OCTOBER 2019 Volume 31 Number 10

Advancing Development & Manufacturing

Pharmaceutical Technology® EUROPE

PharmTech.com

CELEBRATING 30 YEARS ANNIVERSARY

The Demands of the Perfect Dose

API Synthesis
CTM Stability Testing

Formulation
Lipids Enhance Bioavailability

Analytics
Dissolution Testing Basics

Manufacturing
Automating Fill/Finish

Quality/Regulations
The New European Commission

Peer-Review Research
Peginterferon alfa-2b Degradation

SHIMADZU
Excellence in Science

Better Prep!

Keep it simple, stay flexible

The Nexera Prep Series Preparative Purification LC improves productivity tremendously via efficient preparative work using application-specific LC or LC-MS solutions. It provides better prep processes for drug discovery and purification of functional components in pharmaceutical, chemical and food industries.

Ease-of-operation in a flexible set-up
supported by flexible choice of detectors and efficient process automation

Simplifies the fractionation programming
using the LabSolutions software's fractionation simulation function

High sample capacity with a reduced footprint
through a space-saving design with support of custom racks

Fast recovery of highly purified target compounds
by automation of fractionation, concentration, purification and recovery

Preparative LC System

www.shimadzu.eu/better-prep

Pharmaceutical Technology Europe is the authoritative source of peer-reviewed research and expert analyses for scientists, engineers, and managers engaged in process development, manufacturing, formulation and drug delivery, API synthesis, analytical technology and testing, packaging, IT, outsourcing, and regulatory compliance in the pharmaceutical and biotechnology industries.

October 2019

Advancing Development & Manufacturing
Pharmaceutical Technology EUROPE
PharmTech.com

Cover: AndyShell - Stock.adobe.com
Art direction: Maria Reyes

PharmTech.com

Features

DOSAGE FORM TRENDS

12 **The Demands of the Perfect Dose**
Developers are looking to outsourcing partners to provide more specialized expertise and solutions.

API SYNTHESIS & MANUFACTURING

16 **Stability Testing for Small-Molecule Clinical Trial Materials**
Limited guidance and numerous challenges create confusion about the scope and timing of stability testing.

FORMULATION

22 **Overcoming Bioavailability 'Roadblocks' with LBDDS**
A multi-disciplinary approach to lipid-based formulations is needed to overcome limitations with poor solubility.

MANUFACTURING

32 **Best Practices in Handling HPAPIs**
Establishing OEL data and ensuring appropriate engineering controls are crucial aspects of safe handling.

52 **New Technologies for Fill/Finish Streamline Operations**
Advances in parenteral packaging address demands for efficiency and product safety.

QUALITY/REGULATIONS

34 **Using Software in Process Validation**
Software systems can help validate pharmaceutical manufacturing.

38 **Lessons from FDA 483s and cGMP Inspection Data**
Production and process controls, organization and personnel were the top problems found, while packaging and labelling citations increased in 2017 and 2018.

62 **Getting in Touch with New Guidance on Topical Products**
Changing regulatory guidance on generic topical products is expected to lead to an increase in the number of market approvals in the near future.

Peer-Reviewed

26 **Optimizing Manufacturing Based on the Storage Stability of Pegylated Products**
Research into peginterferon alfa-2b's degradation pathways suggest that drug substance be immediately and continuously converted to drug product when the material is in liquid form.

ANALYTICS

46 **The Fundamentals of Dissolution Testing**
In this article, experts discuss the fundamentals of dissolution testing.

50 **Distribution of Data: The Central Limit Theorem**
Using the central limit theorem concerning the distribution of means allows one to justify the assumption of the normal distribution.

SUPPLY CHAIN

56 **Tracking Raw Materials in Biopharma Manufacturing**
Automated, electronic systems improve efficiency and prevent mistakes.

OUTSOURCING

58 **Best Practices for Studying Stability in Biologics**
Industry experts discuss the challenges and regulations of setting up a CGMP-compliant stability testing programme.

Columns and Regulars

6 **Editor's Comment**
The Never-Ending Brexit?

8 **EU Regulatory Watch**
Out with the Old and In with the New European Commission

65 **Exhibitor Profiles**

74 **Pharma Capsules**

74 **Ad Index**

Alliance for Audited Media

Pharmaceutical Technology
EUROPE

PharmTech Group
Editorial Director
Rita Peters
RPeters@mmhgroup.com

Senior Editor
Agnes Shanley
AShanley@mmhgroup.com

Managing Editor
Susan Haigney
SHaigney@mmhgroup.com

Manufacturing Editor
Jennifer Markarian
JMarkarian@mmhgroup.com

Science Editor
Feliza Mirasol
FMirasol@mmhgroup.com

Assistant Editor
Lauren Lavelle
LLavelle@mmhgroup.com

Art Director Dan Ward

Senior Art Director
Marie Maresco

Graphic Designer
Maria Reyes

PharmTech Europe
Editor
Felicity Thomas
FThomas@mmhgroup.com

Publisher
Michael Tracey
MTracey@mmhgroup.com

Sales Manager
Linda Hewitt
Tel. +44 (0) 151 353 3520
LHewitt@mmhgroup.com

Senior Sales Executive
Stephen Cleland
Tel. +44 (0) 151 353 3647
SCleland@mmhgroup.com

Sales Operations Executive
Barbara Williams
BWilliams@mmhgroup.com

VP & Managing Director, MJH Life Sciences™
Dave Esola

C.A.S.T. Data and List Information
Michael Kushner
MKushner@mmhgroup.com

MJH Life Sciences™ Chairman and CEO
Mike Hennessy, Sr

Vice Chairman
Jack Lepping

President
Mike Hennessy, Jr

Chief Strategy Officer & President, Agency Services
George Glatcz

Chief Financial Officer
Neil Glasser, CPA/CFE

Executive Vice President, Operations
Tom Tolvé

Senior Vice President, Content
Silas Inman

Senior Vice President, I.T. & Enterprise Systems
John Moricone

Senior Vice President, Development & Enterprise Systems
John Paul Uva

Senior Vice President, Audience Generation & Product Fulfillment
Joy Puzzo

Vice President, Human Resources & Administration
Shari Lundenberg

Vice President, Business Intelligence
Chris Hennessy

Vice President, Corporate Branding & B2B Marketing
Amy Erdman

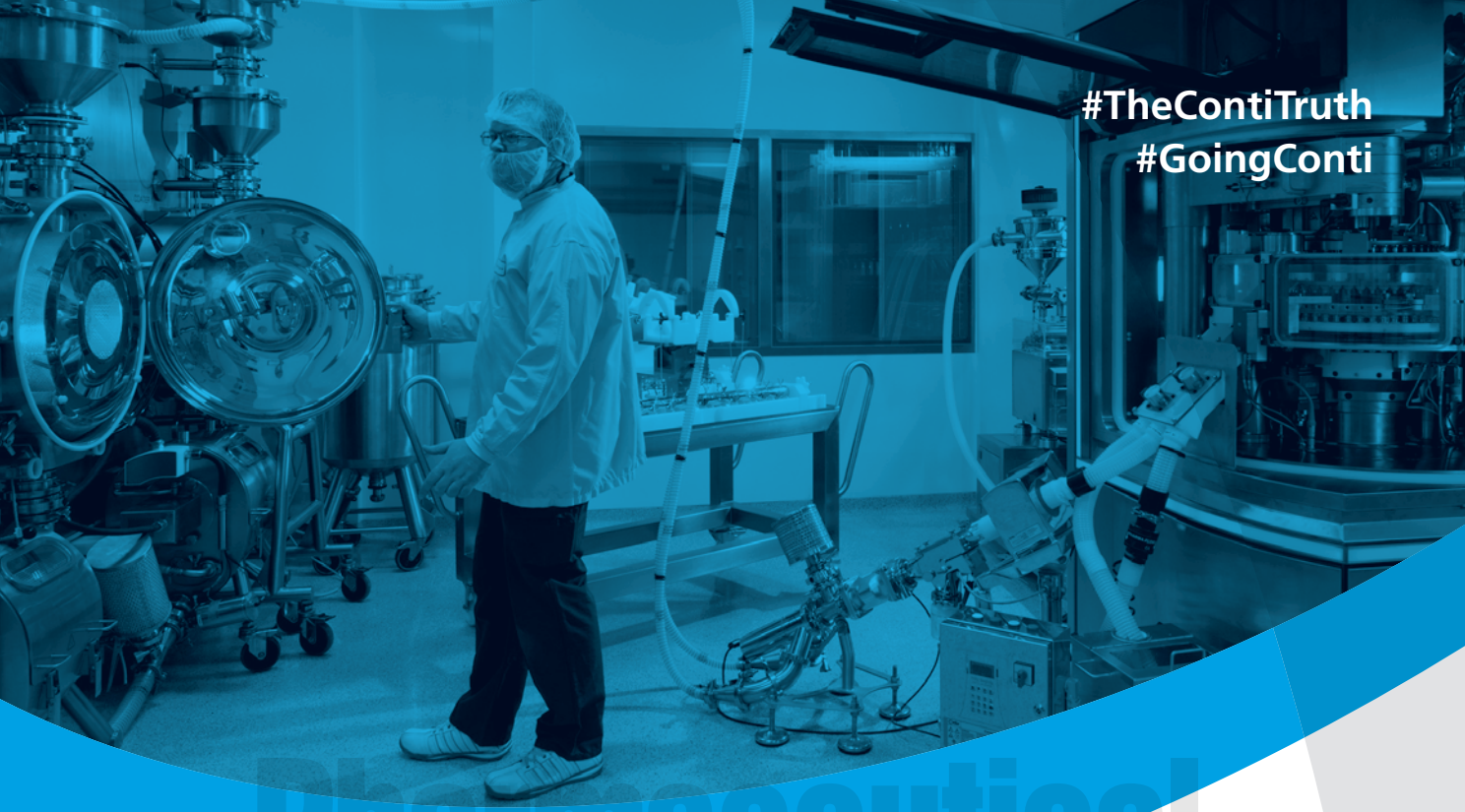
Executive Creative Director, Creative Services
Jeff Brown

Published by
MJH Life Sciences™
Sycamore House, Suite 2
Lloyd Drive
Cheshire Oaks
Cheshire
Ch65 9HQ, United Kingdom
Tel. +44 151 353 3500
Fax +44 151 353 3601

AN MJH life sciences™ BRAND

EDITORIAL ADVISORY BOARD

Above is a partial list of the *Pharmaceutical Technology* brand editorial advisory members. The full board, which includes advisory members of *Pharmaceutical Technology* North America, can be found online at www.PharmTech.com/pharmtech-editorial-advisory-board. *Pharmaceutical Technology* publishes contributed technical articles that undergo a rigorous, double-blind peer-review process involving members of our distinguished Editorial Advisory Board. Manuscripts for editorial consideration should be sent directly to Susan Haigney, managing editor, shaigney@mmhgroup.com.



#TheContiTruth
#GoingConti

Immerse Yourself

… in the Real and Virtual Worlds of Continuous Manufacturing

At the heart of this year's CPhI Worldwide, GEA (stand 110C70) will be presenting a selection of equipment for the batch and continuous granulation, tableting and coating of pharmaceutical products, as well as containment solutions, separation technologies and equipment for materials handling, homogenization and freeze drying.

In the on-stand Continuous Experience room, attendees will be able to journey into the 3D world of virtual reality and take a closer look at the ConsiGma® CDC 50 Continuous Direct Compression system and the ConsiGma® Coater.

For real-world learning opportunity, GEA is also hosting a free-to-attend pre-CPhI event on 4 November in Wommelgem, Belgium. Here, visitors can take part in demonstrations and presentations and benefit from a thorough understanding of our OSD technologies.

Back at CPhI, our experts will be happy to meet you and talk about Quality by Design (QbD) for oral solid dosage production, quality control and process optimization.

Don't miss this opportunity to learn, discover and experience innovative equipment in action with our inspirational people.

GEA engineering for a better world

gea.com

The Never-Ending Brexit?

With no plausibly approvable deal on the table in the UK government at the moment, it is possible that Brexit could be extended even further.

As the United Kingdom fast approaches the deadline for its departure from Europe Union (for the second time), it is possible that Brexit may be delayed even further. The UK government remains at loggerheads, with furore over the recent prorogation, a court ruling stating that the suspension was unlawful, no clear indication a plausible deal will be achievable, and a bill prohibiting a 'no-deal' scenario. Another Brexit extension is becoming a possibility.

However, even if the UK government requests another extension, there is no guarantee that the other countries of the European Union would agree. So, where does this uncertain situation leave the pharma industry both within the UK and across Europe?

Significant changes already

There have already been significant changes as a result of Brexit that have impacted the pharma industry. The relocation of the European Medicines Agency (EMA) from London to Amsterdam was completed in March 2019 and resulted in the agency restricting activities and focusing on core tasks while adjusting to the move and subsequent loss of staff.

Companies have been stockpiling and working on contingency planning to help ensure the supply of medicines post-Brexit is minimally affected. Some pharma companies have stopped investments into the UK altogether, waiting until Brexit is finalized or there is at least some clarity on the situation, and others have opened facilities in countries that will remain in the EU to avoid business disruptions.

Parliamentary bodies and industry associations both in the UK and EU have been releasing guidance information to help pharma companies prepare for Brexit. These types of documents have been particularly prominent for the potential of a 'no-deal' scenario, which is considered to be the 'worst-case' scenario for the pharma industry.

Operation Yellowhammer

In August 2019, the UK government's official report (Operation Yellowhammer) on the probable outcomes of a 'no-deal' Brexit was leaked (1), which highlighted potential disruption to medicines supply that could last up to six months. The Channel port disruptions are underlined as a particular issue of the supply of medicines and medical products, which is an issue that cannot always be overcome by stockpiling as a result of limited shelf-life (2).

Although the government has pledged funding to help with medicines supply in the event of a 'no-deal' scenario, a recent report from the National Audit Office stressed that there is a significant amount left to do so that a steady flow of medicines is assured (3).

Continuous 'no-deal' preparations challenging

The full extent to which the pharma industry will be affected by Brexit is yet to be determined and will very much be influenced by any potential deal that may (or may not) be agreed upon by officials in both the UK and EU. And as UK Prime Minister, Boris Johnson, has firmly stated that his political policy will see the UK leaving Europe on 31 October 2019 with or without a deal, regardless of the Benn Act (a recently passed law that prohibits 'no-deal'), the waters surrounding Brexit seem to be muddier than ever before.

For the pharma industry, however, continuous preparations for a 'no-deal' Brexit is a challenging prospect, as stated by the Chief Executive of the Association of the British Pharmaceutical Industry, Mike Thompson, earlier this year (4). "Leaving the EU with a deal in place remains the best way to minimize any potential disruption to medicines supplies," Thompson said.

References

1. The Guardian, "No-Deal Brexit: Key Points of Operation Yellowhammer Report," *theguardian.com*, 18 August 2019.
2. BBC, "Brexit: What does Yellowhammer Say About No-Deal Impact?" *bbc.co.uk*, 20 September 2019.
3. NAO, "Exiting the EU: Supplying the Health and Social Care Sectors," 27 September 2019.
4. ABPI, "ABPI Response to Government 'No Deal' Guidance," *abpi.org.uk*, 26 June 2019. **PTE**

Felicity Thomas
Editor of *Pharmaceutical Technology Europe*
FThomas@mmhgroup.com

SMA MicroParticle ICS

Non-Viable Particle Counters

THE NEXT LEVEL OF PARTICLE COUNTING

UNMATCHED ENVIRONMENTAL CONTROL

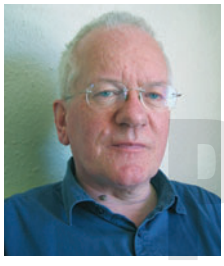
STERILE.COM

For more information, visit our website at **sterile.com/particlecounters**

vai
VELTEK ASSOCIATES, INC.

Out with the Old and In with the New European Commission

A new European Commission is likely, with the support of a new European Parliament, to give a higher profile to healthcare and pharmaceutical matters during its five years in office.



Sean Milmo is a freelance writer based in Essex, UK, seanmilmo@btconnect.com.

The new Brussels-based European Commission, which is due to take over in November 2019, will be playing the powerful role in the European Union of putting forward legislation, which must be approved by the parliament and the council of ministers representing the governments of member states, soon to be reduced to 27 with the departure of the United Kingdom.

The commission will also have a key role in drawing up EU-wide strategies not just in the economic sphere but also the social field, including health. Environmental issues, such as climate change, are being considered at the EU level from an economic and social policy standpoint. The Finnish government has pledged to promote wellbeing during its current six-month presidency of the council of the EU on the grounds that wellbeing is an EU responsibility and is at the core of its raison d'être (1).

Getting more active in healthcare affairs

Authorization of pharmaceuticals is no longer just a matter of ensuring an open, barrier-free market in medicines but is also an instrument of social policy covering areas such as the right to effective healthcare. In fact, certain EU political and social groups believe that social policy should now be given top legal priority so that in the judgments of the European Court of Justice (ECJ) it would be given prominence over purely economic factors (2).

Ursula von der Leyen, a German politician, who has been appointed by EU leaders to be the president-elect of the new commission, has already indicated that she wants the body to be more active in healthcare affairs than its predecessors (3). This could result in stricter controls on pharmaceuticals but could also encourage more innovations in medicines and their production processes. Her healthcare focus was confirmed by her decision to move all responsibilities for pharmaceutical-related activities to the commission's health directorate—DG Health and Food Safety.

The directorate will, for example, take over implementation of regulations for medical devices, including drug–device combinations (DDCs), from the commission's industry and internal market directorate DG Grow (4). Responsibilities for pharmaceutical-related biotechnology and the food supply chain will also be transferred from DG Grow to the health directorate (4). The accountability to the commission of the European Medicines Agency (EMA) will be centralized more clearly within DG Health (4). As a result of all these changes, the commission's duties for the instigation and implementation of pharmaceutical regulations, as well as enacting medicines-linked public health policies, will be concentrated within a single directorate.

The appointments of von der Leyen and her designations of 26 commissioners still have to be approved by the European Parliament. But it is unlikely that the membership of the new commission or the agenda put forward by its president-elect will be radically changed.

Sorting out authorization of DDCs

Among the first initiatives on medicines legislation by the new commission could be sorting out difficulties with the authorization of DDCs under a new medical device regulation (MDR), which is due to come into force in 2020 (5). "I want you to focus on the effective implementation of the [MDR] to protect patients and ensure it addresses new and emerging challenges," von der Leyen told Kyriakides in a letter (5).

The MDR may need to be modified to clarify the role of pharmaceutical agencies in the authorization of DDCs, particularly with respect to quality standards. Medicines authorities have the job of assessing the quality and safety of the drug in the DDC, while certification organizations, called notified bodies (NBs), judge the quality and safety of the device component (6).

In the current text of the MDR or its guidelines there is a blurring of the responsibilities of medicines agencies and NBs in assessing the interaction between the drug and device in a DDC, particularly with single non-reusable integral products such as pre-filled syringes or autoinjectors (7). Pharmaceutical companies have also been complaining about a lack of clarity in what information they are required to give NBs and vice versa.

Another worry is that an insufficient number of NBs will have been designated by the EU to conduct MDR assessments when the new regulation, which replaces a 1993 piece of EU legislation, is due to be implemented

Image Source/Getty Images

Cambrex

Your molecule
Our mission

Drug substance | Drug product | Analytical services

Visit us at CPhI Worldwide
While you're in Frankfurt, discover why we're **the** small molecule company with end-to-end capabilities.

Meet the experts you'll enjoy working with at **Booth 41C10**, November 5-7.

Valeska Taylor
QC Analyst

www.cambrex.com

in May 2020 (8). Certification organizations have to meet tougher criteria to be chosen as NBs under the MDR, which has aroused fears that many will fail the selection process. Only about half the required number could be in operation by the end of this year, according to MedTech Europe, the medical devices trade association (8).

Once chosen, NBs will find that the MDR assessment of products will take longer than under previous legislation because the scope and number of quality, safety, and performance requirements has been increased. Re-certification of an existing product could take up to nine months and even longer in cases of new products (8).

The pharmaceutical and medical device sectors are warning that after MDR is scheduled to come into force in 2020 large numbers of products may have to be taken off the market while the launch of many new ones will have to be postponed because they will be non-compliant (8). This will be at a time when a growing proportion of medicines are being introduced as DDCs because of their greater convenience and effectiveness.

Among the other tasks set by von der Leyen for the health directorate is greater use of Big Data and digitalization to promote health data exchange and research on preventive strategies as well (5). Also, ways should be explored to ensure that Europe has sufficient supplies of affordable medicines to meet its needs. "The pharmaceutical industry (should be supported) to ensure it remains an innovator and world leader," said von der Leyen.

Another assignment for the directorate is the putting forward of a 'Europe's Beating Cancer Plan' to help member states improve cancer prevention and care (5). This should propose actions to strengthen the EU's approach at every key stage of the disease—prevention, diagnosis, treatment, life as a cancer survivor, and palliative care.

Fighting AMR

Perhaps under the new commission, DG Health's top priority will be the fight against antimicrobial resistance (AMR) through the full implementation of the European One Health Action Plan against AMR covering human, animal, and environmental health (5). "Many of today's epidemics are linked to the rise or return of highly infectious diseases," said von der Leyen.

The importance given by the new commission to the enforcement of the EU's One Health Action Plan is strongly supported by the pharmaceutical industry. "Tackling one of the great public health challenges of our time requires collaboration," Nathalie Moll, director general of the European Federation of Pharmaceutical Industries and Associations (EFPIA), said in a blog in September 2019 in response to von der Leyen's call for action (9).

"The One Health approach demands collaboration between the human, animal, environment, and food sectors to address this complex shared problem," Moll continued. "That's why, together with 16 organizations active in human and animal health, we have called for AMR to be at the forefront of EU inter-institutional discussions."

Health campaigners want the One Health Action Plan to be broadened in scope. "This plan lacks concrete targets, so we call on the EU to set targets which are measurable and ambitious," an 18-strong alliance of healthcare non-governmental organizations (NGOs) and patient groups declared in a statement in April 2019 (10).

Curbing antibiotic discharges

Some NGOs have been urging pharmaceutical manufacturers to do more to curb AMR by eliminating it from wastewater discharges from their antibiotics plants. In fact, leading producers of antibiotics are already taking steps to curb antibiotics discharges from their plants. In a survey of international research-based and generic antibiotic manufacturers, the Amsterdam-based Access to Medicine Foundation revealed that 15 out of 18 research-based companies had some form of environmental risk-management strategy aiming to minimize the impact of antibiotic discharges (11). Six of these companies—GSK, Johnson & Johnson, Novartis, Pfizer, Roche, and Sanofi—were the best performers, applying their environmental risk-management strategies not only to their own manufacturing sites but also those operated by third-party manufacturers of APIs and drug products.

The foundation is using data from its surveys to develop a benchmark on anti-AMR actions by pharmaceutical companies to help governments in drawing up procurement policies for medicines. However, even the best performing producers have been reluctant to disclose details of their activities with antibiotic discharges, in particular the metrics they use to put limits on discharges and whether these have been exceeded.

AMR is probably the area in healthcare where the new commission has the opportunity to achieve the most success because of the amount of backing throughout industry for action. But it will be a tough job.

References

1. EU2019FI, "A Competitive and Socially Inclusive EU," *eu2019.fi*, https://eu2019.fi/en/priorities/competitiveness-and-social-inclusion [accessed 30 September 2019].
2. ETUC, "Protocol on the relation between economic freedoms and fundamental social rights in the light of social progress" (Brussels, 18 March 2018).
3. U. von der Leyen, "A Union that strives for more. My agenda for Europe," *ec.europa.eu* (Brussels, September 2019).
4. EC, "European Commission 2019–2014—Allocation of portfolios and supporting services" (Brussels, 10 September 2019).
5. EC, "Ursula von der Leyen, President-elect European Commission: Mission letter Stella Kyriakides, Commissioner-designate for Health" (Brussels, 10 September 2019).
6. EMA, "Medical devices" (Amsterdam, June 2019).
7. EBE and EFPIA, "An Industry Perspective on Article 117 of the EU Medical Devices Regulation and Impact on how Medicines are Assessed," Reflection Paper (Brussels, 12 July 2018).
8. MedTech Europe, "Industry Perspective on the Implementation Status of MDR/IVDR" (Brussels, 14 June 2019).
9. EFPIA, "EFPIA is Ready to Answer EU's Call for Action on Antimicrobial Resistance," Blog (Brussels, 19 September 2019).
10. EU4Health, "Joint position: Europe, let's do more for health!" (Brussels, April 2019).
11. AMR Benchmark, "B Manufacturing and Production," Research Areas, *accesstomedicinefoundation.org*, 13 December 2018. **PTE**

Grifols Partnership
Better together

PARENTERAL CDMO

Grifols **guides** pharmaceutical companies through the process **of switching** from concentrated formula to **pre-mixed solution** in **ready-to-use** flexible bags

Visit us:

November 5th–7th
CPhI Worldwide
Frankfurt, Germany
Booth 121C70

Contact us:

partnership@grifols.com
www.partnership.grifols.com

GRIFOLS

Grifols International, S.A.
Parc empresarial Can Sant Joan, Av. de la Generalitat, 152-158
08174 Sant Cugat del Vallès, Barcelona - SPAIN
Tel. +34 935 712 199
www.grifols.com

HG/CM/0119/0040

The Demands of the Perfect Dose

As the development pipeline becomes more saturated with complex molecules and patient experience becomes more important, developers are looking to outsourcing partners to provide more specialized expertise and solutions.

Felicity Thomas

Oral-solid dosage forms remain the most common drug formulation used within the pharmaceutical industry and, according to market research (1), should continue to experience market growth in the near future. However, a range of factors, such as an amassing focus on biologics, higher proportion of poorly soluble molecules in development, and regulatory pathways, may shift the balance and raise the profile of innovative dosage forms, increasing the requirement for expert skills.

"Pharma's development pipeline is being filled with more sophisticated, harder to make compounds that require complex delivery strategies to administer doses correctly," notes Louis Weber, managing director, Bora Pharmaceuticals. "Demand for specialist expertise has soared, and drug developers are increasingly seeking outsourced solutions to commercialize products."

Overcoming bioavailability issues

A major challenge currently impacting drug development is overcoming bioavailability issues. "Around 40% of all new chemical entities (NCEs) have low water solubility, meaning a strategy for improving poor bioavailability becomes mandatory," emphasizes Manuel Leal, business development director, Idifarma.

"The 'put it in a tablet' dosage form approach that may have worked in the past is no longer effective as molecules require more complex and advanced drug delivery technologies that address insoluble compounds," explains Robert Lee, president, Particle Sciences. "There are a range of technologies to increase bioavailability but for them to be viable, expertise and experience on how to apply them is required so formulations stand a better chance of being effective."

Using solvents, such as isopropyl alcohol, ethanol, and acetone, is a practical way in which developers can improve solubility of most drug substances, notes Weber. "In addition, solvent methods for dispersing drug substances can also be useful to deal with poorly soluble compounds prevalent in today's therapeutic compounds," he says.

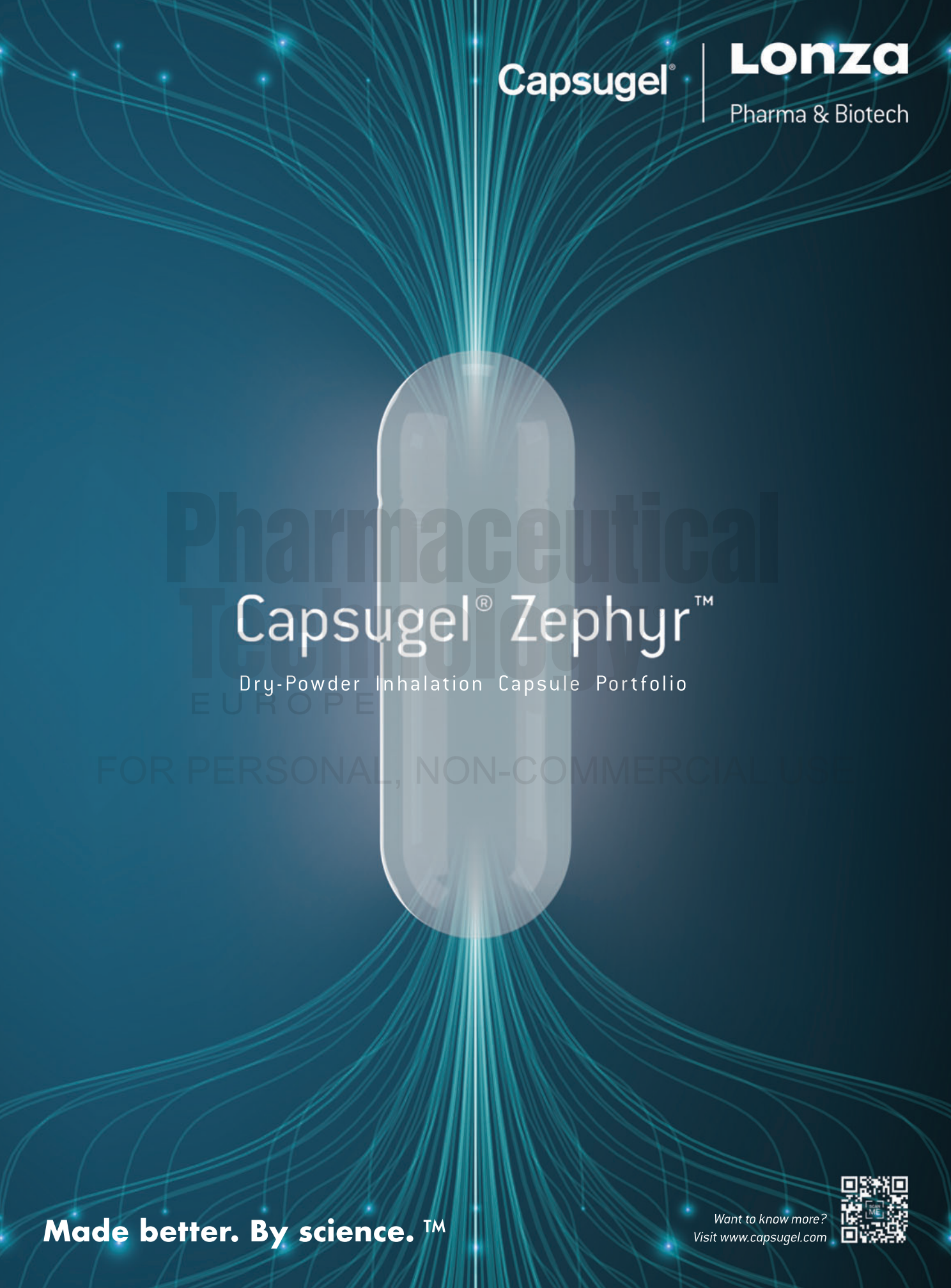
For Leal, there is a need for innovative processes to advance the galenic formulation of finished products as the discovery of new drugs that improve existing therapies has slowed. "Using innovative technologies helps improve the therapeutic arsenal and reduces the reliance on finding new active molecules for the industry," he says. Constant adoption of a variety of strategies that enable enhancement of a drug's absorption is vital for formulation scientists, in Leal's opinion.

Adoption of an orthogonal approach and being open to a variety of methods, particularly during early development was also advised by Lee. "Good development practice starts with the client providing a clear target product profile (TPP), which describes an idealized drug product image, including route of administration, dose, form factor, pH, particle size distribution, and so on," he continues. "Once there is an understanding of the TPP and the physicochemical characteristics of the active, it is possible to assemble potential drug delivery technologies that may achieve the TPP."

"The key to success," stresses Jeremy Drummond, senior vice-president business development, MedPharm, "is to use a holistic approach considering the overall requirements of any formulation; from the properties of the API to the end-use market, patient requirement, and target indication."

AndyShell - Stock.adobe.com

Capsugel® | Lonza Pharma & Biotech



Capsugel® Zephyr™

Dry-Powder Inhalation Capsule Portfolio

Made better. By science. ™

Want to know more?
Visit www.capsugel.com

Advantages of the accelerated pathway

Speeding up the development pathway has obvious benefits for drug developers. Not only can these accelerated routes help shorten the development timeline but can also offer significant cost reductions.

Using the US Food and Drug Administration's 505(b)(2) pathway as an example, Lee highlights that innovative drug dosage forms are being realized thanks to the opportunities afforded by the accelerated development route. "A key advantage of the pathway is the 505(b)(2) sponsor can use clinical data produced by other companies to seek FDA approval without performing all the work required with a traditional new drug application," he says. "This pathway is being used to improve existing drug products with new dosage forms, indications, dosing regimens, and new routes of administration."

In agreement, Weber adds that through accelerated pathways developers are managing to breathe new life into existing products in an economical way. "According to FDA, the pathway allows drug developers a faster route to improve existing drugs, including new dosage forms that are faster acting or that combine two active ingredients in a new way," he comments. "This includes creating new administration routes that enhance therapeutic performance or dose adherence."

Other regulatory bodies also offer accelerated route options, for example in Europe the European Medicines Agency (EMA) allows developers to submit applications via the hybrid procedure, which is considered to be roughly equivalent to 505(b)(2). "The appeal of accelerated pathways is leading drug innovators to rethink existing market medicines and reformulate them in ways that place a greater emphasis on patient centricity," confirms Lee. "This is leading to innovations such as long-acting injectables that require a lower dosing regimen than before or improving the bioavailability of a drug so that it can be delivered via an alternative, more convenient route of administration."

Focusing on the patient

"The patient or consumer must always be at the forefront of any development strategy," stresses Drummond. "It should always be remembered that it is not a drug (i.e., an API) that you give to a patient, but a drug product. For a formulation to achieve a positive clinical outcome and be a commercial success for the developer, the patient must be happy to use it."

In fact, a patient-centric approach to dosage form can be particularly vital when considering specific patient populations. "Traditional dosage forms, particularly tablets, may not always be taken by a patient as prescribed, which can lead to a negative therapeutic outcome and render a course of treatment much less effective," says Lee. "Paediatric and geriatric patient populations are particularly averse to swallowing large tablets and in these cases powders or liquids formation can be much more convenient."

Another way of improving the patient experience and ultimately medication adherence in paediatric patients is through the use of modified-release formulations as they have a narrow therapeutic index and can support dose compliance strategies, confirms Weber. "Most patient groups respond well to taking medications that require fewer doses to be effective (and for longer periods) and reduced side effects from dose fluctuation for example," he notes. "In addition, fixed-dose combination products with multiple APIs and different modified-release profiles can deliver more therapeutic value and better outcomes for both paediatric and geriatric patients."

Adherence issues are also found within patient groups suffering from chronic conditions, specifies Leal. "One answer for chronic disease therapies is to improve the solubility and bioavailability to allow for oral administration, which can improve comfort for the patients and allow them to take the drugs at home," he adds. "A further way of supporting patient-centric approaches to drug dosage forms is through taste masking."

According to Weber, patient-centric principles are being applied in a variety of ways in pharmaceutical development. "Genetic profiling and advanced analytical techniques for example are assisting the personalized/precision medicine approach by providing deep insight into different patient populations and the pharmacokinetic and pharmacodynamic effects of drugs," he says. "Therefore, patients can be more selective in their choice of pharmaceutical products, taking into consideration their efficacy in certain subsets of the populations."

Gaining unique access through outsourcing

As a result of cost-efficiency and patient compliance being major considerations for healthcare providers and payors, solid-dosage forms are still preferred for many pharma products, Leal specifies. "Demand for contract manufacturing of solid forms is, therefore, still strong," he says. "However, there have been vast therapeutic improvements witnessed in smaller patient populations with unmet medical needs, such as oncology."

Oncology treatments tend to require smaller manufacturing volumes and require a higher degree of expertise, such as containment capabilities and agile manufacturing methods, Leal continues. "For traditional contract development and manufacturing organizations (CDMOs), who manage large volumes, these specialist products are very complicated to handle," he emphasizes. "Hence, made-to-measure services can be better provided by smaller independent CDMOs."

In agreement, Lee adds that working with an outsourcing partner for formulation and development can be particularly relevant for non-conventional dose forms. "Dosage forms, such as nasal and ophthalmic, as well as implantable devices and depots, can have additional complexity and regulatory issues for developers to consider," he notes. "Through an outsourcing partner, developers can access expertise and technologies that they do not possess in-house."

A further benefit for Lee is that an outsourcing partner can provide an extension to a developer's available resources. "If there is a backlog or lack of available resources with the client, they can use an outsourcing partner as an extension of their internal development teams," he says.

Flexibility and being able to adapt to any changes that may occur during formulation development is critical to drug development success, stresses Weber. "By partnering with organizations that have experience in commercialization and technical expertise in complex dosage forms

such as modified release or fixed-dose combinations, companies will be able to overcome project challenges in an agile and efficient way," he confirms.

"Specialism is key in the pharma industry. If our clients were to make the investment into their own manufacturing facilities, they would have to dedicate huge amounts of resource and capital," states Leal. "Outsourcing gives a drug developer access to unique skills and support within the supply chain, which means other benefits such as increased speed to market and reduced cost in the long run can be achieved."

Areas of growth

In Lee's opinion, routes of administration that have been previously overlooked will experience future growth. "Nasal delivery can offer an ideal route and increased bioavailability for several drug types, particularly those indicated to treat the central nervous system," he explains. "This route of administration may also be suitable for non-conventional APIs, such as biologics."

For Leal, the increasing prevalence of high-potency ingredients is leading to more growth in demand for outsourcing partners that can effectively manage the associated containment issues. "High potency facilities are capital intensive and containment requirements are stringent," he says. "Therefore, it will be more economical and practical for pharmaceutical companies to work alongside outsourcing partners to develop and manufacture their products in a more efficient manner."

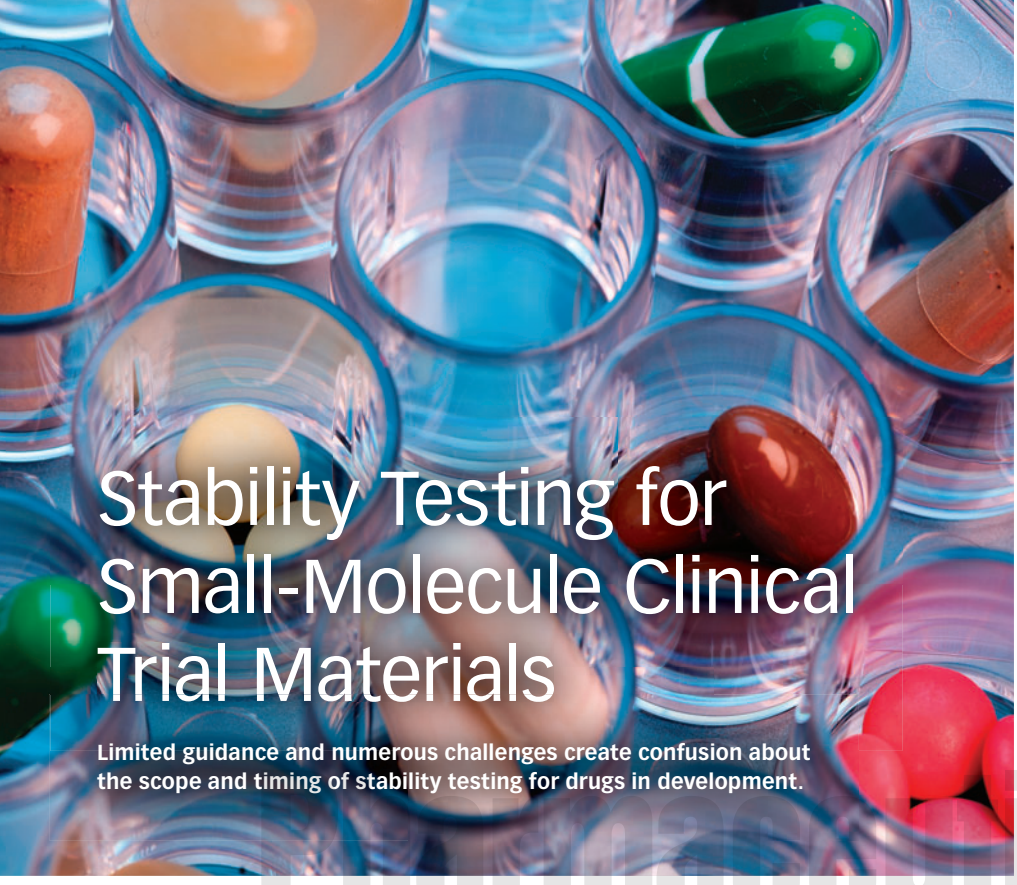
A further trend that Leal believes will be important is that of value-added medicines that are based on well-known molecules with new applications, indications, finished-dosage forms, or strengths. "These drugs are an improvement on the traditional generics, which means more cost, but they remain more economical to develop than medicines based on new chemical entities," he adds.

Currently, there is a trend happening in the industry to use artificial intelligence to mine for APIs to hit relevant newly discovered biochemical pathways, according to Drummond. "A major trend going forward will be the alignment of formulation with information technology and any relevant devices with a focus on making it simple and easy, and even attractive, for the patient to be compliant," he comments.

Ultimately, however, keeping the patient in mind when looking at drug development is and will remain to be of critical importance, emphasizes Lee. "If a patient does not like the dosage form then they are unlikely to take the drug, leading to negative therapeutic outcomes," he concludes. "Dosage forms should appeal, not repel, the target audience."

Reference

1. Future Market Insights, "Oral solid Dosage Pharmaceutical Formulation Market: Emerging Markets of Latin America, APEJ, and MEA to Collectively Hold Over 45% Market Value Share: Global Industry Analysis 2012–2016 and Opportunity Assessment 2017–2027," *futuremarketinsights.com*, market report, 18 July 2017. **PTE**



Stability Testing for Small-Molecule Clinical Trial Materials

Limited guidance and numerous challenges create confusion about the scope and timing of stability testing for drugs in development.

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

The stability of clinical trial materials, regardless of the trial phase, must be understood to ensure patient safety. Stability can be affected by the nature of the API, the production process, the choice of excipients, the container and container closure system, and other factors. Stability testing is therefore essential for demonstrating that the formulations administered to patients in any clinical trial will remain unchanged throughout the duration of the trial. The type and length of stability tests typically depend on the phase of development and the nature of the clinical trial (e.g., use of placebo or comparator drug).

Fragmented regulatory guidance

Various guidance documents from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have been published regarding stability testing of clinical trials materials (CTMs). The language regarding duration of testing in these documents tends to be vague, however. For Phase I trials, FDA recommends monitoring of the stability and quality of the drug during the clinical trial (1). Similarly, EMA recommends an ongoing stability programme be performed with accelerated and long-term storage studies initiated prior to the study (2).

For Phase II and III trials, FDA expects submission of a description of the stability performance and also suggests the development of stability-indicating analytical procedures that will detect significant changes in the quality of the drug product (3). The agency also encourages the completion of stress studies at Phase II, while in Phase III studies these stability studies should be extended to provide marketing application stability data.

While the International Council for Harmonization (ICH) guidelines on stability testing (4) specifically indicate that formal stability protocols do not apply to CTMs and such protocols are not required for clinical stability studies or submission as part of clinical authorization applications, it is highly recommended that companies do conduct stability studies by means of established procedures.

Duration confusion

For CTMs, at a minimum, real-time data must be collected for a sufficient period to demonstrate shelf life for the product in use, as well as cover the duration for any intended clinical trial, according to Alyn McNaughton, technical director at Lonza Pharma & Biotech. The essential purpose of these stability studies, adds Geoff Carr, director of analytical development for Patheon Pharma Services by Thermo Fisher Scientific, is to ensure that CTMs will remain satisfactory over the period that they are intended to be administered to subjects enrolled in the clinical study, which is often dependent on the clinical trial phase.

The duration of a clinical phase will vary depending upon the number of subjects required to complete the study, the therapeutic indication and the data read out period, according to Teresa Iley, director of pharmaceutical development and manufacture for Intertek Pharmaceutical Services. It also tends to get longer as the project progresses, which impacts the required length of the stability study, adds McNaughton.

"As stability testing is commonly on the critical path for any product development, due to the need for real-time data, most stability studies are extended beyond the required time period to gain more knowledge about the product's robustness and potential maximum shelf life. This approach allows an understanding of product supply needs for future clinical evaluation; for example, if additional manufacturing may be required during a clinical study to supplement product supply for batches that will expire during the clinical study, or if the product's shelf life is not long enough for future trials or even for a viable commercial product," he says.

Iley notes that shelf-life justification can be supplemented by data generated from technical batches manufactured in support of clinical trial applications, but it is typically recommended that the actual batches used to supply the trial are also assessed concurrently with the trial.

Initially a CTM is put on stability at both the long-term or storage temperature and under accelerated conditions. If the material is stable under both, the shelf life can be extrapolated up to twice the period covered by

Full solution for irradiated products

- Measurement on bioburden acc. to ISO 11137
- Dosimetric validation / revalidation (dose mappings)
- Validation / revalidation of microbiology (dose audits)
- Physical and chemical tests of product properties after irradiation

November 5–7, 2019 | Frankfurt, Germany

CPhI worldwide®

Visit us at Booth 111B10

www.gerresheimer.com

GERRESHEIMER

the long-term data (5), according to Judy Carmody, founder and principal consultant of Carmody Quality Solutions. "For Phase I trials, for instance, there may be one pull point at three months, which would allow an extrapolated shelf life of six months," she explains.

CTMs for Phase II or III studies are likely to be much closer to the product intended for commercialization, adds Carr. "These trials are usually larger, longer duration, multicenter, and often in multiple countries, so longer-term stability studies (e.g., two years or more) are likely to be more appropriate," he says. In addition, Carr notes that because the formulations are likely to be closer to the intended commercial products, data from these studies may be used as supportive in new drug applications.

The use of accelerated data to justify shelf life longer than real-time data can be a source of confusion, according to McNaughton. "Accelerated data collection provides a means of predicting the shelf life beyond the actual age of the product. However, interpreting any changes in the product impurity profile, relative to the toxicology-based safety information, can prove challenging in situations where the product does demonstrate some instability. It is also critical to ensure that real-time data, when it does catch up to the age of the product at the end of the study, remain in specification," he explains.

Impacts on trial design

The vague guidance regarding stability testing for CTMs can have a number of impacts, including on study designs. For instance, because many companies base their studies on ICH guidelines, especially Q1A(R2) (6), and then make modifications to make protocols more suitable for CTMs, there is often considerable variation in how different companies conduct their studies, according to Carr.

In addition, because it is important to ensure that batches in clinical studies always have the data available to demonstrate they remain in specification during the duration of the trial, it is necessary to continuously update the shelf life as soon as data are available and before the previous shelf life expires, McNaughton stresses. That can be challenging during early-phase studies, but simpler for later-phase trials because more time is available for completing stability studies.

On the other hand, if changes in the chemical or physical stability of a drug product are identified in stability studies, clinical programmes may need to be suspended until new batches can be supplied, according to Iley. She notes that data provided from technical batches can be a good indicator of how clinical batches will perform and could save precious time when planning for contingencies.

The need to re-supply batches may also arise due to factors such as subject recruitment delays or dropouts, changes to dosing regimens, the introduction of new active, excipient, or packaging materials or revision to manufacturing processes. "Using a risk-based approach, it may be possible to undertake bridging studies to justify these changes, but it may also require performance of new or extended analytical studies. Any of these factors can impact the trial design and supporting stability programme," Iley says.

The design of bridging studies will depend on the changes that created the need to perform them, according to Carmody. They typically involve the use of the established analytical methods, with comparison of results to previous data to confirm agreement.

Potential timeline extensions

Any issues identified related to the chemical or physical stability of the drug product could cause a delay to the entire clinical development programme. "A well-designed stability study, initiated early in the programme, will facilitate detection of these issues and lessen any impact they may otherwise cause if not understood and resolved quickly," asserts Iley.

The key challenge is the fact that as candidates progress through the development cycle, typically changes are made to the formulation, manufacturing process, analytical methodology, container closure system, or other aspects. Any such change requires generation of new stability data, according to Carmody. "The new material must also be demonstrated to be stable for the duration of the clinical trial. Any additional time for manufacturing the new CTM further adds to the potential for delays due to the need for additional stability studies," she says.

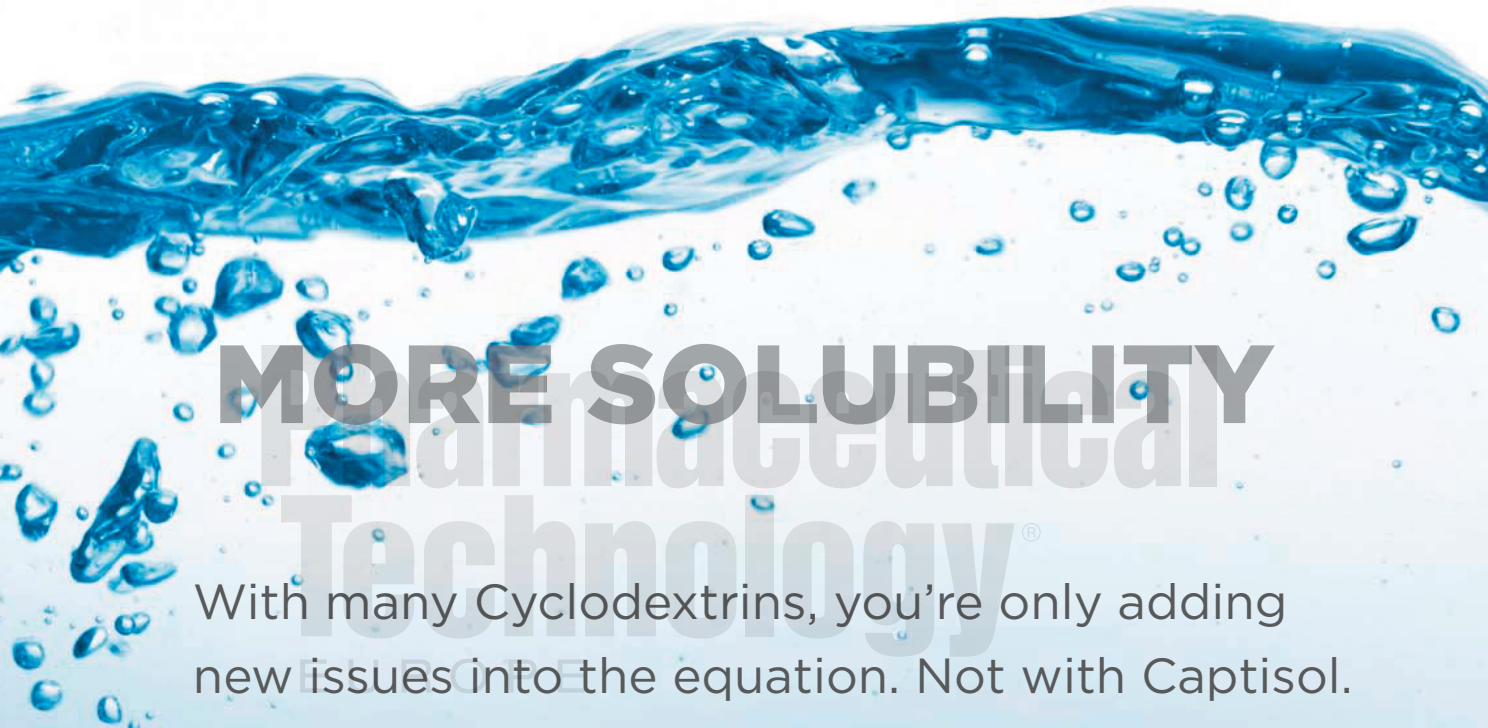
A development programme would, however, take decades if each of these studies were run sequentially to completion, according to McNaughton. "It is necessary to take risks based on limited data from partial studies, which must be done while ensuring that product used in trials remains covered by a stability study that demonstrates it remains within specification," he says.

This necessary approach results in a balancing act of timing and risk with respect to determination of the best time to conduct these studies, and sometimes, when shelf life is limited or not yet known, ensuring a contingency to remanufacture to keep a clinical trial supplied is required. "Careful extrapolation of data obtained from samples stored at accelerated conditions can help predict when additional batches may be required to support clinical studies and therefore allow planning with some level of confidence when manufacturing slots will be required," Iley adds.

There are also often increasing types of stability tests that need to be conducted as candidates move through later clinical trials. For instance, Carmody notes that diluents added to a powder to create a solution for infusion must be subjected to stability studies if the diluent manufacturer cannot provide relevant data. The in-use stability of the solution formed with the diluent must also be demonstrated. This information will impact the product handling protocol for the trial. "In-use studies should therefore be executed during early stages because the results directly impact and inform formulation and process development activities," Carmody says.

API availability is an important factor as well because synthetic route and process development typically proceed in parallel with clinical programmes, according to Carr. "Supplies are often limited around Phase I as synthetic route and scale-up activities have not yet progressed. Limiting stability study duration is important for avoiding wastage of valuable API," he observes. API availability generally increases as candidates move to Phases II and III, so longer-term stability studies can be more readily supported. In addition, Carr

MORE TECHNOLOGY.



MORE SOLUBILITY

With many Cyclodextrins, you're only adding new issues into the equation. Not with Captisol. With revolutionary, proprietary technology, Captisol is rationally engineered to significantly improve solubility, stability, bioavailability and dosing of active pharmaceutical ingredients.

SOLVE PROBLEMS WITH CAPTISOL SOLUTIONS.

CAPTISOL®
A Ligand TECHNOLOGY

CAPTISOL.com

comments that long-term data are more useful at this point because the nature of the API and dosage form is likely to be more representative of future commercial batches.

Complications can also arise in early-phase studies if the product is not tested promptly. In some cases, artificial failures can occur due to product being older than it should when tested, according to McNaughton. "As a result, an incorrect short shelf life can be assigned or the product can even fail specifications during the clinical trial, when in reality it is in specification at the shelf life when it should have been tested. Such situations add expense and uncertainty in a project, and in some cases the risk of withdrawal from the trial and programme termination," McNaughton says.

Method development/ validation challenges

Often during early-phase studies, knowledge of both products and methods are limited, according to McNaughton. "When unknown degradation occurs, or a method does not behave as anticipated due to an unforeseen change, this can lead to pressure on the project. There exists a need to explain the change and justify it as safe for ongoing work or understand quickly that it is a change that does have an impact on product safety," he notes.

Establishing methods at the start of the process and how the method lifecycle progresses (e.g., identification of new impurities, formulation changes) can require careful assessment and may identify gaps in planned studies or potentially initiate new studies, Iley says.

What is important, adds Carr, is the strategy for method development/ validation. Because CTMs are considered GMP at Phase I, at least some validation of analytical procedures is required. Many companies adopt an approach of "phase-appropriate validation" or "qualification" using methods that have only been partially validated. "The objective is to be economic with the resources applied to validation without compromising patient safety," he states.

Quality-by-design approaches to analytical method development/ validation conflict with this strategy, however. Even so, Carr remarks that analytical development can only proceed to a certain extent until the full details of product strength and formulation are known. He suggests that, given the likelihood of limited knowledge regarding potential degradation products and how to set limits for them, the best approach is to use "alert limits" rather than pass/ fail limits or "report results" with no defined limits. "Alert limits may be set applying ICH Q3B(R2) principles (5); an advantage of this approach is that if an alert limit is exceeded, an investigation can be conducted but confirmation of the result does not necessarily require a batch to be rejected, as would be the case with an out-of-specification result," Carr explains. Alert limits are also useful for pharmaceutical performance testing, such as dissolution for solid oral-dosage forms and viscosity for semi solids.

The issue of validation is perhaps one of the most confusing aspects of conducting stability studies, according to Carmody. It is a Catch-22; stability studies and stability-indicating studies (forced degradation of the CTM) should be validated, but validation is typically not completed until Phase III.

"What should be done," Carmody says, "is to understand the target product profile, mechanism of action, and other important characteristics (e.g., solubility, chromophoric, etc.) to identify the most appropriate analytical methods to choose from." The best methods can then be chosen for identification, potency, purity, and impurity analyses and the relevant parameters validated according to regulatory authority expectations. For any deviations, good scientific rational must be documented.

"Even for Phase I CTMs, analytical methods can be developed with the intended use and validation parameters in mind. As important, stability-indicating studies and appropriate methods must be developed to ensure that the possible degradation products for the CTM can be detected," Carmody states.

Carmody also notes it is important that stability programmes be run by qualified personnel with the relevant knowledge. "There are different expectations for stability testing compared to traditional quality control testing. If analytical groups are going to be responsible for stability testing, then the people involved should be trained on the regulations and requirements," she asserts.

Non-API stability testing

While for the most part the focus of stability testing is on the API and formulated drug product, stability testing of placebos and blinded clinical comparators is also important. Stability testing on placebos is not particularly challenging because, in general, it essentially involves appearance testing and tests for other properties that could impact a blinded study.

The same is not true for blinded comparators, according to Carr. These products typically come from other companies. They often have been repackaged in new containers and may even have been manipulated in some way to ensure appropriate blinding for the study. As a result, there is little information available. "Stability testing is likely to be based on comparisons between the unchanged product in the original packaging versus the repackaged blinded product, and it can be very challenging to establish and validate suitable analytical procedures for this type of study," Carr observes.

Comprehensive approach and logical strategy beneficial

A carefully designed study that stratifies the storage conditions, specific tests, and material batches is required to avoid the often-nebulous growth of a stability programme while still generating pivotal development data, according to Iley. "Ensuring strong, validated methods are in place and planning for potential trial extensions in the stability programme design with the inclusion of optional time points and sufficient spare samples to support them is essential," she adds.

The more knowledge of the product and methods that is generated in advance, the more a study can be de-risked, agrees McNaughton. "It is important to ensure sufficient windows for testing are left, before the data are critically required, to allow for investigational work to take place at every time point in the early stages of a product. For this investigational work, there also needs to be sufficient product added to the study to facilitate investigations to examine what may or may not be a critical change," he adds.

It is also crucial to understand what climate zones the product may

be exposed to. "There is little point in generating data for a product in the relatively temperate zone if the product also needs to be used in a tropical zone, and vice versa," says McNaughton. Determining the behaviour of the product components is also key, because if they do not behave according to Arrhenius predictions under accelerated conditions, then a false failure could occur that does not reflect the true performance of the product under its real-time storage conditions.

Using batches of drug product, including any secondary packaging, that have been manufactured to established procedures is also important, according to Iley. "Although requirements may change or vary during the course of product development, the closer to the final processes and procedures, the less influence they may have on the data obtained from the stability programme," she explains. She also says it is best to expect the unexpected and plan for mitigation.

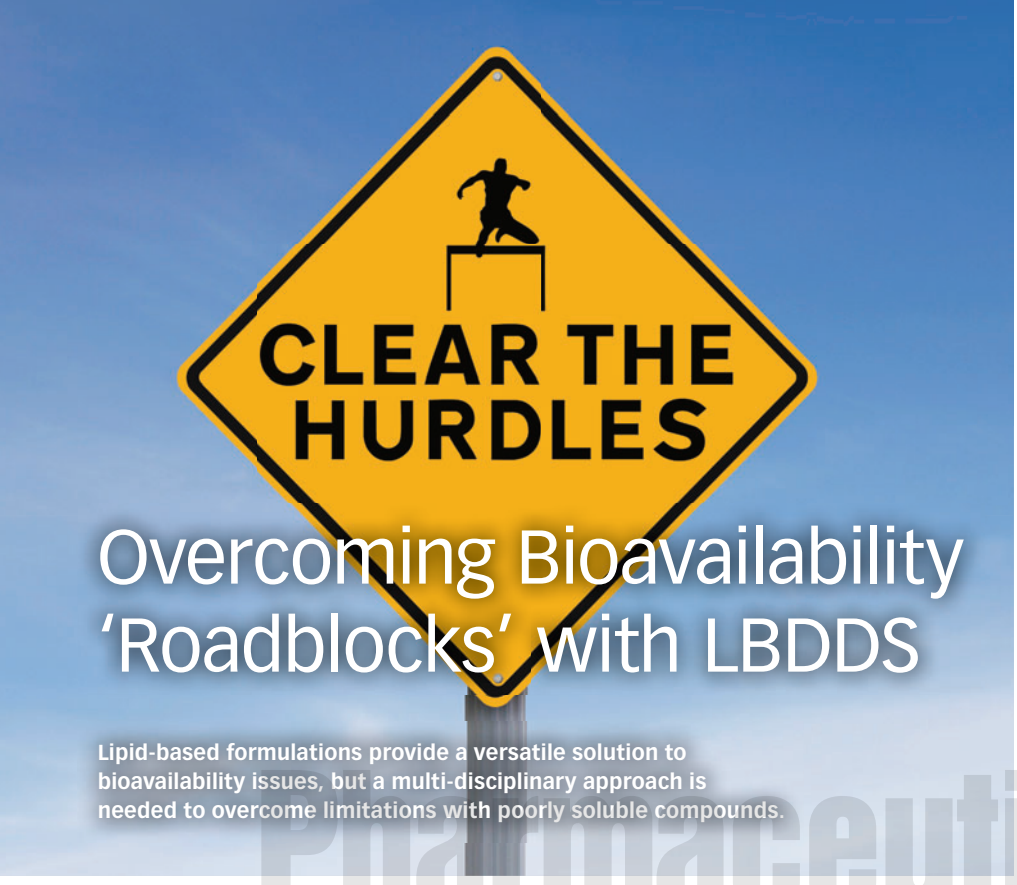
The most important considerations are, according to Carr, to do what is needed to establish the shelf life for CTMs to ensure patient safety and reliable clinical data. It is then important to determine whether it is sensible to extend the study to collect additional stability data that could support a future new drug application filing.

"Full stability programmes must be implemented to address all of the different aspects of clinical trials, from different doses to diluents, placebos, and comparator drugs. An understanding of other potential impacts on stability must also be considered, from critical raw materials to reference standards. All may need to go on stability," Carmody asserts.

Equally important, she says, is consideration of appropriate time points for testing and the trending and statistical analysis of data throughout the testing period. "Shelf life is determined when the stability data crosses specified criteria. That needs to be predicted and not discovered after the fact. It is essential to understand the behavior of the CTM and intervene and make necessary changes if the stability data [are] not trending in the right direction," she concludes.

References

1. FDA, *Guidance for Industry: cGMP for Phase I Investigational Drugs* (Rockville, MD, July 2008).
2. EMA, *Guideline on the Requirements for the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials* (London, Sept. 2017)
3. FDA, *Guidance for Industry: INDs for Phase II and Phase III Chemistry, Manufacturing and Controls Information* (Rockville, MD, May 2003).
4. ICH, Q1A(R2) *Stability Testing of New Drug Substances and Products*, Step 5 version (ICH, 2003).
5. ICH, Q1E *Evaluation for Stability Data*, Step 4 version (ICH, 2003).
6. ICH, Q3B(R2) *Impurities in New Drug Products*, Step 4 version (ICH, 2006). **PTE**



Overcoming Bioavailability 'Roadblocks' with LBDDS

Lipid-based formulations provide a versatile solution to bioavailability issues, but a multi-disciplinary approach is needed to overcome limitations with poorly soluble compounds.

Felicity Thomas

Lipid-based approaches to drug delivery have been extensively researched and have gained importance within the bio/pharma industry for their ability to enhance bioavailability of drug products. This capability to enhance bioavailability is becoming ever more desired in recent times due to the fact that increasing numbers of molecules entering the drug development pipeline are poorly soluble.

"As of late, more than 70% of new chemical entity (NCE) molecules are poorly soluble, with moderate lipophilicity (LogP >2)," says Ravinder Kodipyaka, head, formulation R&D, Custom Pharma Services, Dr Reddy's. "As a result, industry is witnessing opportunities in novel drug discovery for the formulation of new NCEs in lipid-based drug delivery systems (LBDDS) so that bioavailability is improved."

A tremendous solution

"Lipid-based formulations offer a tremendous solution for molecules exhibiting poor solubility and bioavailability," Kodipyaka continues. "These formulations provide excellent solubilization capacity; improve permeation; overcome transporter, enzyme-based inhibitions; and support lymphatic transport, thereby overcoming major roadblocks for achieving optimum bioavailability."

Using lipids to enhance oral bioavailability is a popular choice, adds Michiel Van Speybroeck, head of formulation, Ardena. "When an API is dissolved in a lipid formulation and subsequently administered, the API is presented to the gastrointestinal (GI) fluids in a predissolved form, which avoids slow dissolution from the crystalline form," he notes. "The great advantage that lipids and lipophilic excipients offer over water-miscible solvents is that they are less likely to lose solvent capacity on dilution with the GI fluids. On contact with water, lipophilic excipients phase-separate and form a coarse or finely dispersed emulsion in which the API is sequestered. This protects the API from precipitation in the aqueous phase."

Furthermore, Vincent Plassat, lead product development scientist, Catalent, emphasizes that by delivering drugs in a solubilized form, dose-uniformity can be improved, minimizing patient-to-patient variability. "There is a lot of precedent for the use of lipid-based drug delivery systems (LBDDS) as a result of their value to drug developers and ultimately to patients. LBDDS are extremely versatile because there are many excipients and combinations of excipients that can be used in their development," he explains.

Along with improved dose uniformity, LBDDS are also capable of mitigating food effects (1), Plassat confirms. "For very lipophilic drugs with a LogP value greater than five, formulation of long chain fatty acids can improve lymphatic uptake and bypass the liver. In addition, lipid-based formulations can maintain their solubility throughout the entire journey of the API through the GI tract, allowing higher absorption," he says. "This is unlike non-lipid-based formulations, which exhibit supersaturation, decreased solubility, and lower absorption."

Administration of lipid-based formulations is possible across several routes—oral, injectable, and topical—and depending on the lipophilic nature of a drug, it is possible to determine the optimal lipid delivery system using the Lipid-Formulation Classification System (2), explains Kodipyaka. Employing a suitable lipid excipient component can also aid in modulation of drug release. "The greater the hydrophobicity of the lipid excipient the slower the drug release due to reduced water penetration," he adds.

Being able to control drug release is important so that rapid, high drug plasma level peaks are avoided, which can cause unwanted side effects in patients, notes Ellie Au, product development scientist, Catalent. "A slower release may also protect the drug from degradation in the stomach and facilitate release of the drug throughout the GI tract to improve absorption. Self-emulsifying lipid

formulations typically have faster drug release than those lipid formulations that require digestion. The use of waxes, which are solid at room temperature, creates a matrix for modified release. The drug is therefore released with a controlled kinetic as the matrix slowly erodes," she says.

"Drug release can be further modulated by incorporating pore formers, hydrophilic polymers, and surfactants in the composition or by virtue of a process that creates a more porous structure," Kodipyaka comments. "Drug release is the important determinant to ensure maximum bioavailability at the site of action. Thus, lipid formulations could be tailored to achieve desired drug-release kinetics by careful selection of lipid excipients."

With versatility comes challenges

Lipid-based formulations offer versatility and compatibility in terms of generally recognized safety, route of administration, and capability to overcome bioavailability issues. However, with this versatility, some challenges with LBDDS arise, such as stability issues and drug loading, reveals Karunakar Sukuru, vice-president, Product Development (US & EU) Softgel & Oral Technologies, Catalent.

Drug loading, for example, can be quite low in LBDDS as a result of the improved solubility offered. "Nevertheless, drug loading is a challenge faced by many other bioavailability enhancing technologies," Sukuru adds.

For Kodipyaka, a common challenge associated with lipid-formulations is ingredient stability issues, particularly when using liquid formulations rather than solid forms, and drug precipitation during storage or contact with *in-vivo* GI fluids. "After administration, dilution and digestion effects will lead to a reduction in the solvent capacity of the lipid formulation. As a result, the API that was initially in solution may precipitate, and this may reduce the bioavailability-enhancing potential of the formulation," agrees Speybroeck. "While lipid formulations are generally less susceptible to these effects than those based on water-miscible solvents, some precipitation may still occur. The magnitude of this effect can be assessed using *in-vitro* techniques that consider the effect of formulation digestion."

Lipid-based formulations offer versatility and compatibility in terms of generally recognized safety, route of administration, and capability to overcome bioavailability issues.

Therefore, appropriate design of LBDDS is necessary to ensure that drug precipitation upon exposure to GI fluids is indeed avoided, Sukuru confirms. "Understanding the

mechanism and predicting *in-vivo* performance of LBDDS has gained a lot of attention recently," he says. "Many lipid excipients are naturally derived and contain multiple lipids (e.g., mixtures of mono-, di-, and triglycerides). There may be issues as ratios of lipid components change from batch-to-batch. Because of these variables, it is recommended that drug developers work with experts who have extensive experience and knowledge of the development of LBDDS."

Another challenge experienced with lipid-based formulations is that of Ostwald ripening, which is where small particles dissolve and then re-deposit onto larger particles due to surface energy instability. "Ostwald ripening is a major challenge for lipid-based formulations, particularly for injectable products," says Kodipyaka. "There are a limited number of approved, safe emulsifiers commercially available that can stabilize the emulsion system; hence, it would be very challenging to develop emulsion system with the desired target product profile."

"Finally, while the excipients used to construct lipid formulations are usually quite inert, many of these contain impurities, such as peroxides, aldehydes, or formic acid, that may trigger degradation pathways that are not seen when the same API is formulated in a solid formulation," specifies Speybroeck.

Available techniques and their limitations

Assessing the precipitation risk of lipid-based formulations as a result of dilution and digestion is possible using *in-vitro* experiments. These tests are more complex than standard dissolution tests but are capable of providing a more reliable indicator of lipid formulation performance, notes Speybroeck.

"*In-vitro* lipolysis experiments have been the traditional experiment to study a LBDDS mechanism and correlate it with *in-vivo* performance," confirms Au. "Newer approaches, such as kinetic solubility measurements, are gaining interest to correlate with *in-vivo* behaviour of LBDDS."

Sukuru adds that a main limitation of current techniques that are aimed at overcoming challenges associated with lipid-based formulations is that all the work is undertaken in a closed system, whereas the human body is dynamic and always in motion. "A variety of new techniques and tools are available to quickly evaluate lipid-based formulations. One such tool is fibre optic dissolution testing, which allows for monitoring of dissolution profiles in real-time in a variety of biorelevant media and makes it easier to compare the performance of the formulation without the need for complex and lengthy analytical methods. It is also easier to asses any impact of the media modification," he says. "With such advances in analytical instrumentation, product development can be expedited and made more robust through the generation of data and providing the opportunity to challenge different parameters of the formulation earlier in development."

There is also the emergence of technologies in the field to enhance API loading of lipid-based formulations, adds Speybroeck. "Some researchers have reported on the use of supersaturated lipid formulations (3), whereby the API loading is increased by subjecting the lipid formulation to a heat-cool cycle," he states. "This way, the concentration of API in the formulation is increased beyond its equilibrium solubility, which may lead to several-fold increases in API loading. This technique may be a viable option to reduce administration volume in preclinical and early clinical development. However, the utility for commercial products is more limited given the risk of API precipitation during storage, as the API is present at concentrations above its equilibrium solubility in the formulation."

Regarding ingredients, Speybroeck notes that lipophilic salts are developing within the industry. "While traditional pharmaceutical salt forms are usually developed using small, hydrophilic counterions in an attempt to increase aqueous solubility, lipophilic salts are constructed with large, lipophilic counterions," he says. "These salts may exhibit greatly depressed melting temperatures relative to the free form of the API and therefore also exhibit much higher solubility in lipophilic vehicles."

In terms of unsaturated lipid components, which are prone to lipid peroxidation, formulators can employ saturated medium chain triglycerides along with appropriate antioxidants, explains Kodipyaka. "Excipient compatibility and stress stability studies during early stage development help formulators choose the right excipients according to the degradation pathway of the drug," he says. "Decreased mobility by making semi-solid formulations also can help to physically and chemically stabilize the formulation."

Additionally, alternative ingredients for capsules are coming to the fore, such as the use of hydroxypropyl methylcellulose (HPMC) or polyvinyl alcohol, instead of traditional gelatin-based capsules. "These ingredients are chemically and thermally stable and are less prone to humidity compared to gelatin-based capsules," Kodipyaka confirms. "Furthermore, with the invention of liquid encapsulated micro-spray sealing technology, problems that were common with the conventional banding approach have been resolved."

Size matters

As molecules entering the drug development pipeline are increasing in size and becoming more lipophilic and chemically diverse, solubility challenges are also rising and can lead to a higher level of drug susceptibility to food effects, notes Au. "The broad range of lipid excipients available offer many options to customize formulations to meet the specific needs of the molecule," she says. "Investing time and effort early in

the development of an LBDDS can result in significant savings in time and overall development costs, and often with a better outcome."

With an expanding proportion of drugs gaining fast-track designation, particularly for those therapies aimed at unmet medical needs, the benefits of LBDDS, which were primarily used to introduce life-saving drugs such as HIV proteases and anti-cancer treatments, are apparent, notes Plassat. "For example, within the industry, there has been a growing interest in peptides and other macromolecules due to their high specificity and potency," he states. "The molecules are usually more sensitive to degradation, and lipid-based formulations can provide them with a better environment for long-term stability, and/or protect them from degradation in the GI tract."

Yet, developing a lipid-based formulation essentially remains an empirical endeavour, notes Speybroeck. "Given the plethora of lipids and lipophilic excipients available, initiating a lipid formulation development may seem like a daunting task," he adds. "However, great progress is being made in *in-silico* (computer-assisted) prediction of solubility. Adoption of such techniques may dramatically reduce the initial development effort."

Thanks to these formulation design advancements in addition to new technologies that can enhance API loading and an improved understanding of how lipid-based formulations perform *in-vivo*, Speybroeck anticipates an enhanced adoption of the lipid approach in the future. "I believe we will witness a steady increase in the use of lipid formulations in clinical and commercial drug products going forward," he says.

Taking a lipid-based approach for the formulation and delivery of new molecules with large molecular weights and high lipophilicity has shown great promise, stresses Kodipyaka. "However, technology development and implementation in the area of lipid drug delivery needs to be expedited to catch up with the discovery pace," he summarizes. "A multi-disciplinary approach is required to overcome limitations pertaining to development of lipid formulations for poorly soluble molecules. Knowledge of lipid chemistry, predictive *in-silico* models, nanotechnology, and bio-pharmaceutics coupled with advanced characterization techniques would be helpful in resolving complex issues moving forward."

References

1. R. Savla, et al., *Drug Dev. Ind. Pharm.*, 43 (11) 1743–1758 (2017).
2. V. Jannin, et al., *Indian J. Pharm. Sci.*, 80 (6) 1011–1020 (2018).
3. J. Brouwers, M.E. Brewster, and P. Augustijns, *J. Pharm. Sci.*, 98 (8) 2549–2572 (2009). **PTE**

Optimizing Manufacturing Based on the Storage Stability of Pegylated Products

Chintan Patel, Sanjay Bandyopadhyay, and Gayatri Patel

Research into peginterferon alfa-2b's degradation pathways suggest that drug substance be immediately and continuously converted to drug product when the material is in liquid form.

Depending on the polyethylene glycol reagent and chemistry used to manufacture them, pegylated products may exhibit different degradation patterns under different storage conditions. To ensure product quality, it is essential to prevent degradation, which can occur when temperatures exceed optimal levels during manufacturing, storage, and shipping. To get a better understanding of degradation patterns, research was done to evaluate the stability of pegylated products under various storage conditions.

This article discusses work that was done to examine the effect of repeated freezing and thawing cycles on the stability of peginterferon alfa-2b, and to study its storage stability in frozen as well as liquid form. It also discusses how results might pertain to various other pegylated products. Size-exclusion chromatography, circular dichroism, and fluorescent spectroscopy were all used to evaluate stability under different conditions. Results suggest that storage in liquid form can lead to degradation at temperatures between +2 °C and +8 °C.

Interferons exhibit both antiviral and antineoplastic effects (1). Interferon alfa-2b (Intron A), interferon alfa-2a (Roferon-A), and interferon beta-1b (BETAFERON) are approved for various indications either alone or combined with other agents. Both alfa-2b and alfa-2a types have half-lives of less than 12 hours, necessitating multiple injections (at least three times per week) for the duration of treatment, which can range from three weeks to 24 months (2,3).

Longer-acting versions of both alfa 2b and alfa 2a have been developed to help offset this problem. Examples include peginterferon alfa-2b (Pegintron/ViraferonPeg) and peginterferon alfa-2a (Pegasys). Pegintron/ViraferonPeg has been approved as part of a combination regimen to treat chronic hepatitis C (CHC) in patients with compensated liver disease. Pegasys is indicated for CHC and chronic hepatitis B.

Most of the first generation of pegylated products (i.e., Adagen (Pegademase), Oncaspar (Pegaspargase), Pegintron (peginterferon alfa-2b) and Pegasys (peginterferon alfa-2b) were developed with commercially available acylating PEG reagents (4). Adagen and Oncaspar were prepared using monomethoxy PEG activated with succinimidyl succinate

CITATION: When referring to this article, please cite it as C. Patel et al., "Optimizing Manufacturing Based on the Storage Stability of Pegylated Products," *Pharmaceutical Technology* 43 (10) 2019.

Submitted: 1 May, 2019
Accepted: 14 June, 2019

(mPEG-SS) (5). Pegintron is prepared by conjugating interferon alfa-2b with a single chain 12 kDa PEG activated with succinimidyl carbonate (mPEG-SC), while Pegasys is prepared by conjugating interferon alfa-2a with N-hydroxysuccinimide (NHS) activated 40 kDa branched PEG molecule (6,7). Pegintron is a mixture of biologically active monopegylated positional isomers so that most of the pegylation occurs at the Histidine 34 (His34) residue. Within this residue, a urethane-like bond that is formed by succinimidyl carbonate (SC) conjugation chemistry with the imidazole ring of His34, is hydrolytically labile. In contrast, however, Pegasys is produced utilizing N-Hydroxysuccinimide(NHS) chemistry through amide bond formation. These bonds are not susceptible to spontaneous hydrolysis (8).

For any pegylated interferon, changes in protein temperature stability have been found to depend on the coupling chemistry, degree of pegylation, number of protein subunits, and formulation involved. It is known, for example, that pegylation has no effect on the secondary or tertiary structure of interferon alfa-2b and interferon alfa-2a. Not only the conformational stability of the protein molecule but the stability of the PEG-protein conjugate is important if the drug is to exhibit the desired biological activity and bioavailability. For example, Oncaspar (Pegaspargase), which is produced by conjugating mPEG-succinimidyl succinate (SS) with L-asparaginase, has a short shelf-life when supplied as a liquid solution, where the enzyme activity of L-asparaginase increases upon depegylation (9). In addition, pegaspargase shows different degradation pathways when exposed to high temperature and freeze-thawing stress (10). Pegylated products produced using different PEG reagents and pegylation chemistries (i.e., pegylation with mPEG-SS vs. mPEG-SC) may follow different degradation pathways under different storage conditions. Product may be exposed to sudden temperature excursions during the manufacturing process, storage, and shipping, which can affect product stability. Stability of pegylated products should be evaluated under various storage conditions, considering the nature of the product. The authors researched the effect of repeated freezing and thawing on the stability of peginterferon alfa-2b, as well as the stability of frozen peginterferon alfa-2b and liquid material maintained between +2 °C and +8 °C. Research focused on identifying the degradation pattern of peginterferon alfa-2b under these storage conditions, and were discussed with respect to the stability of various pegylated products.

Maaterials and method

Preparation of peginterferon alfa-2b. Interferon alfa-2b was produced in-house using recombinant DNA technology and pegylated using activated polyethylene glycol with a particle diameter of 12 kDa. Peginterferon alfa-2b was produced by pegylating interferon alfa-2b with 12-kDa monomethoxy polyethylene glycol succinimidyl carbonate (mPEG-SC), to the innovator product, PEGINTRON. PEG conjugation was carried out through integration of a carbamate (urethane) linkage, between N-atoms of the imidazole side-chain of His34 or the μ-NH2 group of N-terminal Cysteine residue, or the ε-NH2 group of Lysine side-chains of interferon alfa-2b and a 12-kDa mPEG-SC molecule.

Pegylation was carried out at pH 6.5 in the presence of a molar-excess amount of mPEG-SC over the protein amount. After pegylation, multiple-column chromatography (using GE's Amersham Biosciences' AKTA) was used to purify the peginterferon alfa-2b, mainly in monopegylated form.

After chromatography, peginterferon alfa-2b was brought into 10 mM sodium succinate buffer using succinic acid and sodium hydroxide (Merck) and maintained at a pH of 6.8. A 0.2-μm sterile filter (Sartopore 2, Sartorius Stedim Biotech GmbH) was then used to filter the protein solution.

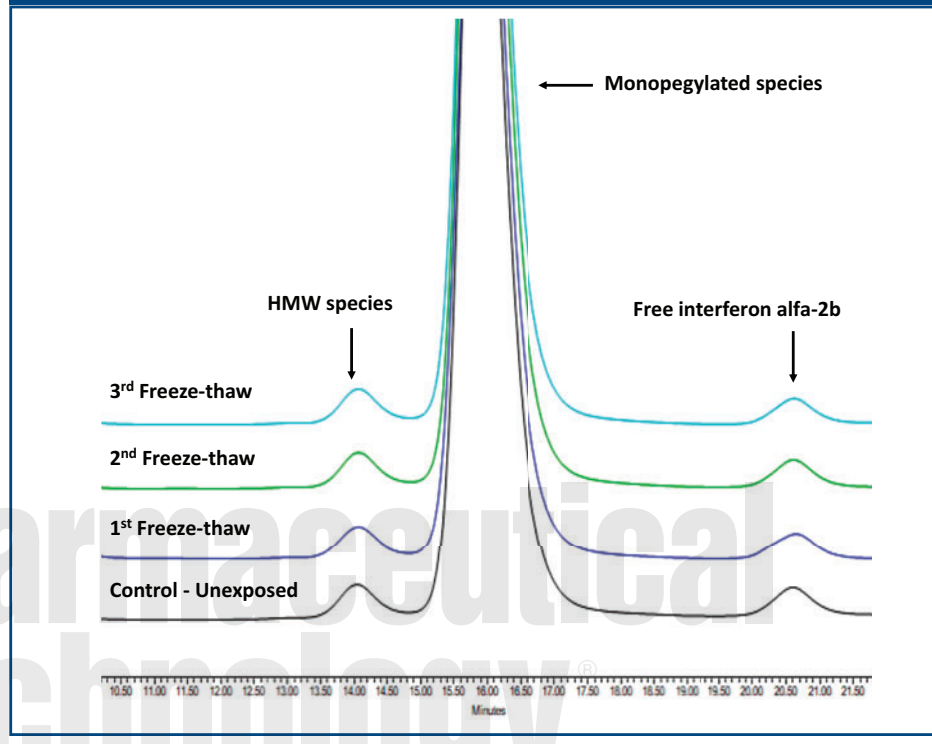
Degradation of frozen vs. liquid peginterferon alfa-2b Peginterferon alfa-2b's degradation pattern was assessed by analysing results of repeated freezing and thawing cycles on the material. To check the effect of repeated freezing and thawing, peginterferon alfa-2b solution was aliquoted with 1 mL solution in a 10-mL container (Thermo Scientific) made of polytetrafluorethylene (PTFE) (Teflon, DuPont). Samples were frozen at or below –70 °C in the deep freezer (Thermo Electron Corporation, Model No.: ULT1740-3-V40). Thawing was done at room-temperature and was considered complete when the frozen mass had been completely converted into liquid. To check the degradation of liquid peginterferon alfa-2b protein, liquid samples were stored between +2 °C and +8 °C in the container, while samples that had been frozen at or below -70 °C were used to determine the stability of frozen material. Samples were withdrawn at different time intervals and analyzed by different test parameters.

Analytical evaluations. The presence of free interferon alfa-2b was assumed to indicate that depegylation had occurred in the test samples. High-performance size-exclusion chromatography (HP-SE), utilizing an ultraviolet (UV) detector, was used to measure samples to determine stability. Measurements were performed on a Shimadzu LC 2010-CHT series HPLC system equipped with a Tosoh Biosciences' TSK gel G3000SWXL column 7.8-mm ID × 30.0 cm/L). Before injecting the sample, the column was pre-equilibrated with 0.2 M phosphate buffer containing 10% ethanol at a pH of 6.8 and a flow rate of 0.5 mL/min at an oven temperature of 25 °C. After the column was equilibrated, 10-μg samples were injected and analyzed in isocratic mode at a flow rate of 0.5 mL/min. Chromatographic separation was monitored at 214 nm utilizing the UV detector.

Test samples exposed to repeated freezing and thawing cycles were also tested to determine the structural integrity of peginterferon alfa-2b protein under these conditions by comparing them with initial sample that had not undergone freezing or thawing. Far-UV circular dichroism (CD) spectroscopy and spectrofluorometry (using a Jasco J-1500 instrument equipped with an MCB-100 Peltier-based temperature controlled assembly) was used to analyze the secondary structure of peginterferon alfa-2b samples.

A smoothing algorithm was used on the CD spectrum for baseline correction, and peak position was identified by using Spectra Manager software. Fluorescent spectroscopy (using a JASCO FP-8300 instrument equipped with a MCB-100 Peltier-based temperature-controlled assembly) was then used to evaluate the tertiary structure of peginterferon alfa-2b protein in the test samples. The temperature of the sample holder was controlled, and samples were incubated at 20 °C for 5 min under stirring conditions. Samples were then excited at 280 nm to capture total intrinsic fluorescence emission. Emission spectra were collected in the range of 300–450 nm. Again, a smoothing algorithm was used for smoothing and baseline correction, and Spectra Manager software was used to identify the maximum peak position.

Figure 1: Overlaid HP-size exclusion chromatograms of peginterferon alfa-2b samples exposed to repeated freezing and thawing in comparison with unexposed initial samples.



Results

Effects of repeated freeze-and-thaw cycles on the stability of Peginterferon alfa 2-B. Peginterferon alfa-2b protein present in 10-mM sodium succinate buffer at a pH of 6.8 was exposed to freeze-thaw stress as described previously. Samples were exposed to three consecutive freezing and thawing cycles and evaluated to determine whether there had been an increase in the level of free interferon alfa-2b by HP-SEC.

Figure 2: Overlaid Far-UV absorbance spectra of peginterferon alfa-2b samples exposed to repeated freezing and thawing in comparison with unexposed initial samples.

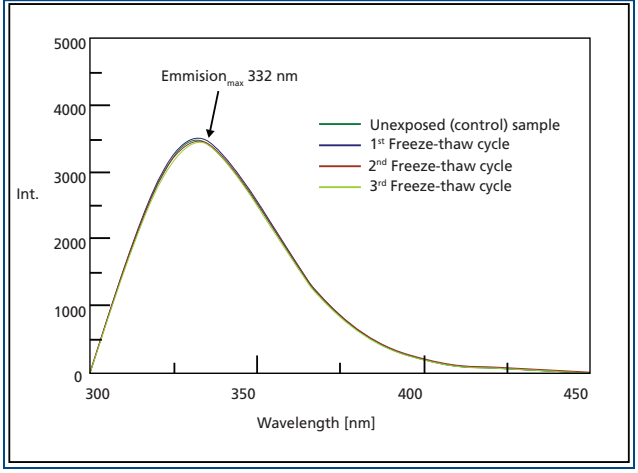


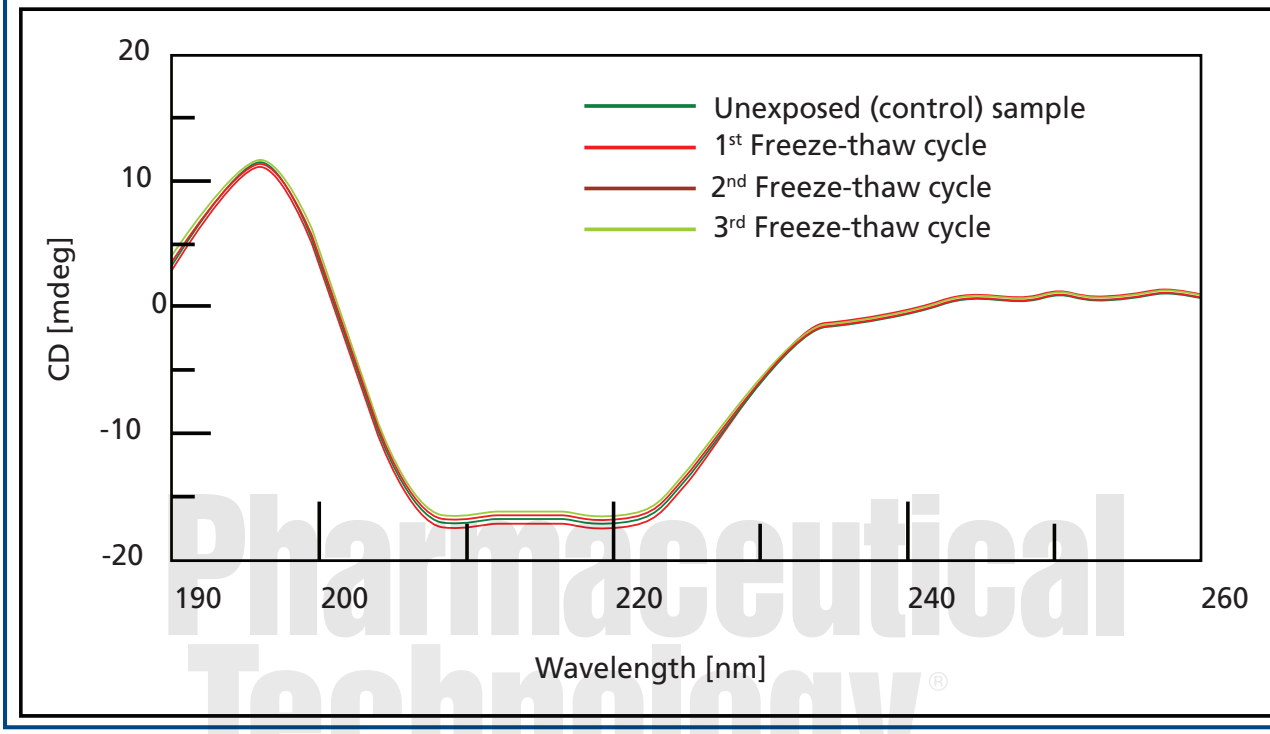
Figure 1 shows the chromatographic profiles obtained with the samples of peginterferon alfa-2b before and after exposure to the freezing and thawing stress. The chromatogram obtained for the test samples exposed to freezing and thawing cycle shows no increase in the peak corresponding to free interferon alfa-2b, indicating no further increase in the level of free interferon alfa-2b upon repeated freezing and thawing compared to the result obtained with the unexposed initial sample.

Secondary structure analysis of the test samples of peginterferon alfa-2b exposed to repeated freezing and thawing was conducted by CD spectroscopy in the far-UV (260–190 nm) region to assess the effect on structural integrity of protein. As illustrated in **Figure 2**, CD spectra obtained with the test samples exposed to repeated freezing, and thawing cycles were observed to overlap with the spectra obtained for the unexposed initial sample in the far-UV region. The overlapping CD spectra obtained with all the samples showed absorbance minima at wavelengths 208 nm and 222 nm, typical for cytokine molecules, which remain unaltered upon repeated freezing and thawing of the peginterferon alfa-2b in presence of 10 mM sodium succinate buffer at pH 6.8.

Figure 3 shows results obtained with peginterferon alfa-2b test samples analyzed by spectrofluorometry to evaluate the effect of repeated freezing and thawing on ter-

ALL FIGURES COURTESY OF THE AUTHORS.

Figure 3: Overlaid fluorescence emission spectra of peginterferon alfa-2b samples exposed to repeated freezing and thawing in comparison with unexposed initial samples.



tiary structure. The fluorescence spectra obtained with the test samples that had been exposed to repeated freezing and thawing were observed to overlap with spectra obtained for unexposed initial samples, indicating no effect on tertiary structure of peginterferon alfa-2b protein.

Stability of peginterferon alfa-2b in frozen vs. liquid form

Peginterferon alfa-2b in 10-mM sodium succinate buffer at pH 6.8 was stored in liquid form between +2 °C and +8 °C, and in frozen form at temperatures at or below –70 °C for three months to check for any increase in the level of free interferon alfa-2b under both the storage conditions.

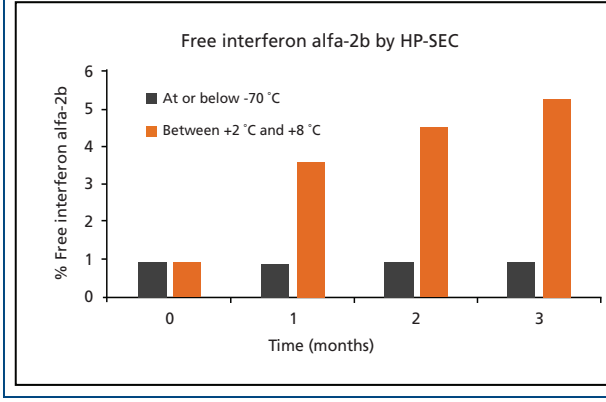
Samples were withdrawn at different time intervals and analyzed by HP-SEC. The level of free interferon alfa-2b in the test samples withdrawn at different time intervals from both the storage conditions is shown in **Figure 4**. When stored as liquid solution between +2 °C and +8 °C, the level of free interferon alfa-2b increased, with time indicating depegylation under these storage conditions.

However, when stored under frozen conditions, even for up to three months, the material showed no significant change in the level of free interferon alfa-2b observed. In a separate study, stability of peginterferon alfa-2b was established at least up to 12 months when stored at or below –70 °C without any significant depegylation.

Discussion

Experimental results demonstrate that peginterferon alfa-2b protein can withstand up to three multiple freeze-thawing cycles without showing any loss of structural integrity and depegylation. When stored under frozen conditions (i.e., at or below –70 °C), the material does not show any increase in level of free interferon alfa-2b for at least three months, showing that no depegylation had occurred. These results stand in contrast to what was observed with the liquid form.

Figure 4: Stability of peginterferon alfa-2b under frozen condition and liquid form: Increase in level of interferon alfa-2b (depegylation) by HP-SEC.



For most biological products, drug substance is generally stored in the frozen form and known to have longer shelf-life of at least about two years before it gets converted into the drug product upon formulation. However, it is known that the manufacturing process of Oncaspar liquid drug product (Enzon Pharmaceuticals Inc.), involves continuous processing of the drug substance to produce drug product wherein the hold time stability of the drug substance material is established between +2 °C and +8 °C.

In a separate study, authors have found that pegaspargase does not show stability upon freezing and thawing (10). Unlike results obtained with pegaspargase, which is a multi-subunit protein highly susceptible to conformational changes upon freezing and thawing, peginterferon alfa-2b produced using mPEG-SC with carbamate linkage showed high stability when exposed to repeated freezing and thawing. These observations suggest that different protein molecules pegylated with different PEG reagents and using different pegylation chemistries may exhibit different degradation patterns when exposed to freezing and thawing stress. Therefore storage conditions during various manufacturing process steps must be selected very carefully, based on the pegylation chemistry utilized, the type of protein molecule involved (i.e., single subunit vs. multiple subunits) and degree of pegylation.

Oncaspar's susceptibility to conformational changes of the protein molecule upon freeze-thawing and depegylation when stored at +2 °C and +8 °C suggests that the drug substance material should be immediately and continuously converted to drug product during fill/finish manufacturing so that the material does not have to be stored.

Based on results obtained with the peginterferon alfa-2b samples stored at or below –70 °C, peginterferon alfa-2b can be stored in frozen form. This allows drug substance and drug product manufacturing to be decoupled, removing the need for continuous processing. The storage stability of peginterferon alfa-2b in frozen form can enhance manufacturing flexibility, particularly for production campaigns in a multi-product facility.

Another pegylated product, Pegasys (peginterferon alfa-2a) which is prepared by conjugating interferon alfa-2a with an NHS-activated, 40-kDa branched PEG molecule with stable amide linkage supplied as a liquid solution with the shelf-life of two years when stored between +2 °C and +8 °C whereas Oncaspar supplied in the form of liquid solution has a shelf-life of only eight months, due to removal of PEG from its protein backbone.

Like Oncaspar, peginterferon alfa-2b remains unstable when stored as a liquid solution between +2 °C and +8 °C and degrades through depegylation as these experiments confirmed. Due to the unstable linkages present in Oncaspar and peginterferon alfa-2b, it is crucial to produce the drug product material as a lyophilized powder and reconstitute it just before the injection.

Conclusion

Peginterferon alfa-2b exhibited stability after repeated freezing and thawing stress cycles, without the addition of any cryoprotectant. No impact was observed on the protein molecule conformation upon repeated freezing and thawing. When stored in liquid form, however, even at +2 °C to +8 °C, peginterferon alfa-2b shows significant depegylation. When stored in frozen form, it remains stable without any depegylation. Pegylated products may exhibit different storage stabilities when exposed to repeated freezing and thawing, based on the PEG reagent and pegylation chemistry utilized. It is thus very important to evaluate the storage stability of pegylated products at various steps of the manufacturing process. Identifying degradation patterns that will occur under different storage conditions can play important role in optimizing both drug substance and product manufacturing process designs.

Acknowledgement

The authors wish to thank Sanjeev Kumar Mendiratta, president, biologics R&D and manufacturing, and Chandresh Bhatt, research associate, biologics R&D, at Cadila Healthcare Ltd.'s Zydus Research Center in Ahmedabad for their scientific and technical guidance.

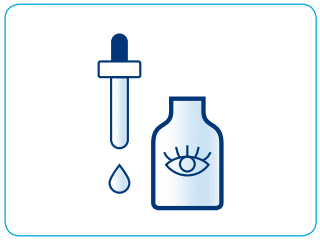
References

1. L. Edwards, *Dermatol. Clin.*19 (1), 139–46 (2001).
2. P. Glue P, et al., *Clinical Pharmacology & Therapeutics* 68(5), 556–567 (2000).
3. A. Kozlowski and J. Milton Harris, *J. Control. Release.* 72 (1–3), 217–224 (2001).
4. P. L. Turecek, et al., *J. Pharm. Sci.* 105 (2), 460–475 (2016).
5. F.F. Davis, "PEG-Adenosine Deaminase and PEG-Asparaginase", in Polymer Drugs in the Clinical Stage, H. Maeda et al, Editors, part of the series *Advances in Experimental Medicine and Biology*, Springer, *Boston, MA*, pp. 51-58 (2003).
6. Y. S. Wang, et al., *Adv. Drug Deliv. Rev.* 54 (4), 547–570 (2002).
7. P. Bailon et al., *Bioconjug. Chem.* 12 (2), 195-202 (2001).
8. M.J. Grace, D. Cutler, *Antivir. Chem. Chemother.* 15 (6), 287-97 (2004).
9. European Medicines Agency, *Committee for Medicinal Products for Human Use, Oncaspar Assessment Report*, November, 2015.
10. P. Chintan, B. Sanjay, P. Gayatri, *Pharm. Tech.*, 43 (4), 40-48 (2019). **PTE**

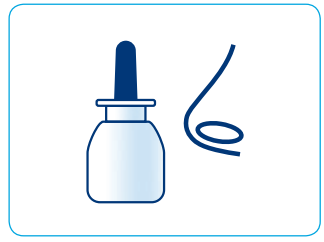
Chintan Patel is researcher and **Sanjay Bandyopadhyay** is vice president, both at Cadila Healthcare Ltd.'s Zydus Research Center in Ahmedabad, Gujarat, India; **Gayatri Patel*** (gayatripatel.ph@charusat.ac.in), is associate professor of pharmaceutics and pharmaceutical technology at Charotar University of Science and Technology, Changa, Gujarat, India.

*To whom all correspondence should be addressed.

Quality. Proven

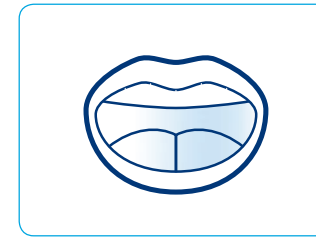


Opthalmics

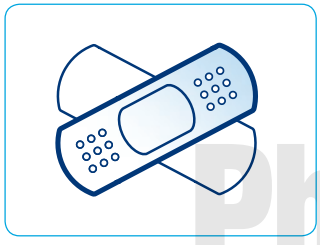


Nasal formulations

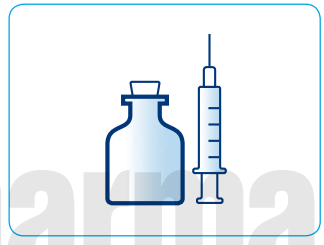
Topical formulations



Oral formulations

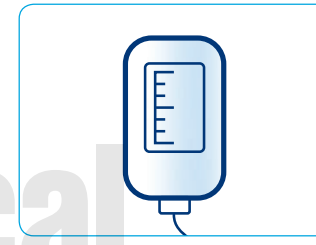


Wound care



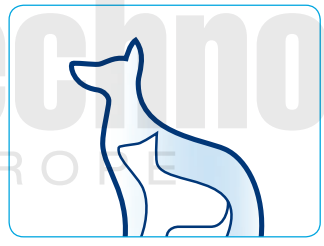
Vaccines

Personal care



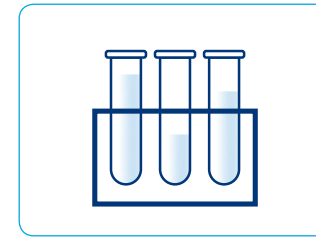
Medical devices

Contraception formulations



Veterinary products

Antiseptic agents



Diagnostic testing and other analysis

Regulations don't compromise. Neither can you.

It's not only the authorities who demand proven quality, purity and traceability every time. You do. That's why our Quats are manufactured to the strictest cGMP regulations, and not a single ingredient is delivered without meeting your own uncompromising standards. Whether it is **Benzalkonium Chloride, CTAB, Cetrimide** or **Strong Cetrimide Solution** for ophthalmic, nasal sprays, topicals, oral products or medical devices, our cGMP Quats can be used as excipients or APIs across a variety of applications. We know that your business depends upon absolute confidence in your supplier – so we've built our business to deliver the reliability you need. **Excellence. Multiplied.**

Learn more about our full range of pharma grade Quats at **novonordiskpharmatech.com**

Visit us at

CPhI worldwide

P-mec InnoPack iCSE FDF

Stand #42D32 (HALL 4.2)

Novo Nordisk Pharmatech A/S

novo nordisk®

Best Practices in Handling HPAPIs

Establishing OEL data and ensuring appropriate engineering controls are crucial aspects of safe handling.

Jennifer Markarian

Handling high-potency APIs (HPAPIs) is increasingly important for drugs such as antibody-drug conjugates, which can have occupational exposure levels (OELs) below 0.1 µg/m³ (100 ng/m³). Contract development and manufacturing organization (CDMO) Piramal Pharma Solutions opened a new wing at its Riverview, MI, USA site in 2019 that is dedicated to the production of HPAPIs with low occupational exposure levels (OELs). Prior to this addition, the site had the containment capability and engineering controls to safely handle HPAPIs with OELs down to 1 µg/m³. The new wing is designed to handle HPAPIs with OELs less than 1 µg/m³ and as low as approximately 20 ng/m³. *Pharmaceutical Technology Europe* spoke with Vince Ammoscato, vice-president and Riverview site head, about some best practices for handling HPAPIs.

Challenges

PTE: What are some of the biggest challenges for handling HPAPIs?

Ammoscato (Piramal): The biggest challenge, especially as a CDMO, is establishing the correct, data-driven, most up-to-date, OELs for chemical entities. Obviously, early on in development, OEL data does not exist, especially if you are looking to make drug substance/API that will be used to establish a toxicology profile (for a toxicology study). As a result, one would involve the product sponsor/client, and our expectation is that the client would give us their thoughts on what the potential OEL could be, based on structural alerts, the proposed indication, and therapeutic effect(s) of the chemical entity. Additional third-party support, such as industrial hygienists/toxicologists, can be employed to propose an OEL based on all those factors.

Industrial hygienists/toxicologists will do an assessment for you, or on behalf of the sponsor, that will establish what the OEL could be for the chemical entity. Otherwise, you would use data like the LD50 [median lethal dose] if available. Our approach is to always default to a more conservative occupational exposure band (OEB) in terms of containment best practice. Safety for our employees is paramount and as a result, we would rather be sure about our containment approach; if the data later suggests a chemical entity is less potent, then you can adjust your containment approach based on the actual OEL.

Our typical client is sophisticated, and I would say only about 20% of projects do not have an OEL at the start. The majority have some level of data and recommend an OEL during the request for proposal process. The OEL is based on data or based on the potential client's internal risk levels. Big Pharma companies, as an example, automatically default an oncology asset to their Category IV or V OEB. This approach offers protection to the sponsor/client by recommending the chemical entity as potent and once data is established, the OEB can be adjusted accordingly.

The other challenge that we are managing is, even though we have been an HPAPI site for more than 30 years, going to the next level (OEB V) of containment—where you start handling chemical entities with OELs in the ng/m³ range—causes safety concerns with employees. We have the appropriate engineering controls and we have put systems and processes in place to be able to handle the highly potent compounds. However, as chemists and EH&S [environmental health and safety] professionals, we know that establishing all the pertinent data is very important and with the appropriate training, our employees continue to feel safe as they work with these highly potent chemical entities.

We have created a culture of safety using industry best practices and have engineered a state-of-the-art facility that makes employees comfortable from a containment perspective.

Best practices

PTE: When handling HPAPIs, what are some of the best practices for engineering controls and measuring the quality of the environment in your classified manufacturing spaces?

Ammoscato (Piramal): The first line of defense is your engineering controls. Proper facility design and engineering, including the heating, ventilation, and air-conditioning systems; approaches to barrier isolation; and the incorporation of

gowning/de-gowning areas are key considerations. Appropriate facilities, engineering controls, and safety protocols are, in fact, increasingly imperative as newer HPAPIs under development have ever declining OELs. Facilities must have controlled air flow (single-pass) and pressure systems with filtration capabilities and airlocks and vestibules around both laboratory and manufacturing suites. The use of closed restricted air barrier systems (RABS), isolators, automated handling equipment, and disposable technologies are increasingly common as means for effectively minimizing the potential for exposure of operators and the environment to potent compounds. The use of appropriate personnel protective equipment (PPE), comprehensive quality management systems, industrial hygiene programs, highly detailed operating procedures, and extensive training programs are also essential. It is really about verified containment more than anything, which requires establishing actual data to prove that the engineering controls you designed and put in place actually work as designed. This verification can be established through surrogate testing of the containment systems.

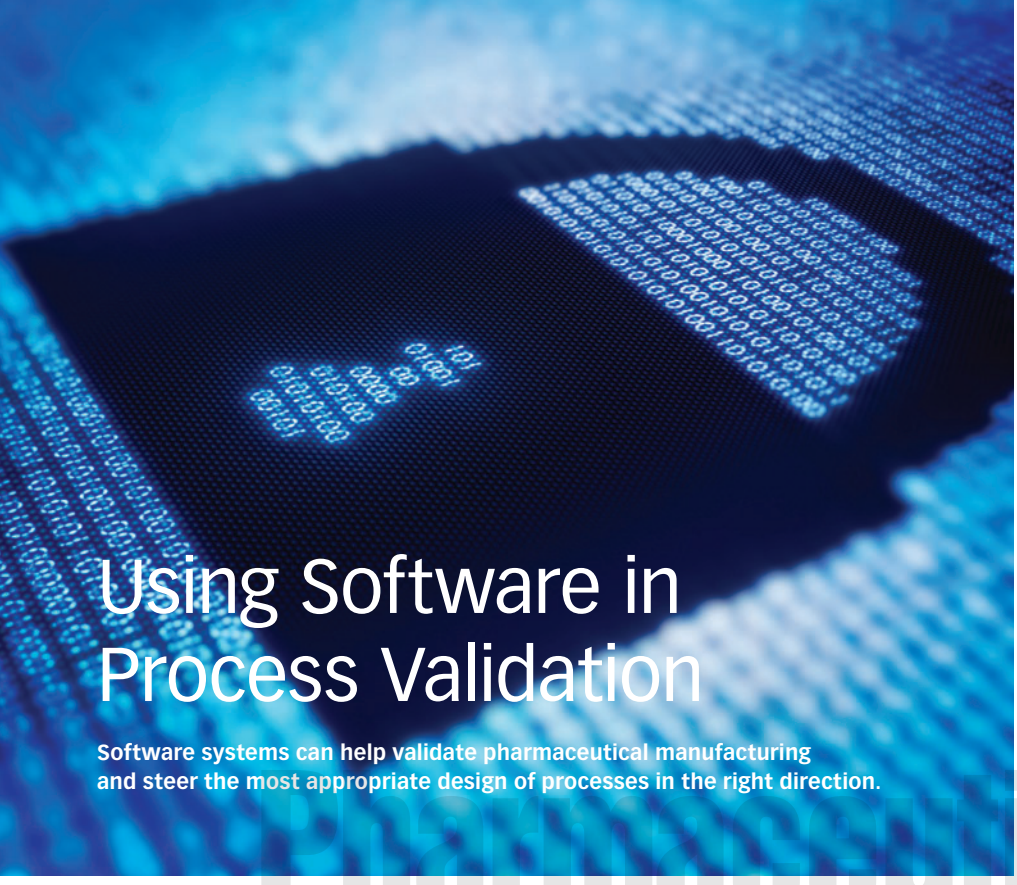
We used surrogate testing with a third-party contractor. They tested all our containment technologies with a surrogate (naproxen) and performed all the required operations when handling a potent chemical entity. Sampling points were strategically placed during the testing to detect any breaches within the engineering containment controls. Having that data to support the engineering containment controls instills confidence in our employees and ensures that we are working safely.

Big Pharma, or the more sophisticated clients, expect you to have dynamic surrogate data [replicating process activities using a surrogate compound] confirming the containment capability for them to bring their projects to your site.

Some of them do EH&S audits as part of their due diligence, not only quality audits. So, during the EH&S audit they might ask for that information. They will ask, 'How do you know that your containment solutions can actually handle down to 20 ng/m^3 in terms of OEL?' Having the dynamic surrogate testing results answers their question.

PTE: What are some of the challenges and best practices in packaging/shipping HPAPIs?

Ammoscato (Piramal): As a site we have always dealt with HPAPIs, so nothing has really changed. You just need to ensure there is no open handling of materials. Packaging is all done within glovebox technology. With regard to shipping, you follow your shipping procedures, with secondary containment systems in terms of the shipping container. We ensure through standard operating procedures that we have all the appropriate documentation and labeling to establish and communicate to the receiving party that the material they are receiving is a HPAPI. You also want to do your due diligence to ensure that the facility you are shipping to can actually handle the HPAPI in terms of receiving it and managing it at their facility. **PTE**



Using Software in Process Validation

Software systems can help validate pharmaceutical manufacturing and steer the most appropriate design of processes in the right direction.

Robert Glaser is chief technology officer at Auvesy, Inc.

Within pharmaceutical manufacturing, the goal of process validation is to build quality into the operation at every step to ensure consistent product quality. It seems straightforward, but how does one achieve this when it involves a myriad of multiple systems (programmemable logic controllers [PLCs], human-machine interfaces [HMIs], control systems, etc.) and requires a team effort that encompasses people from various disciplines within the plant?

It is important to design processes that ensure product quality, safety, and efficacy. Today's software systems can help validate pharmaceutical manufacturing and steer the most appropriate design of processes in the right way. For instance, these systems can deliver clear documentation, provide version control for the multitude of systems in use, and perform backup to ensure all risks are mitigated.

Software systems have become instrumental as validation expands from analytical methods used for the quality control of drug substances and drug products to computerized systems for clinical trials, labelling, or process control. Quality cannot be adequately ensured merely by in-process and finished product inspection or testing. Validation must happen at each step of a manufacturing process, which involves lots of team members from engineers to quality control to compliance officers, etc. to ensure that the finished product meets all quality attributes, including specifications.

Documentation and traceability for compliance

Part of the validation process is in the documentation. There needs to be integrated support for documentation with 100% clarity and traceability. In addition to this, version control of all software systems used within the pharmaceutical manufacturing process is necessary to ensure compliance with current good manufacturing practices (CGMPs). These regulations state that manufacturing processes must be designed and controlled to ensure that in-process materials and the finished product comply with quality requirements that have already been predetermined and assure consistency and reliability (1). The US regulations (21 *Code of Federal Regulations* [*CFR*] Parts 210 and 211) encompass requirements for approving or rejecting processes and specifications that impact drug quality.

In fact, 21 *CFR* 211.22 requires clear, written documentation for quality control and any anomalies or deviations must be justified and documented as well. To meet such compliance regulations, it is crucial to deploy software specializing in version control, backup, and documentation.

In highly regulated industries such as the pharmaceutical industry, the 'four eyes principle', otherwise known as the two-person rule, is a requirement that mandates two individuals must approve an action before it can be taken, and this requirement is also usually managed by the same software system that ensures process validation.

The version control system needs to be vendor-agnostic, which further safeguards that validation is properly addressed.

The four eyes principle gives another reason for deploying a validation software system that is able to integrate seamlessly with a full range of automation devices and equipment commonly in use by pharmaceutical manufacturers and not just tied to one single manufacturer. The version control system needs to be vendor-agnostic, which further safeguards that validation is properly addressed.

Pharmaceutical software systems for process validation

Validation software systems help manage and keep track of all types of activities that take place over the lifecycle of the product and process: whether a piece of equipment designed to manufacture something, a process/recipe to make something, or a computer programme to control something.

With validation, it is instrumental to make sure the process is repeated exactly step by step all the way through and is achieving the end




Nemera

Patient-focused drug delivery devices

Drug Delivery Devices
Innovative developments
Customized solutions
GMP customer IP manufacturing


we put patients first



www.nemera.net
information@nemera.net
Phone: +33 (0)4 74 94 06 54

result within the allowed tolerances. For instance, temperature set points for producing certain drugs would have the processes validated and assigned validation thresholds. For the threshold, each individual step would be assigned a certain range, such as the temperature could fluctuate from five to six degrees or anywhere in-between, but if it crosses over to seven degrees, the process would be flagged and product considered out of specification.

The pharmaceutical industry has a need for validation, which is best done not manually but rather using a sophisticated system. For instance, such software systems will automatically store the new versions or copies as they're made. When a new staff member logs in, the system will know who last notated the file; everything is time-stamped, allowing for a clear audit trail. It also ensures all the correct data are being captured. It can prompt the user to enter notes and/or comments, which are stored by the system and can be provided in real time. This way the user can easily reference why changes were made. Additionally, the system can let the user know if a contractor made changes that were saved to an external drive. The system can alert the person in charge that they need to get a copy of the drive. Currently, this process is often handled manually. In many instances, pharmaceutical companies will use external contractors and then realize thereafter the need for better controls to be put into place. Team leaders see the need for a smart version control and a backup system to safeguard them from any potential problems.

Such systems as described are typically used on a daily basis. They are especially helpful to developers who are making the code changes. With automated validation in place, many issues related to tracking changes go away. For example, when using the validation system, the user would simply log into the system and use the latest copy of the programmeming file from the central repository before beginning work. They wouldn't worry about having the latest version and would have any notes or comments that may need to be addressed. Once done with the day of work, the user would simply save all the changes and essentially put the file back on the shelf and check it back into the system along with any notes or comments.

The validation system should act as an automated backup or scheduler. It should connect to the control network without human involvement.

Automating validation

The validation system should act as an automated backup or scheduler. It should connect to the control network without human involvement. It should automatically reach out to the devices in the network to obtain the current copy that is running on a device and check it against the central repository to ensure its correct. Nothing should happen that is outside of the rules for cGMPs.

In a validation system, there is also flexibility, because the user can choose how frequently they would schedule a backup. Most will do it on a daily or shift basis, so that any and all changes will be noted. For example, perhaps somebody walked up to a controller and put some code on it without letting anyone know. A validation system would pick up on that and flag it. The system will catch vulnerabilities through regular scanning intervals.

The system compares what is actually running on the device to what is assumed should be running there. If changes are noted that are not running, the system will conduct a comparison to determine if there are any issues. It takes into account just the code differences. For example, if there are 10,000 lines running on a controller, the system will simply highlight what is changed and will send that information to an email distribution list so that a manager or decision-maker can decide what action to take.

This change-control methodology focuses on managing change to prevent inadvertent consequences. Certain manufacturing changes (i.e., changes that alter specifications of a drug or a critical device attribute or bioavailability) are mandated to have regulatory filings and prior regulatory approval. Change is an inherent part of the lifecycle of a pharmaceutical product. A change can be an addition to, deletion of, or modification to a manufacturing process, material, product, procedures, or equipment.

Conclusion

Validation is used in the process design stage through commercial production and can provide the scientific evidence that a process can consistently result in delivering a quality product. When manufacturing pharmaceutical drugs, there must an accurate, repeated degree of certainty in obtaining consistent results. A lot of time and money is spent on certifying one individual way of making a particular drug. Digital validation systems help to set a protocol that requires review, signoff, and signatures. The protocol is always checked and authenticated before the process can go into production. Software systems are, therefore, key in the solution to help pharmaceutical companies get to a validated state.

Reference

1. US 21 *Code of Federal Regulations* Parts 210 and 211. PTE

More on data integrity

For more on data integrity, visit PharmTech.com to read the following:

- Keys to Manufacturing Data Integrity www.PharmTech.com/keys-manufacturing-data-integrity
- Can Bioprocessing Achieve Digital Transformation? www.PharmTech.com/can-bioprocessing-achieve-digital-transformation
- Removing Gaps in Data Integrity www.PharmTech.com/removing-gaps-data-integrity-0
- Is Simplification Aiding Data Integrity Compliance? www.PharmTech.com/simplification-aiding-data-integrity-compliance-0

Maximize

Your Molecule's Full Potential

Formulation challenges. Clinical supply hurdles. Limited manufacturing capability or capacity. Market fluctuations and demand surges. Lifecycle management. Risk mitigation. Patent expiry concerns.

At BioPharma Solutions, a business unit of Baxter, we know the high-stakes challenges you face in today's complex parenteral marketplace – and how the work we do is vital to the patients you serve.

That's why we work closely with you at every step to help you achieve your molecule's full potential and your commercialization objectives – building on over 85 years of Baxter innovation, expertise and specialization in parenterals.

Learn more about us at
baxterbiopharmasolutions.com

Baxter

BioPharma Solutions

Lessons from FDA 483s and cGMP Inspection Data

Production and process controls, organization and personnel were the top problems found, while packaging and labelling citations increased in 2017 and 2018.

Ajay Babu Pazhayattil is a management consultant (ajpazha@gmail.com). **Marzena Ingram** is a senior manager, quality and compliance at Eurofins CDMO. **Naheed Sayeed** is deputy director, validation services at Sanofi.

To provide insight into regulatory trends and factors contributing to noncompliance, the authors analyzed data from Form 483 observations issued by the US Food and Drug Administration during routine investigations of finished drug and API manufacturing sites between 2014 and 2018. The goal was to provide pharmaceutical quality compliance professionals, managers, and operators with insights into how they can best strengthen compliance and develop appropriate solutions for key regulatory compliance issues. This article summarizes results of the study.

To review the basics, form 483s are issued by FDA's Office of Regulatory Affairs (ORA), which is responsible for field activities such as site inspections and enforcement (1). ORA inspectors issue Form 483 observations when they find current good manufacturing practice (cGMP) violations during a facility inspection. These observations are then presented to the company's senior managers to notify them of the need to correct compliance deficiencies.

Inspection observations are crucial, because they define the site's state of compliance. Companies that receive 483s are expected to ensure that steps are taken to correct problems and address the observations and any auxiliary systems that are also deficient but not cited. The final establishment inspection report (EIR) then determines the resulting regulatory actions, considering the observations, proposed corrective measures, and evidence collected.

Three different types of observation classifications (2) are possible:

- No Action Indicated (NAI) indicates that no objectionable conditions were found during inspection and that no further regulatory action required.
- Voluntary Action Indicated (VAI) shows that objectionable conditions were found, but the agency is not yet willing to take any regulatory action.
- Official Action Indicated (OAI) shows that ORA will recommend specific actions.

This study used data from FDA's Inspection Classification Database, which was established in 2009 as part of a transparency initiative (3). The analysis used data classified as final, which is updated by FDA and posted on the agency's website each month. Any undisclosed inspections are not captured in the list. The inspectional observation data set files for years 2014, 2015, 2016, 2017, and 2018 provided the full list of audit observations. For instance, the 2014 list of inspectional observations included inspections that ended between 1 October 2013 and 30 September 2014.

FDA recorded a total of 2997 audit observations in 2014, including 645 Form 483s issued for finished formulation and API sites, which, in turn, were classified into nine categories (4):

- Subpart B, organization and
- personnel
- Subpart C, buildings and facilities
- Subpart D, equipment
- Subpart E, control of components and drug product containers and closures
- Subpart F, production and process controls
- Subpart G, packaging and labeling control
- Subpart H, holding and distribution
- Subpart I, laboratory controls
- Subpart J, records and reports.

Table I: 483 observations, final drug product and API 2014-2018.

Year	483 (Drug)	Observations
2014	645	2997
2015	678	3626
2016	691	3500
2017	694	3343
2018	716	3344
Total	3424	16810

IVAN TRAIMAK - STOCK.ADOBE.COM

emergent
biosolutions®

BDS Manufacture | Single-use Platform | Aseptic Fill/Finish | Vials & Syringes | Clinical & Commercial

Protected.

20 SINCE 1998 EMERGENT BIOSOLUTIONS

People, Products & Possibilities

Everyone wants to be protected. With Emergent BioSolutions, you can be sure you are. They have a proven track record as a world-class provider of contract manufacturing services, for both bulk drug substances and sterile injectable drug products. They are dedicated to one simple mission: to protect and enhance life.

See how Emergent protects lives.

ebsi.com/CDMO
800-441-4225 | CDMO@ebsi.com

Figure 1: Final classified form 483 observations, final drug product and API.

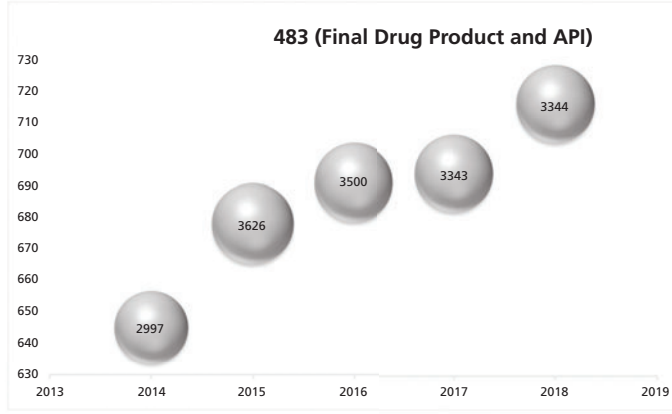


Figure 2: Number of observations by good manufacturing practice (GMP) subsections.

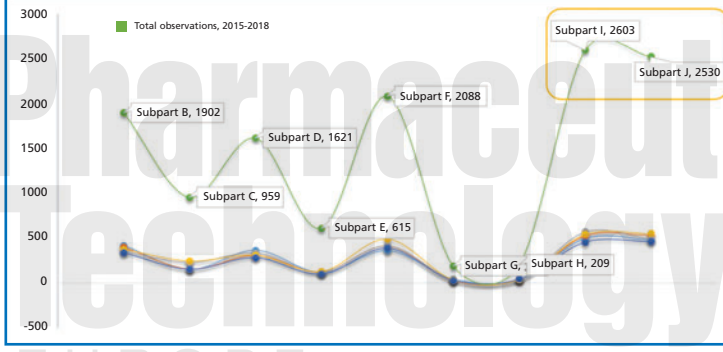
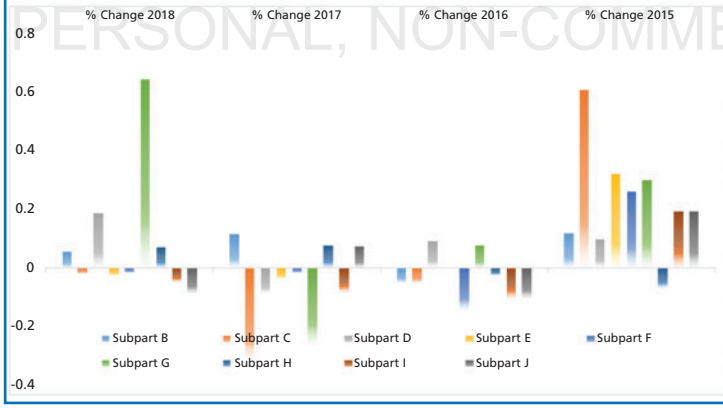


Figure 3: Change of observation types, year over year (in percentages).



The inspection classification database detailed the number of official and voluntary actions (OAIs and VAIs), whether at US manufacturing sites or at sites outside of the United States.

The authors used the Pearson correlation coefficient to identify any positive correlation between the variables, where positive correlation indicates that as the values of one variable increase the values of the other variable increase (5).

Results and discussion

Between 2014 and 2018, the total number of FDA Form 483 audit observations was found to range from 2997 to 3626, with an average of 3362 observations per year. The agency issued a total of 3424 Form 483s, an average of 685 per year. However, 716 483s were issued in 2018, a higher number than seen in previous years (**Figure 1** and **Table I**).

Figure 2 and **Table II** summarize the nine categories of inspection observations and associated subsections. The data provide a clear indication that most 483 observations were related to Subpart I–laboratory controls, which accounted for 2603 observations, and Subpart J–records and reports, with 2530 observations. The other top contributors were Subpart F–production and process controls (with 2088 observations), Subpart B–organization and personnel (with 1902 observations), and Subpart D–equipment (with 1621 observations).

Figure 3 illustrates the percentage changes in the identified observation categories. The most relevant fluctuations would be the increase in FDA observations for packaging and labeling control (Subpart G) in 2017 and 2018. Also noteworthy is the spike in equipment (Subpart

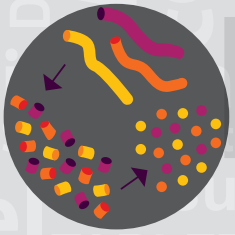
Table II: 483 observations, final drug product and API 2014–2018.

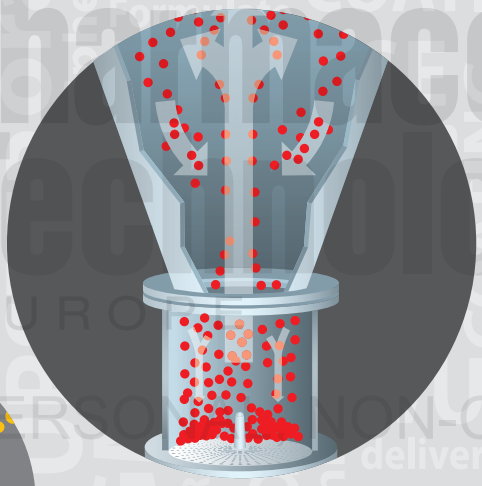
Subpart	Subpart B	Subpart C	Subpart D	Subpart E	Subpart F	Subpart G	Subpart H	Subpart I	Subpart J
2018	424	158	370	124	367	51	45	501	485
2017	401	161	311	127	415	31	42	526	532
2016	359	236	342	132	422	42	39	575	495
2015	379	249	313	132	493	39	40	544	554
2014	339	155	285	100	391	30	43	457	464
Total	**1902**	**959**	**1621**	**615**	**2088**	**193**	**209**	**2603**	**2530**

COATINGS®

Coating Place

Original Wurster Technology





Oradel®

Oral Delivery Innovation

At Coating Place, every coating formulation is customized based on the unique characteristics of the project. Using our **Oradel®** oral delivery techniques, we can achieve a wide variety of release profiles. With over 40 years of experience in the CDMO industry, Coating Place offers technologically advanced Wurster fluid bed coating, high quality coating, linear scalability and superior customer service.

Innovative Development. Experienced Manufacturing.

Coating Place, Inc., 200 Paoli St. • PO Box 930310, Verona, Wisconsin 53593 U.S.A.
+1 (608) 845-9521 • www.coatingplace.com • info@coatingplace.com

D) observations, which went from 311 to 370 between 2017 and 2018. However, laboratory control observations decreased during the same period, which may reflect the implementation of improved system and data integrity laboratory controls.

VAI and OAI trends

VAI and OAI are critical for companies, because they indicate non-compliance and the need for critical actions, which may have implications for product quality and supply. Data showed that there has been a consistent reduction in the issuance of VAI and OAI since 2017, suggesting a higher rate of compliance with regulatory guidance requirements, as found during inspections.

The finished formulation and API site inspection trend (**Figure 4**) indicates a declining domestic inspections trend; however, there was no corresponding increase in foreign site inspections, which may reflect the fact that FDA has adopted a risk-based inspection management process. The data were also analyzed to determine whether there were any correlations between the variables: number of VAI/OAI, number of domestic inspections, and number of foreign inspections.

Based on the Pearson correlation coefficient calculation of X values (domestic inspections) and Y values (number of VAI/OAI), the value of R is 0.9443, suggesting a strong positive correlation between X and Y variables. The p-value is 0.015648, hence statistically significant (<0.05). The correlation was not seen when VAI/OAI numbers were compared with foreign inspection trend. It can be, therefore, concluded that there is a higher tendency to generate VAI/OAI observations if the domestic inspection rate increases.

The Pearson Correlation Coefficient for individual GMP observations associated with the nine subparts (B through J) were analyzed for 2014 through 2018 (**Figure 5 a** and **b**). A positive correlation could be ascertained across laboratory control observations (Subpart I) and records and reports (Subpart J). This may suggest that increased regulatory scrutiny of laboratory controls may have resulted in improved good documentation practices, because there appeared to be an improvement in records and reports observations as well. A summary of statistics is found in **Figure 6**.

Although additional analysis might be required to confirm the correlation, it is safe to assume that laboratory data integrity-based inspection assessment extends from GMP sections Subpart J to Subpart I. As an inspection readiness strategy, organizations should provide equal weight to laboratory electronic controls, procedures, specifications, and methods as well as to data access and integrity (6), and to the storage of raw data and reports, whether electronic or paper.

Conclusion

Analysis of FDA Form 483 observations issued from 2014 to 2018 revealed that the number of 483 forms issued has increased during this time period, while the number of observations has declined. The

Figure 4: Voluntary Action Indicated (VAI), Official Action Indicated (OAI) and domestic, foreign inspections of finished formulation and API sites.

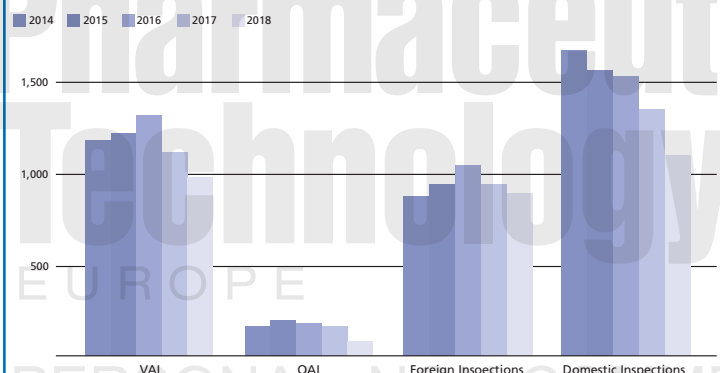


Figure 5a: Pearson correlation coefficient.

X Values	Y Values
1117	1117
1362	1362
1545	1545
1581	1581
1690	1690

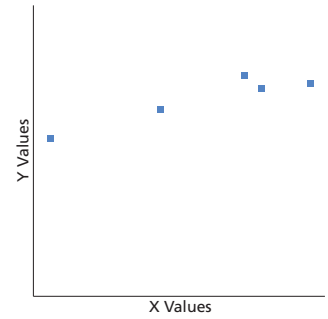


Figure 5b: Result details and calculation.

X Values	Y Values	X and Y Combined	R Calculation
Σ = 7295 Mean = 1459 Σ(X - Mx)2 = SSx = 202014	Σ = 6758 Mean = 1351.6 Σ(Y - My)2 = SSy = 117347.2	N = 5 Σ(X - Mx)(Y - My) = 145385	r = Σ((X - My)(Y - Mx)) / √((SSx)(SSy)) r = 145385 /w √((202014)(117347.2)) = 0.9443

Pfizer CentreOne

Wait a minute. What? Pfizer offers API supply and CDMO services?

Yes, we do. Collaborate with Pfizer CentreOne. And access our manufacturing network for your API and finished dosage form needs.

Welcome to Pfizer CentreOne®. We're a global CDMO embedded within Pfizer and a leading supplier of specialty APIs.

Backed by Pfizer resources, we deliver technical expertise, global regulatory support and long-term supply. For more than 40 years, we've been guiding complex compounds securely and efficiently from development through commercial manufacture.

Listening. Solving. Guiding.

Working together with our customers, we combine our knowledge with open dialogue to solve challenges.

Intelligent collaboration with Pfizer CentreOne.

APIs & Intermediates

Pfizer CentreOne has been a leading provider of specialty APIs. You can count on us to deliver you a high-quality molecule over the long term.

Custom API

Pfizer CentreOne specializes in small-molecule API synthesis. We can perform almost any kind of chemistry you need.

Oral Solids

Pfizer CentreOne excels in the manufacture of oral solid dosage forms.

Sterile Injectables

Pfizer CentreOne is a global leader in sterile injectables fill-finish.

Let's collaborate at
CPhI Worldwide stand 61B10

www.pfizercentreone.com

Figure 6: Summary statistics.

Subpart B--Organization and Personnel		*Subpart C--Buildings and Facilities*		*Subpart D--Equipment*		*Subpart E--Control of Components and Drug Product Containers and Closures*	
21 CFR 221.22-34		21 CFR 221.42-58		21 CFR 221.63-72		21 CFR 221.80-94	
Mean	380.4	Mean	191.8	Mean	324.2	Mean	123
Standard Error	14.99867	Standard Error	20.82162	Standard Error	14.57875	Standard Error	5.949789912
Median	379	Median	161	Median	313	Median	127
Standard Deviation	33.53804	Standard Deviation	46.55857	Standard Deviation	32.59908	Standard Deviation	13.3041347
Sample Variance	1124.8	Sample Variance	2167.7	Sample Variance	1062.7	Sample Variance	177
Kurtosis	-1.14213	Kurtosis	-3.06251	Kurtosis	-0.35406	Kurtosis	3.699224361
Skewness	0.119981	Skewness	0.643347	Skewness	0.454282	Skewness	-1.883361658
Range	85	Range	94	Range	85	Range	32
Minimum	339	Minimum	155	Minimum	285	Minimum	100
Maximum	424	Maximum	249	Maximum	370	Maximum	132
Sum	1902	Sum	959	Sum	1621	Sum	615

Subpart F--Production and Process Controls		*Subpart G--Packaging and Labeling Control*		*Subpart H--Holding and Distribution*		*Subpart I--Laboratory Controls*		*Subpart J--Records and Reports*	
21 CFR 221.100-115		21 CFR 221.122-137		21 CFR 221.142-150		21 CFR 211.160-176		21 CFR 211. 180-198	
Mean	417.6	Mean	38.6	Mean	41.8	Mean	520.6	Mean	506
Standard Error	21.18868	Standard Error	3.854867	Standard Error	1.067708	Standard Error	19.95645259	Standard Error	16.28803
Median	415	Median	39	Median	42	Median	526	Median	495
Standard Deviation	47.37932	Standard Deviation	8.619745	Standard Deviation	2.387467	Standard Deviation	44.62398458	Standard Deviation	36.42115
Sample Variance	2244.8	Sample Variance	74.3	Sample Variance	5.7	Sample Variance	1991.3	Sample Variance	1326.5
Kurtosis	1.767949	Kurtosis	-0.62246	Kurtosis	-1.11727	Kurtosis	0.059894877	Kurtosis	-1.54527
Skewness	1.098318	Skewness	0.566635	Skewness	0.205753	Skewness	-0.425902662	Skewness	0.375057
Range	126	Range	21	Range	6	Range	118	Range	90
Minimum	367	Minimum	30	Minimum	39	Minimum	457	Minimum	464
Maximum	493	Maximum	51	Maximum	45	Maximum	575	Maximum	554
Sum	2088	Sum	193	Sum	209	Sum	2603	Sum	2530

number of VAI and OAI observations issued has also fallen since 2017.

Over this period, there has been a decrease in domestic inspections, and a positive correlation was found between the number of domestic inspections conducted and the number of VAI/OAI observations issued. The highest number of observations were related to Subpart I–laboratory controls and Subpart J–records and reports, Subpart F–production and process controls, Subpart B–organization and personnel, and Subpart D–equipment.

Increased inspection of laboratory controls (Subpart I) may also result in increased good document practices, records and reports observations (Subpart J) based on the positive correlation observed. It is also noteworthy that there was an increase in packaging and labeling control (Subpart G) observations in 2018.

Editor's Note: In the UK and Europe, a risk-based approach to inspections, as well as a mutual recognition agreement (MRA) with FDA, national regulatory bodies in Australia, Canada, Japan and elsewhere, plus agreements with local European authorities, has reduced the number of redundant plant inspections. In 2018, according to EMA, of more than 2500 cGMP inspections, 16 led to the issue of noncompliance statements requiring corrective action plans from the companies involved. Although preliminary guidance was issued early in 2019, questions still revolve around Brexit and how the UK's propsed withdrawl from the European Union would affect the way that cGMP inspections are handled.

Note: This article was prepared by the authors in their personal capacities. The opinions expressed are the authors' own and do not reflect the view of their employer, government, or any agency with which they are affiliated.

References

1. M. Hamburg, *Justification of Estimates for Appropriations Committees Fiscal Year 2016, US Department of Health and Human Sciences*, FDA (2015).
2. FDA, *Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations* (June 6, 2017).
3. FDA, *Transparency Initiative: Draft Proposals for Public Comment to Increase Transparency by Promoting Greater Access to the Agency's Compliance and Enforcement*, FDA Data Transparency Task Force, US Department of Health and Human Services (2011).
4. *Code of Federal Regulations*, Title 21: Part 210, 211: Food and Drugs, Current Good Manufacturing Practices.
5. J. Freeman, T. Young, *Correlation coefficient: Association Between Two Continuous Variables*, Scope Tutorial, (2009).
6. D. Hodgson, F. Maini, et al., *Under the Spotlight: Data Integrity in Life Sciences*, (Deloitte, London, UK 2017). PTE

Specialty expertise in highly potent APIs

Identifying a collaboration partner that can meet the aggressive timelines often associated with highly potent drug candidates is critical. At Lonza Pharma & Biotech, we offer the necessary development, upscaling and manufacturing capabilities under full containment that support API handling to exposure levels to 1ng/m^3.

We also offer particle engineering (particle size reduction and spray drying) under isolation as well as specialized dosage forms designed for highly potent, low dose applications. We have more than 20 years' track record in HPAPI manufacturing and compressed scale-up timelines.

A partner that you can count on for all aspects of your drug program – **Lonza**.

Visit pharma.lonza.com
USA +1 201 316 9200
Japan +81 (0)3 6264 0600
Rest of world +41 61 316 81 11
Email pharma@lonza.com

The Fundamentals of Dissolution Testing

In this article, experts discuss the fundamentals of dissolution testing and highlight the challenges that are surfacing as a result of the increasing numbers of poorly soluble molecules entering the development pipeline.

Felicity Thomas

Because oral solid dosage forms are still the most common way in which drugs are administered, dissolution of the dosage form after it is swallowed, namely the rate at which the active ingredient is released into the body, is a critical facet of drug development. "Dissolution testing is an essential analytical procedure that's required as part of the final release investigation for solid oral dosage forms to control product quality, stability, and batch-to-batch consistency," confirms Meike Eckert, head of Dissolution Laboratories, Evonik Health Care. "As the rate of dissolution can significantly affect bioavailability, the goal of dissolution tests and associated acceptance criteria should be to identify batches with unacceptable bioavailability."

The primary functions of a dissolution test during early stages of development are to characterize therapeutic efficacy, bioequivalence, and bioavailability of API. During later stages of the development process, dissolution testing is also used for quality control (QC) purposes. "The type of dissolution testing performed along with the information required from the testing will change as the molecule progresses from the early stages of development to later in clinical development and towards product registration," says Charlotte Clay, head of Analytical Development, Pharmaceutical Analysis, Quotient Sciences.

Useful at every stage of development

"At the initial stages of characterizing and selecting the API, *in-vitro* dissolution testing can be performed to aid determination of the Developability Classification System (DCS) classification of an API, and in turn provide useful guidance on the best formulation development strategy for a molecule," Clay continues. "In later stages of development, dissolution testing is used as a QC procedure to detect the influence of critical manufacturing variables on a drug product."

During early drug development stages, it is possible to use a biorelevant dissolution method to determine how a formulation may react in media, such as fasted simulated gastric fluid (FaSSGF) and fasted simulated intestinal fluid (FaSSIF), that closely mimics conditions found inside the human body, Clay explains. "This methodology provides a prediction of how a formulation will behave within the body and ensure that the most appropriate formulations are taken forward into clinical trials," she says.

After the optimal formulation has been chosen to progress, dissolution methods specifically aimed at assessing quality and stability are developed. "These methods may not be biorelevant (standard acidic and phosphate buffered medias are typically used), but they are able to distinguish batch-to-batch variability as well as any changes in the formulations' dissolution performance that could affect product stability," Clay confirms.

Once pharmacokinetic (PK) data have started to be collected from clinical trials of the chosen formulation, it is appropriate to develop a biopredictive dissolution method. When used in combination with PK data, it is possible for developers to set up *in-vitro–in-vivo* correlations (IVIVC), which can be used to optimize formulations and determine equivalence for generic or modified versions of originator drug products, states Eckert.

"By following a quality-by-design (QbD) approach, risk assessments and definitions for quality target product profiles can be used throughout the clinical development and commercial lifecycle to identify potentially high-risk formulation and process variables," summarizes Eckert. "Dissolution testing can also achieve an improved product and process understanding to develop an appropriate control strategy."

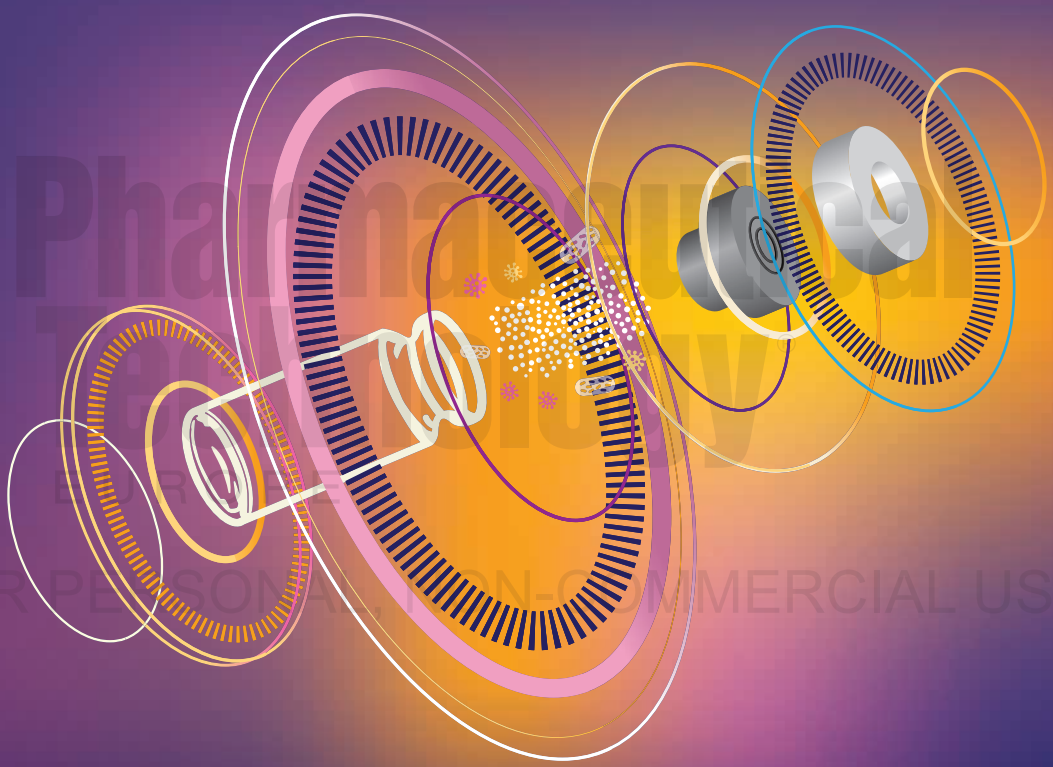
Achieving meaningful dissolution

Of paramount importance for dissolution testing is the assurance that the conditions used for testing are appropriate and correct for the product that is being tested, as well as for the information that is hoped to be gained from the test, stresses Clay. "There are many variables when it comes to dissolution testing from the type of apparatus and the dissolution media used, through to the small but important decisions on parameters, such as paddle/basket rotation speed, the use of sinkers, and the number of sampling time points, to name but a few," she explains. "Small changes to

pda.org/EU/ParPack2020

2020 PDA EUROPE

Parenteral Packaging



25-26 FEBRUARY 2020
BASEL, SWITZERLAND
EXHIBITION: 25-26 FEBRUARY
TRAINING: 27-28 FEBRUARY

CONNECTING PEOPLE SCIENCE AND REGULATION®

REGISTER BEFORE 27 DECEMBER 2019 AND SAVE UP TO €200!

these variables can have a big impact on the data generated; for example, the sinker mesh size used can have a direct impact on the release rate of the formulation, so it is therefore important to control these parameters and specify them in the analytical test method."

Additionally, Clay emphasizes that as a result of an increasing number of poorly soluble molecules entering the development pipeline, the number of ingredients falling into a DCS class II or IV are also rising. "As such, choosing the correct dissolution media where sink conditions can be achieved is becoming more of a challenge when developing dissolution methods," she says.

In agreement, Eckert highlights that it can often be necessary to add solubilizers, such as sodium lauryl sulphate, at an appropriate concentration to achieve meaningful dissolution results when dealing with poorly soluble ingredients. "During the formulation development process, it can be challenging to identify the right dissolution test methods to predict how the target formulation will perform *in-vivo* to reduce risk during future clinical studies," she continues. "Based upon the physicochemical characteristics of the API and the type of formulation, the use of media with different rates of complexity can be employed. These media options can range from plain buffers up to biorelevant media and the potential addition of digestion enzymes."

Defined dissolution apparatus and development of new tools

Currently, there are seven different types of dissolution apparatus defined in the *United States Pharmacopeia* (*USP*)—basket type, paddle type, reciprocating cylinder, flow through cell, paddle over disc, rotating cylinder, and reciprocating disc. Of the seven apparatus, basket type (apparatus I) and paddle type (apparatus II) are most commonly used for oral solid dosage forms but many different product types, from capsules to creams, can be testing using the apparatus defined in the *USP*.

"*USP* Apparatus I and II are the most commonly used dissolution apparatus for solid oral dosage forms and are versatile in enabling the development of many types of dissolution methods, from those for formulation development purposes to those used for QC testing of commercial batches," confirms Clay. "There are also a number of more bespoke dissolution apparatus/techniques being developed and used as drug products become more complex and the search for a more biopredictive technique continues."

In concurrence, Eckert notes that development of newer *in-vitro* tools has occurred as a result of the rising number of APIs with more complex physicochemical characteristics and the more stringent regulatory requirements being demanded for the prediction of *in-vivo* behaviour. "In addition to Apparatus III and IV (reciprocating cylinder and flow through cell), which are candidates for the prediction of detailed gastrointestinal transit with multiple test media or bioequivalent volumes, there is a growing toolbox of other emerging systems that are now offered by university spin-offs, such as Physiolution or other specialized companies for certain specific challenges," she says.

Giving an example, Eckert explains that multiple providers now offer services to combine dissolution testing with simulated mechanical stress. "These combination tests offer additional benefits for dosage forms that are sensitive to mechanical stress, such as delayed release capsules," she adds. "They can also be useful in the development of generic products to compare eroding and non-eroding matrices."

Volumes can be problematic when determining the most appropriate dissolution test to use, stresses Eckert. The commonly used apparatus are limited for use with media volumes of between 500 mL and 1000 mL, which can restrict the physiological relevance. However, using high volumes for dissolution testing can lead to an overestimation of *in-vivo* performance. "To better reflect conditions within the human gastrointestinal tract, the use of mini-paddles combined with smaller vessels can sometimes be advantageous," Eckert says. "However, this method is not yet considered by the pharmacopoeias."

Clay continues by highlighting the fact that there has been an escalating use of modified and non-compendial apparatus in the field of dissolution testing over recent years. "These apparatuses are being utilized to offer novel perspectives on different dosage types, delivery devices, and formulations, with the goal being to make dissolution results more biorelevant," she states. "As a result, previous 'fringe' techniques such as intrinsic dissolution, small-volume dissolution, and dissolutions using enhancer, immersion, or extraction cells are becoming more widely adopted."

Furthermore, advancements in detection techniques are also enabling testing, either online or in real-time, of more complex, multi-component formulations, Clay confirms. With the added capabilities afforded by these new detection techniques, developers can achieve a comprehensive data set, which provides a better understanding of the interactions of APIs and excipients in product formulations.

A harmonized technique

Globally, various pharmacopoeias provide clear outlines for apparatus, procedures, and evaluations that will help developers to fulfil the dissolution testing criteria of regulatory bodies. For example, *USP* has several chapters, including 711, 1092, and 1225, detailing preliminary assessments, method development, analysis, automation, validation, and acceptance criteria (1–3). In *European Pharmacopoeia* section 2.9.3 (4), developers can find information on apparatus, procedures, and evaluations for acceptance criteria also.

"Since 2014, Europe has also started following the *USP* approach of publishing individual formulation monographs containing dissolution methods and acceptance criteria," adds Eckert. "In the US, additional information is also publicly available in the dissolution methods database (5) of the Food and Drug Administration (FDA)."

Further information can also be found on the physical operating conditions of the dissolution testers,

confirms Clay, with guidelines covering dissolution testing for immediate release, delayed release, and extended release drug formulation types. "However, given the complexities of the human body, physiology, and chemical/biological interactions that take place, it can be difficult to solely rely on the dissolution test as a way of predicting how a drug formulation may perform *in-vivo*," she stresses. "The use of biorelevant media can aid such assessments, but there is no way of understanding how closely the dissolution test may predict *in-vivo* performance without performing clinical studies."

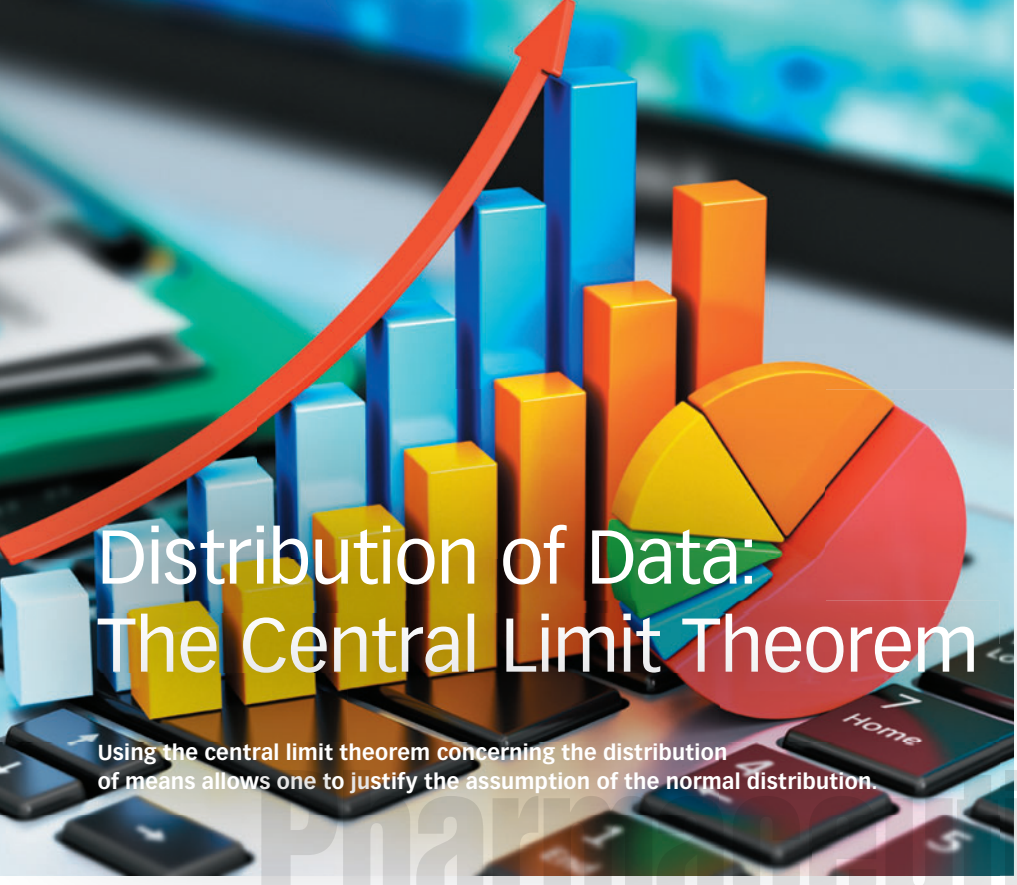
The European Medicines Agency (EMA) also provides guidelines on the investigation of bioequivalence, reveals Eckert. "These guidelines describe the use of dissolution studies to waive a bioequivalence study in applicable cases and the evaluation of similarity of dissolution profiles," she says. "The use of dissolution data in IVIVC approaches is also explained in EMA's guideline (6) on the pharmacokinetic and clinical evaluation of modified release dosage forms."

Because dissolution testing is fundamental for the assessment of the performance of oral formulations and is widely used around the world, much work has been done to create a globally uniform approach. The International Council for Harmonization (ICH) has worked with various pharmacopoeias to harmonize many of the dissolution testing methodologies (specifically *USP* I and II Apparatus) so that they are standardized across many different regions, Clay iterates.

"Dissolution is a harmonized technique across many pharmacopoeias in which dimensions of the equipment used and operating parameters are clearly defined and documented," Clay continues. "Thanks to this harmonization, successful transfer of validated dissolution methods from one laboratory to another is made to be relatively straightforward."

References

1. USP, *USP–NF* <711>, "Dissolution" (US Pharmacopeial Convention, Rockville, MD, 2011).
2. USP, *USP* 35 <1092>, "The Dissolution Procedure: Development and Validation" (US Pharmacopeial Convention, Rockville, MD, 2012).
3. USP, *USP* 36 <1225>, "Validation of Compendial Procedures" (US Pharmacopeial Convention, Rockville, MD, 2012).
4. European Pharmacopoeia, *Ph. Eur.* 2.9.3. "Dissolution Test for Solid Dosage Forms" (European Medicines Agency, London, UK, 2008).
5. FDA, "Drug Databases: Dissolution Testing," www.accessdata.fda.gov/scripts/cder/dissolution/ [accessed 18 Sep. 2019].
6. EMA, *Guideline on the Pharmacokinetic and Clinical Evaluation of Modified Release Dosage Forms* (Brussels, 20 Nov. 2014). **PTE**



Distribution of Data: The Central Limit Theorem

Using the central limit theorem concerning the distribution of means allows one to justify the assumption of the normal distribution.

Chris Burgess, PhD, is an analytical scientist at Burgess Analytica Consultancy Limited, 'Rose Rae,' The Lendings, Startforth, Barnard Castle, Co Durham, DL12 9AB, UK; Tel: +44 1833 637 446; chris@burgessconsultancy.com; www.burgessconsultancy.com.

Analytical people tend not to worry too much about the nature of the distribution of their data. Statisticians, on the other hand do worry. Some 10 years ago, Rebecca Elliott, a senior statistician with Eli Lilly, gave an excellent presentation on some ways users drive statisticians crazy (1). This column is about just one method to prevent that happening, as we do need statisticians occasionally.

The central limit theorem (CLT)—actually theorems as there are more than one—is at the heart of much statistical methodology. The CLT is a lifesaver for analytical data, be it continuous or discrete. The good news is that the part that must be understood is very simple. The really good news is that if the CLT did not exist, many familiar statistical methods would not be valid. The first lesson for analytical people to learn is that, from a statistical point of view, there is a world of difference between individual or replicate data from a sample and means of those data.

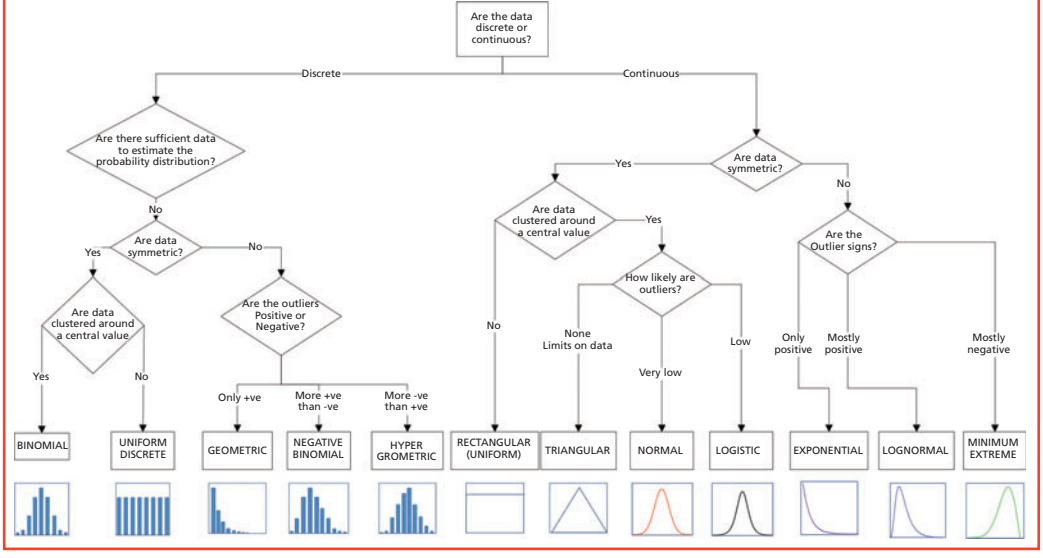
It is visually apparent, therefore, that to use methods based on the assumption of normality would be invalid in many instances. Fortunately, the CLT comes to our aid.

It is the mathematical model (shape) of data population which determines the applicability (suitability) of the statistical methodology. A summary of some commonly met distributions are shown in **Figure 1** (2).

Central limit theorem (CLT)

The simple part of the CLT is that for any sample of N independent determinations, the means of n values tend to a normal distribution irrespective of the underlying population distribution. In addition, the overall or grand mean tends to the population mean. Note that the bigger n is, the more this is true. Unlikely though this seems, some calculations can be performed in Microsoft Excel to demonstrate this property. This is not well described in books on statistics, but *Basic Statistics and Pharmaceutical Statistical Applications* does describe this well, albeit somewhat hidden

Figure 1: Some data distributions for continuous and discrete data (adapted from reference 2).



Scanrail - Shutterstock.com/Figures courtesy of the author

Figure 2: Histogram of the rectangular distribution of the 15 numbers in our data set.

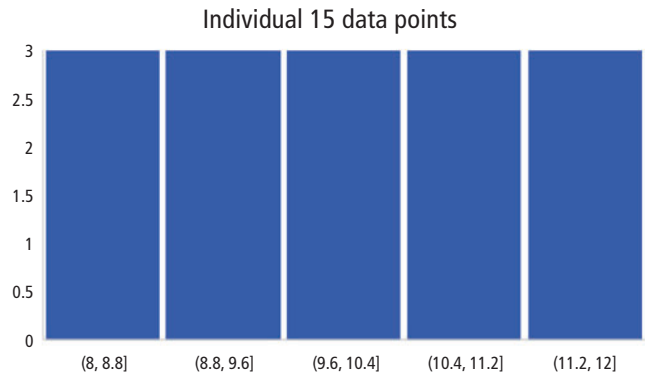


Figure 3: Histogram for the 105 means for n=2.

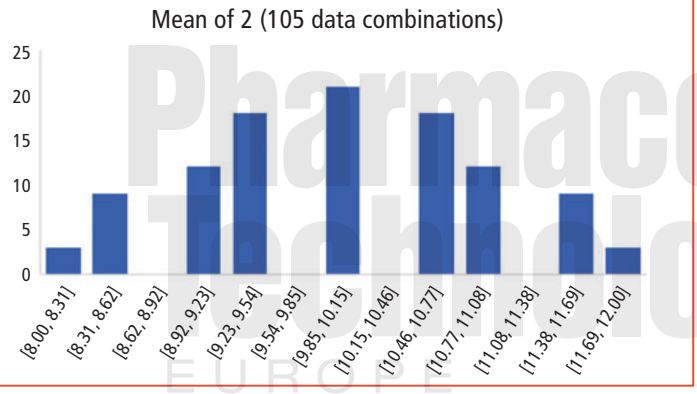
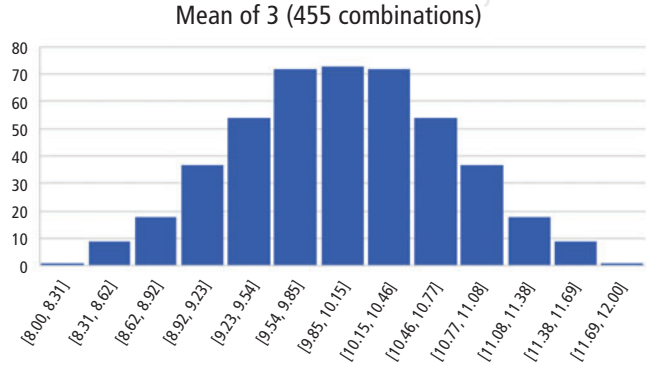


Figure 4: Histogram for the 455 means for n=3.



away in the 800 pages (3). The following is one way to visualize the value of the CLT.

Let us consider a small data set of 15 integer numbers far away from a normal distribution, namely 8,8,8,9,9, 9,10,10,10,11,11,11,12,12,12, which are shown as a histogram in **Figure 2**.

Let us take the decision that n is to be two and we know that there will be 105 means of two combinations of these 15 numbers. In Excel, this would be calculated using the combination formula;=COMBIN(15,2). Sadly, there is no function currently in Excel to list all of these 105 combinations, but fortunately there is a macro available on the Internet to do just that (4). Once you have these combinations listed, then you can calculate the means. The result is shown in **Figure 3**.

Looking good so far; so what about n=3? In Excel, this is calculated from the formula =COMBIN(15,3), which gives 455 combinations. Modifying the macro works well and generates the 455 combinations listing. We proceed as before by calculating the means of 3 resulting in the histogram shown in **Figure 4**.

The approximation to the normal distribution becomes even more apparent. The normal approximation becomes good when n is in the region of 25 to 30. This was demonstrated in an earlier column using the t distribution (5). This particular calculation cannot be performed in Excel because if one used N=50 data points and n=30, one would have 47,129,212,243,960 combinations, which would take, at one calculated mean per second, just under 1.5 million years to achieve even if Excel allowed that many rows.

Conclusion

The central limit theorem concerning the distribution of means allows one to justify the assumption of the normal distribution so that we can use many of the statistical formulae that require normality on our datasets. As long as mean and individual data are clearly differentiated, we will help our statistician colleagues remain sane.

References

1. R. Elliott, "Product Specifications: How to Drive a Statistician Crazy," Pharmaceutical Statistics 2008: Confronting Controversy Conference, Arlington VA, 2008.
2. A. Damodaran, Probabilistic Approaches: Scenario Analysis, Decision Trees And Simulations, people.stern.nyu.edu/adamodar/pdfiles/papers/probabilistic.pdf, Figure 6A.15: Distributional Choices.
3. JE De Muth, *Basic Statistics and Pharmaceutical Statistical Applications*, 3rd edition, page 123 (CRC Press, 2014).
4. Allen Wyatt, Listing Combinations, tips.net, https://excelribbon.tips.net/T011891_Listing_Combinations.
5. C. Burgess, *Pharmaceutical Technology*, 38 (6) (June 2014). **PTE**

New Technologies for Fill/Finish Streamline Operations

Advances in parenteral packaging address demands for efficiency and product safety.

Hallie Forcinio
is *Pharmaceutical Technology Europe*'s Packaging Editor, editorhal@sbcglobal.net.

The global market for injectable drug delivery is growing at a compound annual growth rate of 10.9% (1). A report from Future Market Insights attributes the anticipated growth rate to the rising prevalence of chronic diseases such as diabetes, cancer, and rheumatoid arthritis along with increasing demand for point-of-care devices where prefilled, needle-free injectors are most preferred (1).

Beyond self-dosing, other factors influencing market growth include shorter runs, sensitive products, and labour constraints, which are driving parenteral drug makers to streamline operations. Tactics include maximizing container quality and adoption of ready-to-fill technology. On the equipment side, robotics are assuming a bigger role as are integrated systems. Simulation expedites design and engineering on the front end and supports training, operation, and maintenance functions during and after installation. *Pharmaceutical Technology Europe* reviews new technologies for parenteral packaging, including several displayed at INTERPHEX (2–4 April 2019, Javits Center, New York, NY, USA).

Container features

To address rising demand for ready-to-use (RTU) containers, DWK Life Sciences has developed the Workflow Solutions portfolio of glass and plastic containers, with Solutions Packs for research and for production (2). The Wheaton Complete Pak provides a complete kit of off-the-shelf, RTU packaging components for short runs. Contents include approximately 220 certified sterile and particulate- and endotoxin-free, crimp-top vials in one of three sizes (2, 5, or 10 mL), with seals in red or blue and a coated, uncoated, or lyo stopper. "We are planning an amber version and also planning a ModPak six-pack," says Jay Harkins, senior product manager at DWK Life Science.

For self-dosing, an on-body injector being developed by Nemera combines a disposable needle and drug container with a reusable element that contains the electronics and mechanics. "The device customizes infusion speed and depth of injection and communicates with a smartphone to track doses and provide reminders," says Lauren Mudrak, business development manager at Nemera.

Also under development, the S.A.F.E. Syringe Kit from Morimoto Pharma combines a vial filled with liquid, a pre-attached needle syringe filled with powder, and a compact tube-shaped container. Expected to be commercial in a few years, the design allows injection preparation to be performed inside a closed environment, thereby protecting caregivers from accidental needlesticks and exposure to the drug (3). Dissolving the drug powder inside of the syringe rather than the vial is quicker and ensures all the drug is injected (zero-loss). According to the company, this design also allows a syringe size that is significantly smaller than recent dual-chamber syringes, which makes it easy to administer and lessens patient needle phobia. Because the syringe is returned to the container immediately after administration and extra supplies are not needed, waste is reduced and disposal is safer.

Equipment innovations

Although traditional fill/finish equipment continues to be popular, robotic systems and machines that handle nested, RTU vials, syringes, and cartridges appear to be gaining ground, as they streamline operations by eliminating the need for a washer and depyrogenation tunnel.

New options for handling nested containers include the Dara NFL/2-RDL aseptic filling and closing machine from NJM, a ProMach product brand. Designed for RTU vials and the RayDyLyo cap, the machine handles nests of presterilized vials and eliminates the crimping required with traditional aluminum closures. The machine fills solutions, suspensions, diagnostics, or vaccines in glass or plastic vials in sizes ranging from 2R–50R with dose volumes from 0.1–50 mL and can be programmed for full stopper insertion for non-lyophilized products or half stopper insertion for lyophilized products. Developed for biotech companies and 503B pharmacies, the servo-driven system streamlines the packaging operation to reduce capital costs, minimize footprint, and speed changeover. Volume capabilities

Figure 1: Flexicon FPC60 fill/finish machine from Watson-Marlow Fluid Technology Group uses a peristaltic pump and custom, precision tubing.

suit scale-up through small batch commercial manufacturing.

A highly configurable fill/finish system, the Flexicon FPC60 machine from Watson-Marlow Fluid Technology Group can be set up from outside the cleanroom via wi-fi or hard wiring and automatically adjusts for height and width for hands-free calibration (see **Figure 1**). "We want to remove the operator from the process as much as possible. Operators are the biggest source of contamination," explains Peter Lambert, filling division manager at Watson-Marlow Fluid Technology Group. Each operator also tends to set up the machine differently, so automating changeover eliminates that variability. Compatible with a traditional or single-use product path, the unit handles a range of containers, stoppers, and caps with a minimum of change parts. Designed to handle a range of vial sizes (0.2–100 mL) without change parts, the system outputs up to 45 vials/min. Vibrator bowls for stoppers (injection or lyo) and caps (flip-off or plain) are similarly flexible and capable of handling either 13-mm or 20-mm diameters.

A tabletop fill/seal system for low-volume needs, the EDM3611 from Bausch+Ströbel can be housed in a tent-like disposable isolator. A sterile connection provides air, carbon dioxide, nitrogen, or HEPA-filtered laminar flow. A touchscreen-equipped operator interface houses machine settings and provides 100% in-process control batch recording (4).

Robotics also minimize the need for operator intervention. The GENiSYS R filling and closing system from AST accommodates up to five robots in a compact footprint and minimizes moving parts. Designed to process small batches of presterilized, nested vials, syringes, or cartridges, the machine offers fast, tool-less changeover in less than 30 minutes. A high-definition, user-friendly human/machine interface holds recipes, step-by-step instructions, videos, and standard operating procedures and can eliminate paper documents. An in-process control system ensures accurate fills, minimizes waste, and maximizes product yield.

Decontamination systems

Decontamination systems work in conjunction with fill/finish systems. The Eziflow UV-C aseptic transfer from Ezidock sterilizes to log 6 within minutes using ultraviolet (UV)-C light to ensure that product or components

Figure is courtesy of the author.

transferring to the fill/finish machine are sterile.

Pulsed UV light treatment offers several advantages. Effective against all known microorganisms, including those that are chlorine resistant, the chemical-free process also can remove free chlorine and chloramines, break down ozone, and reduce total organic carbon without leaving any residue, odour, or coating on treated surfaces.

The Pulsed UV Light Chamber Type 411 from Bausch Advanced Technology Group mounts in the wall to serve as a pass-through to the cleanroom. When the door on the cleanroom side is closed, presterilized containers are placed in the chamber. The outer door is closed, and the pulsed-light decontamination cycle runs for approximately 30 seconds. When the cycle is complete, the inner door can be opened and the operator or a robotic arm removes the containers in preparation for the fill/finish process. The compact, easy-to-install system needs minimal maintenance and cleans quickly to minimize downtime. Energy costs are low (5).

The RTDS2 robotic tub decontamination system from Steriline also uses a pulsed UV light and is designed to decontaminate nests of RTU syringes, vials, or cartridges. The robotic arm ensures all tub surfaces are exposed to the lamp flashes. The system can operate as a standalone machine or be integrated with any RTU filling machine, particularly Steriline's robotic nest filling machine (6).

Virtual reality

As Industry 4.0 takes hold, simulation via virtual reality (VR) or augmented reality (AR) is assuming larger roles in machine design, engineering, construction, operation, and maintenance. VR offers an immersive experience in a fully simulated setting; AR overlays digital elements on a real-world environment.

Bausch & Ströbel is already using AR and VR technologies. VR is helping its design teams fix problems in the development phase before machine construction begins. Using VR, the design team can reduce turbulence and areas of low velocities, avoid cross-flows above containers, and show static pressure and upward flow to optimize air-flow and ensure the cleanest possible environment for filling. VR also can help check ergonomic features, such as reachability for machine access by short or tall operators. "VR allows earlier decision making and helps determine if adaptations are needed," explains Florian Naser, an engineer in the Data Processing Organization, Systems Product Creation, Applications at Bausch & Ströbel.

VR can be used to train operators before the machine is installed and whenever new hires come onboard. There are several advantages. VR training doesn't tie up the machine, and all operators are trained the same way. VR can also support maintenance because it can ensure that the proper spare parts are on hand and help optimize machine modifications.

AR also can assist with machine troubleshooting by highlighting the problem area on a tablet computer that is brought to the machine. AR can identify the correct part and part number, zoom in, offer different views, present the virtual view next to the actual machine, and provide visual instructions for the operator or maintenance person, eliminating the need to search through paper-based standard operating procedures. "Nothing is forgotten or out of sequence, and the programme is easily edited if changes are needed," says Naser.

References

1. Future Market Insights, "Global Injectable Drug Delivery Market Revenue Expected to Be Driven by the Rising Prevalence of Chronic Diseases across the Globe," Press Release, 26 July 2018.
2. DWK Life Science, "DWK Life Science Announces Workflow Solutions," Press Release, 27 April 2019.
3. Morimoto Pharma, "Morimoto Pharma Reveals New Exposure Prevention Prefilled Syringe Kits," Press Release, 1 Aug. 2019.
4. Bausch+Ströbel, "Filling with 100% IPC Inside a Sterile Disposable Isolator," Product Data Sheet.
5. Bausch Advances Technology Group, "Pulsed UV Light for Surface Decontamination," https://packexpo-healthcare.com/2019/06/20/pulsed-uv-light-for-surface-decontamination/, accessed 2 Sept. 2019.
6. Steriline, "Robotic Tub Decontamination System RTDS2," Brochure. PTE

USING SIMULATION TO OPTIMIZE FILL/FINISH EQUIPMENT

Digitalization and Industry 4.0 tools are being employed to improve pharmaceutical equipment and systems. An example of this is Optima Packaging's Comprehensive Scientific Process Engineering (CSPE) approach to project planning for its fill/finish systems, which uses simulation for mock-up, engineering design, and design review to speed the design process. Three-dimensional models can be experienced using virtual reality to collect input from users early in the design process.

"The CSPE approach minimizes the risks associated with large plant construction projects by conducting a thorough analysis even prior to the design stage," says Jan Deininger, editor at OPTIMA Packaging Group. Deininger explains that comparable projects are also examined to identify and proactively counter potential risks. During the design phase, designers use simulation to optimize the line layout for accessibility. Developers also use first air flow and simulations of vapourized hydrogen peroxide flow to support a flow-optimized machine design, says Deininger.

The company opened a new facility, the CSPE Center, at its Schwaebisch Hall, Germany site in July 2019 that gives the company space to build, test, and commission multi-story, turnkey, fill/finish facilities. The entire system, including the isolator and filling and closing machines, is assembled, tested under realistic conditions, and approved before it goes to the customer. This integrated factory acceptance testing minimizes unexpected delays at the customer site.

—Jennifer Markarian

30 YEARS

CPhI worldwide®

P-mec | InnoPack | iCSE | FDF | BioProduction

5 – 7 November 2019 | Frankfurt, Germany

30 years of uniting the entire Pharma value chain

The world's largest pharmaceutical exhibition, CPhI Worldwide houses six zones representing each stage of the pharmaceutical supply chain - from APIs, machinery, finished formulations and packaging to outsourcing and biopharmaceuticals.

Uniting over 2,500 international exhibitors, CPhI Worldwide is the place to network and source cost effective pharma solutions from all over the world - in just 3 days, under one roof.

REGISTER NOW! Visit gotocphi.com/mmh

> "Everybody here is seriously doing business, looking for business contacts and actively engaging
>
> **Juan Sarmiento,** Nemera

Meet, network & learn

165+
Countries Participating

2,500+
Exhibiting Companies

100
Hours of Free On-site Content

Tracking Raw Materials in Biopharma Manufacturing

Automated, electronic systems improve efficiency and prevent mistakes.

Jennifer Markarian

Raw material tracking is a crucial component of making a quality product efficiently. Supply-chain visibility and documenting that raw materials meet quality specifications are both important.

"Pharmaceutical and biotechnology companies have similar issues to other industries, but the stakes are much higher because they treat patients," notes Richard Soltero, president of InstantGMP, which offers software for GMP manufacturing. "Each player along the way has an onus to put only quality materials into the supply chain. Every company must remove any poor-quality materials before products end up in the hands of providers and patients. In addition, the complexity of the supply chain makes tracking and tracing materials difficult."

"Maintaining consistent, high quality in both the supply chain for materials and in the end products themselves are two major challenges in raw materials management for biopharmaceutical manufacturers," says Dr. Nandu Deorkar, vice-president, Technology & Innovation at Avantor. "These foundational items can present issues when trying to establish a reputable supply and identify true second sources with suppliers that have well-documented processes."

Best practices

Understanding the supply chain is crucial. "Long lead times can be a challenge for certain raw materials," notes Deorkar. "It is important for manufacturers to work with their suppliers to understand their outlook and foster investments to increase critical capacities worldwide. Additionally, managing the correct methods for packaging and process efficiencies is also critical for handling materials, reducing demands on storage at facilities, and reducing the capital expenditures required at new facilities."

Avantor has implemented flexible packaging sizes to help its biopharmaceutical manufacturing customers. Modular packaging systems enable quicker turnaround for customers to use the materials in production. Preweighed materials in ready-to-use packaging allow companies to reduce storage of bulk or hydrated buffers as well as reducing testing and material handling processes.

Deorkar notes that another best practice is transparency for the supply chain and for management of change procedures for current good manufacturing practice (CGMP) materials. Adoption of electronic data systems enables this practice.

Electronic data

Although the bio/pharma industry has traditionally used paper-based tracking systems, leading manufacturers are transitioning to electronic systems, which offer significant benefits for efficiency and quality, as part of digitalization efforts.

"It's important to have full supply-chain visibility and management of change across the entire supply chain during the manufacturing process, and this is where data [are] coming in to help," agrees Claudia Berron, senior vice-president, Biopharma Production at Avantor. "The new frontier of biopharma is being driven by e-data: the electronic delivery of critical documents related to the material, with full tracking capabilities by package and by pallet. As the industry is adopting this technology, it is benefiting from the experience of other industries that are more advanced in this space."

"Paper-based documentation can be problematic when tracking and managing materials through the production process," explains Soltero. "In a paper-based system with different information kept in different locations, people can find themselves spending valuable time verifying material status and inventory levels or tracking down the right person. Manufacturers can avoid these problems by transitioning to a cloud-based inventory software that automates material tracking, inventory levels, material statuses, purchase orders, and staging materials for production."

Using inventory management software enables automation of material receiving and specifications, says Soltero. Automation eliminates human errors and helps to remove poor-quality materials before they enter inventory, and it can be used to maintain inventory history in real-time. "In InstantGMP's inventory software, each material has a unique profile and a system-generated

Production Perig - stock.adobe.com

receipt number that comes with a barcode label to check materials throughout the production process," explains Soltero. "The real-time status update alerts personnel that material is ready for use, where it is, how much is available, from what vendor, and what the vendor lots are. Every use of inventory or change appears within that material's inventory record."

A new software feature for material resource planning includes the ability to make a picklist. "Through the picklist, manufacturers can start allocating materials for production, setting materials aside to prevent confusion, verifying stock level and material status, preventing double counts, and performing additional quality reviews. Picklists can be used for bridging the tracking gap in assembling kits and for those that want to take advantage of traceability within the software but want to connect data to their legacy system," says Soltero. The software is designed to work in tandem with other systems, including paper-based systems, to help companies that are transitioning to electronic systems. "We understand that a full transition to another system, electronic or not, is a huge undertaking and can be disruptive to production until everything's in place," he says. InstantGMP's software has an inventory import function, and data can also later be added to modules such as software for electronic batch records.

Cell and gene therapy tracking

The emerging space of cell and gene therapy manufacturing, especially patient-specific autologous therapies, requires even more stringent control over raw materials and the entire supply-chain and manufacturing workflow. New systems have been launched to address these specific challenges.

For example, GE Healthcare's Chronicle automation software is designed for cell therapy process development and manufacturing. The software supports real-time data acquisition and notifications for supply chain logistics, electronic batch records, and electronic standard operating procedures (1).

TrakCel supplies software for cell and gene therapy supply-chain tracking and has announced several partnerships with industry members. Most recently, the company announced a collaboration to integrate McKesson's third-party logistics and patient access services with TrakCel's tracking systems (2). In June, TrakCel announced a partnership with Be the Match BioTherapies to integrate services and platforms (3). TrakCel is also a partner in a project in the United Kingdom supported by Innovate UK, the Standard Approach to ATMP [advanced therapy medicinal products] Tissue Collection (SAMPLE programme) (4). The project will study cell and tissue procurement, processing, and storage processes.

Data transfer and insight

GE Healthcare and Amgen announced a digital data exchange programme in early 2019 that aims to use raw material data to increase process understanding of the relationship between raw material variability and process performance (5). The data exchange is intended to improve transparency, identify root causes of variation, and improve quality of both raw materials and the final product. GE Healthcare is developing electronic certificates of analysis (eCoAs) using ASTM International's standard for raw material electronic data (e-data) transfer (6). The ASTM standard grew out of work that originated at Amgen on a standard file format to allow data exchange between raw material suppliers and users (7).

The ASTM e-data standard provides a baseline, but there is work yet to be done, says Berron. "There is still a significant effort required to establish direct e-data connectivity for the electronic delivery of critical documents including CoAs. By enabling CoA e-data instead of PDFs, the data source is ready to retrieve or push to the customer's system, enabling a quick turnaround in troubleshooting efforts and seeding new efforts for predicative analytics of raw material impacts into the process."

"It's all about material control, transparency, and traceability," concludes Soltero. "Non-electronic solutions are rife with opportunities for materials to get lost, to be improperly tested, and to have gaps in traceability. Manufacturers are the last stop in the supply chain before products get to distributors and patients, and that makes it imperative for producers to have complete control and total traceability."

References

1. GE Healthcare Life Sciences, "GE Healthcare Announces Commercial Launch of Chronicle Automation Software for Cell Therapy," Press Release, 15 May 2019.
2. TrakCel, "McKesson and TrakCel Launch Innovative Collaboration to Support Commercialization of Cell and Gene Therapies," Press Release, 11 Sept. 2019.
3. TrakCel, "Be The Match BioTherapies and TrakCel Partner to Standardize Cell and Gene Therapy Supply Chain Solutions," Press Release, 18 June 2019.
4. TrakCel, "Government Boost for Expanding the Use of Cell and Gene Therapies in the UK," Press Release, 18 April 2019.
5. J. Markarian, "Data Insights Improve Process Reliability," *PharmTech.com*, 3 May 2019.
6. ASTM, ASTM E3077-17e1, Standard Guide for Raw Material eData Transfer from Material Suppliers to Pharmaceutical & Biopharmaceutical Manufacturers (2017).
7. C. Undey, "Amgen's Digital Transformation: Linking Raw Material Data from Suppliers to Patients," www.gelifesciences.com/en/us/solutions/bioprocessing/knowledge-center/amgen-linking-raw-material-data-from-suppliers-to-patients, March 2019. **PTE**

AI ENABLES SUPPLY-CHAIN VISIBILITY

Cloudleaf uses intelligent sensor networks, artificial intelligence (AI) with machine learning, and advanced analytics to provide supply chain visibility. The company is expanding its Digital Visibility Platform (DVP) to provide continuous, real-time visibility for the supply chain.

"Currently visibility in the supply chain industry is at best only about 20%. DVP can take this to 100% visibility," claims Mahesh Veerina, CEO of Cloudleaf.

In bio/pharmaceutical manufacturing, the sensors can be attached to raw material containers, which track their location as well as additional environmental information, such as temperature, vibration, and shock. To read more about the use of Cloudleaf's platform in processing blood plasma, see www.PharmTech.com/AI-enables-supply-chain-visibility.

Best Practices for Studying Stability in Biologics

Industry experts discuss the challenges and regulations of setting up a CGMP-compliant stability testing programme.

Susan Haigney

Pharmaceutical Technology Europe spoke with Bhroma Patel, head of product stability, and Baldev Jogi, lead scientist, both at Lonza; and Will Hatcher, senior manager, QC, and Rekha Patel, director, biologics analytical solutions, both at Catalent, about what steps companies need to take when setting up a current good manufacturing practice (CGMP)-compliant stability testing programme for biologics.

Best practices in stability

PTE: What are the first steps for setting up a CGMP-compliant stability programme for biologics?

Hatcher (Catalent): The first step in setting up a CGMP-compliant stability programme is to determine the analytical assays that are stability-indicating and to verify that the method qualification/validation has been performed appropriately to prove that these assays are indeed stability-indicating. After the analytical assays are determined, the next step is to set up the stability strategy, which will include long-term stability at the determined storage condition, short-term stability (accelerated and stressed), and possibly photostability or freeze/thaw studies. It is very important to be conservative with regards to timepoints within a stability study. If the appropriate amount of data [are] not gathered at the appropriate conditions, then it is possible that an entire study would need to be repeated, which becomes extremely time-consuming and costly, and could be detrimental to a regulatory filing timeline.

Bhroma Patel and Jogi (Lonza): An amendment agreement is required between the clients and outsourcing company to see what stages of work [are] required from start to end. This will include objective, activities (e.g., timepoints, temperatures, and intended storage temperature), test methods, and delivery of reports. In addition to this, methods and equipment require validation and specifications put in place prior to starting the stability study.

PTE: What challenges should companies be aware of when setting up a CGMP stability programme for biologics?

Bhroma Patel and Jogi (Lonza): The challenges companies must be aware of when setting up the GMP stability programmemes are that regulatory requirements, such as the ICH [International Council for Harmonization] guideline, are followed throughout the stability programme, from pilot stability studies to drug product studies. Companies may require large facilities for laboratory capacity, storage, as well as stability chambers under different climatic conditions and relative humidity and freezers. In addition, companies are required to develop, validate, and evaluate testing methods and equipment to perform stability studies.

Rekha Patel (Catalent): Companies should ensure that they have redundancies in power, water, and air handling systems as well as appropriate alarm notification systems, to safeguard against possible impacts to the study. To ensure integrity of the study, sample traceability and inventory systems should also be in place. Having a sufficient volume of materials should not be overlooked. Study coordinators should ensure that they have enough materials to progress through the study as well as any investigations or extensions. If special studies are needed, such as freeze/thaw, in-use, forced degradation studies, photostability, etc., proper material amounts should be ensured as volume is often a challenge.

Study coordinators should ensure that methods are proven to be stability-indicating during qualification/validation, are appropriately set up beforehand, and that orthogonal methods are available where appropriate. Analytical methods may change going from early to late phase (e.g., moving from ELISA [enzyme-linked immunosorbent assay]-based to cell-based), and investigators should plan for any bridging activities that may be needed. Appropriate planning also includes a thorough understanding of the study matrix and any special handling required. The timing of the study should be laid out to meet any critical regulatory filings. If planning to file globally, consider testing conditions specific to different regions in the same study, as this will provide sufficient data without the time and cost needed to conduct a separate study.

Regulatory expectations

PTE: What are the specific regulatory requirements for a CGMP-compliant stability programme?

Bhroma Patel and Jogi (Lonza): The specific regulatory requirement for stability programmes for biologics are defined in ICH guidelines with reference to ICH Q1A (R2), *Stability Testing of New Drug Substances and Products*, ICH Q5C, *Stability Testing for New Dosage Forms*, and EMA/CHMP/BWP/534898/2008 rev. 1 corrigendum, *Guideline on the Requirements for Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials*. For recommendations on how to establish shelf life or retest period based on stability studies, ICH Q1E, *Evaluation of Stability Data*, is followed. In total there are six ICH basic guidelines for stability studies, Q1A to Q1F.

Hatcher (Catalent): The regulatory requirements for CGMP stability programmes mainly come from ICH guidelines, specifically: Q7 11.5, Q1A (R2), Q1B, Q1C, Q1D, Q1E, Q5C. There are also regulations from the [US Food and Drug Administration] FDA (21 *Code of Federal Regulations* 211.166) and European Medicines Agency (EMA) (Guideline 3AB5a) that govern what should be contained in a stability strategy. In addition to these regulations, FDA provides guidance that can help determine an appropriate stability study strategy.

With this bolus of information, it can be challenging to determine a clear stability strategy. However, as long as the assays performed are stability-indicating and the stability strategy includes long-term at storage condition, accelerated and stress stability studies, in most cases this can be enough for an initial filing. As a product moves through the clinical lifecycle, photostability and freeze/thaw studies will need to be performed. Additionally, depending on the properties of the product and the results of the stability studies, additional studies may be warranted.

PTE: Can you provide an example of how a company can ensure their stability programme is following regulations?

Bhroma Patel and Jogi (Lonza): Companies can ensure [the] stability programme is following regulations by [creating] standard operating procedures (SOPs) to help set up stability studies and protocol in compliance with regulatory expectations.

A stability programme should be described in the protocol to support the shelf life and storage condition and include:

- Objective/scope of the study (e.g., the stability study results may form part of submissions to the regulatory authorities to support the use of the product in toxicological studies and clinical trials).
- Storage conditions (e.g., intended, accelerated, and stress storage conditions)
- Sampling plan (e.g., samples to be tested at 0, 3, 6, 9, 12, 18, 24, and 36 months)
- Stability indicating parameters for testing of product characteristics, identity, potency, purity, and safety, which have been developed and validated
- Stability test methods (e.g., capillary electrophorsis sodium dodecyl sulfate [CE SDS], image capillary isoelectric focusing [icIEF], gel permeation chromatography [GPC], ELISA), which have been qualified for usage
- Acceptance criteria (e.g., limits for the test results)
- Reference standard to compare the sample against

- Approval process (e.g., approved by quality assurance [QA])
- Stability chambers are serviced, inspected, calibrated, and qualified regularly
- Out-of-specification and out-of-trend SOPs QA regulated
- Evaluation of the acquired data to provide a shelf life
- Trained operators, which includes GMP training and data integrity training annual.

PTE: Can you provide any examples of mistakes companies have made when preparing stability studies for investigational new drug (IND) submissions?

Bhroma Patel and Jogi (Lonza): As a CDMO [contract development and manufacturing organization], the biggest issue we encounter is often around data. For example, companies provide insufficient data and information to support stability of drug substance or information is erroneous due to lack of time to prepare for IND submission. Failure to follow FDA guidance or to submit all the information required from the IND submission checklist is another potential oversight.

Hatcher (Catalent): The main mistake that companies make when setting up their stability strategy is not performing accelerated, stressed, photostability, or freeze/thaw stability studies. Often, a process will change throughout the clinical development of a product, and with these changes comes the need to repeat stability studies. I have seen a trend where companies will not repeat the accelerated or stressed stability; however, they will repeat standard stability at the storage condition for the product. This is a very risky strategy, as regulators will want data to show that the change in the process did not impact the stability of the product, including stressed and accelerated stability studies.

Outsourcing stability

PTE: What are the benefits of outsourcing CGMP stability studies for biologics?

Bhroma Patel and Jogi (Lonza): Companies have access to regulatory experts and can meet the most up-to-date regulatory requirements. Companies can meet their needs and requirements (planning and designing stability studies). [There is] cost saving, as large amount of capital is not required on resources, such as on analytical equipment and stability chambers. [They can] gain scientific and analytical knowledge for data generation, interpretation, and reporting. [Outsourcing] enables companies to focus internal resources on new drug discovery and development.

Hatcher (Catalent): The main benefit of outsourcing CGMP stability studies for biologics is that CDMOs are exposed to many different strategies from sponsors and, therefore, have a good handle on trends in the industry. This level of expertise can be very beneficial for the sponsor and will ensure that the stability programme is compliant and up to date with trends in the industry. Another benefit is the analytical expertise that CDMOs possess because the analysts in a QC [quality control] CDMO laboratory are familiar with several types of analytical methods, which means CDMOs are well placed to help the sponsor troubleshoot methods to make improvements when there are issues.

Outsource facilities also typically have significant storage space and analytical instrumentation. This helps the sponsor know that there will not be equipment or space constraints that could negatively impact their stability programme.

PTE: What are the challenges of outsourcing CGMP stability studies for biologics?

Hatcher (Catalent): The main challenge from a CDMO perspective is when a sponsor changes the stability strategy late in the game. This can be detrimental to the timeline and ultimately could delay approval. Another challenge is balancing cost-savings versus performing stability using a conservative approach. There are times when a sponsor is focused on cost-savings and then limits the stability programme, only to have to come back later and perform the study again. This is why it is very important to perform the study in a conservative manner, to avoid having to repeat.

Bhroma Patel and Jogi (Lonza): Finding a trusted outsourcing partner with the right level of expertise and process knowledge, as well as the right assets and technology is key. Without this, delivery may be late or below expectations, leading to a delay in progressing drug production to the next level. Confidentiality and security are essential to avoid breaches of proprietary information in a multi-customer facility.

Lastly, a strong track record of quality compliance and experience working with regulatory bodies in different jurisdictions is also paramount.

PTE: How can a sponsor company ensure their outsourcing facility is following CGMPs?

Bhroma Patel and Jogi (Lonza): Companies should conduct site audits to verify outsourcing best practices and standards of GMP, also, to check validated systems and processes, and that staff are experienced and properly trained. Checking the FDA, MHRA [Medicines and Healthcare products Regulatory Agency], etc., history of an outsourcing partner as well as the QA procedures in place ensures that an established culture of regulatory compliance and high standards exists.

Hatcher and Patel (Catalent): When outsourcing stability studies, it is important to ensure that the contract provider can meet regulatory requirements. One way in which our company helps reassure clients about CGMP compliance is through on-site customer audits, where auditors can dig into the procedures and processes and verify that appropriate regulations are followed. Having the outsourcing facility provide raw data to the client is also an excellent way to provide transparency and confidence in CGMP compliance.

When working with an outsourcing facility, on-site audits should be performed prior to setting down any studies. In addition, the sponsor should ensure that the stability chambers to be used for the study are on site at the provider location. Lastly, the site's regulatory history should be reviewed to confirm that the site has received approval from all relevant regulatory agencies. **PTE**

How Can You Transform the Patient Experience through Digital Transformation?

ON-DEMAND WEBCAST: Aired Wednesday, September 25, 2019

Register for this free webcast at: http://www.pharmtech.com/pt_p/patient

Event Overview

Due to the high cost of bringing a single new therapeutic to the market, life sciences companies have greater pressure to maximize revenue while staying ahead of the competition. Considering that programs for innovative products are high-risk/high-reward, many companies continue to focus their activities on developing first-in-class treatments. The most innovative among them are turning to novel formulation strategies and delivery systems that can vastly improve the patient experience — the next frontier in drug development.

Nowhere is innovation to enhance the patient experience more critical than with these novel large molecules and the required high-volume injectors to deliver them. Thus, high-tech large-volume wearable injectors in the form of combination products are sure to play a critical role in the future success of these new therapeutics by shifting the point-of-care from hospitals and clinics to the patients' homes.

IASO is a life-sciences showcase for the lifecycle of a combination product in oncology, from upstream thinking to commercialization. In this webcast, experts from Dassault Systèmes will demonstrate the core value of Dassault Systèmes' 3DEXPERIENCE® platform: modeling and simulation, with end-to-end digital continuity and data integrity.

Key Learning Objectives

- Gain insight and knowledge of the life science industry shift toward biologics and the delivery devices required to deliver them
- Gain a high-level understanding of the value the 3DEXPERIENCE Platform can offer to companies bringing innovating combination products (delivery devices) to market
- Learn how the 3DEXPERIENCE platform can be used in each of the following areas: collaborative design, therapeutic design and development, device design and development, manufacturing excellence, enterprise operational excellence

Presenters

Sara Dutta
Life Sciences Industry Business Consultant
Dassault Systèmes

Guillaume Kerboul
Life Sciences Industry Bususiness Consultant Director
Dassault Systèmes

Felicity Thomas
Senior Editor
Pharmaceutical Technology Europe

Who Should Attend:

- CTO SVP Development
- CRO
- Regulatory
- CIO
- VP Research & Development
- VP Manufacturing
- VP Quality
- Director IT
- Director Quality
- Director Product Development
- IT Strategy
- Data Management
- Lab Management
- Computational Science
- Lab Science
- BIO-Research
- Systems Engineering

Sponsored by

DASSAULT SYSTEMES

Presented by

Pharmaceutical Technology EUROPE

For questions or concerns, email kmoore@mmhgroup.com.

Getting in Touch with New Guidance on Topical Products

Changing regulatory guidance on generic topical products is expected to lead to an increase in the number of market approvals in the near future.

Jeremy Drummond
is senior vice-president of business development for MedPharm.

The regulatory landscape governing the approval of generic topical products has been changing significantly in Europe and the United States recently. This is creating new opportunities for generic companies to expand their product ranges in the treatments for the skin, eye, nails, and mucosal membranes.

Historically, the barriers facing companies that have wanted to introduce generic topical products have been sufficiently high to dissuade companies from investing in the product development required. These barriers to investment are now being recognized by governments and payers, and steps are being taken to encourage more topical generic product development.

The use of branded products where generic options are available increases patient expense by an estimated $1.2 billion (€1.1 billion) in the US (1), and similar practices in the United Kingdom are costing the National Health Service £200 million (€227 million) annually (2).

Therapeutic bioequivalence: A major barrier

A major barrier to cost-effective development of topical products has been the historical requirement for clinical trials to demonstrate therapeutic bioequivalence with the reference product. The costs, typically in the millions of Euros, and substantial risks associated with these trials are untenable for many generic topical drug developments because the products often occupy niche markets. These hurdles to development are exacerbated in Europe where the market is split between the member states and ultimately any product needs to be registered in each market.

As with any product development, generic-drug companies need to be confident that they can expect their product to deliver sufficient return on investment. Consequently, many topical products have continued on the market unchallenged by new generic products because of the prohibitive nature of the previously mentioned costs, and risks from any clinical trial.

Regulatory action

So, what are the actions that have been taken by regulators? A few years ago, the Medicines and Healthcare products Regulatory Agency (MHRA) based in the UK, alongside the European Medicines Agency (EMA), made the first step towards changing the regulatory landscape for generic products. They approved at least two topical applications for generic products, one for dermatology and one for nails and accepted that no clinical bioequivalence data was required (3,4). In both of these submissions, the content and physiochemical properties of new topical formulations were exactly matched to those of the originator product. Data had to be presented to demonstrate that the generic and the originator product both had the same critical excipients in the same concentrations and that the physical microstructure of the two formulations was the same. The bioequivalence was effectively demonstrated using *in-vitro* release testing (IVRT) and *in-vitro* permeation testing (IVPT) performance models. *In-vitro* disease activity models were also submitted to support the successful submissions where data were collected using *ex-vivo* human nails and skin. One of these submissions was in relation to a product that contained a steroid as an active ingredient, and the data presented also included an *in-vivo* skin blanching/vasoconstrictor assay study in healthy volunteers.

IVRT measures the release of a drug out of a semi-solid formulation and through a membrane specifically selected not to impede that release. This type of performance testing is analogous to testing the dissolution testing of tablets. Regulatory bodies are increasingly expecting IVRT to be used as a quality tool and as part of all semi-solid release and stability specifications. Traditionally run in vertical diffusion ('Franz') cells, this testing is now being automated to improve throughput and reproducibility.

IVPT measures the penetration into and permeation across human

skin. IVPT is immeasurably more complex than IVRT because of the variability with skin from the same donor as well as donor-to-donor variability.

Disease activity models measure the activity of a drug on a disease-related pathway or an induced infection to establish whether the drug is bioavailable, engages the target, and can act on the desired pathway. In tandem with penetration and permeation testing, these sophisticated models provide the closest analogy to the clinic.

EMA published draft guidelines to be used for the development of generic topical pharmaceuticals at the end of 2018 (5). This draft followed a three-year period where comments on their concept paper, published in 2015 (6), were submitted and reviewed. EMA's guidance utilizes IVRT and IVPT and covers the full range of generic topical products including indications for the eye, nose, and nail, as well as dermal applications. EMA has been collecting feedback from interested parties over the past six months and can be expected to provide an update of the guidance in the coming future, although no timetable has been published.

Disease activity models measure the activity of a drug on a disease-related pathway or an induced infection to establish whether the drug is bioavailable, engages the target, and can act on the desired pathway.

In contrast, the US Food and Drug Administration (FDA) has issued specific guidance documents for several topical products (7). The requirements of FDA and EMA are broadly similar, although there are subtle differences, for example in the statistical treatment of some data. The majority of FDA's draft guidance references back to its draft guidance on acyclovir cream published in 2017 (8). This was the first FDA guidance to offer an *in-vitro* only route for demonstrating bioequivalence.

Relatively complex models

To the untrained eye, these performance testing models may seem to be straightforward lab experiments. They are, in fact, relatively complex with many variables, which can have a significant impact on results. Chilcott *et al.* showed that up to a 30% variation can occur between laboratories using the same IVRT protocol, the simplest of the models (9). Unsurprisingly, regulatory bodies expect a high standard of validation on such bioequivalence tests and in addition to this, the studies must be performed under rigorous levels of quality assurance oversight. As expected from Chilcott *et al.*'s findings, the levels of variability

produced can challenge the limits of these methodologies. There have been reports of some laboratories that have tried to develop suitable IVRT and IVPT methods but have been unable to reach the guidance's thresholds due to a lack of experience. It is important for developers to understand the experimental rigour needed, and have the required experience to generate acceptable data packages. In combination with expertise in the field, the multiple steps and time needed to establish an acceptable level of validation under the appropriate quality standards inevitably means that the costs involved are not insignificant, are typically more than for tablets. Critically they remain much less than the cost of having to do a clinical trial to generate the same bioequivalence data.

Both early adopters and patients can expect to benefit from this new approach to generic-product regulations, as more companies take the opportunity to broaden their footprint in topical product development.

IVPT is particularly challenging. Expertise is required to truly understand how to minimize the inherent variation wherever possible. As drugs increase in size and lipophilicity the levels permeating through the skin can quickly approach the analytical detection limits of even modern liquid chromatography–mass spectrometry equipment. To add to these challenges associated with minimizing data variation, the guidance documents also require that any analytical methods be fully validated, which, experts in the field know, is no easy task. It is also clear even with the utmost care and careful experimentation, getting the data required as written in some product guidance documents can still be a challenge and needs to be a central part of any discussion with regulatory authorities.

Highly knowledgeable partners, with experience in supporting generic clients to manage these challenges, understand how to use *in-vitro* methods as a lower-cost route to demonstrating bioequivalence. Regulators and developers are now starting to appreciate the sensitivity of data from IVRT above those from IVPT when identifying any subtle difference between a new topical generic formulation and the originator product. Experienced practitioners understand that the variability in IVPT data can be mitigated by using fresh tissue and careful handling in particular within single donor samples.

New opportunities

So, while the generics industry is waking up to the new opportunities, they are also learning that the development of topical generic formulations typically requires more specific expertise than oral solid dosage forms due to their more complex nature. There is an increased understanding that the significant investment required is still smaller than trying to demonstrate bioequivalence in the clinic.

Regulators on both sides of the Atlantic, in Europe, and the US, have clearly expressed willingness to provide more clarification to developers as to what is expected in generic submissions; a consequence of the scarcity of generic submissions historically. EMA is continuing to provide developers with product-specific guidance on the suitability of their methodologies and protocols in pre-booked structured scientific advice meetings. Historically, when the applicant provides initial data using the approach they plan to take, these meetings have proved invaluable in providing clear advice on what will be acceptable to an authority. The meetings in particular help clarify areas of uncertainty in the new guidance documents. Similarly, FDA is now open to pre-ANDA (abbreviated new drug application) meetings to discuss specific submissions.

In the latest guidance, EMA has extended the applicability of the *in-vitro* approach from dermal indications to include those for the eye, nail, and nose, and other sites of local delivery (5). Recently, FDA has also announced the introduction of research grants to encourage development beyond skin to other epithelial tissues (10).

The cumulative effects of these changes can be expected to increase the number of market-approved generic topical products in the coming years as desired by the regulatory authorities. Both early adopters and patients can expect to benefit from this new approach to generic product regulations, as more companies take the opportunity to broaden their footprint in topical product development.

References

1. R.J. Desai, et al., *BMJ* 361 (k1180) 3 April 2018.
2. National Audit Office, "Prescribing Costs in Primary Care," *nao.org.uk*, 18 May 2007.
3. MHRA, "Public Assessment Report: Decentralized Procedure—Xemacort 20 mg/g + 1 mg/g Cream (Fusidic Acid and Betamethasone Valerate)," *mhra.gov.uk,* January 2016.
4. MHRA, "Public Assessment Report: Decentralized Procedure—Amorolfine 5% W/V Nail Lacquer, Amorolfine 5% W/V Medicated Nail Lacquer, Amorolfine Hydrochloride 5% W/V Medicated Nail Lacquer, Tinecur 5% W/V Medicated Nail Lacquer, Amorstad 5% W/V Medicated Nail Lacquer," *mhra.gov.uk,* 20 July 2011.
5. EMA, *Draft Guideline on Quality and Equivalence of Topical Products*, *ema.europa.eu*, 18 Oct. 2018.
6. EMA, "Concept Paper on the Development of a Guideline on Quality and Equivalence of Topical Products," *ema.europa.eu*, 2 Dec. 2014.
7. FDA, "Product-Specific Guidances for Generic Drug Development," PSG Database, *accessdata.fda.gov* [accessed 24 Sep. 2019].
8. FDA, *Draft Guidance on Acyclovir*, *accessdata.fda.gov*, Revised Dec. 2016.
9. R. Chilcott, et al., *J. Pharm. Sci.* 94 (3) 632–638 (2005).
10. FDA, "Department of Health and Human Services: Fiscal Year 2020," www.fda.gov/media/121408/download [accessed 24 Sep. 2019]. **PTE**

Alfasigma

Company description

Alfasigma is one of the leading Italian pharmaceutical companies, focused on prescription drugs, self-medication and nutraceutical products. Established in 2015, after the merge of Alfa Wassermann and Sigma-Tau, today has a worldwide presence in more than 90 countries.

In 2018 Alfasigma exceeded 1 billion Euro of turnover, half of which was generated by foreign markets.

Alfasigma's strategy is based on three guidelines which, over the years, have assured the group constant and balanced growth: Research, Technology and Internationalization.

Implementing research and technology to constantly improve its products, opening up new frontiers, extending to new markets.

During the years it has invested heavily in plant and human resources.

As a result of the last investments, two new sterile departments for sterile powder and pre-filled syringes will become fully operational in 2020.

Products and services offered

Alfasigma Contract Manufacturing offers a flexible and versatile range of products and services.

Its products range from lyophilised powders to injectable liquids, pre-filled syringes, topical and oral liquids, semisolids and oral solids. Attention to quality is demonstrated by a long list of certifications: FDA, ANVISA, GCC, PMDA and EUGMP.

Alfasigma Contract Manufacturing handles the development of formulations and processes, optimising the manufacturing process and pharmaceutical formulation. Scaling up and the production of technical and pilot batches, together with the overall validation of the manufacturing process.

The Analytical team offers a wide range of services including the development, transfer and validation of chemical and biological methods, forced degradation and ICH stability studies.

Batch preparation services include the manufacture and packaging of batches for clinical trials, the management of randomisation lists and the release of batches for clinical studies. Alfasigma is also highly experienced in the regulatory aspect.

ALFASIGMA
Contract Manufacturing

Contact details
Alfasigma S.p.A.
Alanno (PE) - Via E.Fermi,1
Pomezia (RM) - Via Pontina, km 30,400
contractmanufacturing@alfasigma.com
manufacturing.alfasigma.com

Hall 12.1, Booth 121D42

Baxter BioPharma Solutions

Company description

Backed by over 85 years of experience in parenterals, Baxter's BioPharma Solutions (BPS) business collaborates with pharmaceutical companies to support commercialization objectives for their molecules. BPS is a premier CMO with a focus on specialized sterile injectable manufacturing designed to meet complex and traditional sterile challenges.

Our state-of-the-art, award-winning facilities have primary locations in:

- The Bloomington, Indiana facility is a leader in sterile contract manufacturing and offers form/fill/finish services and solutions for injectables designed to meet traditional sterile manufacturing challenges.
- The Halle/Westfalen, Germany facility has over 60 years of experience and is recognized as a world-class manufacturer of oncology products and other sophisticated compounds.

Major products/services being exhibited

BPS can support your pharmaceutical needs with a broad portfolio of sterile fill/finish production capabilities, and our reputation is built on the high-quality products we manufacture for our clients in a cGMP environment. Our delivery systems include: prefilled syringes, liquid/lyophilized vials, diluents for reconstitution, cartridges, powder-filled vials, and sterile crystallization. Our drug categories include: small molecules, biologics, vaccines, cytotoxics, highly potent compounds, and ADCs (antibody-drug conjugates). From formulation and development, through commercial launch, our extensive, customized support services can guide you through marketplace complexities, helping you achieve the full potential for your drug molecule. Whether you face formulation challenges, clinical supply hurdles, surges in demand due to market fluctuations, risk mitigation concerns, or patent expiry challenges, we offer tailored and versatile solutions to help achieve your commercialization objectives.

Baxter

Contact details
Baxter BioPharma Solutions
One Baxter Parkway, Deerfield,
IL 60015 USA
Tel. US: +1 (800) 422-9837
International: +1 (224) 948-4770
biopharmasolutions@baxter.com
baxterbiopharmasolutions@baxter.com

Hall 12.1, Stand 121F81

BENEO GmbH

Company description

BENEO is a division of the Südzucker Group, that employs more than 1000 people and has production units in Belgium, Chile, Germany and Italy. www.BENEO.com

Major products/services being exhibited

galenIQ™ (Isomalt), is a water-soluble pharmaceutical excipient filler-binder, derived from sucrose.

In fact galenIQ™ has a sweetness and taste profile that is very similar to sucrose

and therefore galenIQ™ is frequently used to improve the palatability of bitter-tasting active pharmaceutical ingredients (APIs), plant extracts and probiotics.

galenIQ™ is non-cariogenic and shows a low glycaemic index which makes it the optimal choice for the formulation of a broad variety of dosage forms, such as chewable tablets, compressed lozenges, oro-dispersible mini-tablets, effervescents, and cough syrups.

The galenIQ™ range comprises different grades of solubility with varying particle size. galenIQ™ can easily be applied to tablets and powdered formulas, to coat solid dosage forms and as a component in hot melt extrusion processes and liquid applications.

galenIQ™ is manufactured under cGMP conditions according to IPEC-PQG requirements for pharmaceutical excipients and complies with the current Ph. Eur., BP, USP-NF and JP monographs for Isomalt.

galenIQ™
a brand of beneo

Contact details
BENEO GmbH
Maximilianstraße 10,
68165 Mannheim, Germany
Telephone: +49 621 421 170
Fax: +49 621 421 160
contact@beneo.com
https://www.beneo.com/ingredients/pharmaceutical-excipients

Hall 10.2, Booth 102C11

Cambrex

Company description

Cambrex is the leading small molecule company that provides drug substance, drug product and analytical services across the entire drug lifecycle. The company provides customers with an end-to-end partnership for the research, development and manufacture of small molecule therapeutics. With over 35 years' experience and a growing team of over 2,000 experts servicing global clients from sites in North America and Europe, Cambrex is a trusted partner in branded and generic markets for API and dosage form development and manufacturing.

Major products/services being exhibited

Cambrex operates 13 locations across North America and Europe, offering drug substance manufacturing, drug product manufacturing and early stage development and testing services.

Drug substance services include development, scale-up, technology transfer and manufacturing as well as specialist technologies and capabilities such as biocatalysis, continuous flow, controlled substances, solid state science and handling highly potent APIs.

Cambrex's drug product expertise is in the formulation and development of conventional dosage forms including oral solids, semi-solids and liquids; as well as specialist dosage forms such as modified-release, fixed dose combination, paediatric, bi-layer tablets, stick packs, topical and sterile and non-sterile ointments.

Cambrex also offers early clinical phase support to customers requiring smaller quantities of drug substance and drug product supply, in addition to offering standalone analytical services. These include method development and validation, compendial and release testing, stability storage and testing, material characterisation, impurity isolation and identification, fate and purge studies, microbiology, cleanroom services and many more.

Cambrex

Contact details
Cambrex
One Meadowlands Plaza, East
Rutherford, New Jersey 07073, USA
Tel. +1 201-804-3000
info@cambrex.com
www.cambrex.com

Hall 4.1, Stand 41C10

Catalent

Company description

Catalent is the leading global provider of advanced delivery technologies, development, and manufacturing solutions for drugs, biologics, gene therapies, and consumer health products. With more than 85 years serving the industry, Catalent has proven expertise in bringing more customer products to market faster, enhancing product performance, and ensuring reliable global clinical and commercial product supply. Catalent manufactures more than 73 billion doses of nearly 7,000 products annually, or approximately 1 in 20 doses taken each year by patients or consumers globally.

Major products/services being exhibited

Catalent's innovative oral drug delivery technologies include Zydis® fast-dissolve formulations, OptiMelt® hot-melt extrusion, and a broad technology platform for complex controlled release formulations. Since 1933, Catalent has developed over 80% of branded prescription softgel products and continues to deliver breakthrough softgel innovations including OptiShell® and OptiGel® Bio technologies.

The award-winning OptiForm® Solution Suite platform allows developers to formulate oral dose forms by combining high-throughput screening of molecules with the broadest selection of enabling technologies.

Catalent has over 20 years' experience in biologic drug development, including biologics, biosimilars, antibody-drug conjugates and gene therapies. The company's proprietary GPEx® cell line technology generates high-performance, highly stable, production cell lines, and has led to more than 115 drugs in clinical trials and 12 approved products.

In May 2019, Catalent completed the acquisition of viral vector leader Paragon Bioservices, Inc., expanding its biologics drug development, delivery and manufacturing services to include gene therapy.

Catalent

Contact details
Catalent
14 Schoolhouse Road,
Somerset, NJ 08873, USA
Tel. +1 888 765 8846
solutions@catalent.com
www.catalent.com

Hall 12.1, Stand 121A82

DWK Life Sciences

Company description

DWK Life Sciences, represented by SciLabware (a wholly owned company of DWK Life Sciences), manufacture and supply a complete portfolio of standard and bespoke primary packaging solutions and services that meet and exceed the rigorous requirements and expectations of our customers. From tubular glass vials, stoppers and caps for lyophilisation and diagnostic kits, glass tubes and caps for control reagents, dropper bottles, with dropper assemblies or tips and closures for blood grouping reagents and rare antisera, to additional services including depyrogenation, particulate cleaning and barcoding, we can offer our customers a full primary packaging solution, received ready to use.

Visit us on stand 111H20 at CPhI 2019 to find out more.

For further information visit https://www.scilabware.com/en/packaging or email your questions to enquiries@scilabware.com with the subject line Pharma Tech Europe.

Products

- Diagnostic vials, lyophilisation stoppers and cap
- Serum vials and bottles, stoppers and seals
- Dropper bottles and dropper assemblies
- Dropper bottles, tips and closures
- Leak resistant bottles
- High recovery vials
- Glass tubes and caps
- Tubular, moulded glass and plastic universals and bijous
- Ampoules
- Customer bespoke manufactured vials

Premium Services that can be applied to products

- Depyrogenation
- Sterilisation
- Barcoding and Trae weighing
- Particulate cleaning
- Surface treatments
- Custom packaging

DURAN WHEATON KIMBLE
Excellence in your hands

Contact details
DWK Life Sciences
SciLabware Ltd.
Unit 4, Riverside 2, Campbell Road,
Stoke-on-Trent, Staffordshire, ST4 4RJ
Telephone: +44 (0)1782 444406
Fax: +44 (0)1782 940436
enquiries@scilabware.com
www.scilabware.com

Hall 11.1, Stand 111H20

Emergent BioSolutions

Company description

Emergent is a global life sciences company dedicated to one simple mission—to protect and enhance life. For 20 years, Emergent has been dedicated to providing quality services and safety of products for their customers, in an effort to create a healthier world. Emergent develops, manufactures, and delivers a portfolio of specialty products for civilian and military populations that address accidental, intentional, and naturally-emerging public health threats, such as medical countermeasures for biological and chemical threats as well as emerging infectious diseases.

Major products/services being exhibited

As a recognized leader in providing integrated Contract Development and Manufacturing services, Emergent's capabilities support both bulk drug substances and sterile injectable drug products, from Phase I development through commercial scale production.

Drug substance manufacture:

- Clinical & Commercial Scale
- Single-Use Platform (up to 4000L)
- Mammalian Cell Culture
- Viral
- Bacterial Fermentation
- Avian
- Insect
- Process & Analytical Development
- Upstream & Downstream

Drug product manufacture:

- Small Molecules & Biologics
- Viral & Non-Viral Fill/Finish Capabilities
- Clinical & Commercial Scale
- Vials & Prefilled Syringes
- Aseptic Processing
- Terminal Sterilization
- Lyophilization
- Formulation Development
- Material Characterization
- Microbiology
- ICH Stability

emergent biosolutions

Contact details

Emergent BioSolutions
400 Professional Drive
Suite 400, Gaithersburg, MD 20879, USA
Tel. +1 800-441-4225 Fax: +1 484-843-4414
CDMO@ebsi.com
http://www.ebsi.com/CDMO

Hall 12.0, Stand 120A50

GEA Group

Company description

At the heart of this year's CPhI Worldwide, GEA will be presenting a selection of equipment for the batch and continuous granulation, tableting and coating of pharmaceutical products, as well as containment solutions and equipment for homogenization, spray drying and freeze drying.

- Discover our portfolio of single units, modular systems and complete production lines
- Create new opportunities to get your product to market faster with our efficient and reliable process solutions
- Experience the 3D virtual world of continuous manufacturing
- Discuss the developments and technological breakthroughs that will help to define the future of the industry

Major products/services being exhibited

- **Continuous experience:** meet ConsiGma®, the multipurpose platform that has been designed to transfer powder into coated tablets in development, pilot, clinical and production volumes in a single compact unit
- **MODUL Q:** the rotary tablet press that's setting new standards in efficiency, productivity and reliability
- **Mobile PharmaConnect:** this integrated small-scale granulation and drying plant allows a number of diverse process modules to be docked to a single control unit
- **MOBILE MINOR:** installed in almost 2400 plants worldwide, this cross-application spray dryer is compact, robust, reliable and versatile
- **LYOSENSE:** based on multipoint NIR measurements, our technology provides comprehensive, non-destructive evaluation of freeze-dried product cakes in real-time

GEA engineering for a better world

Contact details

GEA Group
Kalscheurener Strasse 92,
50354, Hürth, Germany
Telephone: +49 (0) 2233 6999 0
pharma@gea.com
GEA.com/pharma

Hall 11.0, Booth 110C70

Gerresheimer

Company description

Gerresheimer is a leading global partner to the pharma and healthcare industry. With specialty glass and plastic products, the Company contributes to health and well-being. Gerresheimer operates worldwide and its approximately 10,000 employees manufacture products in local markets, close to its customers. With plants in Europe, America and Asia, Gerresheimer generates revenues of around EUR 1.4 bn. The comprehensive product portfolio includes pharmaceutical packaging and products for the safe, simple administration of medicines: Insulin pens, inhalers, prefillable syringes, injection vials, ampoules, bottles, and containers for liquid and solid medicines with closure and safety systems as well as packaging for the cosmetics industry.

Major products/services being exhibited

The acquisition of Sensile Medical AG allowed Gerresheimer to expand their business model and become an original equipment manufacturer (OEM) for drug delivery platforms with digital and electronic capabilities. Sensecore is small and very precise in dosage. consisting of only two plastic parts, it can be produced at a low cost. Thanks to its high degree of flexibility, it is compatible with a variety of drugs.

Sensile Medical is already working very successfully on projects for diabetics and patients with heart disease and in other treatment areas such as Parkinson's disease. sensile Medical was granted the EC certificate for the wearable micro pump they designed specifically for the treatment of Parkinson's. A European pharmaceutical company has obtained the CE declaration. This makes the product the first micro pump by Gerresheimer's subsidiary Sensile Medical that will be used commercially.

GERRESHEIMER

Contact details
Gerresheimer
KlausKlaus-Bungert-Str. 4,
40468 Duesseldorf, Germany
Tel. +492116181-0 Fax: +492116181295
info@gerresheimer.com
www.gerresheimer.com

Hall 11.1, Stand 111B10

Grifols International, S.A.

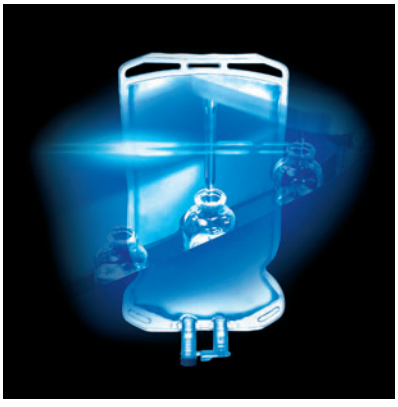
Company description

Grifols Partnership is a business-to-business contract development and manufacturing platform for sterile solutions and lipid emulsions with a long-term experience in producing intravenous solutions for the pharmaceutical industry worldwide.

Over the years we have established successful relationships with customers in global markets, including North America, Canada, Australia and Europe in the following areas:

- Human & Veterinary fields
- New product development
- Generic drug development and manufacturing

Grifols Partnership has two FDA and GMP approved manufacturing facilities in Spain for intravenous solutions that have parametric release certification.



Major products/services being exhibited

We specialize in small molecule intravenous solutions and offer high quality pharmaceutical development and product manufacturing. Our portfolio also includes products which require careful design and assembly including medical devices and bags for blood storage and collection.

Technological capabilities:

- Drug Product Development
- Small Molecule Drug Products
- Terminal Sterilization
- Light and O_2 sensitive products
- Emulsion Technology
- Vials (5 to 50 mL)
- Diluents
- Glass Bottles (50 to 500 mL)
- Flexible Containers (PP bags, 50 to 1000 mL)
- FFS technology for PP bags
- Regulatory Approvals

GRIFOLS
Grifols Partnership
Better together

Contact details
Grifols International, S.A.
Av. de la Generalitat, 152–158,
08174 Sant Cugat del Vallès,
Barcelona, Spain
Tel. +34935712199 Fax: +34935710474
partnership@grifols.com
www.partnership.grifols.com

Hall 12.1, Stand 121C70

Hedinger

Company description

Hedinger is a German company founded in 1843 highly specialized in the supply of pharmaceutical Excipients and APIs manufactured by global chemical companies (e.g., Dow Chemicals, Lanxess, Shell Chemicals, Olin, BP Chemicals, INEOS Phenol).

Our core competence is the GMP-compliant handling along the entire supply chain. We own two sites in Germany—on each site we run a GMP-Laboratory and 4 clean-rooms class D for repackaging and analytical testing. Our System is regularly inspected by the competent local authorities and many pharmaceutical customers (e.g. Novo Nordisk, Sanofi, Boehringer Ingelheim, Eli Lilly, Novartis, MSD, Roche, Pfizer).

Major products/ services being exhibited

Our major services along the supply chain are loading with dedicated equipment, dedicated tank trucks, dedicated tank farms, clean-room repackaging, analytical testing and lot specific COAs released by a QP (Ph. Eur.)

All our products fulfil the highest quality expectations (GMP) and knowing the requirements of our customers, we offer the full regulatory service incl. the possibility of audit reports and quality agreements.

We offer different grades of synthetic Glycerol, Metacresol, Propylene Glycol, Acetic Acid, Isopropanol, Acetone etc. and some aqueous solutions and mixtures.

HEDINGER 1843 A pure decision.

Contact details
Aug. Hedinger GmbH & Co. KG
Heiligenwiesen 26, 70327 Stuttgart, Germany
Tel. +49 711 402050
Fax: +49 711 4020535
info@hedinger.de
www.hedinger.de

Hall 10.2, Stand 102B10

HERMES PHARMA – a Division of Hermes Arzneimittel GmbH

Company description

The oral route is considered a simple and cost-efficient way of drug delivery, primarily using tablets or capsules. However, recent data suggest that difficulties swallowing tablets/capsules are widespread, occur across all age groups, potentially impacting treatment success. Tablets and capsules often fail to keep pace with the evolving needs of modern patients and may no longer be the go-to solution.

HERMES PHARMA is the expert in developing and manufacturing user-friendly oral dosage forms including effervescent and chewable tablets, instant drinks, lozenges, orally disintegrating granules and HERMES NutriCaps. These user-friendly dosage forms

- Are easy to swallow—even for people with dysphagia.
- Taste great—even if the API is bitter.
- Are easy to ingest—even with a large API content or dosage size.
- Can be taken with or without liquids.
- Offer a variety of choices in terms of flavor.
- Improve patient experience through enhanced convenience.
- Allow greater amounts and different combinations of API to be delivered in a single dose, simplifying treatment regimens.
- Help to increase compliance and boost treatment effectiveness.

For over 40 years, HERMES PHARMA has been working with healthcare companies around the globe to expand their product lines and grow their brands. From product development and formulation to manufacturing and regulatory support, we offer expert advice and customized solutions at every point along the pharmaceutical value chain.

HERMES PHARMA is a division of Hermes Arzneimittel GmbH, a German healthcare company with a rich portfolio of successful OTC brands.

HERMES PHARMA
Get the dose right®

Contact details
HERMES PHARMA – a Division of Hermes Arzneimittel GmbH
Georg-Kalb Strasse 5–8,
82049 Pullach im Isartal, Germany
Tel. +49 89 79102 261
info@hermes-pharma.com
www.hermes-pharma.com

Hall 12.0, Stand 120D81

Capsugel® | Lonza Pharma & Biotech

Company description

Capsule Delivery Solutions, part of Lonza Pharma & Biotech, is the leader in capsule-based solutions and services, proudly offering Capsugel® products. With the largest production and supply chain footprint in the industry, we provide the highest quality and deepest regulatory expertise to our 2,000 pharmaceutical customers, globally. Our unique combination of science, engineering, formulation and capsule expertise enables us to optimize the bioavailability, targeted delivery and overall performance of our customer's products. We partner with them in over 100 countries to create novel, high-quality and customized solutions that meet their needs and patients' evolving preferences.

Major products/services being exhibited

With a diverse portfolio including gelatin, HPMC, and specialized clinical capsules, we are a global leader in capsule development and manufacturing, bringing unmatched products and technical support to our worldwide customer base. We provide the widest array of non-animal based specialty polymer capsules. Our capsules portfolio includes:

- **Immediate release:** Coni-Snap® Gelatin, Vcaps® Plus, Vcaps® Gen C, Plantcaps®
- **Modified release:** Vcaps® Enteric, DRcaps™
- **Dry Powder Inhalation capsules - Zephyr™:** Gelatin: Coni-Snap® Gelatin and Coni-Snap® Gelatin-PEG; HPMC: Vcaps® and Vcaps® Plus
- **R&D portfolio:** PCcaps®, DBcaps®, Colorista®
- **Patient Centric and Life Cycle Management:** Coni-Snap® Sprinkle, Press-Fit®, Licaps®, DUOCAP®

As we continue to grow our offering, stop by our booth: 102A70, to learn more about Capsugel® Zephyr™ dry-powder inhalation portfolio; Lonza Engine™ equipment portfolio; and other innovative capsule technologies.

Capsugel® | Lonza Pharma & Biotech

Contact details
Capsugel® | Lonza Pharma & Biotech
Rijksweg 11, B-2880 Bornem, Belgium
Tel. +33 389 205 725
Fax: +32 (0) 3-889-26-22
solutions.emea@lonza.com
https://www.capsugel.com/market-segments/biopharmaceuticals

Hall 10.2, Stand 102A70

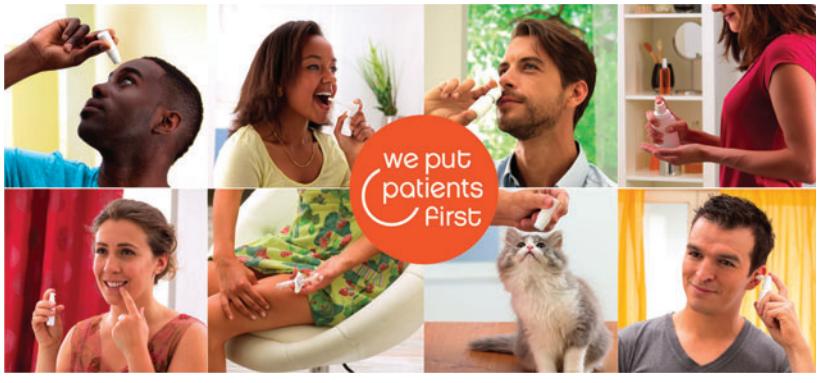
NEMERA

Company description

Nemera is a world leader in the design, development and manufacturing of drug delivery devices for the pharmaceutical, biotechnology and generics industries. Nemera always puts patients first, providing high-quality solutions that have a demonstrable impact on patients' health.

Nemera's vision is to be the most patient-centric drug delivery device company.

Nemera's newly branded Insight Innovation Center, with offices in North America and Europe provides consultative services to support your overall device strategy. Providing user research, Human Factors, User Experience design, and Design for manufacturing, the Insight Innovation Center can help you navigate your device strategy for both novel and platform solutions. Users are at the center of everything that we do in our effort to always put patients first.



Major products/services being exhibited

Nemera offers a comprehensive portfolio of products and services across ophthalmology, nasal, inhalation, dermal, transdermal and parenteral delivery:

- Ophthalmic (multidose eye droppers for preservative-free formulations)
- Nasal, Buccal, Auricular (pumps, valves and actuators for sprays)
- Parenteral (auto-injectors, pens, safety devices & implanters)
- Dermal and transdermal (airless & atmospheric dispensers)
- Inhalation (pMDIs, DPIs)

Nemera

Contact details
NEMERA
20, Avenue de la Gare,
38290 La Verpillière, France
Telephone: +33 4 74940654
information@nemera.net
www.nemera.net

Hall 11.1, Booth 111C52

Novo Nordisk Pharmatech A/S

Company description

High-purity GMP quaternary ammonium compounds

Novo Nordisk Pharmatech A/S is a leading worldwide supplier of recombinant insulin for cell growth media and pharmaceutical grade quaternary ammonium compounds (Quats) for the pharmaceutical, biopharmaceutical and personal care industries. Our Quats are manufactured to the strictest cGMP regulations, and not a single ingredient is delivered without meeting your own uncompromising standards. Whether it is Benzalkonium Chloride, CTAB, Cetrimide or Strong Cetrimide Solution for ophthalmic, nasal sprays, topicals, oral products or medical devices, the products are manufactured to the highest cGMP standards (ICH Q7), and in both product areas the company has distinguished itself for:

- Global regulatory compliance
- Consistent high quality
- Extensive regulatory documentation
- Continuous availability
- Secure global supply chain
- High levels of service and support

Major products/services being exhibited

- Benzalkonium Chloride (BKC, BAK, BAC) CAS. No. 8001-54-5,
- Cetrimide CAS. No. 1119-97-7,
- Cetrimonium Bromide (CTAB) CAS No. 57-09-0
- Strong Cetrimide Solution CAS No. 1119-97-7

Novo Nordisk Pharmatech A/S

Contact details

Novo Nordisk Pharmatech A/S
Koebenhavnsvej 216, 4600 Koege, Denmark
Tel. +45 5667 1000
Fax: +45 5667 1000
nnprinfo@novonordiskpharmatech.com
www.novonordiskpharmatech.com

Hall 4.2, Stand 42D32

Pfizer CentreOne®

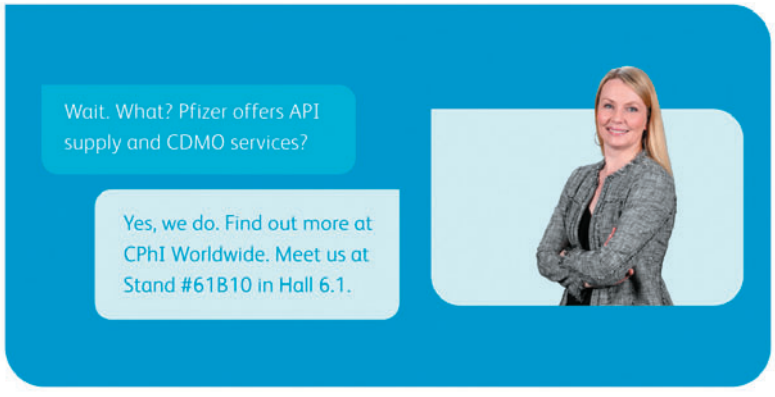
Company description

Pfizer CentreOne is a global CDMO embedded within Pfizer and a leading supplier of specialty APIs. Our global manufacturing network includes more than 35 sites across six continents. Backed by Pfizer resources, we deliver technical expertise, global regulatory support and long-term supply. For more than 40 years, we've been guiding complex compounds securely and efficiently from development through commercial manufacture.

Working together with our customers, we combine our knowledge with open dialogue to solve challenges. Intelligent collaboration with Pfizer CentreOne.

Major products/services being exhibited

Pfizer CentreOne will have its experts on hand to discuss its contract development and manufacturing capabilities, including small molecule APIs, oral solids, sterile injectable fill-finish and biologics. Pfizer CentreOne will also have experts available to answer questions about specialty APIs and intermediates.



Pfizer CentreOne

Contact details

Pfizer CentreOne®
235 E. 42nd Street, New York, NY 10017, USA
Telephone:
Contract manufacturing (International):
+1-224-212-2267 (US)
APIs & intermediates:
The Americas: +1-269-833-2296 (US)
Europe, Middle East, Africa: +32-27157578 (Belgium)
Asia Pacific: +65-64190240 (Singapore)
pfizercentreone@pfizer.com
www.pfizercentreone.com

Hall 6.1, Stand 61B10

Röchling Medical

Company description

Röchling Medical is an innovative developer and manufacturer of components, systems and complete OEM-products for various medical applications such as fluid management, surgery, diagnostics and pharmaceutical. We manufacture at six locations worldwide under clean room conditions.

For our pharmaceutical customers, we develop and produce high-quality, customized plastic primary packaging solutions, as well as application aids and drug delivery systems for the simple and safe dosing and administration of drugs. We also offer a broad spectrum of standard packaging options for a variety of dosage forms for the human pharma and animal health markets.

Our product portfolio is complemented by a comprehensive range of services along the whole process chain, including packaging, sterilization and regulatory support.

Major products/services being exhibited

- Our technologies: multi-layer extrusion blow molding, injection blow molding, injection stretch blow molding, injection molding
- Our services: product design and development, inhouse tooling, industrialization and high-volume manufacturing, assembly, quality assurance, packaging and sterilization, regulatory support

Visit our stand to learn more about:

- Sympfiny®—our award-winning oral delivery system for dosing and dispensing multiparticulate drugs
- Our expertise in co-extrusion and collapsible bag technology (example application: API containers for soft mist inhalers)
- Highlights from our standards programme: 10–50 mL round nasal spray bottles for 20 mm snap on pumps—officially approved by Aptar and Nemera; ophthalmic bottles range for Aptar OSD; new eyedropper bottles series with retained tamper-evident ring

Röchling

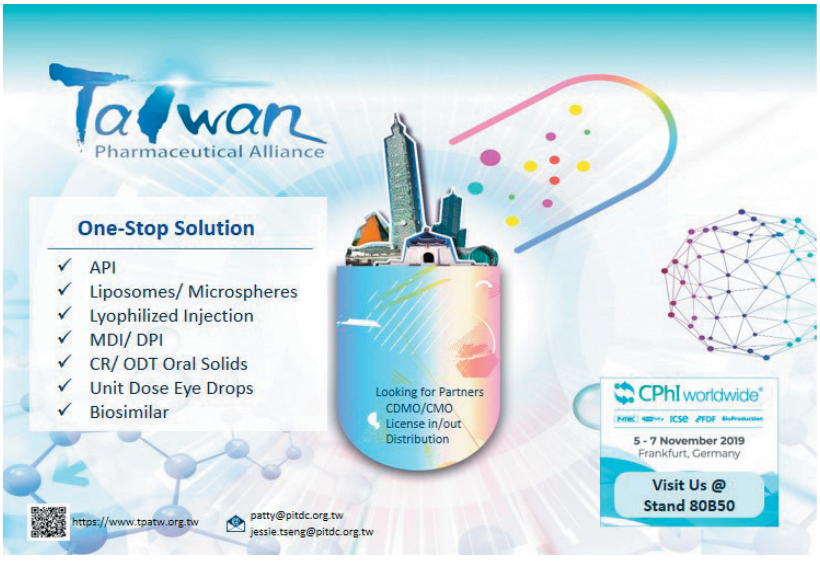
Contact details
Röchling Medical Neuhaus GmbH & Co. KG
Waldweg 16, 98724 Neuhaus am Rennweg, Germany
Telephone: +49 3679 72606-0
sales.deneu@roechling.com
roechling-medical.com

Innopack, Hall 11.1, Stand 111D20

Taiwan Pharmaceutical Alliance

Company description

Taiwan Pharmaceutical Alliance (TPA) comprises several Taiwan-based manufacturers, including API & FDF (small entity & biosimilar). TPA facilities pass PIC/S GMP. Products are marketed in US, EU, Japan & ASEAN etc. TPA is your trustworthy partner in the dynamic markets.



Major products/services being exhibited

TPA provides quality products with affordable price. Niche products include liposome & microsphere, OROS Tablets/ ODT, high potent soft gel, MDI/ DPI, eye drops, patch, biosimilar etc. Services include CDMO/CMO, license in/out, and trading etc.

Taiwan Pharmaceutical Alliance

Contact details
Taiwan Pharmaceutical Alliance
7F., No.9, Wuquan Rd., Wugu Dist., New Taipei City 248, Taiwan (R.O.C.)
Tel. +886-2-6625-1166 Ext. 5216
Fax: +886-2-6625-1177
jessie.tseng@pitdc.org.tw
www.tpatw.org.tw/en/

Hall 8.0, Stand 80B50

GE Healthcare Partners with Companies and Academia to Expand PET Tracer Portfolio

GE Healthcare announced that it is partnering with several companies and academic institutions with the aim of developing a portfolio of targeted oncology positron emission tomography (PET) tracers.

It is hoped that the PET tracers will be able to better predict and monitor responses to immunotherapies through accurate screening of immune mechanisms in real-time. The portfolio will contain tracers for biomarkers that are associated with tumors as well as the presence and state of T cells.

Three company deals have already been signed, one with Indi Molecular for a CD8 T-cell marker, another with Affibody Imaging for a programmed death-ligand-1 (PDL-1) cell expression marker, and the third with AdAlta for a Granzyme-B activated T-cell marker. After proof-of-concept for these tracers has been achieved, they will be used in a clinical setting to improve the success rate and efficiency of immunotherapy clinical trials. Ultimately, this should enable accelerated time-to-market for immunotherapies.

Further to the company partnerships, GE Healthcare is working with Vanderbilt University Medical Center, under a five-year partnership deal, to investigate the role of PET in immunotherapies. Through this partnership, the organizations will be looking to develop artificial intelligence powered apps and PET tracers that will be used to aid physicians in the identification of the most appropriate treatment for patients on an individual basis.

Source: GE, "GE Healthcare Expands Oncology PET Tracer Portfolio–Aims to Improve Patient Response Rates to Immunotherapies," Press Release, 24 Sept. 2019.

UK Biotech Receives CARB-X Award Worth US$9.2 Million

Procarta Biosystems, a biotech company based in the United Kingdom, has received an award from global non-profit partnership, CARB-X, potentially worth US$9.2 million, to be used for the development of antibiotic precision medicines.

The UK-based biotech revealed that it will be granted an initial non-dilutive funding of US$2.2 million through the CARB-X award and with the opportunity of gaining a further US$7 million should certain milestones be met. Procarta will use the money to advance its proprietary oligonucleotide-based antimicrobial platform and will specifically target infections caused by Gram-negative ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species) pathogens.

"This new award from CARB-X recognizes the value of the novel modalities in our pipeline and their potential to precipitate a paradigm shift in antimicrobial treatments," said Andrew Lightfoot, chief executive officer of Procarta in a press release. "We are delighted to have support from CARB-X recognizing the importance of developing new antibiotics to combat antimicrobial resistance."

"This award from CARB-X follows closely on a €1.5-million (US$1.7-million) investment from the Novo Holdings REPAIR Impact Fund. Together, these new funds will be used to progress our lead asset, PRO-202, and to develop our proprietary drug discovery platform to build a pipeline of antimicrobial agents to cover the ESKAPE pathogens," Lightfoot added.

Source: Procarta Biosystems, "Procarta Receives Carb-X Award Of Up To $9.2 Million," Press Release, 17 Sept. 2019.

Ad Index

COMPANY	PAGE
Alfasigma SpA Div Contract Manufacturing	53, 65
Ametek Brookfield	23
Aug. Hedinger GmbH & Co. KG	21, 70
Baxter Healthcare Corp.	37, 65
Beneo GmbH	15, 66
Cambrex	9, 66
Catalent Pharma Solutions	67, 76
Coating Place	41
CPhI	55
Curtis Health Caps Sp. Zo.o.	49
Dassault Systèmes Ltd	61
Emergent BioSolutions	39, 68
GEA Process Engineering NV	5, 68
Gerresheimer AG	17, 69
Grifols International SA	11, 69
Hermes Arzneimittel GmbH	59, 70
Ligand	19
Lonza Biologics Inc.	13, 45, 71
Nemera Services	35, 71
Novo Nordisk Pharmatech A/S	31, 72
PDA	47
Peter Huber Kaltemaschinenbau AG	33
Pfizer CentreOne	43, 72
Röchling Medical Neuhaus GmbH & Co. KG	73, 75
Scilabware Ltd	25, 67
Shimadzu Europe	2
Taiwan Pharmaceutical Alliance	63, 73
Veltek Associates	7

Röchling

Medical

Your Innovative System Partner

For plastic primary packaging and drug delivery devices.
Technical product development, clean room manufacturing,
and regulatory services – all from a single source.

Diagnostics

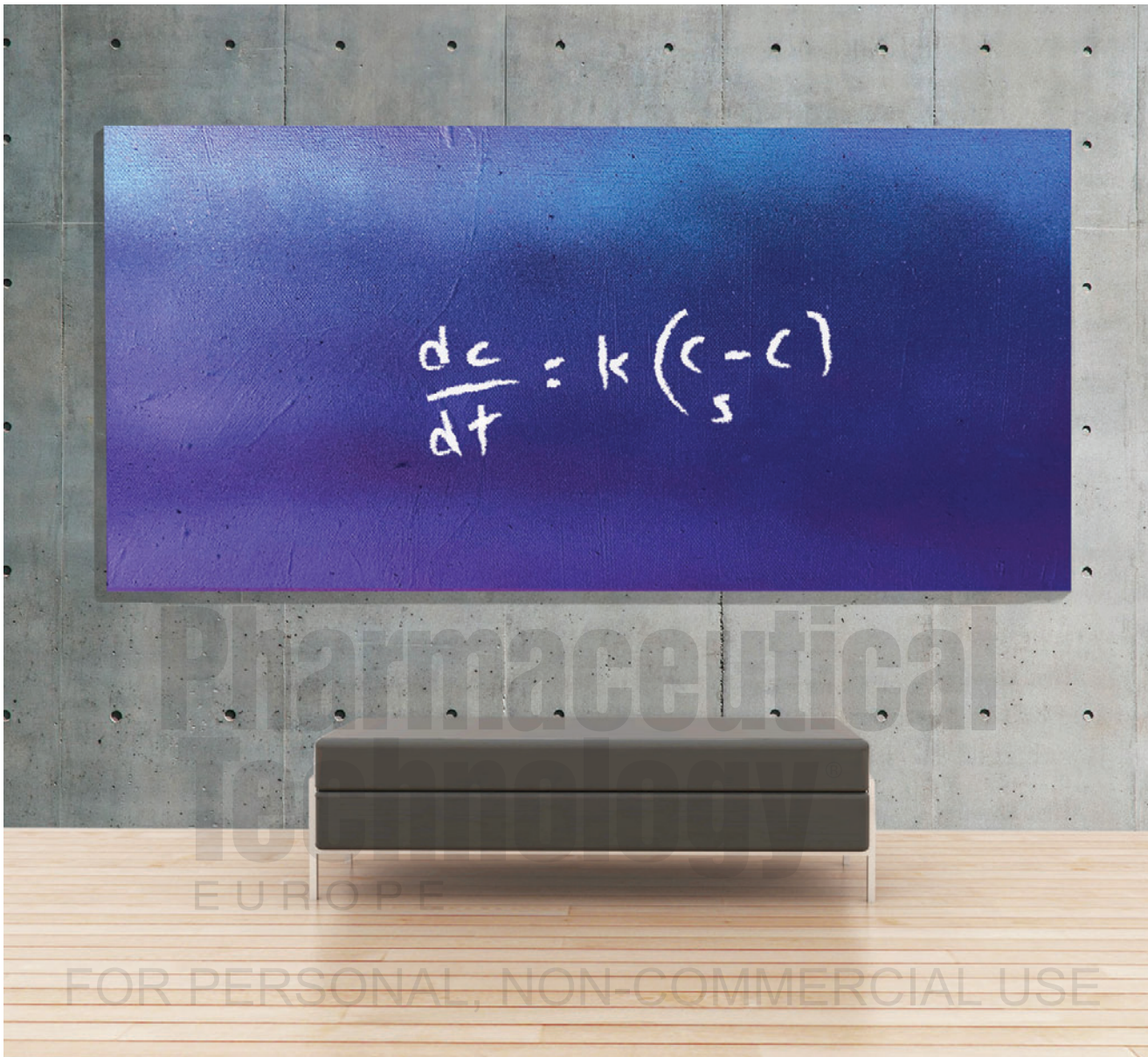
Fluid Management

Pharma

Surgery & Interventional

Röchling Medical. Passion for Health.
www.roechling-medical.com

Visit us at CPHI
5–7 November 2019
Hall 11.1 | Stand D20



SOLVING BIOAVAILABILITY IS SCIENCE. DESIGNING TREATMENTS IS ART.

Successful formulations for better bioavailability are built on robust science, superior technologies and the art of drug design.

Catalent's expertise in solving thousands of solubility challenges with the broadest toolkit of formulation and delivery technologies, coupled with integrated screening, clinical manufacturing and supply, will help get your molecules into clinic faster, turning your science into reality. **Catalent, where science meets art.**

Catalent®

us + 1 888 SOLUTION (765-8846) **EU** 00800 8855 6178 catalent.com/solubility