different formulations containing preservatives were tested for live microorganism viability over six weeks after compounding.

Material and methods

The low immunogenic strain of P. acnes (probiotic bacterial active) and phage that attacks pathogenic P. acnes (microbiome editor) were provided by Phi Therapeutics. Two gelled aqueous products were made with the intent of formulating cosmetically elegant products: hydroxyethyl cellulose (HEC) at 1.5% w/w and polyacrylic acid polymer or carbomer (Carbopol 980, Lubriloz) at 0.75% w/w, both titrated with propylene glycol until isosmotic (~285 mOsm/kg). Both gels were prepared with the following preservative systems: preservative free, methylparaben (0.1%) and propylparaben (0.02%), phenoxyethanol (1.0%), and potassium sorbate (0.2%). In addition, two solution products were made: an 80:20 water:propylene glycol blend (w/w) and an 80:20 water:ethanol blend.
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blend (w/w). Both solution blends were considered self-preserving. The pH of all the products were taken, but no pH modifiers were added. Active viability and stability testing were conducted every two weeks after addition of active microorganism by diluting the formulated products to a known concentration of active microorganisms and plating them out. 

**Results**

When added individually to the probiotic formulations, the parabens, phenoxyethanol, and potassium sorbate completely deactivated the product gelled with HEC or Carbopol by more than 99.95% within the first four weeks of compounding with the HEC gelled water (non-preserved) product performing no better than 20% propylene glycol product.

The parabens, phenoxyethanol, and potassium sorbate in isotonic HEC formulations did not deactivate the phage six weeks after compounding. Formulating the phage with ethanol or propylene glycol up to 20% solvent did not have any effect on phage activity (see Figure 3).

As shown in Figure 4, however, the use of a negatively charged polymeric gelling agent (polyacrylic acid polymer) did deactivate the phage by about 95% two weeks after compounding and caused more than 99.95% loss in phage titer by four weeks.

**Discussion**

The basis for microbial enumeration testing (*USP* <61>), tests for specified organisms (*USP* <62>) and antimicrobial preservative effectiveness (*USP* <51>) of topically applied non-sterile pharmaceutical products is the statement in US 21 Code of Federal Regulations (CFR) 211.113(a) that “Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed” (6). It should be noted that a topical probiotic product should not have greater difficulty in passing *USP* <61> or *USP* <62> than topical products containing non-living actives. For topical probiotics, the living microorganism active is not “objectionable” and thus is not required by *USP* <61> to be below 1000 CFU. Likewise, the absence of pathogens such as *Staphylococcus aureus* or *Pseudomonas aerogenesis* as determined by specified organisms of *USP* <62> is necessary for the safety of any topically applied pharmaceutical. It is passing antimicrobial preservative effectiveness testing (*USP* <51>) that is the biggest hurdle to the development of a topical product containing a living microorganism as the active.

As seen for the probiotic *P. acnes* strain used in the first case study,
only the addition of 20% propylene glycol was reasonably tolerated by the living microorganism active. The parabens, phenoxyethanol, potassium sorbate, and ethanol, when added individually to the probiotic formulation, deactivated the product by more than 99.95% within four weeks of compounding. The 20% propylene glycol liquid initially lost 90% activity at two weeks, but remained at a very consistent level of activity from two weeks through to six weeks. While a certain segment of the probiotic active appears susceptible to the cell membrane function interference exerted by a glycol, sufficient quantities of viable probiotic remain to manufacture an efficacious topical product. Blending propylene glycol with other glycols to optimize antimicrobial activity has been an area of active research within the field of dentistry (7). The results of the first case study, combined with the literature concerning the bactericidal activity of propylene glycol, indicate that addition of glycols to a fluid suspension of probiotic P. acnes is a reasonable development strategy for complying with 21 CFR 211.113(a).

As expected, the phage was more resilient to the addition of preservatives to the formulation. Addition of ethanol to the formulation did not appear to have any effect on the phage. The parabens, phenoxyethanol, potassium sorbate, and propylene glycol did not appear to deactivate the phage six weeks after compounding. The use of a negatively charged polymeric gelling agent did deactivate the phage by approximately 95% two weeks after compounding and caused more than 99.95% loss in phage titer by four weeks. Obtaining a preserved bacteriophage probiotic topical gel is possible provided that an uncharged gelling agent such as HEC is used as the thickener.

Conclusion
The phage has the capacity to tolerate a wide range of typical pharmaceutical preservatives, and it appears possible to formulate a cosmetically elegant final product if a nonionic gelling agent (such as HEC) is used. However, formulating a final product containing the probiotic P. acnes will be challenging, and certain amounts of care will need to be taken in working with the bacteria and choosing the best method of preserving the final product. Nonetheless, bacterial levels in the 20% propylene glycol aqueous solution have been relatively stable from weeks 2–6, indicating that this is a reasonable development strategy. From the results obtained from these two case studies, it can be concluded that it is possible to formulate a preserved topical product containing living microorganisms.

References
According to the modern requirements of the European Union’s Good Manufacturing Practice for Medicinal Products, a manufacturing authorization holder should guarantee the suitability of excipients included in the finished medicine. For this purpose, a formalized, documented assessment of risks associated with safety, quality, and function for each excipient should be carried out. Though the EU-GMP guidelines give an indicative list of parameters that should be taken into consideration when assessing the excipient risks, none of the known and cited sources specifies how to perform such an assessment. The present article, therefore, describes a new, combined, quantitative method for assessing excipient risks that has been developed by the authors as one possible risk evaluation method. This method represents a combination of a quantitative risk assessment (based on the risk index method) and a qualitative risk ranking method. The risk components related to safety, quality, and function of excipients as well as parameters included in them are considered, and the score points are assigned to each excipient. The developed method was used for excipient risk assessment of some marketed finished medicines manufactured by Ukrainian pharmaceutical enterprises.

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to guarantee the quality of the excipients is quite complicated because the manufacturers of excipients mostly aren’t MAHs and are not covered by regulatory GMP-inspections. Moreover, such manufacturers may refuse to be audited by MAHs. Thus, one way a MAH can determine if an excipient is of appropriate quality and can be used safely in finished drug manufacturing is by doing a risk assessment.

An overall risk assessment should take into account the requirements of other relevant quality systems to determine the origin and the intended use of the excipients, as well as previously recorded cases of defects in their quality. A system of an overall assessment and management of excipient risks is incorporated in the pharmaceutical quality system of a finished medicine manufacturer. All actions within excipient risk assessments are documented and are subject to GMP inspection. A risk management approach has been implemented in pharmaceutical manufacturing for more than 10 years, and methods and tools that can be used in the risk management process are described in International Council for Harmonisation (ICH) Q9 (6). This list, however, is not exhaustive and could be expanded using other tools or combinations. Numerous examples of risk assessment methods and tools are described (7, 8), but information about which approach is useful for excipient risk evaluation and details of how this evaluation could be done are lacking. This article, therefore, aims to provide such information.

The guidelines (3) establish the fundamental principles that should guide a finished medicine manufacturer in the excipient risk assessment and note that the instruments and methods described in ICH Q9 (6) can be used for this purpose. The guidelines (3) provide an indicative list of parameters that should be taken into consideration when assessing the excipient risks, but in the authors’ opinion, it is not complete and the parameters included in a particular risk component need more in-depth study and additional individual assessment. In a previous publication (9), the authors have considered the possible algorithms for the risk assessment of excipient function in every particular pharmaceutical formulation. The present work was aimed at the development of a quantitative, combined method for the overall risk assessment of excipients that can be applied by industrial pharmaceutical enterprises.

**Risk method development**

The method developed by the authors is a combination of a quantitative risk assessment based on the use of the risk index method using scores (10) and a qualitative risk ranking method. The quantitative characteristic used in the first stage ensures the objectivity of the assessment and a more accurate characterization of the risk level. The qualitative ranking method applied in the second stage enables interpretation and further practical use of such an assessment. Applying the method using quantitative analysis of the risk components and the parameters included in them determines a risk category as low, medium, or high risk.

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**Figure 1:** Low-, medium-, and high-risk areas (respectively, from left to right) derived from the risk components: safety (S), quality (Q) and excipient function (F), expressed in score points from one to three.
To develop this method, the following tasks were performed:

- The components that affect the excipient risk and that can be considered as independent variables were studied.
- A set of parameters within each of the risk components was determined.
- A scoring system for the parameters, and accordingly for the risk components, was established.
- An algorithm for the quantitative assessment of the risk components was developed.
- Low-, medium-, and high-risk areas in the resulting three-dimensional space were determined.
- From the three-dimensional space in the risk assessment, one can move to a simpler and more understandable qualitative rank (low, medium, or high risk).

The guideline (3) identifies quality (Q), safety (S), and function (F) of excipients in a finished medicine as the components that affect excipient risk. Each of the risk components for an individual excipient is represented in the form of coordinate axes in three-dimensional space: Q, S, and F (see Figure 1). The total risk index (TRI) is calculated using Equation 1:

$$TRI = S \times Q \times F \quad [Eq. 1]$$

For simplicity, a three-point scale (from one to three) is used for each component.

In turn, each of these components includes a number of parameters, which can be designated by the letter that corresponds to the component name and the index that corresponds to the parameter number. For example, Q3 denotes the third parameter related to the quality component, and F1 to F7 denotes the parameters of the excipient function component (see Tables I–III). Each of these parameters is quantified from one to three points, and the risk value is calculated for the components S, Q, or F as the arithmetic mean of the parameters included in each of the components. To decrease the error of the overall risk assessment, when calculating the arithmetic mean of the parameters at the stage of component assessment, one should not round the obtained values to whole numbers. Rounding should be limited to the first significant digit after the decimal point. By substituting such values into the formula (1), a more accurate assessment of the overall risk index is obtained, and the resulting value is rounded to whole-number values at the final stage of the calculation.

Table I: Instructions for assigning parameters and score points to the Safety (S) excipient risk component.

<table>
<thead>
<tr>
<th>Safety (S)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spongiform encephalopathy:</td>
<td>$S_1$</td>
</tr>
<tr>
<td>Raw materials of animal origin are used for the manufacture of excipient</td>
<td>1</td>
</tr>
<tr>
<td>Raw materials of animal origin are not used for the manufacture of excipient</td>
<td>3</td>
</tr>
<tr>
<td>Potential for viral contamination:</td>
<td>$S_2$</td>
</tr>
<tr>
<td>Impossible</td>
<td>1</td>
</tr>
<tr>
<td>Possible but not significant for this particular pharmaceutical form</td>
<td>2</td>
</tr>
<tr>
<td>Possible and significant for this particular pharmaceutical form</td>
<td>3</td>
</tr>
<tr>
<td>Potential for microbiological or endotoxin/pyrogen contamination:</td>
<td>$S_3$</td>
</tr>
<tr>
<td>Exipient has a synthetic origin and is resistant to microbial contamination</td>
<td>1</td>
</tr>
<tr>
<td>It is possible, but not significant for this particular pharmaceutical form</td>
<td>2</td>
</tr>
<tr>
<td>It is possible and significant for this particular pharmaceutical form, in</td>
<td>3</td>
</tr>
<tr>
<td>raw materials of animal and/or vegetable origin are used in the excipient manufacturing process or the excipient could serve as a substrate and stimulate the growth of micro-organisms</td>
<td></td>
</tr>
<tr>
<td>Potential for any impurity originating from the raw materials (e.g., aflatoxins or pesticides):</td>
<td>$S_4$</td>
</tr>
<tr>
<td>Raw materials of vegetable origin are not used in the excipient manufacturing process</td>
<td>1</td>
</tr>
<tr>
<td>Raw materials of vegetable origin are used in the excipient manufacturing process</td>
<td>3</td>
</tr>
<tr>
<td>Potential for any impurity generated as part of the process and carried over (e.g., residual solvents and catalysts):</td>
<td>$S_5$</td>
</tr>
<tr>
<td>Low potential for such an impurity</td>
<td>1</td>
</tr>
<tr>
<td>High potential for such an impurity</td>
<td>3</td>
</tr>
<tr>
<td>Sterility assurance for excipients claimed to be sterile:</td>
<td>$S_6$</td>
</tr>
<tr>
<td>The excipient sterility is ensured</td>
<td>1</td>
</tr>
<tr>
<td>There are some problems with the excipient sterility ensuring</td>
<td>2</td>
</tr>
<tr>
<td>The excipient sterility is not ensured</td>
<td>3</td>
</tr>
<tr>
<td>Potential for any impurities carried over from other processes, in absence of dedicated equipment and/or facilities:</td>
<td>$S_7$</td>
</tr>
<tr>
<td>Low potential for such impurities</td>
<td>1</td>
</tr>
<tr>
<td>High potential for such impurities</td>
<td>3</td>
</tr>
</tbody>
</table>
High risk: $12 \leq \text{TRI} \leq 27$  

[Eq. 4].

Additional requirements may be used when assigning a category. For example, if the value of at least one of the components ($S$, $Q$, or $F$) is three, then the overall risk in any case cannot be attributed to a low risk area, but should be attributed to the medium or high risk. It should also be understood that although Figure 1 gives an idea of the risk areas in the chosen three-dimensional space, it is rather simplistic, because in practice, calculated values of risk components will not be round numbers, but non-integral values, as described previously.

**Defining component parameters.** An important aspect of risk assessment within the framework of this algorithm is identifying the parameters that are included in each of the risk components. Certainly, the choice of the main parameters should be guided by the normative document (3), but it insufficiently defines which parameters are included in each of the components. In addition, the normative document does not contain a clear separation of the parameters included in the individual components of excipient risk. In the authors’ opinion, for some components, the listed parameters should relate to another risk component. For example, the following parameters are assigned to the functional characteristic of excipients in the finished medicine (3):

- The pharmaceutical form and use of the finished medicine containing the excipient
- The excipient function in the finished medicine (examples are given)
- The proportion of the excipient in the finished medicine composition
- Daily patient intake of the excipient
- Any known excipient quality defects/adulterations, both globally and at local company level
- Whether the excipient is a mixture
- Known or potential impact on the critical quality attributes of the finished medicine
- Other factors affecting patient safety.

In the authors’ opinion, a parameter associated with defects of excipient quality or adulterations refers not to a functional characteristic, but to the quality risk component ($Q$). Moreover, the parameters referred to the safety and quality risk components in the guidelines (3) are not separated and are given in one list. Understanding how these parameters relate to precisely those risk components is unclear, and additional information is needed. To better define the $F$ component, the authors used the approach of the European Pharmacopoeia (Ph.Eur.) Chapter 5.15 “Functionality-related characteristics of excipients” (11). Although this chapter is not mandatory, it is useful in the authors’ excipient risk assessment method. The authors also added several parameters to the $Q$ component.

### Table II: Instructions for assigning parameters and score points to the Quality ($Q$) excipient risk component. Parameters not included in guidelines (3) are in italics.

<table>
<thead>
<tr>
<th>Quality ($Q$)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control of transportation and storage conditions, including cold chain management:</td>
<td></td>
</tr>
<tr>
<td>No cases of non-observance of established conditions for transportation and storage upon delivery</td>
<td>1</td>
</tr>
<tr>
<td>Only one case of non-observance of the conditions for transportation and storage as delivered</td>
<td>2</td>
</tr>
<tr>
<td>More than one case of non-observance of conditions for transportation and storage upon delivery</td>
<td>3</td>
</tr>
<tr>
<td>Supply chain complexity:</td>
<td></td>
</tr>
<tr>
<td>Direct supply chain from excipient manufacturer</td>
<td>1</td>
</tr>
<tr>
<td>Supply through one distributor</td>
<td>2</td>
</tr>
<tr>
<td>Supply through two or more intermediaries</td>
<td>3</td>
</tr>
<tr>
<td>Stability of the excipient:</td>
<td></td>
</tr>
<tr>
<td>No problems with stability of the excipient</td>
<td>1</td>
</tr>
<tr>
<td>Problems with stability of the excipient</td>
<td>3</td>
</tr>
<tr>
<td>Assurance of package integrity:</td>
<td></td>
</tr>
<tr>
<td>No package defects or integrity failure have been identified</td>
<td>1</td>
</tr>
<tr>
<td>A few single cases of package defects have been identified</td>
<td>2</td>
</tr>
<tr>
<td>Multiple cases of significant package defects have been identified</td>
<td>3</td>
</tr>
<tr>
<td>Related to the excipient quality defects or adulterations, identified both globally and at a local company level:*</td>
<td></td>
</tr>
<tr>
<td>No defects and adulterations have been identified</td>
<td>1</td>
</tr>
<tr>
<td>Single defects have been identified</td>
<td>2</td>
</tr>
<tr>
<td>Adulterations have been identified</td>
<td>3</td>
</tr>
<tr>
<td>Results of sterility input control for the excipient claimed to be sterile:</td>
<td></td>
</tr>
<tr>
<td>At least one recorded case of a nonconformance of the excipient in this parameter</td>
<td>3</td>
</tr>
<tr>
<td>Any excipient defects recorded during reported period, which were identified in the input control:</td>
<td></td>
</tr>
<tr>
<td>A proportion of identified defects less than 1%</td>
<td>1</td>
</tr>
<tr>
<td>A proportion of identified defects from 1% to 10%</td>
<td>2</td>
</tr>
<tr>
<td>A proportion of identified defects more than 10%</td>
<td>3</td>
</tr>
<tr>
<td>Results of input control for the critical quality attributes of the excipient (e.g., identification, pyrogenicity, toxicity):</td>
<td></td>
</tr>
<tr>
<td>At least one recorded case of a nonconformance of the excipient</td>
<td>3</td>
</tr>
<tr>
<td>Results of input control for significant quality attributes of the excipient (e.g., assay content, impurity content, microbiological purity):</td>
<td></td>
</tr>
<tr>
<td>At least one recorded case of a nonconformance of the excipient in this parameter</td>
<td>3</td>
</tr>
</tbody>
</table>

*This parameter was included in $F$ in the guidelines, but here is included in $Q$. 

**DEFINITION OF $Q$ COMPONENT**

A parameter associated with defects of excipient quality or adulterations refers not to a functional characteristic, but to the quality risk component ($Q$). Moreover, the parameters referred to the safety and quality risk components in the guidelines (3) are not separated and are given in one list. Understanding how these parameters relate to precisely those risk components is unclear, and additional information is needed. To better define the $F$ component, the authors used the approach of the European Pharmacopoeia (Ph.Eur.) Chapter 5.15 “Functionality-related characteristics of excipients” (11). Although this chapter is not mandatory, it is useful in the authors’ excipient risk assessment method. The authors also added several parameters to the $Q$ component.
The final step in developing risk assessment algorithm was to determine what points (and in what cases) should be assigned to each of the parameters included in each risk component. **Tables I–III** list the instructions and the point values developed by the authors.

**Method validation**

Assessment of the authors’ method for the risk assessment of excipients in finished medicines was carried out by four Ukrainian manufacturers of finished medicines. At least five specialists at each company participated.

The risk assessment for excipients in a medicinal product (Insular Stabil) produced by one of these companies (Arterium) is presented in **Table IV** as an example. This medicinal product is produced in the form of a suspension for injection, in which 1 mL contains 100 IU of human recombinant insulin. The authors’ method was used to obtain values of the S, Q, and F risk components for each excipient (see **Table IV**). The TRI value of each excipient, listed in **Table IV**, was calculated according to **Equation 1** using the values of the parameters from **Tables I–III**. The arithmetic mean was calculated and rounded to two significant digits. The TRI value for each excipient was rounded at the end of the calculation.

To transition from a quantitative assessment to a qualitative rank, the authors used the inequalities in **Equations 2–4**. As shown in **Table IV**, only protamine sulphate is characterized in expert assessments by an average risk level (i.e., the value is in the range of $6 < \text{TRI} < 12$); other excipients have a low risk level (i.e., TRI value < 6).

From this and similar assessments carried out at the other companies, the

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**Table III: Instructions for assigning parameters and score points to the excipient function (F) risk component. Parameters not included in guidelines (3) are in italics.**

<table>
<thead>
<tr>
<th>Excipient function (F)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmaceutical form and use of the finished medicine containing the excipient:</strong></td>
<td>$F_1$</td>
</tr>
<tr>
<td>External (topical) administration</td>
<td>1</td>
</tr>
<tr>
<td>Oral administration</td>
<td>2</td>
</tr>
<tr>
<td>Sterile pharmaceutical product</td>
<td>3</td>
</tr>
<tr>
<td><strong>Technological function of the excipient in the finished medicine composition</strong></td>
<td>$F_2$</td>
</tr>
<tr>
<td>Functionality-related characteristics are absent in the European Pharmacopoeia (Ph. Eur.) monograph or are not significant</td>
<td>1</td>
</tr>
<tr>
<td>For this particular excipient function in the pharmaceutical form</td>
<td>2</td>
</tr>
<tr>
<td>Not more than 2 functionality-related characteristics, described in the Ph. Eur. monograph, are related to this particular excipient function</td>
<td>3</td>
</tr>
<tr>
<td>Three or more functionality-related characteristics described in the Ph. Eur. monograph are related to this particular excipient function</td>
<td>4</td>
</tr>
<tr>
<td><strong>The proportion of the excipient in the finished medicine composition:</strong></td>
<td>$F_3$</td>
</tr>
<tr>
<td>Proportion of the excipient does not exceed 10%</td>
<td>1</td>
</tr>
<tr>
<td>Proportion of the excipient is between 10% and 40%</td>
<td>2</td>
</tr>
<tr>
<td>Proportion of the excipient exceeds 40%</td>
<td>3</td>
</tr>
<tr>
<td><strong>Daily intake of the excipient administered with the finished medicine to a patient</strong></td>
<td>$F_4$</td>
</tr>
<tr>
<td>Up to 100 mg</td>
<td>1</td>
</tr>
<tr>
<td>From 100 mg to 500 mg</td>
<td>2</td>
</tr>
<tr>
<td>More than 500 mg</td>
<td>3</td>
</tr>
<tr>
<td><strong>Whether the excipient is a mixture:</strong></td>
<td>$F_5$</td>
</tr>
<tr>
<td>The excipient is not a mixture, but an individual substance</td>
<td>1</td>
</tr>
<tr>
<td>The excipient is a premixed blend of two individual substances</td>
<td>2</td>
</tr>
<tr>
<td>The excipient is a premixed blend of more than two substances</td>
<td>3</td>
</tr>
<tr>
<td><strong>The impact of the excipient (its function) on providing established biomedical requirements to the finished medicine:</strong></td>
<td>$F_6$</td>
</tr>
<tr>
<td>The excipient does not affect biomedical requirements</td>
<td>1</td>
</tr>
<tr>
<td>The excipient function is directly linked to providing biomedical requirements to the finished medicine</td>
<td>2</td>
</tr>
<tr>
<td><strong>Known or potential impact of the excipient on the critical quality attributes of the finished medicine:</strong></td>
<td>$F_7$</td>
</tr>
<tr>
<td>The finished medicine meets specification criteria even when a proportion of the excipient is changed by $\pm 50%$ of the nominal</td>
<td>1</td>
</tr>
<tr>
<td>The finished medicine meets specification criteria when a proportion of the excipient is changed by not more than $\pm 25%$ of the nominal</td>
<td>2</td>
</tr>
<tr>
<td>The finished medicine meets specification criteria when a proportion of the excipient is changed by not more than $\pm 10%$ of the nominal</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table IV: The results of the risk assessment for the excipients included in the medicinal product “Insular Stabil”.**

<table>
<thead>
<tr>
<th>No</th>
<th>Excipients, included in the medicinal product composition</th>
<th>Risk components</th>
<th>Total risk index (TRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$S$</td>
<td>$Q$</td>
</tr>
<tr>
<td>1</td>
<td>Protamine sulfate</td>
<td>1.7</td>
<td>1.9</td>
</tr>
<tr>
<td>2</td>
<td>Di-Sodium hydrogen phosphate dehydrate</td>
<td>1.4</td>
<td>1.6</td>
</tr>
<tr>
<td>3</td>
<td>Glycerol</td>
<td>1.6</td>
<td>1.7</td>
</tr>
<tr>
<td>4</td>
<td>Meta-cresol</td>
<td>1.3</td>
<td>2.0</td>
</tr>
<tr>
<td>5</td>
<td>Phenol</td>
<td>1.3</td>
<td>1.6</td>
</tr>
<tr>
<td>6</td>
<td>Water for injections</td>
<td>1.4</td>
<td>1.3</td>
</tr>
</tbody>
</table>
authors found that only some of the excipients included in the corresponding finished medicines have an average (medium) risk level. The overwhelming majority of the examined excipients were of low risk, and none of them were of high risk.

Conclusion
A new method for assessing the risks of excipients in the finished medicine composition has been developed and can be used as one of the possible methods for excipient risk evaluation. This method represents a quantitative assessment of risks using the scoring system within the risk indexes with subsequent ranking and transition to the final qualitative assessment of the excipient risk level. The advantage of the method is more objective quantitative evaluation that uses a comprehensive list of parameters. The authors’ method has been introduced at one of the Ukrainian enterprises as a component of the standard operating procedure for assessing the risks of excipients that are part of the finished medicines produced by this enterprise.

This work is the first stage in solving a more general task of establishing an appropriate set of good manufacturing practices requirements for excipients used in the manufacture of finished medicines. The authors plan to publish further approaches to solving this broader problem.

References

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*To whom all correspondence should be addressed.
Stability testing is essential for maintaining the integrity and quality of biopharmaceuticals and for assessing an accurate shelf-life. It is an important aspect of quality control and an important step in evaluating product safety and efficacy. It is also important for examining how critical quality attributes (CQAs) of a drug substance vary with time under different environmental factors.

Drug packaging to ensure shelf-life

Through stability testing, pharmaceutical companies can ensure the most suitable packaging and/or container closure for the storage and distribution of biopharmaceutical products, according to Russell Crothers, supervisor, Sample Control Unit, Alcami.

“With the right storage, appropriate shelf life determined, and distribution methods in place, the quality of active pharmaceutical ingredient (API) and drug products is safeguarded,” Crothers says.

In addition, understanding potential degradation routes in relation to storage environment is an important factor in establishing the CQAs of a pharmaceutical or biopharmaceutical, according to Ashleigh Wake, director, Biological Services, Intertek Pharmaceutical Services.

“Ultimately, this understanding ensures that the optimal quality control strategy is in place to monitor the continued efficacy and safety of any therapeutic,” Wake says.

“Imagine the situation where, in the first instance, the degradation route of a molecule had not been assessed through forced or ‘stressed’ studies. Not understanding this pathway could lead to failure in identifying pertinent degradation products [that] impact the safety and/or efficacy of the product and thus need to be controlled during product release,” says Wake.

Wake goes on to note that if the potential formation of impurities is not evaluated prior to the release of the product, then methods will not be in place to monitor levels. This could lead to a rise or change in profile, which might not be detected until an “effect” in patient population is observed.

More so, without understanding the stability both of drug substance and drug product, the shelf life cannot be effectively established. This may not only risk the safety and efficacy of a product supplied to patients but can lead to unrealistic or even untenable pricing, especially for biologic molecules, which are expensive to produce, thus impeding their availability,” she adds.

Stability test design

There are several important factors to consider when designing and conducting stability studies. “Safety, quality, and product efficacy work together in stability studies of APIs and finished drug products. Through stability testing, pharmaceutical companies have the ability to identify and trend shelf life and their effects on efficacy as samples are exposed to time, light, and temperature,” Adam Keisker, supervisor, Laboratory Support Services, Alcami, states.

From a chemical perspective, scientists look for separation of the chemical compound into elements or simpler compounds.

Degradation factors that are fundamental to consider for the efficacy and shelf life of APIs/finished drug products include physical, chemical, and microbiological factors. Physical factors encompass changes to the physical nature of the drug, such as appearance, properties, hardness, brittleness, and particle size, that occur in tablets, capsules, and semisolids.

From a chemical perspective, scientists look for separation of the chemical compound into elements or simpler compounds or a change in the drug’s chemical nature via hydrolysis, oxidation, isomerization, polymerization, or photodegradation, according to Keisker.

Finally, microbiological contamination of a product,
depending on the type of microbe and its level of toxicity, can also play a role in the design and functions of the studies, he adds.

The strategy used for testing product stability is the most important consideration in the design of a pertinent study, according to Wake.

“If, prior to a formal stability evaluation, work is not performed to understand all potential degradation routes of the molecule through stressed studies, methodologies cannot be effectively chosen for inclusion in the formal study to encompass assessment of degradation product formation and thus all such species monitored,” says Wake.

“For any drug substance or product, an effective stability study cannot be designed on a ‘tick box’ approach for analytical assessments to be included for testing at timepoints,” she adds.

Wake adds that all stability programmes should include methods to confirm identity, assay, purity, and impurities. “However, the choice of the actual analysis and number/mode of methods utilized cannot be a ‘standard set’, but should be designed on a bespoke basis.”

**Degradation factors that are fundamental to consider for the efficacy and shelf life of drugs include physical, chemical, and microbiological factors.**

“Choice of storage condition or conditions should also be carefully determined prior to initiation. [International Council for Harmonization (ICH)] Q1 and Q5C (1,2) provide guidance on study design for pharmaceutical and biopharmaceutical products and should be the basis for all design; however, the eventual programme requires considered input,” explains Wake.

As an example, Wake points out that, if the intended storage condition is refrigerated, this condition should be considered as the long-term storage condition to be evaluated for a minimum of 12 months, typically longer. An accelerated condition would then, in most instances, relate to storage at 25 °C/60% relative humidity (RH) for six months and, importantly, the need for assessment at 40 °C/75% RH, would not typically be required.

“Logistically, the amount of material, drug substance, and/or drug product required to support what can be as long as a five-year programme with multiple time points needs to be considered at onset. Not only should this include a realistic amount for the defined programme, but should incorporate a minimum of an additional 25% to act as back-up material in case of re-test,” Wake says.

“In addition, ICH guidance requires that a minimum of three batches of material be included in formal stability studies, again this can put pressure on sample requirement and timely availability,” she adds.

**Strategic stability testing**

Having a strategic approach and considering a plan for a “worse-case” scenario is important to addressing the challenges of stability testing and to conducting a successful testing programme. It is also important to approach each study with a bespoke, considered design for storage and testing, rather than a “tick box” approach, Wake says.
Perhaps the biggest challenge is to ensure that the testing programme incorporates sufficient analytics to ensure all potential and known degradants are continually monitored. When considering complex molecules, such as biologics, the complexity of degradation and the number of potential routes makes this assignment extremely difficult,” Wake explains.

If a potential impurity is missed and later seen to appear, this may detrimentally affect the integrity of the stability study. In a worst-case scenario, the missed impurity may require re-testing, which would introduce significant delay to product registration, Wake notes.

“Knowing all the ways a finished product or API could be affected by degradation is crucial in performing successful stability tests,” according to Keisker.

“For instance, stability studies are executed to simulate climatic effects. The studies are based on where the products are going to be sold. From those studies, scientists are able to better establish a shelf life of the medicine, determine the best way to store the medicine, and ultimately help ensure the safety of the consumer,” Keisker explains.

Analytical methods for effective stability testing vary from drug product to drug product. The design of stability studies must take into account the product form, container type, and packaging, Keisker notes.

“For example, commercial drug product testing would include studying the degradation effects from the conditions on both the drug product and the container it is sold in,” he says.

“There are many variables but it ultimately depends on the client and their interests as well as requirements for the climate zone they intend to sell their product,” Keisker adds.

In terms of methodology, most small-molecule pharmaceutical stability study programmes are typically based around the need for some analysis that is dependent on the presentation of the substance or product, such as, for example, water content only being necessary on lyophilized or solid material, Wake says.

For biologics, the nature of the stability testing to be included in any programme differs and is driven by the complexity of biologic molecule structure.

Not all analytics will be required at each timepoint, their inclusion would be driven by the likelihood of change, for example, sterility is typically assessed at six-month intervals, unless a specific indication warrants more frequent analysis. Typical methodologies for certain quality attributes are illustrated in Table I.

In comparison, for biologics, the nature of the stability testing to be included in any programme differs, driven by the complexity of biologic molecule structure. In many ways, biologics require a more diverse analytical capability, according to Wake. Defining a typical stability testing protocol is consequently more difficult, but as a minimum would include assessment of the quality attributes shown in Table II.

“Other criteria such as process related impurities, solvents, metals, etc. are typically not included in a stability programme but determined on product release. Again there can be exceptions where there is a potential for the amount of such species to increase on storage,” says Wake.

In-use stability testing

In the case of multi-dose product types, in-use stability testing can be used. The intent of an in-use stability study is to simulate the use of the product in practice, taking into consideration the filling volume of the container, any dilution/reconstitution before use, the hold-time before use, and various diluents that could be used for administration, Crothers says.

<table>
<thead>
<tr>
<th>Quality attribute</th>
<th>Typical methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Visual, pharmacopoeia method</td>
</tr>
<tr>
<td>Sub-visible particles</td>
<td>As advised in ICH Q4B Annex 3 (R1)</td>
</tr>
<tr>
<td>pH</td>
<td>Potentiometry, pharmacopoeia method</td>
</tr>
<tr>
<td>Identity</td>
<td>Mass spectrometry, spectroscopy (NMR/FTIR) or chromatographic retention time.</td>
</tr>
<tr>
<td>Assay</td>
<td>HPLC or GC with suitable detection</td>
</tr>
<tr>
<td>Purity</td>
<td>HPLC or GC with suitable detection</td>
</tr>
<tr>
<td>Impurities</td>
<td>HPLC/GC/IC/ICP—impurity dependent</td>
</tr>
<tr>
<td>Sterility</td>
<td>Microbiology or container closure integrity. Pharmacopoeia method.</td>
</tr>
<tr>
<td>Endotoxin and total viable count</td>
<td>Microbiology—Pharmacopoeia method</td>
</tr>
</tbody>
</table>

ICH is International Council for Harmonization. NMR/FTIR is nuclear magnetic resonance/Fourier-transform infrared spectroscopy. HPLC is high-performance liquid chromatography. GC is gas chromatography. IC is ion chromatography. ICP is inductively coupled plasma. Source: Intertek
The purpose of conducting in-use stability testing is to establish a period of time during which a multi-dose product may be used while retaining quality within an acceptable specification, once the packaging is open or broached, Wake says, citing the European Medicines Agency’s definition of the term (3).

“In-use stability testing can therefore be considered for multi-dose product types, as assessment of the continued efficacy and safety (as defined through CQA testing) of a pharmaceutical (or biopharmaceutical) drug product once in its final administration form,” Wake says.

Typically, an in-use assessment is performed on a minimum of two batches of material, with, ideally, one batch taken from a near end-of-shelf-life product. The protocol involves reconstituting the drug product to its administrative form and testing over a pre-defined storage period at the condition recommended.

“The analytics performed will be in line with those identified for long-term and accelerated storage studies with perhaps a greater influence on microbial criteria and potential impurities derived from pertinent environmental factors, for example, impurities formed through oxygen exposure which is unavoidable in a multi-dose format,” according to Wake.

Establishing an effective in-use shelf-life is of significant benefit. Without it, a multi-dose product design becomes significantly less practical in terms of ensuring patient safety and product efficacy in this format,” Wake explains.

Table II: Quality attributes and typical methodologies for biologics.

<table>
<thead>
<tr>
<th>Quality attribute</th>
<th>Typical methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Visual, pharmacopoeia method</td>
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<td>Sub-visible particles</td>
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</tr>
<tr>
<td>pH</td>
<td>Potiometry</td>
</tr>
<tr>
<td>Identity</td>
<td>Mass spectrometry, immunochemical approach or chromatographic/electrophoretic retention/migration time.</td>
</tr>
<tr>
<td>Assay</td>
<td>HPLC or GC with suitable detection or immunochemical approach</td>
</tr>
<tr>
<td>General impurities</td>
<td>Reverse Phase HPLC SDSPAGE</td>
</tr>
<tr>
<td>Impurities (Aggregates)</td>
<td>Size exclusion chromatography (SEC), Analytical ultracentrifugation (AUC), Electrophoresis and/or dynamic light scattering (DLS)</td>
</tr>
<tr>
<td>Impurities (Charge variants)</td>
<td>Electrophoresis and/or ion exchange chromatography</td>
</tr>
<tr>
<td>Receptor binding</td>
<td>Surface plasmon resonance (SPR)</td>
</tr>
<tr>
<td>Higher order structure</td>
<td>Circular dichroism (CD) and/or spectroscopy (NMR or FTIR).</td>
</tr>
<tr>
<td>Potency</td>
<td>Cell based assay, based on mode of action.</td>
</tr>
<tr>
<td>Sterility</td>
<td>Microbiology or container closure integrity. Compendial approach.</td>
</tr>
<tr>
<td>Endotoxin and total viable count</td>
<td>Microbiology. Compendial approach.</td>
</tr>
</tbody>
</table>

ICH is International Council for Harmonization.
HPLC is high-performance liquid chromatography.
GC is gas chromatography.
SDS-PAGE is sodium dodecyl sulfate polyacrylamide gel electrophoresis.
NMR/FTIR is nuclear magnetic resonance/Fourier-transform infrared spectroscopy.
Source: Intertek

Supply, which can lead to the product being non-viable in terms of patient access,” Wake explains.

References
Robert Iser, vice-president of PAREXEL Consulting, spoke with *Pharmaceutical Technology Europe* about the role quality agreements play in outsourcing.

**Roles and responsibilities**

**PTE:** What is a drug company’s responsibility when it comes to ensuring the quality and safety of products or ingredients manufactured at a contract facility?

**Iser:** Although a drug company (or an application sponsor or marketing authorization holder) is ultimately responsible for ensuring that products available for patients and caregivers meet quality and safety expectations, the assurance of quality and safety of products and ingredients manufactured at a contract facility is a shared responsibility between the drug company and any contracted facility. Both parties must adhere to the expectations set out by the appropriate regulations and guidance to ensure that the products are manufactured in accordance with current good manufacturing practices (CGMPs), meet the necessary quality standards, and are safe and effective throughout a product’s lifecycle.

As noted in the current FDA [US Food and Drug Administration] guidance on quality agreements (1), ‘when all parties clearly understand their CGMP-related roles and manufacturing responsibilities, the owners who use contract facilities, contract facilities that provide services to owners, and, ultimately, patients who take the drugs manufactured under these arrangements may benefit in many ways … each party engaged in the manufacture of a drug is responsible for ensuring compliance with CGMP for the manufacturing activities it performs.’ This demonstrates the importance of putting together a sound quality agreement and clearly defining roles and responsibilities of the company and the contract facility.

**PTE:** What are the most important aspects of a quality agreement?

**Iser:** There are a number of important aspects for quality agreements between a drug company and a contract manufacturer. It is vital that the following aspects are clearly stated and agreed upon:

- The CGMP-related roles and responsibilities of the company and the contract manufacturer, including final approval for manufacturing activities
- How deviations and out-of-specification results will be investigated, communicated, and resolved
- How changes that may need to be made to the manufacturing process, equipment, analytical methods, specifications, etc., are managed.

It is important to consider these aspects, along with other recommendations found in current guidance, when developing and implementing agreements with contract facilities.

**Regulatory expectations**

**PTE:** What are the European expectations regarding quality agreements?

**Iser:** The European Commission published a revision to the European Union Good Manufacturing Practices (GMPs) (Chapter 7) (2), effective in 2013, to provide expectations for outsourced GMP-regulated activities. The revised GMP guide includes many of the same topics as found in the current FDA guidance for industry including roles and responsibilities of the contract giver (the drug company) and the contract acceptor (the contract facility), assessment of a facility to carry out outsourced activities, communication of information that is necessary to carry out the outsourced activities, change control expectations, etc. A company looking to enter into a quality agreement should utilize this guide.

**PTE:** What are FDA’s expectations regarding quality agreements?

**Iser:** FDA published a final guidance for industry in November 2016 on quality agreements with contract manufacturers (1). The guidance was developed as a collaborative effort with the Centre for Drug Evaluation and Research (CDER), the Centre for Biologics Evaluation and Research (CBER), the Centre for Veterinary Medicine (CVM), and Office of Regulatory Affairs (ORA) and lays out the current thoughts and expectations that FDA has for quality agreements.

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**Susan Haigney**
agreements. It is strongly recommended that companies refer to this guidance when initiating a new quality agreement or if they are reviewing an existing quality agreement with a contract facility.

It should also be noted that ICH (International Council for Harmonization) Q7 (3) includes helpful information regarding quality agreements with API manufacturing sites, which is augmented by FDA’s quality agreement guidance. Companies developing combination products should review the expectations found in the guidance on Current Good Manufacturing Practice Requirements for Combination Products, as it relates to contract facilities and quality agreements (4).

Companies that are being inspected by a regulatory agency should have available any applicable quality agreements so that they may be provided to the investigator/inspector upon request.  
—Robert Iser, PAREXEL Consulting

PTE: Do regulatory agencies want to see copies of quality agreements when performing inspections?

Iser: Per FDA’s current guidance on quality agreements, ‘quality agreements may be reviewed during inspections,’ and current regulations in the United States and Europe, as well as other regions, include expectations for the outsourcing of manufacturing activities. As such, companies that are being inspected by a regulatory agency should have available any applicable quality agreements so that they may be provided to the investigator/inspector upon request.

Creating quality agreements

PTE: What mistakes are companies making when drafting quality agreements?

Iser: There are some common mistakes that occur when companies are drafting quality agreements. First, roles and responsibilities of the drug company and the contract manufacturer are not always clear, especially when it comes to stating and agreeing on the quality unit’s responsibilities. Second, some agreements are interpreted in a manner that deviates from CGMP expectations (e.g., a contract manufacturer interprets that they do not need to perform an investigation of an out-of-specification result that they generate since the drug company is responsible for release of commercial batches), which may lead to observations being cited during an inspection. Third, a mechanism to periodically assess and revise—if necessary—the agreement is not always included in agreements. Lastly, some quality agreements include commercial contract or business aspects and should only focus on quality management aspects as laid out in current regulations, such as US 21 Code of Federal Regulations (CFR) 211 (5) or guidance documents such as ICH Q7 (3) or Q10 (6). Additional helpful information on avoiding these mistakes can be found in FDA’s current guidance for industry (1).

PTE: How can drug companies and contract manufacturers create quality agreements that clearly outline each company’s responsibilities?

Iser: The best way for drug companies and contract manufacturers to create quality agreements that clearly outline each company’s responsibilities is to follow the recommendations for roles and responsibilities that are found in current guidance documents. Current agency documents clearly lay out expectations for documenting roles and responsibilities that are directly linked to the quality unit responsibilities included in CGMPs, and pharmaceutical quality system aspects found in health authority guidance and ICH guidelines.

PTE: Can you give a real-world example of when a lack of a quality agreement or a poorly-written quality agreement led to a FDA 483 and/or warning letter?

Iser: It is important that a quality agreement between a drug company and a contract facility clearly defines roles and responsibilities related to CGMP activities. It is equally important, as stated in the FDA guidance, ‘that quality agreements cannot be used to delegate statutory or regulatory responsibilities to comply with CGMP.’ It is likely that FDA would cite a company for deviating from CGMP expectations due to adherence to an inadequate quality agreement that violate the tenets of the GMPs.

A real-world example of a FDA 483 observation related to quality agreements is a contract testing facility being cited for not following a quality agreement regarding the destruction of remaining samples with
the authorization of the contracting company. This ties back to the importance of establishing clearly defined roles, adhering to the roles under an agreement, and how it fits with the CGMP expectations.

It is important that a quality agreement between a drug company and a contract facility clearly defines roles and responsibilities related to CGMP activities.

—Robert Iser, PAREXEL Consulting

FDA guidance further states (as part of case examples), ‘no matter whom tests the products, the owners’ quality units are ultimately responsible for ensuring that the products are manufactured in accordance with CGMP. A quality agreement does not change that. FDA could cite the owners … for failing to evaluate, qualify, audit, and monitor their contract facilities.’

A recent example of a quality agreement citation in a warning letter (7) was related to a quality agreement with the firm’s contract manufacturer that didn’t include provisions for sterilization processing along with other quality agreement provisions that were not being routinely followed. Although this warning letter was related to a device and should follow the purchasing controls expectations found in 21 CFR 820.50 (8), it also shows that clarity around roles and responsibilities and adherence to an approved quality agreements are important aspects that need to be considered when a company develops and implements a quality agreement with a contract facility, and may be assessed while an FDA investigator is on site.

Companies that are looking to develop combination products should consider how the current 21 CFR Part 4 regulations (9) impact their quality system and operations and are encouraged to read the current FDA guidance on GMPs requirements for combination products (4) for further information as the guidance includes language on entering into quality agreements, where ‘quality agreements may, for instance, specify expectations as to which facility will perform what activities and develop and maintain what documentation needed to demonstrate compliance with particular CGMP requirements … for example, an owner may contract for the manufacture of the final combination product with a contract manufacturing facility, and detail in the supplier agreements the CGMP responsibilities and approaches for that facility.’

Overall, the best way to avoid inspectional observations that may lead to a warning letter is to initiate quality agreements that use the recommendations found in current health authority quality agreement or outsourcing guidelines, are reflective of CGMPs, and are part of an effective pharmaceutical quality system.

References
5. 21 CFR 211
6. ICH, Q10 Pharmaceutical Quality System (ICH, April 2009).
8. 21 CFR 820.50
9. 21 CFR Part 4 PTE

MORE ON QUALITY AGREEMENTS

The following articles on quality agreements, including commentary from the US Food and Drug Administration, can be found on PharmTech.com:

• Good Quality Agreements Support Compliance with CGMP
Drug manufacturers can improve use of quality agreements in contract manufacturing.

• Quality Agreements: Managing Global Relationships
A robust quality agreement and good communication scheme can help avoid and alleviate regulatory concerns.

• The Importance of Quality Agreements
Pharmaceutical Technology asked Siegfried Schmitt, principal consultant at PAREXEL, about the importance of quality agreements in the sponsor/contractor relationship.
www.PharmTech.com/importance-quality-agreements

• Quality Metrics and CMO Agreement
FDA’s focus on the quality culture and its request for quality metrics may ensure a successful company-CMO relationship.
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Improving Operations in the Lab

New and emerging products advance bio/pharma laboratory operations.

Amber Lowry

Staying up to date on the most advanced technologies is important for improving operational tasks, especially in the laboratory. The following is a sampling of the latest products available to optimize laboratory operations for biological products.

Automated fraction collector

The NGC Fraction Collector from Bio-Rad Laboratories provides flexibility and collection capacity for analytical or preparative chromatography applications when used with the company’s NGC Chromatography System (1). Features include a benchtop Peltier cooling module for temperature-sensitive biomolecules and an optional enclosure to protect samples from environmental conditions while allowing full access during a run. Because the enclosure is optional, the same fraction collector can also be used for reverse-phase chromatography applications.

The unit, which runs on ChromLab 5.0 Software, allows researchers to choose how to collect and when to access their fractions. The system can be activated to collect based on slope, percent of buffer from pump B, pH, and detector signals. According to the company, front-to-back dispensing provides access to fractions before method completion for improved speed of downstream analysis. Researchers can also choose the type of collection vessel they prefer for each phase in a method, including deep-well plates, tubes, bottles, and carboys (with prep-rack adaptors for large-scale purification). Adding two new fraction collectors to each NGC System can further expand capacity, according to a company press release.

Bioreactor control system

Automated Control Concepts’ (ACC) Lab Owl is a bioreactor control and information system that integrates laboratory instrumentation for data collection and analysis for labs using cell culture and fermentation applications (2). Its user-friendly interface can be used with bench-top bioreactors in development labs, in pilot plants, and in manufacturing, according to company. The system is available in flexible and scalable form factors to meet the needs of labs dependent on bioreactors for cell culture and fermentation experiments.

Cell counting device

Corning and CytoSMART Technologies, a company spin-off from The Netherlands’ Eindhoven University of Technology that manufacturers ultra-compact, live-imaging systems and cell counters for biological laboratories, have partnered to simplify mammalian cell counting in laboratories (3). The new Corning Cell Counter uses technology developed by CytoSMART and offers enhanced speed for automated cell counting. The device, which is exclusively supplied by Corning, will be available through Corning’s global sales team and worldwide distribution network.

Cell counting is a crucial subcultivation step in the cell-culture workflow, according to the companies. Many laboratories still perform manual cell counting using a haemocytometer or a counting slide viewed under a microscope. In comparison, the Corning Cell Counter returns an accurate and precise digital cell count in a few seconds. The device can accommodate the standard reusable haemocytometer or disposable slides, but microscopic viewing in order to perform the cell count will no longer be needed, as stated by Corning.

Freeze dryer for life science labs

The Freezemobile freeze dryer from SP Scientific is suited for high-quality preparation of peptides, proteins, plant materials, and organic tissue (4). Unlike many traditional freeze dryers that employ coil condensers, these freeze dryers use a smooth-walled condenser that enables fast defrost and removal of ice for faster turn-around time and also alleviates vapour port ice blockages other systems are prone to, according to the company.

The freeze dryer is offered in 25- and 35-liter condenser sizes and is suitable for labs with multiple users, as well as labs with high quantity of product through-put. The device has a -85 °C condenser to enable the removal of a variety of solvents and can be configured for exact user processing requirements.
Individual samples can be added or removed without interrupting the instrument, thereby enabling users to continue their experimental process without having to wait for another freeze dryer to become available. The freeze dryer also includes a range of single- and multi-tiered horizontal "T" type manifolds, which can be used to dry multiple flasks simultaneously, and provides an optimized platform for drying large quantities of samples in bulk flask format. To improve the laboratory operating environment, the freeze dryer can also be supplied with a low noise, oil-free vacuum pump, as stated by SP Scientific.

Additionally, the company offers a control system that offers a range of control features to meet the demands of various applications. Vacuum levels, condenser temperature, ambient room temperature, and component status are all displayed on a clear LCD display, while alarms warn of any unwanted process deviations.

The company’s Freezemobile Shell Bath helps to decrease manifold freeze-drying time. The tool rotates sample flask on its axis, thereby coating the interior surface of the flask with frozen product. According to the company, this increases the surface area of the product-to-energy input, as well as vapour removal helping to reduce the freeze-drying process to the shortest time possible when utilizing flasks and a manifold system.

**Quaternary LC System**

The Acquity Arc Bio System by Waters, a specialty measurement company, is engineered to enable transfer and improvement of bioseparation analytical methods regardless of the liquid chromatography (LC) platform on which the original method was developed, according to the company (5). The system’s platform allows biopharmaceutical laboratories to transfer methods between labs as well as from one LC instrument platform to another while maintaining method integrity.

The system can run reversed-phase, ion exchange, size exclusion, and hydrophobic interaction LC methods with minimal carryover and maximum recovery of biomolecules, as stated by the company. Flow paths are made of non-stainless-steel and iron-free, bio-inert materials that can minimize undesirable protein interactions and maximize system robustness under salt and pH extremes. Multi-flow path technology delivers plug-and-play compatibility with high-performance liquid chromatography (HPLC) or ultra-high-performance liquid chromatography (UHPLC) methods through a selectable dwell volume that matches the dwell volume of the original instrument. The company states that this minimizes the time needed for laboratories to redevelop methods from internal and external partners.

Waters reports that in addition to replicating established HPLC assays, the system can improve the sensitivity, resolution, and speed of chromatography methods by leveraging recent 2.5–2.7-micron particle column technologies. These include the company’s BioResolve RP monoclonal antibody (mAb) Polyphenyl solid core columns for the reproducible analysis of intact or sub units of mAbs and antibody-drug conjugates. The system also supports previously developed “legacy” methods on traditional 3–5-micron HPLC columns, as stated by the company.

The system is controlled through Waters Empower 3 and MassLynx software and also features Auto Blend Plus technology that automatically blends up to four solvents in any combination or proportion. The auto blend technology also allows the operator to programme in pH and ionic strength for ion-exchange or size exclusion-based methods, or programme in the organic solvent concentration and pH for reversed-phase gradient separations. This significantly reduces human error and the task of preparing buffered mobile phases manually, according to the company.

**References**

Transporting sensitive pharmaceuticals is a risky and complex business. “The lower deck conditions of a Boeing plane or the inside of a typical intermodal freight container are a long way from the GMP-validated cleanrooms and controlled laminar-flow environments of the pharma production environment,” says Alan Kennedy, founder and executive director of TEAM UP, an organization that focuses on pharma supply chain issues.

According to the International Air Transport Association (IATA), the global pharmaceuticals logistics market is valued at €52.3 billion ($US 64 billion) and is one of the most regulated, expensive, and fragile cargo markets in the world today (1), says Kennedy.

Pharmaceutical transport typically combines different modes, explains Kennedy. Air transport, prized for its speed and flexibility, is used mainly for long distance, intercontinental distribution of the most valuable therapeutics, he says, while road is the most widespread method and is also used to connect with both air and sea freight. Rail remains an insignificant factor. This may change, however, Kennedy says, as new “silk route” rail connections between Asia and Europe are established (2).

Ocean: Cold Chain’s Cinderella?

Ocean transport may conjure 1940’s images of the days when most people still crossed the ocean by ship. It has historically been the Cinderella of pharma distribution, says Kennedy, but, IATA notes that 3.5 million metric tons of pharmaceuticals are still shipped by sea each year, compared with 0.5 million metric tons by air (3).

Over the past five years, ocean transport has taken on much greater visibility in the pharma industry. Cost competitiveness is one factor driving increased acceptance, he says, since it is up to 80% less expensive than air transport.

In addition, Kennedy notes, although it takes much longer than air travel, ocean transport is often more reliable, because it involves fewer product handoffs. Products remain stored and untouched for longer periods throughout their journey (in air travel, they must be taken off the plane and held in various staging areas, increasing the chance of temperature excursions). According to some studies, air freight accounts for 80% of all reported temperature excursions, compared with 1% for sea journeys (4,5).

In addition, air product makes it impossible to monitor product in real time, because US safety regulations require that data loggers and other transmitting devices be switched off during transport.

Risk reduction

A 2013 report by analysts from The Seabury Group (7) found significant quality-control problems with air freight. As a result, Kennedy says, air cargo carriers began to set higher standards, establishing the IATA Centre of Excellence for Independent Validators (CEIV) Pharma programme to interpret general European Union and other good distribution practice (GDP) rules specifically for air shipment of pharmaceuticals (8).

That same year, the EU extended GDP regulations to cover controlled room temperature (CRT) products, which must nominally be kept from 15–25 °C, which only accelerated a switch from air to ocean transport, Kennedy says.
Alan Kennedy, executive director of TEAM UP, shared perspectives on Poseidon and ocean transport with Pharmaceutical Technology Europe.

PTE: Why was Poseidon established and what do you hope to achieve with the programme?

Kennedy: Like-minded individuals at the 2017 European Temperature Controlled Logistics Conference agreed that, in order for any degree of wholesale, across-the-board improvement in the pharma-cold chain, there would need to be more alignment between supply-chain stakeholders.

Poseidon’s model is built around some of the principles of supply-chain collaboration and integration that are being successfully applied in other industries. Instead of a supply chain, Poseidon is a supply network that involves all of the stakeholders responsible for transporting pharmaceutical products.

Currently, 19 companies are involved in the Poseidon project, including eight pharmaceutical manufacturers. Driven by pharmaceutical companies, the programme is designed so that each pharma firm and its shippers, logistics companies, and suppliers sit around the same table as equal partners. A network partner agreement governs the relationships between all these parties, and they work together as a single team with common goals, rules, risk sharing, and performance incentives.

Poseidon is putting together an end-to-end integrated network for pharma logistics. We hope that the model will serve as a template for pharmaceutical companies in their quest for more efficient, more competitive, and more concerted supply chains that are fit for purpose in today’s rapidly changing and increasingly regulated environment.

Leveraging improved technology

PTE: How are you connecting the many stakeholders who would be involved in ocean transport?

Kennedy: A cloud-based Poseidon Collaboration Hub enables members to communicate in real time or whenever needed. With stakeholders around the world, this arrangement promotes the sharing of information and facilitates multiparty project management, enabling online group meetings and access to documentation, 24/7.

PTE: What types of technology (e.g., temperature and condition monitoring) are being refined for ocean transport, and how would they differ from solutions that were developed for air transport?

Kennedy: The challenges of sea freight broadly mirror those of air, although some of the protection and monitoring equipment had to be adapted to the different time parameters and operating conditions. For example, one of our participants, DowDuPont, is currently exploring new cargo-cover materials for ocean freight use.

Real-time product monitoring at sea

One of the advantages of sea freight is that it offers better shipment visibility so that shippers can monitor the geographical position and physical condition of freight in real-time. At this point, Poseidon is only using Maersk smart reefers and US-built Klinger redundancy reefers.

For air freight, the US Federal Communications Commission requires transmitting devices such as data-loggers to be auto-switched off during flight for safety reasons. Although the loggers continue to capture data during the flight, this information can only be retrieved later. As a result, there is reduced opportunity to receive alerts or to intervene quickly to fix a potential problem, such as an unexpected temperature excursion, that might compromise product quality.

PTE: Are insurance costs more of an issue for sea than air freight?

Kennedy: Ocean transport insurance can sometimes be perceived as a black hole by shippers, who tend to be more comfortable with the comprehensible and comprehensive insurance provisions associated with air freight. Shipping lines, for instance, tend to apply inconsistent liability limits, which, in any case, are invariably much lower than the typical value of a full container consignment of pharma products. It’s a problem that currently bas many otherwise suitable products from being shipped by water. Poseidon is actively addressing this issue and has brought the insurance industry into negotiations from the project’s start. As a result, Poseidon can now offer a wide-ranging insurance framework specially devised to provide adequate indemnity for all pharma shipment values.

PTE: Have there been any regulatory changes regarding ocean shipment or position pronouncements by the World Health Organization (WHO) or other global authorities on ocean transport of pharmaceuticals?

Kennedy: GDP legislation is indiscriminate, non-prescriptive and applies universally to all transport modes. So, the same standards must be met by all (The IATA CEIV programme is simply a translation of these general regulations to make them more air-freight-friendly).

Although a high proportion of vaccines are currently transported by sea, the use of ocean freight has not yet been officially endorsed by WHO due to concerns surrounding the perceived implications of a ‘total’ loss situation (i.e., where a huge volume of urgent vaccines or drugs might be lost in a single event). WHO is expected to review this position, however, in light of Poseidon insurance provisions.

PTE: Have there been any detailed risk benefit analyses of ocean transport performed recently?

Kennedy: Different pharmaceutical companies have launched proprietary pilot studies to ascertain savings and quantify results. However, Poseidon is working with several pharma manufacturers to design and implement the largest ocean freight transport validation exercise to date. This study will involve multi-container intercontinental shipments of different pharmaceutical dosage forms (oral solid dosage forms, vial parenterals, and topical creams), which will be rigorously monitored and documented. This exercise will be completed by June 2018.

PTE: Are there types of pharma companies that tend to rely more on ocean transportation? What interest are you seeing in the industry?

Kennedy: For the first time, the 2017 IQPC Temperature Controlled Logistics conference in London included a Sea Freight Focus Day. This event was sold out, and 70% of attendees worked at pharmaceutical manufacturers, almost all seeking to enter sea freight or to upgrade their sea freight usage.

Most of Big Pharma is already shipping some of its products by sea. However, these companies typically deal in huge volumes that lend themselves well to full container load (FCL) shipments. Small- and mid-sized pharma companies, which contribute half the industry’s total output, do not currently have access to a GDP-compliant less than container load (LCL) service, also known as ‘groupage’ or shared container service. Therefore, many of these smaller companies are forced to ship products by air. We expect this restriction to be lifted once Poseidon introduces its GDP-compliant LCL service later this year.

Poseidon plans to introduce a GDP-compliant LCL service later this year, and we expect this service to fill a huge, currently unmet need in the pharmaceutical logistics market.
“More recently, with economic pressures mounting, big pharma companies have begun to look more closely at transportation. It is emerging as an area where significant savings are possible, which has created an even greater incentive for manufacturers to change modes of transport,” says Kennedy.

Shipping high-end products

So far, most of the growth in pharma’s use of ocean transport has been around relatively low value, high-volume products such as solid-dose tablets, generics, APIs, and excipients. However, advocates see that it also has potential to handle more sensitive large-molecule biologics as well as personalized medicine therapies.

AstraZeneca shipped nearly 70% of its products by sea in 2017. In 2012, it had shipped 5% of its products that way.

Among ocean transport’s strongest pharma advocates is AstraZeneca, which has increased the percentage of products it ships by sea from 5% in 2012 to nearly 70% in 2017 (9). Eli Lilly, which has been conducting studies of ocean transport of biologicals, has found that transporting products by sea saves 80% in costs. Lilly also found that sea transport reduces the carbon footprint, reduces staffing requirements, packing and storage needs, and also reduces the impact of vibration and shock on materials during transport (10).

Partnering with vendors

Lilly has partnered with Modality Solutions for protocols and reports, with Q Products for thermal covers, and with Sensitech, using TempTales, temperature monitors that allow for simultaneous tracking of both temperature and location.

One test involved simulating worst-case scenarios for a 40-foot reefer transporting 18 pallets of placebo, evaluating temperatures ranging from 0–115 °F. The studies used the Locus Traxx GPS and Lansmont’s Saver to monitor any shock and vibration effects on products.

Tests compared results trucking product to Long Beach, CA, a two-to-three-day trip, with shipping product to Australia, a 45-day trip one way. A Bayer study (11), meanwhile, showed ocean transport plus trucking to be an efficient way to transport pharmaceuticals inland in Brazil. Logistics efforts in that country can be challenging because they involve long distances overland, and, in some areas, potential security issues.

In 2016, at the European Temperature Control Logistics Conference, a number of stakeholders in pharma cold-chain shipping, joined forces to form TEAM UP. Their aim was to explore ways to improve the shipping of pharmaceuticals through collaboration and better use of available IT, temperature and condition monitoring, and communications technology.

Poseidon established to improve sea transport

In January 2018, TEAM UP established Poseidon, a network involving the different types of companies involved in the ocean transport of pharmaceuticals (see Sidebar). Its 19 current members include eight pharmaceutical manufacturers as well as shippers, logistics specialists, and technology vendors.

Led by pharmaceutical manufacturers but involving shippers, logistics companies, and suppliers as full partners, the group is focusing on applying best collaborative and integration practices and the latest technology to address any performance gaps that separate ocean from air and other transportation modes.

Technology vendor members currently include Maersk, H. Essers, Marsh, DowDuPont, AmSafe Bridport, Klinge Corp., Pelican Biothermal, Sonoco Thermosafe, Logtag Recorders, and Controlant. Members are working on a number of new projects, including a major validation study that is expected to be completed by June 2018.

In addition, Poseidon is introducing new insurance programmes, designed to make the process of insuring ocean freight simpler and more straightforward. The group will also introduce new container options especially designed for small-to-mid-sized pharmaceutical companies, who are often locked into using air transportation due to limited options.

References

AirBridgeCargo Airlines

AirBridgeCargo is an international cargo carrier with an in-depth knowledge of the healthcare and pharmaceutical industry. We have developed special abcPharma product, providing active and passive solutions for transportation of time-sensitive products and guaranteeing transparency, traceability and compliance with IATA TCR and CEIV certification rules. Exact temperature monitoring from acceptance to delivery with special packaging solutions and thermal blankets for palletized shipments, modern fleet of Boeing 747 freighters with three compartments enabling different temperature settings from 4 °C to 29 °C, and dedicated, skilled staff trained in handling healthcare products—ABC offers value-added services for pharmaceutical products, powered by digital technologies in the interest of its customers. On top of this, ABC introduced 24/7/365 Control Tower (CT) operation to monitor and manage transportation of special cargo consignments, including pharmaceutical products. From vaccines, laboratory equipment, MRI/MRT machines to blood samples, and beyond—we, at ABC, will always find the best logistics solutions to cater your needs and expectations.

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Contec’s Mop Head Saturation System allows mop heads to be presaturated prior to being passed into the controlled environment. This eliminates the need for any water to be passed into the clean-room. Small and compact, the stainless steel cart with twin 8L buckets is ideal for small to medium-sized cleanrooms.

Being lightweight and manoeuvrable, the cart is easy to use. Fitted with autoclavable castors, the whole cart can be autoclaved before use. In order to make the system highly efficient and cost effective, the mop heads used need to be fast-wicking and highly sorbent.

Contec has developed a new flat mop head to be used as part of the system; Contec Quiltex I Polyester Mop Heads. They are manufactured from 100% 2-ply polyester around a rayon core so are ideal for even the highest grade of cleanroom as they generate small numbers of particle and fibres.

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**Midilab RC**

Midilab RC by DIOSNA is a highly flexible laboratory processor that is built in modular design. The device is designed for plug-and-play operation and the modular design offers a rapid change (RC) between the fluid bed module and the tablet coater module. Each module as well as the basic unit are moveable and can be connected without using any tools. For both modules different material bowl sizes are available, whereby the fluid bed module can handle batch sizes from 600 g to 9 kg and the tablet coater module can handle 2 kg to 16 kg batches. For better process monitoring both modules are equipped with inspection glass. Another highlight is the swivelling and tilting operator terminal with stainless steel housing which allows flexible adjustment for the operator. The installation is possible in line, at a corner as well as through the wall.

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**PIM 941–Particle Inspection Machine**

The Rommelag PIM (Particle and Cosmetic Inspection Machine) for full automatic control of Blow-Fill-Seal containers uses a superimposed agitation pattern including vibration for the detection of free moving particles. This method causes a particle in the ampoule to move. The PIM inspects the containers with cameras, comparing three or more pictures before and after the vibration. This shows any particles inside the ampoule that have changed the location. A side effect of this process causes a tremendous reduction of impeding bubbles within the containers. Additionally, the PIM offers a set of extension modules inspecting for cosmetic defects like deformations, discolorations, black and white spots, and other geometrical alterations along with a fill level check. In its maximum configuration the PIM is a fully automatic 360 degree quality inspection tool and defect sorting machine. Even more, the PIM protociling features allowing the creation of an individual customized batch report and comprehensive statistics and trending screens.

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This year celebrating the 50th anniversary of its presence in Europe, Shimadzu emphasizes its Excellence in Science approach through the release of the new i-Series Plus integrated HPLC. The i-Series Plus highlights the company’s position of a world leader in analytical instrumentation. This compact solution covers conventional to ultra-fast LC analysis. Application-specific solutions are available within the product range such as the Cannabis Analyzer for potency testing of primary active components of cannabis for medical use. It offers a simple procedure, complete with a column, methods, batches, and report templates. With the i-Series Plus, pretreatment operations have been automated, such as the processes to dilute samples and add reagents. This results in less mistakes and measurement errors and ensures highly reproducible and reliable data in the analysis of pharmaceuticals and foods.

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In-house experts can help select the right systems and suppliers, making validation and compliance easy, says Siegfried Schmitt, principal consultant at PAREXEL.

Q. We are planning to upgrade several of our automated systems in production and in the laboratories. These upgrades are necessary so that we can implement functionality like audit trails, which are now required to achieve data integrity compliance. We contacted suitable vendors and some have now offered to sell to us fully US 21 Code of Federal Regulations (CFR) Part 11 and data integrity-compliant software packages. Such a package seems like a very good deal, but it is not offered by the majority of suppliers. Can you give some insight on how other companies address this situation?

A. You are in a very typical situation where not all your automated systems are of a technical standard that make compliance with the applicable regulations possible, unless you upgrade or replace certain systems. It is an unfortunate fact that there are still vendors out there who make misleading claims, either out of ignorance, or worse, knowingly. The only party that can legally commission and operate a computerized system in a fully compliant manner is the system owner (i.e., someone within your organization). Only you know how you are going to use the specific system and for what purpose. No vendor can do this for you. Therefore, automated system suppliers can merely offer to sell you systems that are designed and built in a manner that allows you, the customer, to operate them in a compliant manner (e.g., complying with 21 CFR Part 11 or other regulatory requirements).

Let me give you an example to clarify this: You may purchase a system upgrade that provides audit trail functionality. Although the vendor gives you an audit trail as you requested, you may choose not to activate it (perhaps because it slows the system down too much). Now you may be in a non-compliant situation. Or, you decide to activate the audit trail, but upon review you find that it is not in human readable form, or that it only captures a fraction of the transaction, or that the amount of data in the audit trail is so overwhelming that it becomes unmanageable.

Savvy companies have in-house experts with a sound understanding of the regulations covering automated systems, how to perform computerized systems validation, and how to optimally harness the vendors’ expertise. These experts will put together the user requirement specifications (URS) for the various systems. The URS is the document that will steer how the system (or system upgrade) will help you to operate in compliance with the regulations (i.e., what it takes to make sure that data are trustworthy and your system is fully validated). In the URS, companies will specify what they expect from the audit trail (e.g., it must be human readable, sortable, exportable, searchable, etc.).

The URS also forms the basis for the testing requirements, namely the testing by the users. Users may be quality unit personnel who need to verify that on an analytical instrument the series of injections for an analysis tally with the method, or that there were no rogue injections. Only these people will know what they are looking for and how they want to perform their review. Your system vendors are now tasked with providing you with a system that meets your needs, and not just a ‘one-size-fits-all’ solution.

Don’t be lulled into a false sense of security by sales promises; instead, make sure you have experts at hand who can help you select the systems and suppliers who best meet your needs. Once you do this, you will find that validation and compliance even with the most demanding regulations become not only possible, but exciting. PTE
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