JUNE 2020 Volume 32 Number 6

Advancing Development & Manufacturing

Pharmaceutical® Technology EUROPE

PharmTech.com

The Value of Connected Drug Delivery

Development
Fast-Dissolving Dosage Forms
Abuse-Deterrent Formulations

Manufacturing
Avoiding Disinfectant Residue

Analytics
Bioanalytical Study Partnerships

Supply Chain
Onshoring Ingredient Sourcing

Operations
Intelligent Packaging

Peer-Review Research
Alleviating Subcutaneous Injection-Site Pain

European Pharmacopoeia

New supplements (10.3-10.5)

Essential to market your products in Europe, and beyond

SUBSCRIPTIONS **NOW OPEN!**

- **Legally binding in 39 European countries** and **applied in more than 120 countries** worldwide.
- Provides **new and revised texts**.
- Delivers **crucial information** for European markets **earlier** than any other Pharmacopoeia.
- Available in **print and electronic versions**, with **direct access** to complementary information (**EDQM Knowledge Database**).

Product information and pricing
https://go.edqm.eu/pheur10th

Orders
www.edqm.eu/store
orders@edqm.eu

Online HelpDesk and FAQs
https://go.edqm.eu/HDpubs

www.edqm.eu

edqm
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

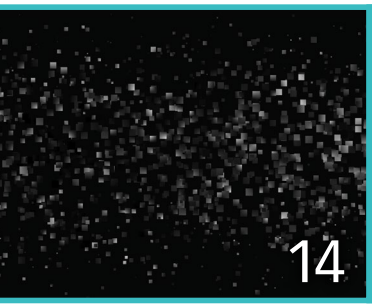
COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

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.

June 2020

Pharmaceutical Technology EUROPE

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



PharmTech.com

Features

COVER STORY: DRUG DELIVERY

10 **Better Connected: The Value of Connected Drug Delivery**
Connected delivery solutions can provide value to industry and patients, through improved medication adherence and outcome optimization.

DEVELOPMENT

14 **Formulating for Convenience and Compliance**
The correct mix of excipients is crucial to the success of fast dissolving/orally disintegrating dosage forms.

18 **Reducing Risk with Abuse-Deterrent Formulations**
Increasing prevalence of drug misuse and abuse is driving a heightened and more stringent approach to abuse-deterrent formulations.

MANUFACTURING

28 **Why Do Disinfectant Residues Matter?**
Consider how to assess the risks of disinfectant residues and understand their possible sources.

ANALYTICS

32 **The Importance of Partnering for Bioanalytical Studies**
Bioanalytical studies are an important aspect of biologic drug development that may necessitate partnering with bioanalysis experts.

OPERATIONS

36 **Intelligent Packaging Promotes Interaction with Patients**
Technology advances improve online productivity, authenticate product, and boost patient adherence.

SUPPLY CHAIN

38 **Securing the Supply Chain**
The global COVID-19 pandemic has highlighted the need for the pharmaceutical industry to strengthen its supply chain.

Peer-Review Research

21 **Approaches to Alleviating Subcutaneous Injection-Site Pain for Citrate Formulations**
The authors will discuss how formulations containing citrate compare to other buffers in reducing subcutaneous injection-site pain and discuss a formulation and excipients selection strategy that formulators can use to mitigate the risk of injection-site pain.

Columns and Regulars

5 **From the Editor**
A Little More Respect

6 **European Regulatory Watch**
A Strategic Shake Up in Europe's Medicines Sector

40 **Ad Index**

42 **Ask the Expert**
Following Guidelines During a Crisis

Pharmaceutical Technology EUROPE

PharmTech Group
Editorial Director
Rita Peters
RPeters@mjhlifesciences.com

Senior Editor
Agnes Shanley
AShanley@mjhlifesciences.com

Managing Editor
Susan Haigney
SHaigney@mjhlifesciences.com

Manufacturing Editor
Jennifer Markarian
JMarkarian@mjhlifesciences.com

Science Editor
Feliza Mirasol
FMirasol@mjhlifesciences.com

Assistant Editor
Lauren Lavelle
LLavelle@mjhlifesciences.com

Creative Director, Publishing
Melissa Feinen

Senior Art Director
Marie Maresco

Graphic Designer
Maria Reyes

PharmTech Europe
Editor
Felicity Thomas
FThomas@mjhlifesciences.com

Publisher
Michael Tracey
MTracey@mjhlifesciences.com

Sales Manager
Linda Hewitt
Tel. +44 (0) 151 705 7603
LHewitt@mjhlifesciences.com

Senior Sales Executive
Stephen Cleland
Tel. +44 (0) 151 705 7604
SCleland@mjhlifesciences.com

Sales Operations Executive
Barbara Williams
BWilliams@mjhlifesciences.com

VP & Managing Director, MJH Life Sciences™
Dave Esola

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

MJH Life Sciences™ Chairman and Founder
Mike Hennessy, Sr

Vice Chairman
Jack Lepping

President and CEO
Mike Hennessy, Jr

Chief Financial Officer
Neil Glasser, CPA/CFE

Executive Vice President, Operations
Tom Tolvé

Executive Vice President, Global Medical Affairs and Corporate Development
Joe Petroziello

Senior Vice President, Content
Silas Inman

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

Senior Vice President, Audience Generation & Product Fulfillment
Joy Puzzo

Vice President, Human Resources & Administration
Shari Lundenberg

Vice President, Business Intelligence
Chris Hennessy

Executive Creative Director, Creative Services
Jeff Brown

Published by
Multimedia UK, LLC
Sycamore House, Suite 2
Lloyd Drive
Cheshire Oaks
Cheshire
Ch65 9HQ, United Kingdom
Tel. +44 151 705 7601

AN MJH life sciences BRAND

Subscriptions:
Pharmaceutical Technology Europe is free to qualified subscribers in Europe.
To apply for a free subscription, or to change your name or address, go to PharmTech.com, click on Subscribe, & follow the prompts.

To cancel your subscription, please email your request to mmhinfo@mmhgroup.com, putting PTE in the subject line.

Please quote your subscription number if you have it.

For reprints contact Michael Tracey, mtracey@mjhlifesciences.com.

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.

A Little More Respect

Pharma's reputation is being boosted in light of the current COVID-19 pandemic efforts.

The pharma industry's reputation with the global public has been patchy at best, with various scandals being highlighted in the press over the years giving rise to scepticism over the integrity of companies, particularly 'Big Pharma', working to develop therapies. However, in light of the recent efforts to combat COVID-19, some polls are showing an upswing in the public's perception of the industry.

A long-term issue

The issue of reputation in the bio/pharma industry has been considered for many years now. Gallup, a global analytics and advice firm, for example, has evaluated the opinion of the pharma industry since 2001, finding that the view of the industry by Americans has been overwhelmingly negative in nearly two decades (1). According to research from GlobeScan, stakeholders have a tendency to believe that the pharma industry's reputation is poor, with a particularly negative environment seen in Canada and the United Kingdom caused by campaigns from non-governmental organizations or films (2).

In one of the latest polls from Gallup, published in 2019, the pharma industry had dropped to the bottom of the list in terms of public opinion in the United States (1). And, the problem of pharma's reputation is not isolated to North America. In Europe, and particularly focusing on the UK, PatientView highlighted that factors, such as Brexit, were causing lower public opinion of the industry's reputation in 2018 (3).

Opinion is softening

According to Talking Medicine's Pharma Reputation Thermometer, there has been a 'softening of negative public opinion' in the UK towards the industry during the COVID-19 pandemic (4). Results of the health-tech data company's research, which will be repeated on a monthly basis to track changes in attitude to the industry, has shown small improvements across each reputation measure—trust, transparency, product usefulness, patient-centricity, and overall industry recommendation—from before COVID-19 to May 2020 (4).

"For many reasons, the pharmaceutical industry has always suffered from negative perceptions among the general public. However, these latest findings show that there have been improvements on a number of key reputation measures," said Jo Halliday, CEO and founder, Talking Medicines, in the press release (4). "Maybe we should not be too surprised, given the situation we find ourselves in, pinning our hopes on the industry finding a vaccine and antigen tests and drugs to be able to create a 'new normal' for society. However, based on these results, it seems as if pharma has an opportunity to develop a closer and more open relationship with people and communities."

Great effort required

As pharma companies continue to forge ahead, collaborating with others that may be considered as competitors in a 'normal' situation, there is a chance that the overall reputation of the industry can be further improved. However, the task of developing and delivering an effective vaccine for COVID-19 is by no means a small feat and will require great effort from the industry as a whole.

"Not only does the science have to be on our side if we are to quickly find a coronavirus vaccine, but we also have to find ways of being able to produce hundreds of millions, possible billions of doses of the new vaccine," said Thomas Cueni, director general of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), in a press release (5). "The only way to deliver on our promise of safe, equitable, affordable coronavirus vaccines is for science and collaboration on a global scale to prevail. Be in no doubt, our member companies are fully engaged in the race to find a vaccine. We are fully committed to playing our full role within existing partnerships on the basis that we wholeheartedly embrace the goal of providing new coronavirus vaccines for all."

Stay alert, safe, and healthy.

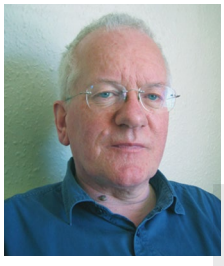
References

1. Gallup, "Big Pharma Sinks to the Bottom of US Industry Rankings," Press Release, 3 Sep. 2019.
2. GlobeScan, "The Pharmaceutical Industry; Issues & Reputation," Intelligence eBrief, 4 July 2013.
3. PatientView, "Pharma Reputation in 2018—Among UK Patient Groups—Falls Due to Brexit and Other Factors," Press Release, 16 July 2019.
4. Talking Medicine, "Pharma's Reputation Shows Uplift During Pandemic," Press Release, 27 May 2020.
5. IFPMA, "Pharma Partners in Efforts to Give Coronavirus Vaccine for Everyone," *ifpma.org*, Press Release, 28 May 2020. **PTE**

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

A Strategic Shake Up in Europe's Medicines Sector

The EU's pharmaceutical strategy has the potential to shake up the policies and regulations of the region's medicines sector.



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

The European Union has started drawing up a pharmaceutical strategy, which will be closely linked to a new EU industrial strategy and could trigger a shake-up of policies and regulations in the European medicines sector. Broad changes in some parts of the EU's pharmaceuticals regulations have been on the cards since the European Commission (EC) introduced a regulations improvement programme (REFIT) five years ago to simplify legislation and make it less burdensome for business without compromising policy objectives (1).

A major driving force behind the pharmaceutical strategy, being drawn up by the EC for consultation due to start by the end of 2020, will be a desire to reverse Europe's loss of its position as the global leader in the development and production of new medicines. Today almost half of global new drug treatments originate in the United States, according to the European Federation of Pharmaceutical Industries and Associations (EFPIA) in a report in March 2020 backing a new EU industrial and pharmaceutical strategy (2).

In 2014–2018, only 25% of new drugs emanated from Europe (2). "[This] represents a reversal of the medical innovation landscape [25 years ago]," commented Nathalie Moll, EFPIA director general in the introduction to the document. At the same time, a growing number of new treatments are being approved first in emerging markets, such as China, she pointed out. "Both [strategies] bring the future of Europe's life-sciences sector into sharp focus and represent a unique opportunity to work together to re-establish Europe's global leadership in medical innovation," she added.

This ambition will require pharmaceutical policies and regulations, which will incentivise new investment in R&D and processing technologies, particularly those based on digitalization and artificial intelligence (AI). Also, the policies and regulations will have to be in line with key objectives of Europe's industrial strategy, being at the forefront of the global fight against climate change and protection of the environment.

Europe does currently have a strong position in vaccines R&D and manufacturing, which could be useful in the international competition among medicine producers for leadership in the development of vaccines to combat COVID-19. However, the COVID-19 crisis has also highlighted Europe's dependence on imported APIs and generic medicines made in China and India. In volume terms around three quarters of Europe's API requirements come from these two countries (3).

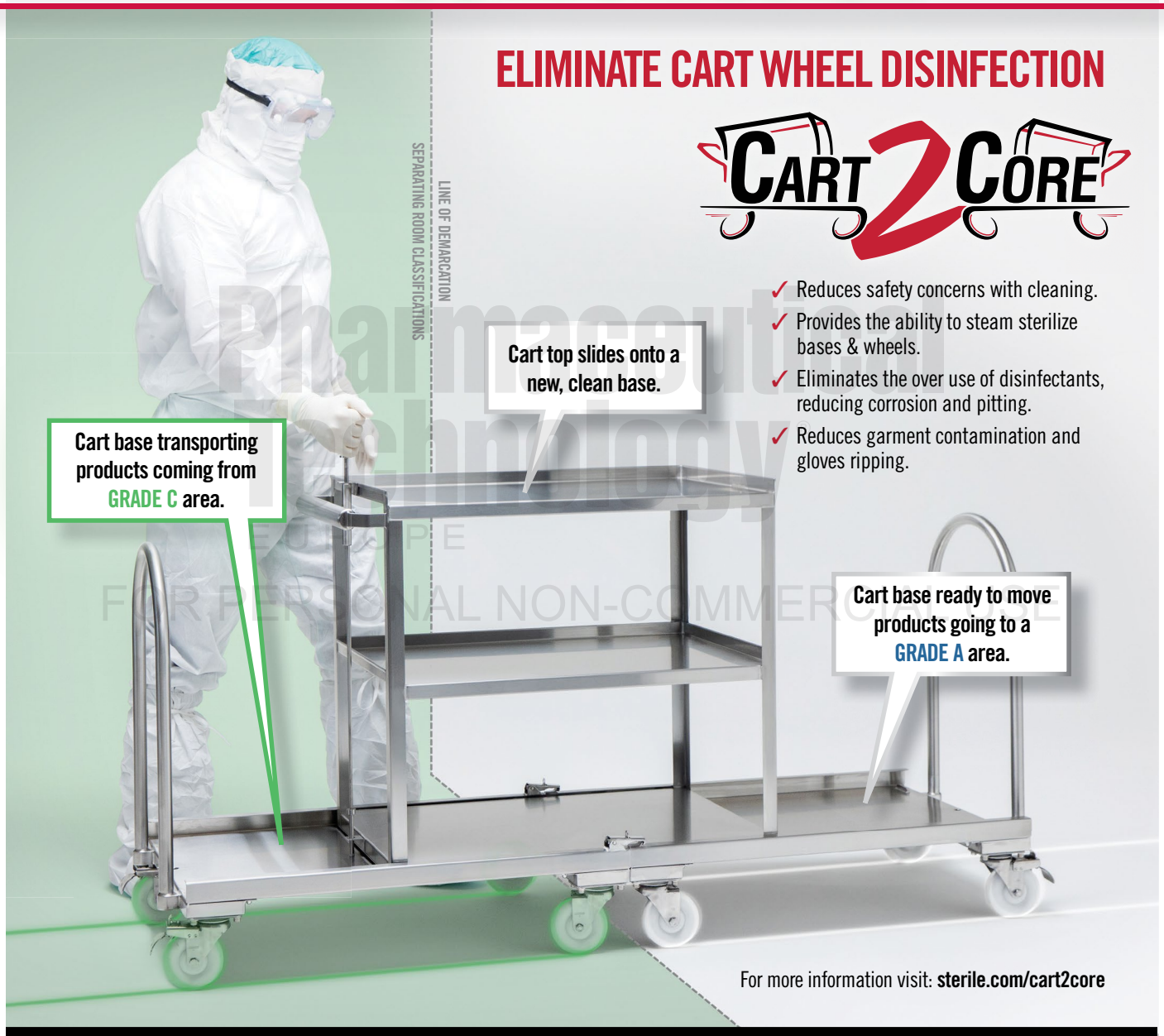
Medicines supply shortages

Partly as a result of plant closures in China and India, there have been shortages of some essential medicines in Europe, such as drugs for treatment of COVID-19 patients in intensive care units (ICUs). Some EU member states have been banning the export of some crucial hospital medicines to other European countries during the COVID-19 crisis. Despite the EU being a free trade area, Union rules give member states the freedom to take virtually whatever measures are necessary to protect public health within their borders. There have been hoarding and stockpiling of COVID treatments by individual countries even though they have had relatively low infection rates of the virus.

"We have a situation in which countries have more supplies of certain drugs then they have needed while other countries were suffering from shortages of these medicines," explained Adrian van den Hoven, director general, Medicines for Europe, the main trade association for generic medicines and biosimilars producers and suppliers. "The COVID-19 pandemic has confirmed that the main cause of drug shortages is not problems with production but difficulties of allocation," he told *Pharmaceutical Technology Europe*. "This is an issue which ought to be dealt with by the pharmaceutical strategy."

COVID-19 prompted some industrial groups to make their own arrangements for sorting out medicines' shortages. Medicines for Europe, for example, has been acting as an *ad hoc* coordinator of its members to enable them to divert hospital products to countries where they were most needed, explained van den Hoven. It even brought in management consultants A.T. Kearney to help

MOVE PRODUCTS NOT CONTAMINATION



ELIMINATE CART WHEEL DISINFECTION

CART 2 CORE

- ✓ Reduces safety concerns with cleaning.
- ✓ Provides the ability to steam sterilize bases & wheels.
- ✓ Eliminates the over use of disinfectants, reducing corrosion and pitting.
- ✓ Reduces garment contamination and gloves ripping.

For more information visit: **sterile.com/cart2core**

vai
VELTEK ASSOCIATES, INC.

Veltek Associates, Inc.
15 Lee Boulevard
Malvern, PA 19355

Patents: sterile.com/patents

STERILE.COM

create a modelling system for forecasting where there would be the strongest demand for specific medicines, he added.

The EC had to be asked to lift rules on competition and labelling of packaging to make the redirection of medicines legally possible, according to Medicines for Europe. "Current regulations need to be altered so that the EC can organize the allocation of medicines during crises like the COVID-19 pandemic," said van den Hoven. "The commission is the right body to take on that role."

Prior to COVID-19, the European Medicines Agency (EMA) and the Heads of Medicines Agencies (HMA) representing national licensing authorities, had created an HMA/EMA taskforce on medicines availability (4). Its job was to help regulatory authorities ensure continued availability of medicines at times of shortages.

But the taskforce lacked enough clout to provide fast-track capability during major emergencies. So, in March 2020, the commission created an EU Executive Steering Group to manage shortages during serious events, such as pandemics. The group is chaired by the EC with EMA acting as an official central coordinator.

The EC has made clear that a key objective of the pharmaceutical strategy is to establish a more streamlined structure for handling big emergencies in the post-COVID-19 period. The new strategy will focus on the "availability, affordability, and security of supply of pharmaceuticals [which] has been highlighted by recent events linked to the coronavirus disease outbreak," the commission said in a communication issued in March 2020 (5).

The aim to incorporate lessons learned from the COVID-19 crisis in the pharmaceutical strategy may explain delays in the publication of a roadmap on the strategy, due in March 2020. The pharmaceutical committee of the EC's health and food safety directorate (DG Sante) was told in March 2020 that it would be given details for the strategy by the end of the year. This may now be put back.

The plan was that the publication of the roadmap would open the way to detailed discussions on the strategy with the committee, consisting mainly of representatives from EU member states. This would enable the committee to be "an important forum of interaction" on the contents of the document, according to a report on the committee's March meeting.

Encouraging investment in API manufacturing

The issue of shortages is still seen as being closely tied to limitations to Europe's manufacturing capacity, particularly with APIs. It is acknowledged by industry that there is a need for a regulatory framework that would encourage more investment in the modernization of production processes.

More could be done to exploit the strengths of European-developed technologies, perhaps through additions to the existing range of regulatory financial and other incentives, extension of intellectual property rights, more protection of technological data, and greater market exclusivity, such as that applied to orphan drugs.

With APIs, for example, Europe is heavily reliant on Chinese and Indian imports for bulk actives. But in the global marketplace, it is well positioned in the development and manufacture of more advanced APIs, which account for much of Europe's one-third share of worldwide actives output (2).

More than three quarters of APIs used in the manufacture of innovative medicines in Europe are sourced in the region with a further 11% coming from the US and only 9% originating from Asia, according to EFPIA figures (6). "European producers can be incentivised to focus on the development and production on APIs for crucial medicines and whose manufacture is complex and difficult," said van den Hoven.

Broader key features

The pharmaceutical strategy will also reflect broader key features of the industrial strategy, such as the EU's quest for international leadership in digitalization and AI and in green technologies. The EC hopes that an acceleration of digitalization across EU industry will help boost the European Green Deal by helping the development of green technologies and lower carbon footprints.

The current trend in the pharmaceuticals sector is for the expansion of digitalization from manufacturing processes through to clinical trials, pharmacovigilance, and disposal but in a way that ensures that wastewater, for example, can be reused because it is free of pharmaceutical residues.

Cost-saving increases in regulatory efficiencies through the wider application of IT systems have enabled faster assessments of variations approvals. The high cost of submitting approvals for variations in APIs can be decreased by IT initiatives under which information on active ingredients is stored in the same dossier so that the producer or supplier of the APIs apply for variation approvals rather than individual medicine manufacturers.

These would be proposals on authorizations, which would involve EMA or national licensing agencies. But a lot of changes put forward by the pharmaceuticals strategy could lead to the EC being given more direct responsibilities in the medicines sector, which may be opposed by member states.

References

1. EC, "Better Regulation: Delivering Better Results for a Stronger Union," *ec.europa.eu*, Communication, 14 Sep. 2016.
2. EFPIA, "EU Industrial and Pharmaceutical Strategy: An Opportunity to Drive Europe's Health and Growth," *efpia.eu*, Press Release, 9 March 2020.
3. European Fine Chemicals Group, "Addressing the Acute and Complex Issue of Medicines Shortages," *efcg.cefic.org*, Briefing Paper (September 2019).
4. HMA, *HMA/EMA Task Force on Availability of Authorized Medicines for Human and Veterinary Use* (Amsterdam, 2020)
5. EC, "A New Industrial Strategy for Europe," *ec.europa.eu*, Communication, 10 March 2020.
6. EFPIA, "EFPIA Statement Following the Call with EU Commissioner Kyriakides," *efpia.eu*, Press Release, 18 May 2020. **PTE**

LIQUID CAPTISOL®

Now offering Aseptic-filled Liquid Captisol.

Facilitate your drug discovery and development activities with Liquid Captisol. Liquid Captisol is a 50% aqueous concentrate of Captisol® (Betadex Sulfobutyl Ether Sodium USP/NF) that has been aseptic-filled into 250 mL plastic bottles. The product will help you to move quickly into phase solubility studies, formulation development or safety studies. Now quickly dilute to your desired concentration and determine solubility or dose preclinically. Captisol has been used extensively to provide improved solubility, stability, bioavailability and dosing of challenging ingredients. Liquid Captisol is protected under our all-aqueous patented process and included within our extensive safety database. Accelerate your drug discovery and development and order non-clinical grade Liquid Captisol.

CAPTISOL.com

Better Connected: The Value of Connected Drug Delivery

Connected delivery solutions can provide value to industry and patients, through improved medication adherence and outcome optimization.

Felicity Thomas

As the world becomes more heavily reliant on connected devices, it is little wonder that the connected drug delivery devices market is set to witness significant growth in the coming years. According to market research, the sector is expected to grow at a compound annual rate of 35.4% in the forecast period of 2019–2026 (1). Suggested drivers of this projected market growth include a rise in the number of patients suffering with chronic diseases globally, increasing emphasis on preventive care, a general shift towards connected devices rather than manual ones, and improved procedural outcomes offered through connectivity (1).

Delivering drugs through connected devices, such as auto-injectors, smart inhalers, and closed-loop solutions, has been documented as a potential way of improving patient adherence and reducing dosing errors, particularly in the home setting (2–5). "It is widely recognized that the effectiveness of drug delivery devices can be compromised by adherence and patient use error, the likelihood of which are impacted by numerous factors," confirms Andreas Meliniotis, director, device development, Vectura. "Tracking and reporting use via connected devices can highlight use errors and compliance with therapies, and, therefore, can be used as a tool as part of the process towards improvement in the delivery of almost any therapy."

Most critical aspects of connectivity

"The most critical aspect to connected drug delivery is improving patient adherence to get desired outcomes from prescribed medications," says Bill Welch, chief technology officer, Phillips-Medisize. "First and foremost, connected drug delivery is about creating an engaging experience so that patients have the best tools and technology available to help manage their disease."

Traditionally, the connectivity interface was built into the delivery device, such as medication reminders, timers, and alerts, notes Welch; however, with smartphone apps, it is now possible to further enhance the patient experience and the ability to share information. "With patient permission, information can be shared to the patient's healthcare providers and even family members," Welch continues. "This dynamic enables the entire care team and loved ones to be equally invested in the patient's health to improve adherence and outcomes within the greater scope of a connected care ecosystem."

Lawton E. Laurence, director, Radical & Disruptive Innovation, West Pharma Services, iterates the

importance of defining the limits of connectivity. "Connectivity is communication. Communication among devices, among stakeholders, and then between those two groups. Connectivity is not a panacea for the pain of poor patient adherence," he says. "Without an intimate understanding of your target patient population, device connectivity may only shine a spotlight on the overall weaknesses of the product. Consider it as a tool that can help you more effectively collect information and execute on the appropriate mitigation strategies for your patients."

"Tracking and reporting use via connected devices can highlight use errors and compliance with therapies, and, therefore, can be used as a tool as part of the process towards improvement in the delivery of almost any therapy."

—Andreas Meliniotis, Ventura

However, once the appropriateness of a drug–device combination product for a specific patient population has been discerned, using connectivity to then target specific issues underlying non-adherence can be exceptionally effective, Laurence adds. "In the distilled words of Lord Kelvin, 'What gets measured, gets managed' and there is no doubt that transforming the drug delivery space from one of ephemeral delayed reaction to a data driven ecosystem of aligned stakeholders is the core promise of connectivity," he states.

"In order to consider the impact of connectivity on adherence, we should first explore what factors affect adherence," remarks Meliniotis. By way of an example, Meliniotis referenced a research paper on inhaler adherence, which noted that although adherence can simply be defined as to how a patient follows a prescription, there are many variables, such as dose frequency, taste, and route of administration, that can actually influence the use of a medication (6).

"With regards to therapies where connected drug delivery can provide otherwise non-existent feedback, connected devices can provide both feedback and metrics to encourage patients to comply, changing their mind-set," Meliniotis continues. "Gamification can be used, which uses an app or other feedback interfaces to encourage compliance, and there are suggestions that to ensure long-term compliance, constantly changing aspects, (i.e., new targets or ongoing metrics) can keep patients interested, and have a longer-term effect than more basic systems."

"To be sure, the ability of connectivity to improve patient adherence in the short term has discrete merit; however, the real payback is how we can leverage the information to feed the next generation of drug-device combination products," adds Laurence. "The first movers will be privy to a treasure trove of usability information and their ability to operationalize that intelligence will position them to be the leaders in the next generation."

Focus areas

"Connected drug delivery should be focused on areas where the impact can be the largest," explains Meliniotis. "One example is by providing immediate feedback to a therapy that would otherwise be unavailable, for instance, an asthma maintenance therapy, where adherence may be poor due to no immediate decline in health, rather than insulin injections for diabetes, where adherence is generally high due to immediate severe outcomes."

Adoption of connected solutions is already being seen in the fields of certain rare and orphan diseases, where there is a high cost per patient per year, Welch confirms. "Outcomes are important as payers move pharma toward performance-based contracts. Having confidence in patient adherence and the ability to get the best outcomes has, therefore, never been more important," he adds. "Connected drug delivery can help facilitate outcome optimization by providing real data to healthcare providers to enable better informed treatment decisions."

Other areas that can particularly benefit from connected drug delivery solutions include chronic diseases that need to be managed hourly or daily and for patients that require more acute care or rescue devices for emergency use, Welch notes. "Better ways to manage chronic, orphan, and emergency conditions with connected drug delivery are being looked at currently," he says. "It is not a 'one-size-fits-all' solution, rather the connected health ecosystem must be built for the disease and patient population."

According to Laurence, the bio/pharma industry is just beginning to tap into the opportunity afforded by connected drug delivery solutions to create value for its diverse stakeholders, with some therapeutic areas that were 'early adopters' demonstrating transformative changes. Some examples of changes from 'early adopters' include the Type I diabetes market where the stakeholders demanded transformation to have connectivity between devices, or with therapies for respiratory problems where connected inhalers are used to offer

"Outcomes are important as payers move pharma toward performance-based contracts … Connected drug delivery can help facilitate outcome optimization by providing real data to healthcare providers to enable better informed treatment decisions."

—Bill Welch, Phillips-Medisize

the histogram of doses and inform whether the drug was delivered appropriately, he notes.

"Some therapies can be impacted significantly by user technique, and identifying this can have a dramatic effect in the efficacy of treatment, particularly if it prevents a patient being prescribed a medication at a higher level in order to compensate," agrees Meliniotis.

Taking into account how bio/pharma companies investing in connectivity could drive superior solutions in the future, Laurence stresses that one of the most underreported opportunities in connected devices relates to clinical trials. "If you want to study the adherence of your patient population and even access unassailable retrospective dose data, a mere notification in their patient-facing app presents a revolution in cost and time to collect that data," he states. "It may be feasible to look at how changes in formulation, device characteristics, or nurse interventions impacted a patient's adherence. Gone will be the days of supposition reaction; connectivity will usher in data-driven therapy evolution."

"It is increasingly important to be able to prove quantitatively the value being wrought in [advanced] therapies. Pay for results and accountable care organization models are becoming more commonplace and connected drug delivery devices will be another wave of the same swell."

—Lawton E. Laurence, West Pharmaceutical Services

Potential limitations

There are a couple of prominent limitations of connected drug delivery solutions, namely cost and environmental waste, explains Welch. "When electronics and sensors are added to make a traditional mechanical drug delivery device digitally connected, this drives up the cost. So, it is important to find a balance between the value of data and patient adherence versus the added cost of the electronics and sensors," he notes. "Likewise, while the traditional single-use or disposable devices may have cost production advantages, companies and consumers should also consider the impact of a disposable device on the environment."

It is the industry's dependence on disposable devices that Laurence states as being the most insidious of limitations. "It is imperative that a sustainable solution is found that can improve a patient's experience while reducing the burden on the ecology," he says. "Another pressing barrier to connected solutions is patient trust in what will be done with the data collected by the device. Success will be unattainable if industry acts in a clandestine fashion on this matter. Every moment the security of drug delivery devices is called into question will be the nucleus of setbacks in our mutual goal to improve the standards of the patient."

With many connected drug delivery solutions currently taking the form of an 'add-on' feature to an existing product, functionality is limited somewhat as the base device has not been originally designed with connectivity in mind, asserts Meliniotis. "As time progresses, delivery devices are likely to be increasingly designed with connectivity in mind, which could open up possibilities for integrated connectivity of high functionality add-on devices," he states.

Tips, tricks, and trends

Some key considerations when developing a connected drug delivery device include optimization of the patient experience, significant market research to achieve a detailed target product profile, and taking a holistic approach with platforms and technology providers. Data privacy and security must also be considered thoroughly, particularly in light of the current focus in this area, continues Welch. "Pharmaceutical drug delivery devices are highly regulated and you have to be cognizant of the diligence and development rigor required on the device, the app, and the data access portals to meet the underlying regulatory criteria," he says.

Looking at potential trends for the future, Laurence noted the movement toward advanced therapies, which is driving elevated prices. "It is increasingly important to be able to prove quantitatively the value being wrought in these therapies," he says. "Pay for results and accountable care organization models are becoming more commonplace and connected drug delivery devices will be another wave of the same swell."

For Meliniotis, the full potential of connected devices will only start to be unlocked once 'true adherence' is measurable. "Once devices are capable of measuring signals from the patient, monitoring 'true adherence', and automatically administering or prompting administration of medication, it will be possible to attain a closed feedback loop, which could ultimately optimize efficacy for patients individually," he states. "Once the benefit of connected devices has been clearly demonstrated, pharmaceutical companies will invest more heavily in this field."

"Another avenue for future trends is to consider the impact of prescription digital therapeutics as a combination with traditional injectables," adds Laurence. "Like many things, it's possible the combination of the two is significantly more powerful than either could be alone."

Sustainability is high on the agenda for the future in Welch's opinion. "There's a real push from the industry, especially in the European regulatory environment, to manufacture products that are more sustainable and environmentally friendly from both a raw material utilization standpoint, but also in

regard to the supply chain, logistics, and transportation considerations," he adds. "Developing connected devices that achieve a balance between disposable and reusable will, therefore, be highly desirable. Sustainability, connectivity, and cost must all come together to address the trends shaping the future of patient care with more efficient drug delivery that leads to better outcomes."

"It would be difficult to describe a future state where every therapy wouldn't benefit from connectivity," Laurence continues. "The back-end infrastructure to convey the value to the stakeholders isn't necessarily available today, but I'm quite certain it will be."

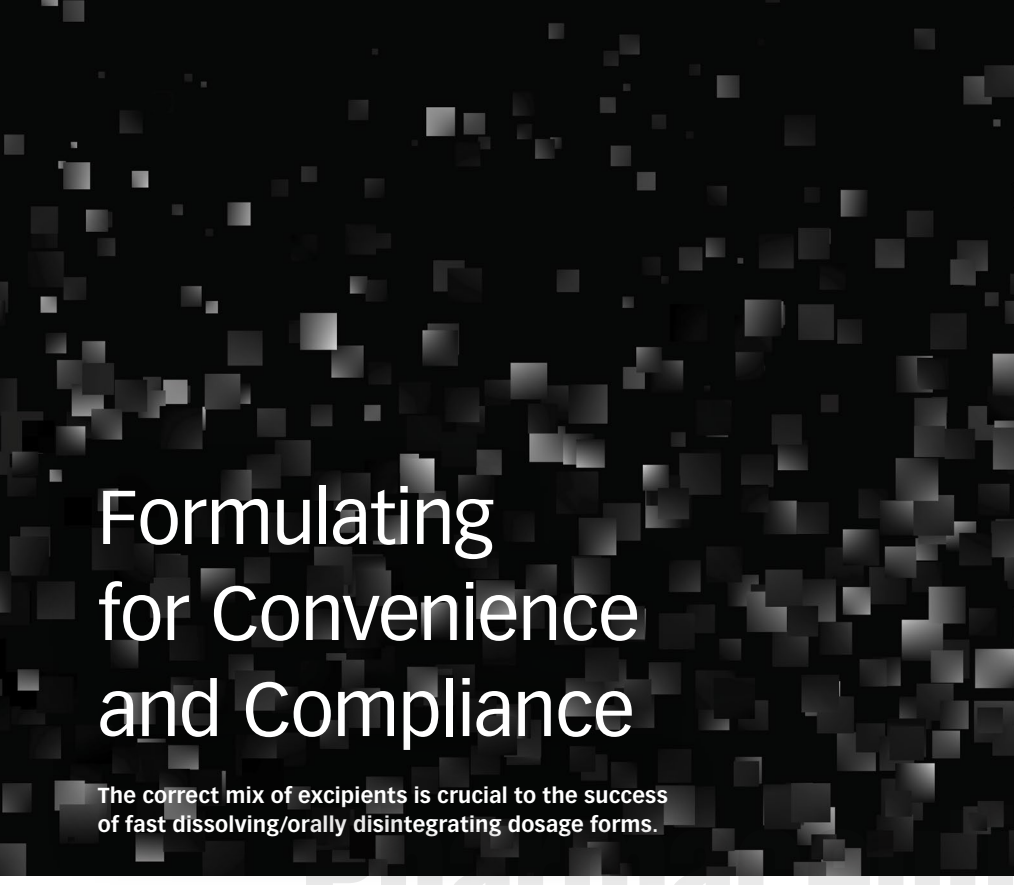
Even though it is now possible, as it never has been before, to easily track aspects of drug delivery, it must be remembered that the effectiveness of any treatment is a combination of numerous factors, emphasizes Meliniotis. "As the availability of connected devices increases, so the effect of this data-driven therapy adjustment is likely to become increasingly apparent, which in turn will increase the desire to connect more therapies," he says.

"At the end of the day, it's all about accountability," confirms Welch. "There are several dimensions of connected health that contribute to the overall picture. Creating a better user experience with a connected drug delivery device that drives higher patient engagement and ultimately improves health outcomes is the end game. To get there, everyone involved must assume a level of accountability."

For pharmaceutical companies, accountability lies in providing drugs and connected delivery systems that can demonstrate improved outcomes supported by data, while the device manufacturers are accountable to their pharmaceutical partners to design and develop innovative products that optimize patient engagement, lower the cost of connectivity, and reduce waste, Welch emphasizes. "As the world becomes more connected, we all must do our part to keep the population—and the environment—healthy," he concludes.

References

1. Fortune Business Insights, "Connected Drug Delivery Devices Market Size, Share, and Industry Analysis, By Type (Injectable Devices and Inhalation Devices, and Others), By Technology (Bluetooth, NFC, and Others), By End User (Homecare Settings and Hospitals), and Regional Forecast, 2019–2026," *fortunebusinessinsights.com*, Market Report (November 2019).
2. I. Kleiter, et al., *BMC Neurol.*, 17 174 (2017)
3. B. Bittner, et al., *Med. Devices (Auckl.)*, 12 101–127 (2019).
4. A.H. Chan, et al., *Lancet Respir. Med.*, 3 (3) 210–219 (2015).
5. A. Blanco-López, et al., *J. Endocrinol. Invest.*, Open Access Article, Published Online 1 April 2020.
6. J.R. Jardim and O.A. Nascimento, *Med. Sci.*, 7 (4) 54 (2019). PTE



Formulating for Convenience and Compliance

The correct mix of excipients is crucial to the success of fast dissolving/orally disintegrating dosage forms.

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

Today, drug formulators must not only consider patients outcomes when developing new products but should also focus on the overall patient experience. Four main factors address the patient experience, according to Sarath Chandar, chief science officer with SPI Pharma: convenience, compliance, safety, and efficacy. Orally disintegrating tablets (ODTs) and other fast-dissolving oral dosage forms address the first two factors—and to some extent efficacy as well—from the standpoint of sublingual delivery, which can lead to increased bioavailability for poorly soluble APIs.

Patient-centric formulations

Convenience is increased with ODTs and fast-dissolving products across all patient populations. "Paediatric patients benefit from this group of products because they dissolve faster than what they are able to spit-out and can also be mixed with foods for easy administration. These products can also be taken without water, so they are also amenable for adults on the go," says Krizia Karry, global technical marketing manager at BASF Pharma Solutions.

The fact that ODTs do not need to be washed down with water provides additional benefits as well. ODTs are, for instance, attractive to those who do not want to swallow liquids or hard tablets because they are feeling nauseous, adds Ralph Gosden, head of product development at Catalent Swindon. They are also useful when there is a need for rapid drug release, such as to relieve a headache, according to Torkel Gren, science and technology officer for Recipharm. "Orally disintegrating products are an ideal platform for delivery of active ingredients for the treatment of pain, allergies, diarrhea, Parkinson's disease, travel-related illness, and other indications where rapid dosing and absorption is required," he observes.

In addition, ODTs can help patients who have an aversion to swallowing a tablet or capsule, and those who find it extremely difficult to take standard tablets because they may have dysphagia or other problems with swallowing (e.g., the elderly and infirm), Gosden notes. "Patients suffering from mental impairments can benefit as well," he adds, "as they will sometimes deliberately avoid taking medications or pretend to have swallowed a standard tablet or capsule by hiding it in their mouth to spit out later—a practice referred to as 'cheeking'. This tactic is nearly impossible with an ODT as it disintegrates quickly and completely."

Other benefits of orally disintegrating products in some cases are higher bioavailability and the fact that faster drug uptake can be achieved, according to Gren. "Instantaneous disintegration allows the drug to be dissolved and absorbed more rapidly, and for drugs that can be absorbed via the mucous membranes within the oral cavity, it can help to avoid the harsh environment within the gastrointestinal tract and bypass first-pass metabolism by the liver."

Films, granules, and tablets

Orally dissolving products include tablets, granules, and films. "For tablets, the most common manufacturing technology is direct compression into tablets or minitablets," Karry asserts. The use of 3D printing is also being explored for the production of ODTs, Gosden notes. "Granules are mostly produced via fluid bed granulation/drying and twin-screw granulation to ensure adequate size control. On the other hand, films are cast and dried on moving Teflon membranes from solutions or suspensions of APIs and soluble polymers," Karry comments. More advanced technologies are often protected by patents, which may restrict competition, according to Gren. "In addition," he stresses, "a more complex technology should not be used if it does not result in significantly better product properties."

Thin film strips are a delivery technology that can be used for both systemic and local delivery by oral, buccal, and sublingual routes, according to Gosden. "Although they

dissolve rapidly in the mouth and are considered self-administrable, the application of thin-film strips is somewhat limited as the maximum dose that can be formulated for delivery via the digestive tract is only in the 20–50 mg range," he says.

In addition, Chandar adds that the US Food and Drug Administraton has not approved many thin-film products for pharmaceutical applications because the strips can stick together, resulting in the patient taking multiple doses at once. This challenge has been addressed by individually packaging the oral strips, according to Karry.

The distinguishing properties between orally dissolving products are the form factor and drug delivery methods (e.g., sublingual, buccal, oral, etc.). "The form is selected taking into consideration the target population and the API solubility. For example, a drug dissolved in a polymeric matrix in the form of a fast-dissolving film may avoid first-pass effects through buccal drug delivery and thus show higher bioavailability due to the design of the drug product," Karry says.

Distinguishing features

To be successful, orally disintegrating formulations must have certain features. The most important property is rapid—within 30 seconds or less—disintegration or dissolution in the oral cavity with or without water, according to Chandar. Because they are placed in the mouth, they also ideally should have a pleasant mouth feel that is creamy rather than chalky. An attractive taste is also ideal, which requires taste masking if the API is bitter, which many are.

Excipients: The most important component

Excipients are the most important part of orally disintegrating/fast-dissolving products, according to Karry, because they ensure good sensory properties and adequate technical performance. "When developing conventional tablets, the drug developer will focus on a limited number of characteristics that are easy to measure quantitatively, such as hardness, friability, disintegration, and *in-vitro* dissolution. When working with ODTs, several parameters that are difficult to measure are affected by the excipient," Gren explains.

"Examples include creating a clean mouth feeling, or creaminess and overall good palatability, as opposed to grittiness and lingering bad flavours, all the while leading to tablets with high tensile strength, low friability, and fast disintegration," Karry says. She also points out that the interplay between tensile strength and disintegration is particularly important, because the stronger the tablet, the lower its porosity and the slower it disintegrates. "In this case, having both an efficient binder and a super-disintegrant is necessary for good performance of the drug product," she comments.

Compressed tablets require super-disintegrants, which either swell or wick up saliva, disrupting the tablet's structure and encouraging dispersion, according to Gosden. Other important excipients include binders and fillers, according to Karry. Numerous other excipients can also be added to impart specific properties, such as lubricants, sweeteners, colours, and flavourings. "However," Gosden notes, "some of the additional ingredients that may be required to manufacture the tablet can impede its disintegration. For example, if high levels of lubricant are necessary, the particle size must be carefully considered. If the particle size is too large, then the tablet may give a gritty and unpleasant mouthfeel as it disperses."

Certain excipients also enhance the bioavailability of poorly soluble APIs (e.g., Biopharmaceuticals Classification System [BCS] II and IV) by helping to increase the dissolution rate, according to Chandar.

Selecting the right excipients

The type and amount of excipient needs to be carefully selected in order to get the right balance between a number of technical characteristics, including stability, flavour, and mouthfeel, Gren comments. It is particularly important to choose the right filler(s), he says, because the filler is often present in large quantities and has a significant impact on the taste and mouthfeel of the product. "A judicious use of quality-by-design and multivariate methods are helpful here," notes Gren.

Some excipients found in orally dissolving products such as sweeteners and flavouring agents are not normally used in conventional tablets, according to Gren. "Here it is extremely important to work in close collaboration with the marketing professionals when selecting the type and amount of all excipients, but especially the flavouring agents. The taste of the product should be developed in order to suit the intended patient population," he says. "In my experience, sugar alcohols, mannitol in particular, are extremely useful in orally disintegrating products; they provide sweetness and pleasant mouthfeel and also have relatively favourable technical properties," Gren observes.

The most important excipients are those that ensure adequate technical and sensorial performance, notes Karry. She lists binders to give strength to the formulation, super-disintegrants to ensure fast hydration and disintegration, taste-masking polymers to decrease the interaction between the bitter or acidic drugs and tongue receptors, and flavours, which are used as needed based on the target population and to stimulate saliva secretion. Strawberry and apple flavours stimulate more saliva than cinnamon, for example.

"The absolute most important excipient for these products, in my opinion, are disintegrants," Karry says. "As a patient, I can accept having a bad tasting medicine—there are many out there already—but what I cannot accept is having a bad taste in my mouth for minutes or hours. Disintegrants help to ensure this does not happen. They enable complete drug product disintegration

in the mouth so that the small particles can be swallowed, and if designed right, they clean our mouth as well," she explains.

Karry notes that studies have shown that both particle size and shape play an important role in mouthfeel. Hard irregular particles are perceived as larger than soft and smooth particles (1), while particles of 100 µm in size are perceived as creamy or fatty and thus activate salivary secretions and swallowing (2).

"These studies demonstrate that a systematic science-based approach is needed when formulating orally disintegrating products," Karry concludes.

For lyophilized ODTs, Gosden says the most critical excipients are those that form the porous structure, specifically gelatin and mannitol. "While the freeze-drying process is under way, it is important to ensure that all of the mannitol remains crystalline, or there will be a risk that the finished dosage form will collapse during storage," he explains.

Chandar notes that for poorly soluble APIs, surfactants and plasticizers are used for bioavailability enhancement. He stresses, though, that no excipient should be used unless there is a demonstrated need and each ingredient in an ODT formulation should be justified.

It is also worth noting, according to Gosden, that some excipient suppliers have developed proprietary blends of excipients in ready-to-use form (i.e., co-processed excipients) for the creation of compressed ODTs.

Synergies with co-processing

Co-processed excipients based on microcrystalline cellulose (Prosolv ODT from JRS Pharma) and mannitol (Ludiflash from BASF and Pharmaburst from SPI Pharma) have been increasingly used in orally disintegrating/fast-dissolving products owing to their ease of use and overall particle characteristics, according to Karry. "In particular," she observes, "those containing mannitol have the advantage that this alcohol sugar has a negative heat of solution and upon dissolving in the mouth imparts a cooling effect with a sweet taste. Mannitol is also amenable for ketogenic diets (important for epileptic patients) and diabetics (due to the low carbohydrate count)."

Co-processing, unlike simple blending or mixing, of different excipients, enables the enhancement of functional performance, according to Chandar. "Whether via spray drying, granulation, congealing, or other methods, co-processing—when done effectively—creates synergies between the excipients involved, leading to unique properties and functionality not achievable any other way," he states.

As an example, Chandar points to SPI Pharma's latest addition to the Pharmaburst line (500), in which the excipients are subjected to a three-step process that includes spray drying and granulation. "The result is a microplate structure of the combined excipients that exhibits a 30–40% improvement in compactability compared to simple, physical mixing. This higher compactability opens up a broader design space for formulating robust ODTs by providing a much higher API carrying capacity of up to 500–600 mg," he remarks.

Other important advances

Catalent has developed Zydis Ultra, a next-generation ODT technology that provides better taste-masking properties in a lyophilized ODT combined with an increased drug loading capacity, according to Gosden. A coating is applied to the outside of micronized API particles (as small as 100 µm in diameter) using a dry-coating process.

"Gelatin forms the overall polymeric structure of the tablet, while mannitol increases robustness and makes the tablet look aesthetically elegant. Both ingredients dissolve readily in saliva, giving a quick-acting, melt-in-the-mouth experience for the patient," Gosden says. In addition, he observes that unlike compressed ODTs, they are not reliant on the use of super-disintegrants to provide rapid dispersion. Instead, the rapid disintegration results from the way in which lyophilized ODTs are manufactured as well as the formulation of excipients.

BASF, meanwhile, has developed Kollidon CL-SF, a superfine disintegrant with unique properties for ODTs, according to Karry. "This super-fine version of crospovidone was specifically designed to provide formulators a disintegrant that generates upon hydration smooth particles that are less than 100 µm for a non-gritty, melt-in-your-mouth feeling," she explains.

Separately, Karry notes that many companies in South America and Europe are moving to twin-screw granulation methods for

On-Dose Technology Authenticates Drug Products

SoteriaRx, a platform of on-dose technologies and detection services from Colorcon, uses a lock and key mechanism. The coated or printed dosage form is the 'lock' and the detection method—unique taggants specific to the customer that can be used on multiple drug products—is the 'key". Microtags are incorporated into the pill, providing a barcode that can be digitally read and recorded for instant authentication. The system can be used to track medicines from plant to patient, providing a new level of supply chain authenticity and transparency, the company reported in a press statement (1).

Reference

1. Colorcon, "Colorcon, Inc. Launches SoteriaRx On-Dose Authentication Technology Platform," Press Release 14 May 2020.

—*The editors of* Pharmaceutical Technology Europe

manufacturing fast-disintegrating granules. “Twin screw allows for better control of granule size and is easily converted and integrated into continuous manufacturing processes,” she says.

Regardless of the technology, the advantageous properties of new and more advanced excipients should be balanced against the higher costs that are often associated with them, asserts Gren. “For example,” he comments, “a more expensive excipient may allow you to avoid complex process steps and hence reduce manufacturing costs. As a result, the overall costs must be considered.”

Compatibility and flexibility are important

As with any formulation, one of the biggest challenges to developing orally disintegrating/fast-dissolving products is ensuring API-excipient compatibility. “Even though the majority of the excipients are pharmacologically inert, sometimes physical and chemical interactions between the API and excipients can occur that affect the stability, safety, and efficacy of the drug,” Gosden explains.

For fixed-dose combinations involving two or more APIs, the question of whether the APIs are chemically compatible or prone to interact when combined must also be considered. Catalent addresses this issue when using its Zydis technology by using two or more homogenous formulations that are dosed sequentially under different conditions prior to freeze-drying. “This approach addresses issues of incompatible APIs/excipients and temperature-sensitive APIs,” says Gosden.

ODT formulators should also prioritize exploring the relationship between tensile strength, friability, and disintegration, according to Karry. “Tensile strength is lower for ODTs compared to regular tablets due to fact that you need higher porosity for solvent uptake and core hydration. Similarly, disintegration tests are decent *in-vitro* predictors of palatability as patients prefer dosage forms that do not linger in their mouth for too long,” she adds.

Given the wide range of APIs and the drive to develop more patient-centric formulations including orally disintegrating fast-dissolving products, it is also important for formulators to have access to broadly flexible platform technologies that can be used for multiple drugs, Chandar asserts. “An antiretroviral drug may require a very high dose, while a cardiovascular therapy may need minimal loading. A universal excipient platform that can be used for both types of formulations and generate robust tablets that don’t apart when the patient opens the package dramatically simplifies the process,” he comments.

Chandar goes on to note that excipient technologies that provide rapid dissolution and can also aid in enhancing bioavailability are particularly attractive given than nearly 75% of pipeline candidates fall in BCS Class II or IV. In addition, ODT excipient technologies if designed appropriately may even be able to facilitate the oral delivery of some smaller biologic drugs— notably peptides—by enabling sublingual dosage forms that dissolve under the tongue in just five seconds, avoiding first-pass metabolism in the liver.

References

1. L. Engelen, et. al. *J. Texture Studies*, online https://doi.org/10.1111/j.1745-4603.2005.00022.x. (19 September 2005),
2. J. R. Stokes, M. W. Boehm, and S. K. Baier, *Current Opinion in Colloid Science*, 18(4), 349–359 (August 2013). **PTE**

Reducing Risk with Abuse-Deterrent Formulations

Increasing prevalence of drug misuse and abuse is driving a heightened and more stringent approach to abuse-deterrent formulations.

Felicity Thomas

Possibly the most publicized and well-documented form of drug misuse and abuse has been that of opioids—prescription pain-relief medicines. The opioid crisis, which has impacted the global health community for several years, has paved the way for increased demand in abuse-deterrent formulations from pharmaceutical developers.

Abuse-deterrent formulations essentially have the potential to provide an effective way of reducing the capabilities of an end-user to abuse or misuse a medical therapy, while maintaining the drug's clinical benefit. To explore the topic of abuse-deterrent formulations in more detail, *Pharmaceutical Technology Europe* spoke with Angela Moore, scientist, Analytical Development, Alcami.

In need of risk mitigation approaches

PTE: Could you discuss some of the reasoning behind abuse-deterrent formulations and why there may be an increase in interest in this area?

Moore (Alcami): Doctors continue to prescribe opioid medications for pain management, generating an inevitable association with abuse and addiction. Government officials and pharmaceutical professionals alike are in need of risk mitigation approaches.

In the United States alone, there have been estimates, released by the US Department of Health and Human Services (HHS), revealing that in 2018 over 47,000 citizens died from an opioid overdose and that two million people in the country were suffering from an opioid use disorder (1). The economic costs associated with the opioid epidemic have been estimated at $504 billion (€453 billion), according to analysis by Johns Hopkins University Bloomberg School of Public Health (2). And, the issue of opioid addiction is not isolated to the US, with countries worldwide experiencing significant healthcare costs associated with prescription opioid abuse, such as those experienced in the five largest European countries as reported by Shei *et al.* (3).

Pharmaceutical companies have responded to this need through more stringent abuse-deterrent formulations and studies. Although abuse-deterrent does not equate to 'abuse-proof,' medications that contain abuse-deterrent properties make it more difficult for abusers to obtain the euphoria associated with common manipulation techniques.

Current approaches

PTE: Currently, what abuse-deterrent formulation approaches are available and what are the benefits and/or limitations to these approaches?

Moore (Alcami): The current products on the market that contain abuse-deterrent labelling approved by the US Food and Drug Administration (FDA) fall into two categories of abuse-deterrence: physiochemical and opioid/antagonist. Physiochemical abuse-deterrent properties include products that are formulated to resist crushing, chewing, and physical manipulation. They contain excipients that will 'gel' upon contact with solvents to make them difficult to inject intravenously. Opioid/antagonist products contain the active opioid intended for therapeutic use and also a sequestered antagonist so that if the product is manipulated intentionally it will release a chemical that will prevent the user from feeling the euphoric effects of the opioid.

There are benefits and challenges to both physiochemical and opioid/antagonist abuse-deterrent formulations. Benefits of physiochemical formulations include having physical barriers that make it more difficult to resist tampering and manipulation. Abusers avoid these formulations as they cannot easily crush and/or inject the drug. One of the biggest challenges of these types of formulations, however, is that there are still drug abusers who find ways to abuse these products. The excipients that are present in the formulations to prevent abuse can cause many health issues if injected. For example, OpanaER (Endo Pharmaceuticals) was an extended-release oxymorphone hydrochloride oral drug product. The

drug was approved by FDA in 2006 but was being abused mainly by insufflation. The drug was reformulated in 2010 with physiochemical properties intended to be resistant to intranasal and intravenous routes. However, in June 2017, FDA requested OpanaER to be removed from the market as abusers had moved from insufflation abuse to injection abuse (4). The reformulated drug product was being shared between multiple users for injection. OpanaER was directly linked to outbreaks of Hepatitis C (New York, 2011), thrombotic thrombocytopenic Pupura-like (TTP) illness (Tennessee, 2012), and HIV (Indiana, 2015) (5,6).

A benefit to opioid/antagonist abuse-deterrent formulations is that the drug product contains a sequestered antagonist within the formulation. If the drug product is administered to patients as intended, it will work therapeutically. However, if a drug abuser tried to crush or manipulate the drug, the sequestered antagonist would be released and block the euphoric effects of the opioid. However, these abuse-deterrent products are not 'abuse proof'. Drug abusers have found ways to chemically extract the opioid from the antagonist with common household solvents to still abuse these formulations.

Another challenge that is related to all of the eight approved, abuse-deterrent opioid products that are on the market is cost. The products are all name-brand and expensive to patients. There are currently no FDA-approved generic equivalents to abuse-deterrent formulations, and insurance companies are reluctant to pay the extra expense for an abuse-deterrent opioid when the cost is vastly different from generic non-abuse-deterrent equivalents.

Close regulatory scrutiny

PTE: Are there specific regulatory challenges that should be considered when approaching abuse-deterrent formulations?

Moore (Alcami): FDA is closely scrutinizing all new abuse-deterrent products and current opioid products that are on the market now. There are comprehensive, in-depth testing requirements prior to approval of these products. For example, *in-vitro* testing of products intended to prevent abuse can take six months to a year to complete thousands of extraction, manipulation, and syringe studies.

After this testing is complete, the products are then verified in a clinical setting in humans, where clinical subjects purposely take a product as intended and then in an abused form and rate their 'drug liking', which is if they enjoy the product recreationally and if they would take the drug again.

Post-approval, FDA also requires all pharmaceutical companies that manufacture prescription opioids commercially to participate in the REMS program (Risk Evaluation and

Mitigation Strategy) where they monitor the abuse of commercially marketed opioid pharmaceuticals.

As each formulation and mode of abuse can be different, there is only FDA published guidance, *Abuse Deterrent Labeling—Evaluation and Labeling Guidance for Industry*, published in April 2015 that pharmaceutical companies can use as a guide for completing the required tests. Companies must work closely with FDA to ensure the testing performed is adequate and that study designs are acceptable. It is not uncommon for FDA to request additional testing at each stage of studies, which takes considerable time and expense to execute.

Evaluating effectiveness

PTE: How can the effectiveness of an abuse-deterrent formulation be evaluated?

Moore (Alcami): Current FDA guidelines for determining abuse-deterrence of a drug product involve four main studies termed Category 1, 2, 3, and 4.

Category 1 testing involves laboratory manipulation and extraction studies. In these studies, the product is evaluated and compared to currently marketed formulation(s) for the ability to defeat or compromise the abuse-deterrent properties. This testing is performed *in-vitro* and provides physical characteristics of the product and its ability to resist crushing, grinding, melting, and so on, to inhibit nasal abuse. Extraction studies provide information on the product's ability to isolate the antagonist, or resist abuse by injection, or, in larger volumes, resist abuse by ingestion.

Category 2 testing involves pharmokinetic studies in healthy humans. The product's *in-vivo* properties are evaluated by comparing an intact formulation against the manipulated formulation through one or more routes of administration. Comparator products are also evaluated for comparison.

Category 3 testing evaluates the clinical abuse potential of the product. These are large, complicated *in-vivo* studies that are generally conducted with recreational drug users as test subjects. These test subjects are screened prior to the study to ensure that they are able to distinguish between active drug and placebo in a drug abuse setting. In these studies, the test subjects are provided with the drug product being developed and suitable comparators. The drugs are administered through the route of abuse that is being studied (i.e., oral or intranasal) and the patients provide not only pharmokinetic data, but also subjective data on the drug liking (how high they are) and if they would take the drug again.

Category 4 assessment is a post-approval study that determines if the product has resulted in meaningful reductions in abuse, misuse, or adverse clinical outcomes (addiction, overdose, and death). These evaluations are conducted by the product manufacturer. Currently, there are no products on the market that contain the Category 4 label for abuse-deterrence.

Many considerations

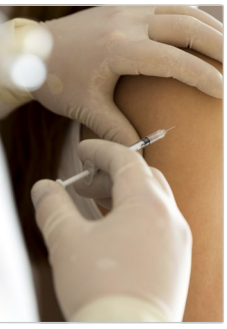
PTE: What trends, potential new approaches, and considerations do you foresee as being important in the field of abuse-deterrent formulations in the near future and why?

Moore (Alcami): One of the biggest trends in abuse-deterrent formulations is the development of abuse-deterrent generic products. FDA has published guidance for industry, *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*, for companies that are developing generic products comparable to the approved abuse-deterrent products on the market (7). The intention of the guidance is to reduce the amount of testing required for the generic product by showing equivalence or superiority to the name-brand product in laboratory-based, abuse-deterrent tests so that human trials (Categories 2 and 3) are not required. Additionally, any new opioid drug that is being developed must demonstrate resistance to abuse in order to grant FDA approval.

There are many considerations for manufacturers developing abuse-deterrent opioid formulations. Most importantly, the product must be considered safe and effective, and it must adhere to all regulatory manufacturing and testing guidelines. From a chemistry and biologic perspective, the product must resist dose dumping and abuse, but still release the active ingredient when ingested as intended. From the commercialization perspective, key considerations are developing a product that has a competitive advantage over what is on the market today. The company must differentiate their product so that they can answer the question: 'What product characteristics will make a doctor want to prescribe the new product over what is on the market?' Furthermore, insurance companies, governments, and patients must be convinced that the new product is worth more compared to cheaper, non-abuse-deterrent products on the market.

References

1. HHS, "What is the US Opioid Epidemic?" *hhs.gov*, Epidemic Informatic last updated 4 Sept. 2019 [accessed 12 May 2020].
2. D.H. Lin, et al., *JAMA Netw. Open*, 1 (2) e180235 (2018).
3. A. Shei, et al., *Clinicoecon. Outcomes Res.*, 7 477–488 (2015).
4. FDA, "FDA Requests Removal of Opana ER for Risks Related to Abuse," *fda.gov*, Press Release, 8 June 2017.
5. H. Mehmood, et al., *J. Investig. Med. High Impact Case Rep.*, Published Online 31 Jan. 2018.
6. Endo Pharmaceuticals, "Opana ER—Oxymorphone Hydrochloride Tablet, Extended Release," *endo.com*, Prescribing Information [accessed 12 May 2020].
7. FDA, *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products Guidance for Industry*, Guidance Document (November 2017). **PTE**



Approaches to Alleviating Subcutaneous Injection-Site Pain for Citrate Formulations

Arvind Srivastava, Ger Brophy, and Meera Agarkhed

Subcutaneous (SC) injection provides flexibility in dosage form, options for self administration, and may also help reduce drug cost while increasing patient compliance. Biopharmaceuticals delivered via SC injections are commonly formulated at an acidic pH with a variety of stabilizing agents and buffers, including histidine, phosphate, and citrate. The authors will discuss how formulations containing citrate compare to other buffers in reducing SC injection-site pain and discuss a formulation and excipients selection strategy that formulators can use to mitigate the risk of injection-site pain.

Subcutaneous (SC) injection is a method of administering medication as a bolus under the skin, into the tissue layer between the skin and the muscle (1). It is often viewed as an alternative to oral administration for drugs which may degrade when exposed to gastric acid and enzymes in the body. Intravenous (IV) infusion requires a special arrangement (such as infusion set, pump, etc.) as well as the involvement of a health care provider, making its use in at-home treatment limited. For frequent administration in the treatment of chronic diseases, such as asthma and arthritis, the development of SC dosage forms is valuable to improve ease of administration, reduce costs, and increase patient compliance (2).

SC injection is currently the most common route of self-administering drugs, such as proteins and peptides (1). In these applications, patients are not administered drugs, but rather formulations that contain a drug. Subcutaneously injected drugs are often formulated in non-physiological conditions to improve or maintain product efficacy and stability throughout product shelf life (1, 3, 4). Biopharmaceuticals intended for SC injection are commonly formulated at acidic pH with a variety of stabilizing agents (4, 5). A typical SC formulation composition includes buffers (e.g., citrate, histidine, phosphate, acetate), tonicity adjusting agents (e.g., dextrose, glycerol, sodium chloride), antimicrobial preservatives (e.g., m-Cresol, phenol, benzyl alcohol) and stabilizers (e.g. salt, amines, buffers) and viscosity-reducing agents (e.g., arginine, histidine, polysorbate, human serum albumin, surfactants, zinc chloride) (6).

Injection-site pain challenges in the development of an SC formulation

While SC injection has numerous benefits, one potential drawback is that it may cause pain at the injection site. This may be caused by different factors, including buffer type, pH, temperature, viscosity, injection volume, tonicity, individual experience, speed of injection, needle size, anatomical region, and formulation (2, 7, 8, 9, 10).

CITATION: When referring to this article, please cite it as A. Srivastava, et al., "Approaches to Alleviating Subcutaneous Injection-Site Pain for Citrate Formulations," *Pharmaceutical Technology* 44 (6) 32–37 (2020).

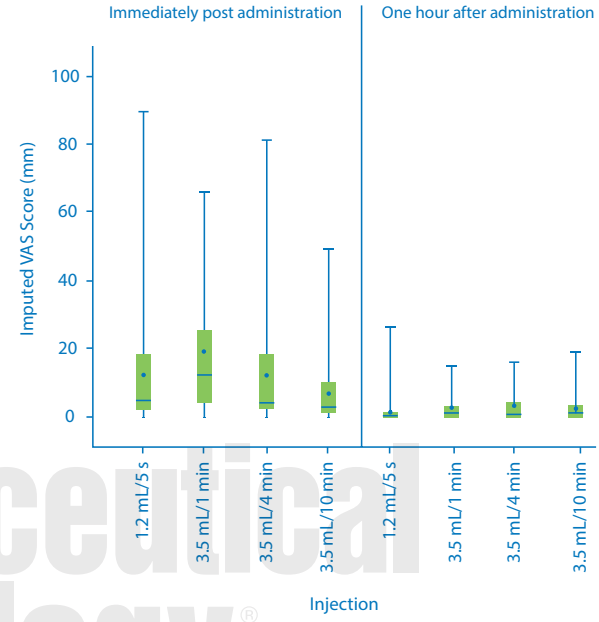
Submitted: 18 Nov 2019
Accepted: 18 Dec. 2019

An inherent limitation of SC dosage form is the injection volume. The maximum volume that can be administered is typically less than 2 mL (2, 5), because the area available under the epidermis and dermis are limited in such a way that the injection of large volume creates high back pressure. Considering this limited maximum injection volume, SC administration of monoclonal antibodies (mAbs) at a high dose necessitates the development of stable, high-concentration formulations which may also have high viscosity. As viscosity increases, the time and pain at the site of the injection increase as well, making treatment challenging to administer while also negatively affecting patient compliance (11).

Pain at the injection site is also protein-specific (2). As reported by Schmitt *et al.* (12), a prospective, randomized, double-blind study demonstrated increased painfulness of subcutaneous injections for treatments of anemia. The study evaluated the effects of SC delivery of darbepoetin-α (commercially marketed as Aranesp, a trademark of Amgen) compared to epoetin-β (commercially marketed as NeoRecormon, a trademark of Roche) in children. The higher injection pain with darbepoetin-α, which cannot be explained by differences in injected volume, needle properties or patient anxieties, must therefore be related to the nature of the injected fluids per se (12). The meticulous standardization of and the higher injection pain with the preparation and injection procedure, as well as the double-blind design of the study, largely ruled out any interference by technical factors (e.g., needle, injected volume) or psychological factors (e.g., previous adverse experience with one of the drugs or biased pain expectation towards the new drug). Darbepoetin-α was usually diluted with twice as much saline as epoetin-β; this factor should, if anything, have reduced injection pain with darbepoetin-α. Hence, it is highly likely that the difference in perceived pain is related to the specific composition of the two medications (12).

In another example, a single-center, crossover study was designed to compare visual analog scale (VAS) scores associated with three 3.5-mL SC injection durations to that associated with a 1.2-mL SC bolus injection and to investigate tolerability, swelling, and leakage from the injection site (13). Results are shown in **Figure 1**. The study demonstrated that, immediately after administration and one hour later, a SC injection of 3.5 mL of a viscous placebo buffer, with the characteristics of a typical protein formulation, administered over one minute was associated with more pain than a 1.2-mL bolus injection. Administered over 10 minutes, it was associated with less pain than the bolus injection. The differences were not considered clinically meaningful, suggesting that it may be possible to reduce the number of injections per biotherapeutics treatment through the injection of larger SC dose volumes using a prefilled syringe, auto-injector, or another personal injection device (13).

Figure 1. Visual-analog scale (VAS) pain scores by treatment, immediately and one hour after administration. Dots represent means, boxes represent the first quartile to the third quartile with lines showing medians, and whiskers indicate ranges.



Use of citrate in SC formulations and its impact on injection-site pain

Formulation plays an important role in controlling pain at the injection site. For example, a histidine buffer is known to be less prone to cause pain upon injection compared to a phosphate and citrate buffer (2, 9, 10, 11). **Figure 2** shows the results of a double-blind study of 54 healthy individuals who were injected with recombinant human growth hormones in two different commercially available solutions (histidine and citrate). An experienced nurse performed the injections pairwise (right and left thigh). A majority of the participants (38/54) reported that the citrate buffer caused more pain than the histidine buffer (11).

It is hypothesized that the pH of the injection site might not drastically change upon injection unless the formulation contains strong ions as buffering agents (1). This is supported by a study where it was reported that the pain patients experienced upon injection was more serious for citrate than for histidine or saline (11). Since citrate is a strong ion, whereas histidine and saline are not, it is possible that the pH shift within the SC tissue upon the administration of the buffers is more significant with citrate than with saline and histidine, resulting in a more painful injection (1).

Results of a randomized, double-blind, crossover study indicated that the epoetin alfa formulation using a sodium phosphate buffer was associated with less injection-site discomfort and a shorter duration of pain than the formulation containing a citrate buffer (14). An epoetin alfa formulation

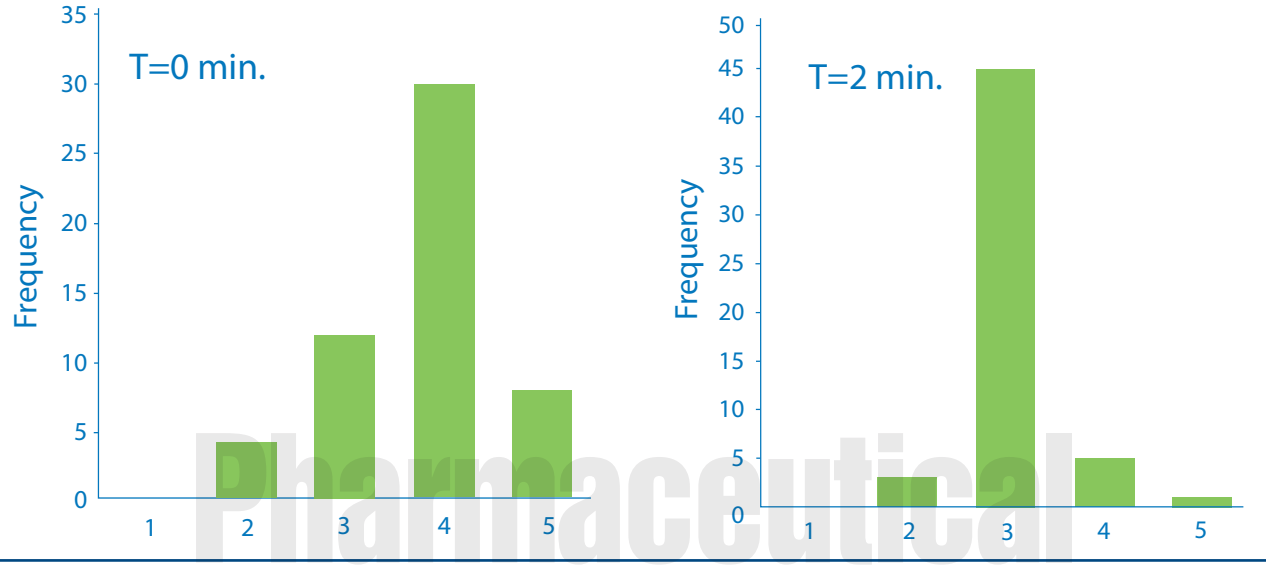
emergent
biosolutions®

Perfecting Your Formula

Navigating the choppy waters of drug development and manufacturing can be challenging. Having an experienced hand at your side who's guided others to their destinations before can make all the difference. Wherever you are in your journey, let us know the challenges you're facing and our CDMO team of experts will customize a pathway to your success.

Learn more at emergentcdmo.com.

Figure 2. Perception of pain at time (T) = 0 min. (left panel) and T = 2 min. (right panel) after injection of histidine versus citrate solutions. The citrate solution caused more pain than histidine (P = 0.002). Score 1=histidine solution caused much more pain than citrate solution; Score 2 = histidine solution caused more pain than citrate solution; Score 3 = no difference in pain after the two injections; Score 4 = citrate solution caused more pain than histidine solution; Score 5 = citrate solution caused much more pain than histidine solution.



using sodium phosphate as the buffer may provide an advantage in local tolerability and compliance (13). These findings are consistent with other reports in the literature (15, 16). Human insulin-like growth factor I (hIGF-I) formulated at isotonic conditions with sodium chloride (NaCl), ranging in pH from 6 to 7 with phosphate buffer concentrations of 5 to 50 mM, was investigated to determine subcutaneous injection pain and local tolerance (redness, paleness, and edema). The discomfort at the injection site was lowest with 10 mM phosphate, pH 7. Injection of the buffer at pH 6 (50 mM phosphate) caused significantly more pain than using 10 mM phosphate, whereas the pain at pH 6 using 10 mM phosphate did not differ significantly from that experienced in the injection of the solution at pH 7 using either 10 mM or 50 mM phosphate. The hIGF-I itself did not seem to cause pain. The authors conclude that for subcutaneous injections at non-physiological pH, the buffer strength should be kept as low as possible to avoid pain upon injection. The authors also hypothesize that when a non-physiological pH must be used for stability reasons, lower buffer strength enables more rapid normalization of the pH at the injection site (17).

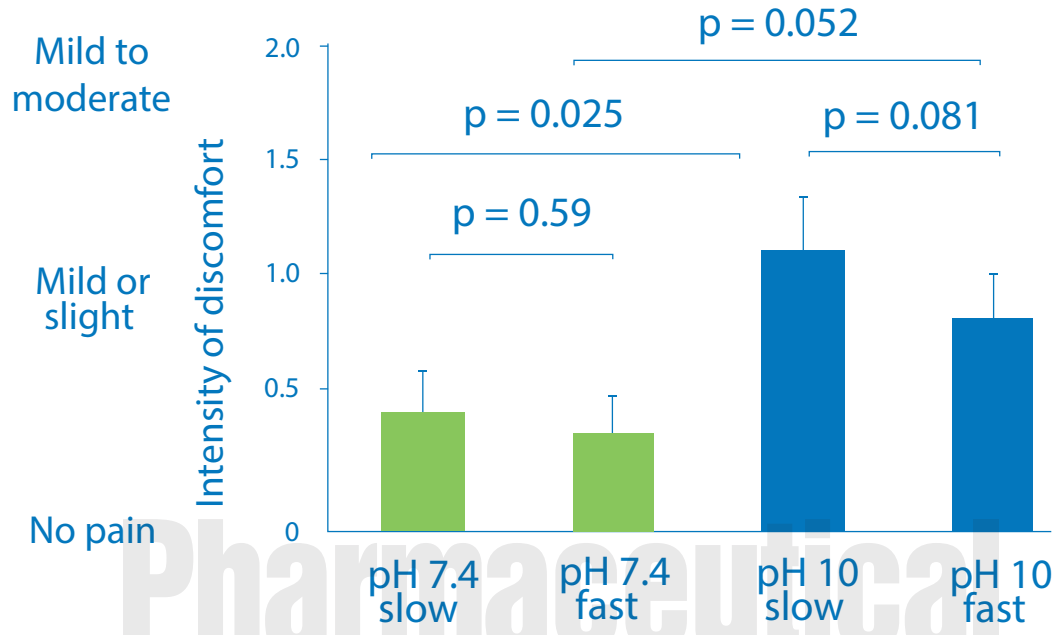
A single-blinded study with 42 adult volunteers employed at a tertiary care center was performed to determine the impact of administration rate and buffering on the pain associated with subcutaneous infiltration of lidocaine (18). Each subject received four lidocaine injections:

- slow, buffered (SB)
- slow, unbuffered (SU)
- rapid, buffered (RB)
- rapid, unbuffered (RU).

Buffering was accomplished by mixing 1% lidocaine with 8.4% sodium bicarbonate in a 9:1 ratio. Slow administration was 30 seconds and rapid was five seconds. Needle size (27-gauge), injection depth (0.25 inch), lidocaine volume (1.0 mL), and temperature (room) were the same for each of the four injections. In all four conditions, the needle remained in the forearm for 30 seconds to ensure blinding. The main outcome measure was the mean pain score for each condition, as recorded on a 10 cm visual analog scale. The lowest pain scores (mean ± SE) were recorded for the SU and SB conditions at 1.49 ± 0.29 and 1.48 ± 0.26, respectively, and they were significantly lower than the scores for RB (2.34 ± 0.28; $P < 0.01$) or RU (3.11 ± 0.33; $P < 0.001$). Each of the slow conditions was reported to be the "least painful" of the four significantly more often than either rapid condition. By this largest blinded study to assess administration rate and the pain of a local anesthetic, the authors found that administration rate had a greater impact on the perceived pain of lidocaine infiltration than buffering (18).

Clinical trials on anakinra (commercially marketed as Kineret, a registered trademark of Swedish Orphan Biovitrum) and related studies in rats demonstrated a correlation between drug concentration, dose level and buffer (19, 20, 21). The vehicle (buffer) and the concentration of anakinra were found to be the cause of mast cell degranulation leading to injection site-related reactions (19, 20). In one of the dose-finding studies with anakinra (21), it was also noted that the injection-site reactions (ISR) were dose-related. ISRs were experienced by 28% of subjects in the placebo group and by 19%, 38%, 56%, 64%, and 63% in the groups receiv-

Figure 3. Results regarding intensity of discomfort after fast or slow subcutaneous administration of albumin at pH 7.4 or pH 10 in normal human subjects. Data are presented as mean + standard error of the mean.



ing anakinra at 0.04 mg/kg, 0.1 mg/kg, 0.4 mg/kg, 1.0 mg/kg, and 2.0 mg/kg, respectively (19, 21).

These studies also demonstrated that the potential reasons for pain upon injection could be related to the buffer (citrate) at a non-physiological pH (6.5 vs. 7.2) and the presence of the surfactant polysorbate 80 (19). Polysorbate 80, used in the formulation of anakinra, is also present in erythropoietin and has been shown to cause hypersensitivity reactions in patients (22). In another study, tolerability of neutral verses alkaline (pH 10) formulation of human albumin in 10 volunteers was compared. Results are shown in **Figure 3**. The discomfort associated with alkaline pH, especially when delivered slowly, was more than the neutral pH (23).

Buffer selection during formulation for reduction or prevention of injection-site pain

Formulation and the buffers used in the process play an important role in controlling the pain at the injection site, as demonstrated in literature. A histidine buffer is known to be less prone to cause pain upon injection when compared to phosphate and citrate buffers (2, 9, 10, 11, 19). As outlined earlier, a double-blind study of 54 healthy individuals injected with recombinant human growth hormone in two different commercially available solutions (histidine and citrate) with isotonic saline as a reference demonstrated that the formulation using the citrate buffer was more painful to inject than the formulation in the histidine buffer (11). Additionally, as outlined in the randomized, double-blind, crossover study with epoetin alfa, the formulation using a sodium phosphate buffer was associated with less injection-site discomfort and a shorter duration of pain than the formulation containing a citrate buffer (14). These studies (11, 14) demonstrate that histidine and phosphate are better buffers than citrate for subcutaneous formulations.

Buffering strength has also been shown to affect the level of subcutaneous injection-site pain. Since biopharmaceuticals intended for SC injection are commonly formulated at an acidic pH level with a variety of stabilizing agents (4, 5), keeping the buffer strength as low as possible can help avoid pain upon injection (17) since subcutaneous injections occur at a non-physiological pH level. Buffer-free formulations can minimize subcutaneous injection-site pain. Therapeutic proteins require buffering to maintain solution pH, stability, and efficacy while proteins (e.g., antibodies) have their own buffering capacity. MAbs at higher than 50 mg/mL concentrations typically don't require conventional buffering excipients to control the pH as required at a low concentration (24). Adalimumab (commercially marketed as Humira, a trademark of AbbVie Inc.), was recently reformulated in a citrate-free buffer to minimize the injection-site pain in the treatment of rheumatoid arthritis (25). The mean values of "overall pain at the time of injection" VAS were 6.7 (±2.4) for the existing formulation and 1.6 (±1.7) for the citrate-free formulation, indicating that overall pain at the time of injection was significantly alleviated with the citrate-free formulation (25). Results are shown in **Figure 4**. The mean values of "pain 10 minutes after injection" VAS were 3.1 (±2.8) for the existing formulation and 0.4 (±0.9) for the citrate-free formulation, indicating that pain 10 minutes after injection was also

Figure 4. Injection site pain for adalimumab at the time of injection and after 10 min. of injection in citrate and citrate-free formulations.

Injection site pain	Visual analogue scale (VAS)	
	Citrate formulation	New citrate-free formulation
At the time of injection	6.7±2.4	1.6±1.7
10 min. after injection	3.1±2.8	0.4±0.9

significantly alleviated with the citrate-free formulation (25).

Injection durations (18) and injection volumes (22) are other measures to reduce injection-site pain. As demonstrated by Scarfone *et al.* in a single-blinded study with 42 adult volunteers to determine the impact of administration rate and buffering on the pain associated with subcutaneous infiltration of lidocaine, slow administration with a duration of 30 seconds was reported to be less painful than the rapid administration duration of five seconds (18). As reported by Anderson *et al.*, in an open-label, multicenter, randomized comparative study of novel (20 mg/0.5 mL) versus marketed (20 mg/1.0 mL) formulations, the mean immediate VAS total pain score was significantly lower after administration of 20 mg/0.5 mL glatiramer acetate (GA) injection compared with the 20 mg/1.0 mL GA injection. The lower immediate VAS pain score associated with the novel formulation was consistent over all 14 days of the study, indicating that the improvement in injection pain did not diminish over time. The reduced VAS pain score associated with the novel formulation was also evident five minutes post-injection (26). As evidenced by their study, reducing the volume may also provide a moderate benefit. The incidence and severity of local injection site reactions (LISRs) within five minutes and 24 hours post-injection were significantly less for the novel formulation than the marketed formulation. Moreover, even though most patients reported some LISRs following injection of either formulation, a greater percentage of patients treated with the reduced volume solution reported no symptoms within five minutes and 24 hours after injection (26).

Finally, surfactants and excipients may also play a part in increasing or decreasing site pain. Surfactants, such as polysorbate 80, may cause hypersensitive reactions in patients at the site of subcutaneous injection (22), highlighting the fact that polysorbates, which are usually present in protein formulations, need to be controlled properly to prevent hypersensitivity to the drug upon subcutaneous injection. Excipients such as sorbitol can reduce injection-site pain (27) as suggested by large clinical trial studies of Synolis V-A (hyaluronic acid and sorbitol, Synolis), a visco-antalgic formulated with 4% sorbitol that demonstrated reduction in injection-site pain (27). The antioxidant effect of sorbitol may also play a role in rapid and strong pain reduction in patients with osteoarthritis, therefore influencing function recovery and medication intake reduction (27). Viscosity-reducing excipients such as amino acids and salt (7) are also expected to reduce injection-site pain due to the injection of a high viscous solution.

Several drugs have been co-formulated with a recombinant protein to minimize injection-site pain due to a large-volume injection. Trastuzumab (commercially marketed as Herceptin SC, a trademark of Roche Genentech) and rituximab (commercially marketed as Rituxan Hycela, Rituxan SC, and MabThera SC, all trademarks of Roche Genentech) are formulated with the proprietary recombinant human hyaluronidase PH20 enzyme (rHuPH20; Halozyme Therapeutics, San Diego, CA) to overcome administration time and volume barriers associated with existing SC therapeutic formulations. The rHuPH20 works by degrading the glycosaminoglycan hyaluronan (HA), which plays a role in resistance to bulk fluid flow in the SC space, limiting large-volume SC drug delivery, dispersion, and absorption (28).

Conclusion

Subcutaneous (SC) injection is a viable alternative for patients requiring frequent treatments because they may be administered by the patient outside of a health care setting. In spite of these advantages, associated injection-site pain is a leading cause of patient noncompliance. The root cause of injection-site pain can be traced back to choices made in the buffering agents, surfactants and other excipients used during drug product (formulation) design. Biopharmaceutical manufacturers may be able to mitigate injection-site pain caused by drug product composition by choosing more appropriate solution conditions to reduce viscosity, pH, and buffering strength in their formulations.

It is well-known that making changes in drug product composition during late-phase development or post-marketing is expensive and comes with a number of regulatory risks. For these reasons, formulators should proactively engage with their chosen chemicals and excipients suppliers

early in the process, long before drug product development has been completed and the product composition is locked. Such partnerships between biopharma manufacturers and chemical suppliers to better identify and, if necessary, develop optimal materials for their product can help ensure drug product development that meets a drug target product profile while improving patient outcomes.

References

1. H.M. Kinnunen and R.J. Mrsny, *J Control Release* 182, 22–32 (2014).
2. S. Goswami, et al., *Antibodies* 2, 452–500 (2013).
3. S. Ohtake, Y. Kita, and T. Arakawa, *Adv Drug Deliv* Rev 63, 1053–1073 (2011).
4. W. Wang, et al., *J Pharm Sci* 96, 1–26 (2007).
5. L.H. Bookbinder, et al., *J Control Release* 114, 230–241 (2006).
6. S. Pramanick, S. Singodia, and V. Chandel, *Pharma Times* 45, 65–77 (2013).
7. L.A. Gatlin and C.A.B Gatlin, "Formulation and Administration Techniques to Minimize Injection Pain and Tissue Damage Associated with Parenteral Products," in *Injectable Drug Development: Techniques to Reduce Pain and Irritation*, P.K. Gupta and G.A. Brazeau, Eds. (Interpharm Press, Denver, CO, 1999), pp. 401–425.
8. A.W. Yu, et al., *Int J Artif Organs* 21, 41–43 (1998).
9. A.M. Kappelgaard, et al., *Horm Res* 62, 98–103 (2004).
10. T. Laursen, B. Hansen, and S. Fisker, *Basic Clin Pharmacol Toxicol* 98, 218–221 (2006).
11. D.S. Tomar, et al., *mAbs* 8, 216–228 (2016).
12. C.P. Schmitt, et al., *Nephrol Dial Transplant* 21, 3520–3524 (2006) .
13. C. Dias, et al, *AAPS PharmSciTech* 16, 1101–1107 (2015).
14. K.J. Taub, et al., *Can J Hosp Pharm* 52, 24–29 (1999).
15. L.A. Frenken, et al., *Am J Kidney Dis* 22, 553–556 (1993).
16. L.A. Frenken, H.J. van Lier, and R.A. Koene, *Nephrol Dial Transplant* 9, 1295–1298 (1994).
17. J. Fransson and A. Espander-Jansson, *J Pharm Pharmacol* 48, 1012–1015 (1996).
18. R.J. Scarfone, M. Jasani, and E.J. Gracely, *Ann Emerg Med* 31, 36–40 (1998).
19. C. Kaiser, et al., *Rheumatol Int* 32, 296–299 (2012).
20. A. Bendele, et al., *J Lab Clin Med.* 125, 493–500 (1995).
21. S. Cohen, et al., *Arthritis Rheum* 46, 614–624 (2002).
22. R.H. Steele, et al., *Nephrology* (Carlton) 10, 317–320 (2005).
23. W.K. Ward, et al., *Clin Drug Investig* 32, 433–438 (2013).
24. P. Garidel, B. Pevestorf, and S. Bahrenburg, *Eur J Pharm Biopharm* 97, 125–39 (2015).
25. T. Yoshida, et al., *Mod Rheumatol* 29, 1–5 (2019).
26. G. Anderson, et al., *J Neurol* 257, 1917–1923 (2010).
27. F. Radenne, *Abstracts/Osteoarthritis and Cartilage* 22, S57–S489 (2014).
28. K.W. Locke, D.C. Maneval, and M.J. LaBarre, *Drug Deliv* 26, 98–106 (2019). **PTE**

Arvind Srivastava, PhD*, arvind.srivastava@avantorsciences.com, is technical fellow, and **Ger Brophy**, PhD, is executive vice-president, Biopharma Production; both are at Avantor. **Meera Agarkhed** was a senior manager, Technology & Innovation, at Avantor.

**To whom all correspondence should be addressed.*

Why Do Disinfectant Residues Matter?

Consider how to assess the risks of disinfectant residues and understand their possible sources.

Madison Hoal is Global Technical Consultant, and **Donald Singer** is Senior Microbiology Technical Consultant, both at Ecolab Life Sciences.

In aseptic manufacturing, the application of cleaning and disinfection agents reduces contamination to an acceptable level for the grade of cleanroom and prevents cross-contamination from surfaces that are part of or adjacent to good manufacturing practice (GMP) manufacturing operations.

There is systemic complacency within the industry regarding the cleaning and disinfection products used and the associated programme. A common response within industry when asked about the rationale for a given cleaning regime is: "We have always done it that way." When a review of the associated environmental monitoring trends demonstrates a degree of control, everyone is satisfied.

Historically, cleaning has been the "residual contaminant" removal step and disinfection has followed, often at times leaving the disinfectant on the surfaces indefinitely. Legacy cleanroom environments were often following the old adage that "visible disinfectant residues on the surface are a preventative measure." But this rationale may be changing. The authors have seen a prolonged and increased concern from regulators over residues left from disinfectants post-application.

Current industry thinking, along with recent compliance mandates (1), is that any residual chemical is a potential chemical or particulate contaminant to a process and possibly to product. This renewed focus has led a change from legacy thinking to a consideration of how to assess and address disinfectant residues, including an evaluation of what properties other than efficacy, such as residue profile, should be considered for cleaning and disinfectant products.

Considering risk

Product quality risk. The presence of a disinfectant residue represents a risk to product quality as either a physical or chemical contamination risk, which is why products such as alcohols are commonly used in close proximity to open product, as they leave little or no residues.

For aseptically produced and low-bioburden products, contamination control is intertwined within the quality system, facility design, and process validation. The US Pharmacopeial Convention (USP) says (2):

"The removal of residual disinfectants should be monitored for effectiveness as a precaution against the possibility of product contamination."

Cleanrooms are typically designed to facilitate contamination control for pharmaceutical products at the point in the manufacturing process where internal controls are most important. The highest risk products, sterile injectables, require product contact surfaces to be contamination-free and are commonly subjected to validated sterilization processes. Adjacent surfaces on production machinery and containment equipment (e.g., isolators or restricted access barriers) can be decontaminated, with the assurance that residual agents are removed, to prevent possible cross-contamination during the filling process where product is minimally exposed.

Biopharmaceutical cleanrooms can range in use from bulk manufacturing, containing large tanks/vessels and complex purification equipment, to fill/finish operations for sterile injectables. The concern with residual disinfectant cross-contamination into product processing is a moderate risk in bulk manufacturing areas, unless product processes are directly adjacent to a decontaminated surface, such as a fermentation tank with any size hatch that can open. Filling operations are similar in high risk to the sterile injectable.

Cleanrooms used for cell therapy manufacturing may have more containment features to protect the live cells and inherently short manufacturing times, yet there are still many surfaces that need to be part of the contamination control strategy. These surfaces are disinfected routinely with expectations that no residue exists that can be carried by operators (on their gloves or gowns) or mobile equipment from one activity to

another in the manufacturing suite(s). Appropriate choice of disinfectants is also crucial when using single-use bags containing live cells throughout the lifecycle of a cell therapy.

Despite the expectation that no disinfectant residue exists in these critical and adjacent manufacturing areas of any type of pharmaceutical operation, broad-spectrum disinfectants and sporicidal agents used in these same areas often leave residue, which may or may not be visibly apparent.

The new draft of Annex 1 contains a specific regulatory guidance statement about disinfectants, which highlights that cleaning programmes should be effective at removing disinfectant residues. This expectation is in line with the developing expectations of industry and with historical regulatory observations. Annex 1, section 4.36 says (1):

"The disinfection of cleanrooms is particularly important. They should be cleaned and disinfected thoroughly in accordance with a written programmeme. For disinfection to be effective, prior cleaning to remove surface contamination should be performed … Cleaning programmes should effectively remove disinfectant residues."

Regulatory risk. Regulatory compliance is always a business expectation because of its impact on final products and the patients who are the primary customers. Regulatory inspections follow the legal requirements stated in practical terms as current good manufacturing practices (CGMPs). Inspectors have authority to interpret CGMPs when they evaluate a manufacturing operation.

Evaluation of cleaning and disinfection practices are part of the CGMP inspection. Most evaluations of the cleaning and disinfection programme are based on visual observation. Inspectors will not only indicate and question visual observation of residues from product, but they also will note disinfectant-type residues. Since cleaning validation usually relates to product contact surfaces, most non-product contact surfaces do not have a quantitative analysis of residues. Thus, the visual observation of residue by an inspector is often generalized and unqualified as to its identification as a residue from manufacturing products (actives or excipients), cleaning, or disinfection. Notation of colour and location is often the extent of an observation, which leaves the identification of the residue and the subsequent corrective action with the manufacturer. In most situations, residue of any kind becomes an observation/finding from the inspection with a requirement to identify and mitigate/prevent future occurrence.

Health and safety risks. Another aspect to consider is the health and safety risk disinfectants may have on cleanroom operators and cleaning technicians. All disinfectants are by their very nature toxic to living organisms; however, these chemicals are an effective and safe tool when handled appropriately with adequate safety measures in place. Training on proper storage, mixing, handling, and application procedures is essential.

The interaction between some disinfectants can lead to undesirable risks to cleanroom operations. If the cleaning and disinfection programme does not address disinfectant residues prior to applying different chemistries, there is a potential for chemical interactions between the chemistries in use (3). For example, a chlorine-based disinfectant applied after a phenolic-based disinfectant may result in the release of toxic chlorine gas. Additionally, these chemical reactions may also interfere with the disinfectant's efficacy. The presence of disinfectant residues may also reduce the biocidal activity of disinfectants subsequently applied to the surface. This may result in frequent environmental excursions or increased recovery of microorganisms that the cleaning and disinfection regime should have been effective at managing throughout the facility.

Disinfectant residues can also interact with one another, causing sticky or slippery floors. Both outcomes pose a risk of slips, trips, and falls to cleanroom operators. In addition, the presence of sticky floors may also lead to the accumulation of debris on the surfaces posing a gross contamination risk. It is imperative that pharmaceutical manufacturers review their cleaning and disinfection programme to ensure that a residue removal step is incorporated when changing or rotating between different disinfectants, such as prior to sporicides.

Facility risk. Cleanroom operators are sure to have seen evidence of disinfectant residues, such as an oily sheen on stainless steel or the chalky white powder on the floor coving. Other effects from the use of disinfectants on cleanroom surfaces can be rouging on stainless steel or the reduction of the epoxy floor sheen.

In cleanrooms, disinfectant residues are often monitored, or measured, visually. These residues, if not managed preventatively, can cause degradation to the facility over time, which can lead to costly reconstruction or require deep cleaning measures.

A significant source of facility degradation tends to be rotational sporicides. Due to effective use levels of sporicidal formulations, these chemicals tend to be corrosive in nature and can quickly age a facility if not appropriately managed. It is crucial that the residues of these types of chemicals are removed from the surface after the appropriate contact time to avoid degradation over time. However, it should be noted that residue should not only be removed from cleanroom surfaces where the residue is visibly apparent, such as on stainless steel and glass, but also on surfaces where the residue may not be visibly apparent, such as non-reflective surfaces.

Consumption of time and resources. The disinfection residue removal process is likely to require additional time and resources in the form of increased cost of labour and

supplies to remove residues, which in turn leads to reduced production time and productivity.

Factors leading to residue

Disinfectant residues need to be removed from the cleanroom environment, but most disinfectants have some degree of residues. It begs the question: How can cleanroom operations meet the regulatory requirements without impacting their production schedule and targets?

Several aspects of the cleaning and disinfection programme can be reviewed to reduce the impact and/or risk posed by disinfectant residues, such as introducing a residue removal regime, reviewing application techniques, and choosing low-residue formulations.

Insufficient or non-existent residue removal. All disinfectants, with the exception of some isopropanol and hydrogen peroxide formulations, leave some amount of residue on the surface, which will require routine residue removal.

Cleanroom disinfectants are typically aqueous-based formulations and are therefore readily dissolvable in water. Thus, the best solvent to remove disinfectant residues is water. Normally, this is water for injection or purified grade water, depending on the location and risk to the cleanroom. However, water poses another risk to the cleanroom: origin or potential for microbiological growth. To address this concern, 70% alcohols are commonly used in critical environments. While 70% alcohols are disinfectants, they are also used to reduce the build-up of other disinfectant residues.

The effectiveness of the residue removal step should be assessed for each disinfectant used in the site's cleaning and disinfection programme. The frequency of the residue removal will depend on the means of application and the disinfectant formulation.

Over-application. When applying disinfectant to cleanroom surfaces, the end-user should be cautious of oversaturating a surface. Over-application can be the result of many common challenges within the cleanroom. One challenge is achieving the validated contact time. A heavy application of disinfectant may seem like a way to achieve the validated contact time. However, by oversaturating a surface, more disinfectant is being applied, resulting in more disinfectant residues building-up over time.

Another common challenge is improper use of the cleaning and disinfectant tools. The user should seek cleaning and disinfecting tools that apply the disinfectant in a controlled manner, such as an effective wringer and a defined saturation level for wipes. If controls are not in place, variability in application can result among operators, which in turn can impact effectiveness of the cleaning and disinfection programme. Over application can also impact the frequency of the residue removal programme.

The effectiveness of the residue removal step should be assessed for each disinfectant.

Manufacturing sites should also ensure that their cleaning and disinfection personnel are adequately trained to apply disinfectants in a cleanroom setting. This includes training on the saturation level of mops and wipes, as well as how controlled application is important on surfaces. Multiple coatings and overlapping the same surface do not only serve as a potential cross-contamination issue, but also contribute to disinfectant residue build-up.

Disinfectant formulation. It is important to be aware of and understand the formulation of a disinfectant when applied to a particular surface for consideration about potential residues. Good practice utilizes high quality pharmaceutical grade water (e.g., water for injection) for dilution of disinfectant concentrate. Following a manufacturer's label for the volume of water to use when diluting disinfectant concentrate is critical, and any variation can influence the occurrence of residue and performance. Disinfectant stability may be related to incorporated inactive ingredients in the formulation, yet also may influence residue occurrence. Compatibility of the disinfectant on a particular surface is another parameter.

Consider the intended purpose that the disinfectant was formulated to serve. Some cleaning and disinfection products intended for GMP environments may have been originally formulated for clinical or hospital settings that are more commonly highly soiled environments. Although these products are available for use within a cleanroom environment, these products will be formulated to address greater soiling and contamination than would be anticipated in the average pharmaceutical cleanroom. Therefore, it is likely that these types of disinfectants will contain a higher degree of surfactants and actives than are necessary to control and maintain a classified cleanroom; all contribute to the residue profile of the product.

Conclusion

Disinfectant residues pose various risks to the cleanroom environment, which is why the industry and regulatory groups have a renewed focus on the effective removal of their residues. End-users can combat disinfectant residues in many ways, such as implementing a routine residue removal programme, instituting "low-residue" disinfectant formulations, and focusing on operator training to control application.

References

1. EC, EudraLex, Volume 4, EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Annex 1, Manufacture of Sterile Medicinal Products, Draft (2020).
2. USP, *USP* General Chapter <1072> "Disinfectants and Antiseptics", *USP 42–NF 37*, Rockville, MD (2019).
3. *The CDC Handbook: A Guide to Cleaning and Disinfecting Cleanrooms*, T. Sandle Ed. (Grosvenor House Publishing Ltd, London, England, 2012). **PTE**

Excipient Science in Protecting Moisture Sensitive Drugs

ON-DEMAND WEBCAST

Aired: Wednesday, June 3, 2020

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

Presenters

Dr. Ali Rajabi-Siahboomi
VP & Chief Scientific Officer
Colorcon, USA

Dr. Jayesh Parmar
General Manager – Formulation Technologies
Colorcon, USA

Moderator

Rita Peters
Editorial Director
Pharmaceutical Technology

Event Overview

With heightened scrutiny by regulators and patient advocacy groups about the potential presence of impurities and degradants in medicinal products, it is imperative to effectively manage moisture, as it is known to be the main cause of degradation leading to impurities in solid-dose formulations.

Moisture issues occur before and beyond the packaging. During this webcast, experts will explore the role of core ingredient selection, manufacturing conditions, and on-dose packaging (film coating). Discover science-based practical solutions for formulators to manage the impact of moisture in the dosage form.

Key Learning Objectives

- Understand fundamental interactions between moisture and core ingredients
- Gain insight into how excipients can be used to help stabilize drug formulations
- Discover how to enhance stability from core to coating

Who Should Attend

- Formulation development scientists
- Analytical scientists
- Stability coordinators
- Production departments
- Regulatory departments

Sponsored by

Colorcon®

Presented by

Pharmaceutical Technology EUROPE

For questions or concerns, email
mdevia@mjhlifesciences.com

The Importance of Partnering for Bioanalytical Studies

Bioanalytical studies are an important aspect of biologic drug development that may necessitate partnering with bioanalysis experts.

Feliza Mirasol

Bioanalytical studies are an important aspect in biologic drug development because data from these studies are needed to define the characteristics of potential new biologic molecules. Bioanalyses data are also an important inclusion in regulatory filings, which drives the need for outsourcing partners who have in-depth experience in developing and conducting the appropriate bioanalytical assays for a project as well as experience interacting with regulatory authorities.

Pharmaceutical Technology Europe spoke with Robert Kernstock, PhD, director, Immunoassay Laboratory Services at ICON, and Neelanjan Bose, PhD, Director of Bioanalytical Chemistry at Emery Pharma, both contract research organizations (CROs), about the need for bioanalytical testing programmes and regulatory strategies for potential new biologics.

Importance of bioanalytical studies

PTE: Why is it so important to conduct bioanalytical studies during the development process of a new biological therapeutic?

Bose (Emery Pharma): Bioanalytical studies, which are designed to provide estimates for concentration of drugs and biologics in pre-clinical and clinic studies of the therapeutic molecule or their metabolites, are critical for various aspects of human clinical pharmacology, studies related to bioavailability (BA)/bioequivalence (BE) evaluation, and some nonclinical studies requiring concentration information for pharmacokinetics, toxicokinetics, or biomarkers. Bioanalytical work serves to supplement pivotal studies and aid in the decision-making process for approval, safety, and/or labelling of a drug or biologic; in short, without proper bioanalytical data, the therapeutic product would not be approved.

Kernstock (ICON): Beyond the regulatory requirements for conducting bioanalytical studies, the scientific importance of the data that these assays generate is invaluable. Bioanalytical assays provide information on certain safety aspects of the therapeutic in determining the maximum tolerated dose. Pharmacokinetic (PK) scientists use the data to determine exposure, half-life, and other pharmacological parameters, which are used to guide decisions on how often and how much of a therapeutic should be given for efficacy without undue toxicity.

Bioanalytical assays extend beyond simply measuring drug concentrations over time but are also used to assess drug efficacy by way of pharmacodynamic (PD) endpoints (i.e., biomarkers). Biomarker assay results may provide early indicators of efficacy, or even safety issues. They can also be used to stratify patients to predict responders or non-responders. Another key bioanalytical assay for biotherapeutics is the assessment of immunogenicity (both wanted and unwanted). For vaccine development, a positive immunogenicity result may be considered to be potential evidence that the vaccine is working as intended. Unwanted immunogenicity is much more complicated as the impact of anti-drug antibodies may impact the pharmacokinetics, efficacy, and safety, and has to be looked at down to the individual patient level.

Regulatory particulars

PTE: What type of data/information in particular do global regulatory authorities require from bioanalytical studies?

Kernstock (ICON): For any regulated bioanalytical study to occur, a validated method is required. FDA [the US Food and Drug Administration] has issued guidance documents detailing the scope of bioanalytical method validation required for PK/PD endpoints, but it is also important to consider other regional guidance documents (e.g., European Medicines Agency, Pharmaceuticals and Medical Devices Agency [Japan], Agência Nacional de Vigilância Sanitária

[Anvisa] [Brazil], etc.) when conducting method validations. The general assessments for method validation consist of accuracy, precision, selectivity/specificity, linearity, robustness, and stability.

Depending on the type of assay, certain parameters may be added or removed to meet the assays' context-of-use, and the analytical acceptance criteria may also vary. For immunogenicity assays, a statistical report or summary is required to justify your cut point(s). A well-described validation plan detailing the experiments and a priori acceptance criteria should be written and approved resulting in a bioanalytical report summarizing the experiments in tables, descriptions of deviations, and any pertinent conclusions. A quality statement from a quality assurance unit is typically included in the report for any regulated work.

Once the methods are validated, the sample analysis commences that follows bioanalytical plans and/or standard operating procedures (SOPS). The reported data typically contain information on subject (or animal) number, dose/treatment group, time point, and analytical result. A listing of assay performance characteristics, which include tables of assay control results, run summaries, and calibration curve results, are typically provided. Additional information, such as incurred sample reanalysis results and sample condition (e.g., hemolyzed) may also be included.

Bose (Emery Pharma): On a broader perspective, FDA requires PK, toxicokinetic, or biomarker concentration evaluation through bioanalytical studies. It is critical that the data [are] generated via phase-appropriately validated methods (i.e., the methods are 'fit-for-purpose') and in many cases adhere to [US] *Code of Federal Regulations* (*CFR*), 21, Part 58 (21 *CFR* 58), Good Laboratory Practice for Nonclinical Laboratory Studies (1). These involve much experimentation, data curation and storage, quality review, personnel training, and generation of SOPs—all related documentation should be available for review by FDA, along with the bioanalytical report.

On a global scale, requirements and expectations around regulated bioanalysis generally follow the same thread as FDA, but with specific regional differences. Most jurisdictions have independent bioanalytical method validation guidance.

Early development considerations

PTE: What types of approaches or strategies are best to plan out early on in the drug development process?

Bose (Emery Pharma): Bioanalytical studies are challenging to design and plan properly at the onset of the drug/biologic development process, as they involve samples from multiple pre-clinical species, tissue types, and human-derived samples with a diverse (and in most cases unknown) genetic and metabolic makeup. The bioanalytical methods need to be robust enough to work with the variability that comes with such a diverse set of samples.

It is thus important to anticipate these challenges early on while in the R&D phase, and develop sample preparation protocol(s) and method(s) that can work with such diverse types of samples, varying sample amounts, and be able to account for less-than-ideal sample handling during shipment and storage. It is also preferable to start the method validation process early that ensures that the data are reliable. While FDA guidance suggest that the level of validation should be appropriate for the intended purpose of the study, it is often helpful and cost-effective in the longer term to expand validation a bit beyond that so as to get better prepared for the later development process.

Kernstock (ICON): Early in clinical development, it is important to understand the context-of-use for your bioanalytical assays, what type of therapeutic you have, and how your clinical studies are going to evolve. For instance, if you think your lowest effective concentration of your therapeutic is 500 µg/mL (trough levels), then developing an immunogenicity assay that is tolerant to high levels of therapeutic would be a critical consideration early in development. Whether or not your Phase I study is going to be in patients or healthy volunteers is another important consideration.

Similarly, the disease-state biomarker assays may require different sensitivities than if it was in a normal population. Understanding the sensitivity requirements for your PK assay is also important. Intravenous administration of the therapeutic may require a less sensitive assay in your serum samples, whereas an ocular injection of the therapeutic will require a very sensitive serum PK assay to measure circulating drug levels. When conducting a preclinical toxicology study, the PK assay may not need a very low limit of quantitation since the therapeutic will be dosed at high(er) levels, and the immunogenicity assay may not have a confirmatory tier as an immune response is expected from a foreign protein. Perhaps you have a novel cell therapy, and a flow cytometer is used to collect 'cellular kinetics'. This means special handling instructions to analyze the samples within the demonstrated stability window, or the use of additives in the collection tube to stabilize study samples.

Best practices

PTE: Are there any 'best practices' procedures or steps you can recommend for beginning a bioanalytical study programme for a new therapeutic?

Kernstock (ICON): There are a few best practices to consider, including identifying an appropriate blank matrix pool, testing disease-state selectivity as early as possible, and having a good supply of

excellent critical reagents identified and appropriately characterized. Addressing these considerations will go a long way to avoiding future analytical headaches. Understanding the mechanism of action of your drug and how it relates to the sample. For instance, if the drug target is a soluble cytokine that is abundant in serum and plasma, don't be surprised if your selectivity experiment fails. More importantly in that case, what matrix pool are you using for your standard curve? Is the pool stripped of the cytokine, or did you use a surrogate matrix that doesn't contain the interfering molecule?

Bose (Emery Pharma): FDA's 2018 guidance on bioanalytical method validation (2) is a great place to start. Additionally, while still in draft form, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) M10 *Bioanalytical Method Validation* guidance (3) has been a decade-long collaborative initiative of analytical sciences and regulatory agencies around the globe; it is among the best resource currently available to plan for, and design bioanalytical studies.

Expert partnership benefits

PTE: Why is it important, or even necessary, for some biopharma companies to partner with an outsourcing partner for the purpose of bioanalytic studies?

Bose (Emery Pharma): Method development in bioanalytical studies is a black box to many, requiring intense training and somewhat intuitive understanding of how analytes behave in diverse biological matrices. It is important to note that, unlike standard analytical studies, bioanalyses involve highly complex and largely undefined biological matrices, with likely millions of compounds that can interfere with specific and accurate concentration evaluation.

The required knowledge and expertise to successfully navigate bioanalytical studies may not be acquired quickly in-house, particularly when the regulatory landscape around bioanalyses changes regularly. Additionally, most bioanalytical studies are moving towards mass spectrometry (MS)-based analyses, which involve instrumentation that is too expensive to acquire for many companies and require specialized training for use and data analyses.

Furthermore, most bioanalytical studies involve conducting the work under good laboratory practice (GLP), thus, the analytical laboratory must adhere to 21 *CFR* 58. This requires companies having a quality system in place, regular audit of the facility, maintaining documentation, training records, instrument qualification, and so on, all of which often becomes too cumbersome for many biopharma companies with limited operational budget. It is thus much simpler to partner with an outsourcing contract research organization (CRO) with expertise in bioanalyses, which already have an established quality system and the required experience in interaction and data presentation to FDA and other regulatory bodies.

Kernstock (ICON): Partnering with contract laboratories can be extremely beneficial, and there are a number of reasons for doing so. The capacity in your own lab may have been exceeded and the need to outsource work to a partner lab would be necessary. Your own lab may be lacking in certain analytical equipment or experience, and a contract lab would be able to provide that service and expertise. CROs are particularly useful to smaller biotechs as the CROs can provide valuable consulting services and an expanded scope of service offerings such that they can be a 'one-stop-shop' for all of your bioanalytical needs. CROs have a very deep understanding of bioanalysis based on the number and diversity of assays they have developed. This is reflected in their scientific expertise as well as their understanding of global regulatory practices, since they are more frequently audited by multiple regulatory agencies; these factors end up benefitting all of their clients.

References

1. CFR Title 21, Part 58 (Government Printing Office, Washington, DC).
2. FDA, *Bioanalytical Method Validation Guidance for Industry* (CDER, May 2018).
3. ICH, M10 *Bioanalytical Method Validation, draft version* (26 Feb. 2019). **PTE**

More on bioanalytics

For more on bioanalytics, read the following articles on *PharmTech.com*:

- **Detecting Contamination in Cell Therapies**
  www.PharmTech.com/detecting-contamination-cell-therapies
- **Building Data Quality In Generates Quality Data Out**
  www.PharmTech.com/building-data-quality-generates-quality-data-outensuring-quality-data-process-monitoring-and-control
- **Implementation of Autocorners Algorithm for Retrospective Process Monitoring**
  www.PharmTech.com/implementation-autocorners-algorithm-retrospective-process-monitoring
- **The Benefits of Outsourcing Stability Testing**
  www.PharmTech.com/benefits-outsourcing-stability-testing

Dry Powder Inhalers: Key Considerations for Combination Product Development

ON-DEMAND WEBCAST

Aired: Wednesday June 24, 2020

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

Presenter

Andreas Meliniotis
Director, Device Development
Vectura Group plc.

Moderator

Rita Peters
Editorial Director
Pharmaceutical Technology

Event Overview

Dry powder inhalers are an important technology for the delivery of therapies for both respiratory and non-respiratory disease areas. The development of such drug-device combination products is highly complex and several factors can have a significant impact on the success of the program. This webcast discusses the key considerations to reduce risk when developing a DPI product from early clinical trials through to scale-up, and provides insights for both novel and generic development programs.

Key Learning Objectives

- Understanding different options for dry powder inhaler technology
- Key considerations for DPI product development
- Manufacturing strategies for seamless transition and scalability from lab to commercial scale
- Relevant regulatory guidance and risk-based approaches to process development and device design
- Device strategies for novel and generic inhaled development programs

Who Should Attend

- Pharmaceutical and biotech companies developing inhaled medicines (new chemical entities and/or generics)
- Manager/Director/Senior Director/Vice President/SVP, R&D
- Manager/Director/Senior Director/Vice-President/SVP, Product Development
- Manager/Director/Senior Director/Vice President/SVP, Procurement and Sourcing
- Manager/Director/Senior Director/Vice President/SVP, Inhaled Device Development

Sponsored by VECTURA

Presented by Pharmaceutical Technology EUROPE

For questions or concerns, email mdevia@mjhlifesciences.com

Intelligent Packaging Promotes Interaction with Patients

Technology advances improve online productivity, authenticate product, and boost patient adherence.

Hallie Forcinio
is *Pharmaceutical Technology Europe's* packaging editor, editorhal@cs.com.

With the evolution of interactive "intelligent" technologies such as near-field communication (NFC), radio frequency identification (RFID), and two-dimensional barcodes, patients can interact with pharmaceutical products in unprecedented ways. Such "smart" packaging offers the potential to improve patient adherence, safety, and therapeutic success.

Tracking drug products

"[Using smart packaging,] wrong applications are prevented, counterfeits can be reliably detected and rejected, processes are automated and secured, and relevant information is available at the point of use," explains Arne Rehm, product manager RFID/NFC Solutions at Schreiner MediPharm. The technology also supports traceability throughout the processing, packaging, and distribution process as well as implementation of Industry 4.0.

Rehm reports, "UHF [ultra-high frequency] RFID offers the advantage of being able to track a large number of individual products or packaging units at once. For example, all products can be recorded within a few seconds for inventory monitoring, which is far superior to optical or manual processes in speed and accuracy." NFC allows large amounts of data to be stored almost invisibly on the product. It works particularly well in situations where graphic space is scarce and is well-suited for labels for small containers with narrow radii. "A key aspect here is certainly the high level of digital counterfeit protection that can be provided at the same time," says Rehm.

He notes, "RFID and NFC labels have become more powerful and cheaper in recent years. In addition to the greatly improved reading range of new chip generations in the UHF range, various new functionalities have been integrated, from security to sensor technology."

A DataMatrix code is the basis for Smart Containers from SCHOTT North America. Laser marking a unique code on the bottom of each vial enables traceability throughout the entire manufacturing process. The unique DataMatrix code is applied during vial manufacturing. After hot forming, advanced laser technologies create the code and inextricably link it to the container. Coded containers may be scanned at various points during the fill/finish process, including after loading, washing, depyrogenation, filling/checkweighing, stoppering, crimping, and labelling, as well as before secondary packaging. "To ensure ease of use, the Smart Container code can be read by conventional camera equipment," says Diana Löber, global product manager vials at SCHOTT. "Moreover, as the unique identifier is positioned at the bottom of a vial, there is no need to install multiple cameras or to turn the container," she explains.

Scanning the code supports implementation of Industry 4.0 and helps pharma manufacturers unlock the power of machine vision and big data analytics by enabling optimal monitoring and traceability of the vial manufacturing and fill/finish processes. "This means that the technology supports and improves reject management and line clearance, reducing the risk of mix-up and optimizing lyophilization processes and container-based targeted recalls," says Löber.

Caregivers and patients also benefit. With a unique code on each vial, if a product quality problem arises and a recall is necessary, it is easier to identify which vials need to be recalled and remove them more quickly from the marketplace. "This ensures patient safety and high quality up until the drug is administered," concludes Löber.

For labelled containers, particularly vials and syringes with small radius curves, Schreiner MediPharm offers labels equipped with RFID technology, which relies on flexible electronics from PragmatIC instead of rigid silicon chips. "Until now, conventional RFID/NFC solutions have mainly been utilized in high-value use cases," said Dr. Thomas Schweizer, president of Schreiner MediPharm. "Due to the cooperation with PragmatIC, we are now able to offer attractively priced, smart pharma

labels even for high-volume and low-cost medicines," he reported (1).

For smart cartons, a partnership between Schreiner MediPharm and Edelmann, a folding carton producer, incorporates digital features for fast, reliable product authentication and product protection. BitSecure copy detection technology prints a small, digital security feature based on a high-resolution, random pattern whose intricate details are not discernible by the naked eye. The pattern can be authenticated quickly using a smartphone or handheld reader and analyzed via related software. A closure seal with an integrated NFC chip and an irreversible void effect combines analogue and digital technologies, offering double tamper evidence. Before the seal's initial opening, the user reads the NFC chip using a smartphone and related app to confirm product authenticity. Opening the package without peeling off the seal causes it to break along the perforation. If the NFC chip is read again, the smartphone will warn the packaging has been opened previously. The chip also may link the user to interactive applications for patient information and assistance (2).

Sensors for inhaled products

For inhaled products, which are sometimes difficult to dispense correctly, Sanner and Amiko Digital Health are partnering to equip dry powder inhalers with advanced sensor technology. Amiko's Respiro platform tracks device usage in real-time and facilitates adherence by ensuring the medication is administered following the right technique. "Our digital health tools assist healthcare professionals and empower patients to achieve better respiratory treatment results," said Duilio Macchi, chief executive officer and co-founder of Amiko, in a press release (3).

Contin. on page 41

Beyond packaging

Smart technologies are not limited to packaging but also can be incorporated directly on solid dosage forms. One technology from TruTag Technologies adds an invisible barcode to each pill. It relies on functionalized microparticles of silica, a US Food and Drug Administration-approved pharmaceutical excipient, which forms an invisible, edible, and high-security optical 3D barcode, known as TruTags. In the case of tablets, TruTags barcodes are added as part of the existing film coat (via standard pan-coating processes) or applied through an immediate-release clear topcoat. "TruTags do not impact the release profile or stability of the product nor do they impact tablet elegance," reports Dr. Michael Bartholomeusz, CEO at TruTag Technologies. In the case of capsules, TruTags barcodes are mixed into existing inks and applied directly on capsules using a standard printing process.

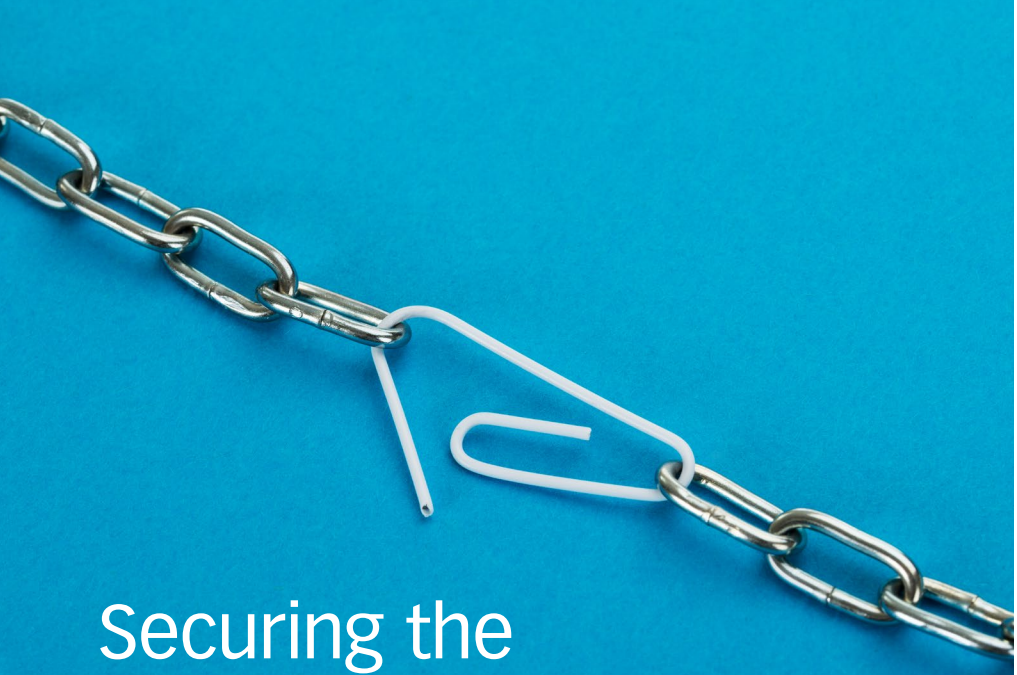
TruTags barcodes can be read by a proprietary, enterprise-level portable or handheld unit or a mobile phone equipped with a downloadable app. Bartholomeusz says, "While this phone-based reader can also be used by the brands and manufacturers, it is especially useful as a consumer tool to ensure the authenticity of the product … and as a patient interaction tool for the pharma companies."

According to Bartholomeusz, "the TruTag solution can bring profound value to several stakeholder groups—specifically in the area of quality, safety, and security." He explains, "For patients, the adoption of TruTags on tablets and capsules offers a tangible path toward the mass digitalization of medicines and a future where patients can interact directly with their medicines via cell phones. The potential value of this interaction has been well-documented and includes the ability to: ensure patients are getting the correct product in the correct dosage; communicate prescribing information; monitor and influence patient adherence; and record adverse events and link them directly to specific product batches ([for a] risk evaluation and mitigation strategy)."

TruTags barcodes facilitate instant and unequivocal identification of products anywhere in the supply chain, which is critical when there is a suspect event. It enables manufacturers and brand owners to determine whether the problem is related to an internal quality failure, an external supply chain issue, or third-party criminal actions such as counterfeiting, diversion, or sale of expired products. Knowing the cause of the problem allows a pharmaceutical company to take specific corrective action. "While efforts to serialize packaging certainly help with this process, once tablets and capsules are removed from their original packaging, serialization is rendered ineffective," adds Bartholomeusz. Barcoded tablets or capsules can be identified throughout the product's entire lifecycle.

In addition, on-product marking offers benefits for clinical trial administrators, payors, regulators, and law enforcement. Tagging materials with TruTags barcodes permits instant, unequivocal authentication at any stage in the clinical trial and reduces the chances of error in the allocation and administration of medication particularly in double-blinded trials. This ensures "the right patients are taking the right drugs at the right dosage without impacting blinding," explains Bartholomeusz.

For payors, he says, "The adoption of an on-dose sensor such as TruTags offers the potential for improved patient communication and intervention where patients become non-compliant. Improvement in adherence levels will improve treatment efficacy and reduce losses in the healthcare system." For regulators and law enforcement, he concludes, "The adoption of an on-dose marking for controlled prescription drugs (such as opioids) … would allow enforcement agents to more effectively identify drugs and prosecute [wrong-doing]."



Securing the Supply Chain

The global COVID-19 pandemic has highlighted the need for the pharmaceutical industry to strengthen its supply chain.

Felicity Thomas

The global population is ageing, the prevalence of chronic conditions is rising, and medicines are becoming more widely accessible globally, which are all leading to greater demand and growth in pharmaceuticals and pharmaceutical ingredients. According to market research, the API market is expected to experience a compound annual growth rate of 6.7% in the forecast period of 2020–2027 (1).

Production of pharmaceutical ingredients has gradually shifted over the course of several decades to Asia, rather than Western-based countries, which has been driven largely by cost savings. This global access to supply has been largely beneficial to the industry and patients alike, expanding access to medicines for many more people around the world.

A gradual shift

"Beginning in the 1980s, the pharmaceutical industry experienced a gradual shift in the manufacturing of some APIs and finished drug products from Western-based countries to China and India. This transition not only better served growing regional demand across Asia for high-quality healthcare products, but helped to reduce drug manufacturing costs," confirms Dr. Andreas Meudt, vice-president of exclusive synthesis for the Health Care business line of Evonik. "The low-cost benefits of manufacturing APIs and drug products within Asia has helped to turbocharge the generic drug industry and expand global access to a range of lower-cost medication options," says Meudt.

One of the most obvious changes to the pharmaceutical manufacturing supply chain has been the increased reliance on external partners for the development and commercialization of products, notes Lonnie Barish, vice-president, business development and marketing, Bora Pharmaceuticals. "The shift has been positive for patients, allowing consumers to benefit from lower cost drugs from US Food and Drug Administration (FDA) and European Union (EU) inspected current good manufacturing practice (cGMP) facilities while still maintaining quality, innovation, and allowing efficient drug development and commercialization routes," he says.

"Companies have been engaging offshore, international manufacturing partners for several reasons. The initial drivers have been accessing lower cost supplies and proximity to emerging markets," Barish continues. "While managing costs has been a central theme, access to capacity, technical capabilities, and cutting-edge science at high quality CGMP facilities have also prompted many offshore partnerships, especially for more commoditized and high-volume products."

Through the purchase of former 'Big Pharma' facilities, many offshore contract development and manufacturing organizations (CDMOs) are now capable of offering high levels of product quality, Barish stresses. "However, the nature of pharma is increasingly global, and whether offshore or not, CDMOs must compete internationally on a number of challenging fronts," he adds. "If a supplier can offer flexible scale and capacity, efficient processes, and specific technologies and capabilities all designed to optimize manufacture of a drug product, then that CDMO is already providing distinct advantages."

In addition to the move to offshore manufacturers, companies have also been outsourcing more complex APIs and drug products to specialized contract manufacturing organizations (CMOs) and CDMOs. "One reason for this change is that an increasing number of APIs are highly complex, with many requiring more than a dozen steps for synthesis. Most require a range of advanced technologies that go far beyond the realms of classical chemistry," explains Meudt. "In many cases, there are only a few CMOs in the

world that have the necessary core competencies to manufacture such complex APIs. These CMOs tend to have a Western-centred global manufacturing network. In addition to these CMO sites providing proximity to core regional healthcare markets, pharmaceutical companies also benefit from the reliability of these CMO partners when it comes to quality consistency, supply security, and intellectual property protection."

Strategic changes

However, in the advent of a global pandemic, such as that of COVID-19, potential vulnerabilities in the current pharmaceutical supply chain have been highlighted (2). In a position paper from the European Fine Chemicals Group (EFCG), concerns on the potential threat of medicines shortages as a result of the dependency on Asian countries for APIs, which is stated as being close to 80% for EU medicinal products, were laid out (3). A possible three-part solution to preventing drugs shortages in the future was specified in the paper, including a plan to "bring critical off-shore technology back to Europe" (3).

Even in cases of less complex APIs, and with some products being considered essential to the provision of patient care, a shift in strategy is being seen across the industry, asserts Meudt. "Rather than seeking short-term, price-sensitive supply contracts with a range of CMOs, many companies are instead prioritizing long-term supply relationships with a short-list of preferred CMOs," he says. "While manufacturing cost will always be important, pharmaceutical companies are increasingly selecting their long-term CMOs based upon other factors including security of quality and supply, regulatory track record, data control, and environmental sustainability. Regardless of geography or price, customers want CMOs that can deliver long-term value and peace-of-mind."

COVID-19 has elevated the issue of API and drug product supply further to industry and governmental bodies, Meudt continues. "Healthcare systems are coming to recognize that domestic or regional access to API manufacturing, together with national safety stocks for essential medicines, must be a strategic imperative to maintain continuity of supply during future pandemics or other globally disruptive events," he says.

India and China are currently in a strong position as many of the necessary raw materials that are required to manufacture certain APIs are only available in those regions. "However, it is becoming increasingly apparent to many European and North American leaders that they must re-evaluate their regional API, intermediate, and drug manufacturing capabilities to further reduce the risk of critical supply chain breakdowns occurring in the future," Meudt asserts. "Close interaction between pharmaceutical companies, CMOs (such as Evonik), industry groups, and governments will be required to ensure that the regional supply of APIs to local healthcare systems can be better maintained even during periods of global crisis."

"The current COVID-19 pandemic has re-focused the spotlight on the preparedness and resiliency of pharma's contract manufacturing and API supply chains. Offshore or domestic suppliers are going to have to redouble their efforts to assure reliability, redundancy, and quality," emphasizes Barish. "Going forward, I think there will be significant pressure on pharmaceutical companies to strengthen their own supply lines, obtaining secondary sites, and additional partners."

Furthermore, increasing regulatory scrutiny is another factor affecting outsourcing decisions by pharmaceutical companies. "The ability of a CMO to prevent product contamination, avoid occupational exposure to highly potent APIs, minimize emissions, and maintain the integrity of pharmaceutical manufacturing data are all growing areas of scrutiny," Meudt confirms.

Transitioning activities

Typically, a pharmaceutical company will employ one of two potential strategies to transfer manufacturing activities from one region to another, explains Meudt. "For APIs used with already commercial products, companies will undertake a multi-year process to shift at least some portion of the manufacturing to an alternative local CMO," he says. "Although, it is more common that companies simply revise their manufacturing strategy for pipeline drug products before they reach late-stage clinical trials and commercial approval. Either way, the company will typically have a shortlist of prospective CMO candidates within a local region that have the necessary competencies, capacity, and regulatory track record."

Transference of API manufacturing from a CMO in one site to another in a different region can aid in the improvement of supply continuity, but Meudt stresses that this sort of change should only be done with a CMO that can demonstrate a track record in areas, such as capacity expansion, process and equipment harmonization, and quality management, so that any potential risks are minimized. "It can further help to reduce supply chain risk if the CMO is either backward integrated in the production of some of the associated raw materials required to manufacture the API or has experience in the qualification of other prospective suppliers," he adds.

It can take several years for a company to transfer manufacturing from one region to another, typically between three to five years, notes Meudt. During the transition period, companies must perform the review and selection process for a new CMO partner, complete audits and technical transfer, as

well as implement the processes to support scale-up to the required clinical or commercial volumes. "Around two years are also required to complete the regulatory approval process," Meudt says. "While the COVID-19 situation may incentivize companies and governments to try and accelerate such transfers, it is of critical importance that key process steps are maintained to the highest quality and regulatory standards. Qualified teams with technical experience in the technical transfer process for such APIs and drug products are important."

A global and complex system

As the current global pandemic has made clear the critical issue of API and drug product manufacturing, there have been concerns raised by industry officials globally about the potential risks of losing access to essential medicines. "Comments from officials within several governments worldwide indicate that countries could in future choose to prioritize the supply of locally manufactured APIs and drug products for use within their own healthcare systems," states Meudt. "Fortunately, the global pharmaceutical supply chain appears to have held up well to-date due to normal stockpiling strategies and the continued operation of core manufacturing and logistical activities."

Given the fact that the pharmaceutical supply chain is a global and highly complex system, Meudt iterates that the current status quo of ingredients manufacturing will largely stay the same. "Pharmaceutical manufacturing capacities will continue to expand across North America, Europe, China, India, and other markets to meet the growing healthcare demands of local populations," he notes. "In parallel, CMOs within each country or region will continue to specialize in their respective areas of core competence."

Agreeing, Barish adds that there will inevitably be a place for both onshore and offshore manufacturing simply due to the global nature of the pharma industry. "There will always be some products, controlled substances for example, that cannot be produced in certain facilities in a specific market," he says. "Other reasons, such as drug strategy and cost will have an impact as to where manufacturing takes place. A novel drug with a smaller batch size, for example, may not be suited to offshore manufacture as the economies of scale will not be beneficial."

Asia is expected to continue to be a primary source for the world's generic APIs and drug products; however, Meudt specifies that there are also expectations that some companies, with a strong manufacturing presence in Asia, may seek to further reduce short-to-medium term supply chain risk by having a larger percentage of their total global production requirements either made, or stockpiled, in Europe or the United States. "For new complex APIs or highly specialized drug products, it is expected that most production will continue to occur at established sites that have the right capabilities, quality culture, and record for project execution," he adds. "This shift not only reflects the need to reduce regulatory risk and improve proximity to key healthcare markets, but the advanced technologies and precise processes that CMOs need to possess to successfully commercialize such APIs and finished drug products at desired levels of quality."

Simultaneously, Meudt predicts that regional and national governments will further encourage companies to increase the manufacture of essential APIs and drug products at local sites to ensure preparedness in any future pandemics. "It is likely that many governments will review what financial incentives can be put forward to accelerate investment by pharmaceutical companies and CMOs to further strengthen regional capacities," he says.

"As we move into a post-COVID-19 world, managing supply chain risk must become integral to business planning, risk management, and long-term drug strategy," summarizes Barish. "It is therefore important to engage with partners that offer logistical advantages, whether they be domestic or offshore, and can contribute to the security and reliability of the drug supply."

References

1. Grand View Research, "Active Pharmaceutical Ingredient Market Size, Share, and Trends Analysis Report by Type of Synthesis (Biotech, Synthetic), by Type of Manufacturer (Captive, Merchant), by Type, by Application, by Region, and Segment Forecasts, 2020–2027," *grandviewresearch.com*, Market Analysis Report (February 2020).
2. EFCG, "API Manufacturers Address Critical Medicines Shortages Leaving Europeans and Americans Vulnerable and Dependent on Asian Supplies," *efcg.cefic.org*, Press Release, 12 March 2020.
3. EFCG, "Addressing the Acute and Complex Challenge of Medicine Shortages," *efcg.cefic.org*, Position Paper (January 2020). **PTE**

Ad Index

COMPANY	PAGE
Catalent	44
Colorcon	31
Council of Europe EDQM	2
Emergent BioSolutions	23
Ligand	9
PDA Europe	17
Peter Huber Kältemaschinenbau AG	13
Shimadzu Europa	43
Vectura	35
Veltek Associates, Inc.	7

Operations — *Contin. from page 37*

The partners have designed the plastic part that houses the electronic components, completed prototypes, and set the stage for production. "The engineering of these plastic parts for serial production was quite a challenge," notes Ursula Hahn, head of Product Management at Sanner. Although commercialization is likely to take some time due to the many sales channels and stakeholders involved, Sanner is confident the add-on will be accepted and successful. In addition, Hahn predicted, this technology "…will certainly be transferred to further areas of application in the near future."

Another respiratory product partnership, this one between Aptar Pharma and Sonmol, an adherence specialist based in Shanghai, seeks to increase patient engagement and provide better treatment outcomes for asthma and chronic obstructive pulmonary disease. The resulting Smart Inhalers will be marketed primarily in China and other Asian markets (4).

Blister pack monitoring

One intelligent packaging technology that's already commercial is the I-Smart wallet from Schreiner MediPharm, which is based on the child-resistant and tamper-resistant Dosepak carton from WestRock. A microchip applied to the blister pack uses NFC to send a signal to a smartphone to alert the patient to take his/her medication and monitors adherence. Janssen Cilag, the winner of the award in the Equipment Innovation Category in the International Society for Pharmaceutical Engineering's 2019 Facility of the Year Competition, runs the I-Smart wallet on equipment from C-Matic and ECCT. On the line, one machine automates and performs virtually every step in the packaging function. Capable of being remotely controlled, the line is designed to be flexible enough to run a range of dosage forms and blister designs for quick changeover and speedy product launches. The result is shorter cycle times, lower labor and material costs, higher capacity, and enhanced process compliance and reliability (5).

For the patient, medication intake is electronically documented (time and dose). "When the patient pushes a tablet out of the blister, data are generated in real-time, such as the time of removal, the dose or, optionally, the respective cavity," explains Uwe Braun, product manager of Patient Compliance Monitoring Solutions at Schreiner MediPharm. These data are automatically stored in the package and transmitted to a database via a smartphone app or a reader using NFC or Bluetooth.

For Janssen Cilag, the I-Smart Wallet was customized for its drug. "All electronic features were integrated without any change of the existing package design," reports Braun. As a result, end-user convenience could be assured because the blister pack use and push-through forces remained unchanged.

Inline readers on I-Smart wallet production lines and pharmaceutical packaging lines verify all functionalities are working before finished packages are released. "Additionally," Braun says, "specific data such as lot number, ID codes, and medication name can be stored on the chip inside the package. Finally, a full digital track-and-trace system with security features can be added optionally.

The future

Smart packaging will continue to enhance patient safety and counterfeit protection. Hahn predicts, "Track-and-trace will also develop further to ensure a more transparent supply chain." She also believes demand for integrated smart devices will expand so caregivers and patients will know when a dose was taken and that it was administered correctly.

With technology evolving and prices declining, "We … see many opportunities for RFID and NFC labels," adds Rehm. He predicts, "The possibility of integrating sensor functionalities (temperature, humidity, etc.) will enable a large number of new applications at unit level."

References

1. Schreiner MediPharm, "Schreiner MediPharm and PragmatIC Announce Strategic Partnership for Smart Pharma Labels," Press Release, 5 Dec. 2019
2. Schreiner MediPharm, "Schreiner MediPharm and Edelmann Group Develop Demo Version of Smart Packaging Solution," Press Release, 28 March 2019.
3. Sanner, "Sanner and Amiko Partner to Develop Digital Solutions for True Medication Adherence," Press Release, 13 Feb. 2018.
4. AptarGroup, "Aptar and Sonmol Partner to Develop Digital Platform for Respiratory-Related Therapies," Press Release, 21 April 2020.
5. ISPE, "2019 Category Winner for Equipment Innovation Janssen Cilag SpA," *www.ispe.org*, iSpeak Blog, 18 July 2019. **PTE**

Ask the Expert — *Contin. from page 42*

"CDER [the Center for Drug Evaluation and Research] recommends that in taking such measures, firms plan to carefully monitor indicators of product quality to note any unfavorable trends or shifts as a result of the implementation of the Plan. CDER also recommends that firms retain samples for testing at a later date in cases where testing is reduced or omitted because of lack of resources" (2).

While it is important to act quickly and efficiently during a crisis, the process and product must still be manufactured in accordance with appropriate regulatory requirements. Before you make any drastic changes to SOPs or eliminate process steps you need to read the FDA guidance document, prepare a proper risk assessment, and justify why the removal of the requirement from the SOP does not impact patient safety and product quality. The documentation you provide and the assessments you perform to address some of the extraordinary situations facing you and your colleagues in the effort to produce necessary medical drugs should give you confidence that you have acted appropriately and within the regulations to fulfil patient needs.

References

1. EMA, *Guidance on the Format of the Risk Management Plan (RMP) in the EU–in Integrated Format*, EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2 Human Medicines Evaluation (EMA, 31 October 2018).
2. FDA, *Draft Guidance for Industry: Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products* (CDER, March 2011). **PTE**

Following Guidelines During a Crisis

Products must be manufactured in accordance with appropriate regulatory requirements, even during a pandemic, says Susan J. Schniepp, executive vice-president of post-approval pharma and distinguished fellow, Regulatory Compliance Associates.

Q. I am in the quality department and am responsible for investigations, and I have been working from home due to the COVID-19 pandemic. The investigation standard operating procedure (SOP) requires me to perform face-to-face interviews with people and to complete the investigation within 90 days. Working remotely to conduct the interviews is taking much longer, and I am afraid I'll miss my deadlines. Could I eliminate the interview requirement until I am able to return to the facility?

A. I certainly understand the challenges of trying to conduct remote face-to-face interviews and the need to try and streamline processes during times of crisis, but now is not the time to take unnecessary, undocumented shortcuts with any of your procedures. My recommendation is that you step back from your frustration with the situation. Focus on the elements you need to conduct a thorough investigation and look at finding alternative means to fulfil the SOP requirements as defined in your contingency plan. If you do not have a contingency plan in place, you should immediately develop one and include appropriate risk-based information. The European Medicines Agency has a guidance on the format for a risk management plan that might help you get started on this activity (1).

To determine how you might make your operations more efficient during crisis times, I further suggest you review the US Food and Drug Administration's (FDA's) draft guidance titled, *Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products* (2). The guidance document states, "This guidance is intended to encourage manufacturers of medically necessary drug products (MNPs) and any components of those products to develop contingency production plans to use during emergencies that result in high absenteeism at production facilities" … "The guidance provides considerations for the development and implementation of a plan for production of MNPs during a crisis, including specific elements that should be included in the plan."

The contingency plan you develop should include information regarding the company's prevention and risk mitigation processes. The guidance states, "These preventative measures can include steps to prepare personnel such as:

- "Educating employees on topics such as, in the case of a pandemic, personal hygiene (hand washing and coughing and sneezing etiquette), social distancing, and appropriate use of sick leave
- "Encouraging employees to get immunized as appropriate by providing information on local vaccination services or by offering on-site vaccination services, if reasonable
- "Providing information for and encouraging employees to develop family emergency preparedness plans
- "Reviewing CGMP [current good manufacturing practice] regulations regarding appropriate sanitation practices and restriction of ill or sick employees from production areas (see 21 *CFR* [*Code of Federal Regulations*] 211.28)" (2).

The guideline also recommends "that manufacturers, when evaluating activities that might be reduced in frequency, delayed, or substituted by a suitable alternative, first identify and consider activities that are intended by the CGMP regulations to provide controls not connected with the manufacturing of any specific batch. Examples include:

- "Production equipment routine maintenance
- "Utility system performance checks and maintenance (e.g., air temperature, lighting, compressed air)
- "Environmental monitoring of facilities such as cell culture, harvesting, and purification rooms during production
- "Stability testing for certain drug products and components
- "Periodic examinations of data and of reserve samples" (2).

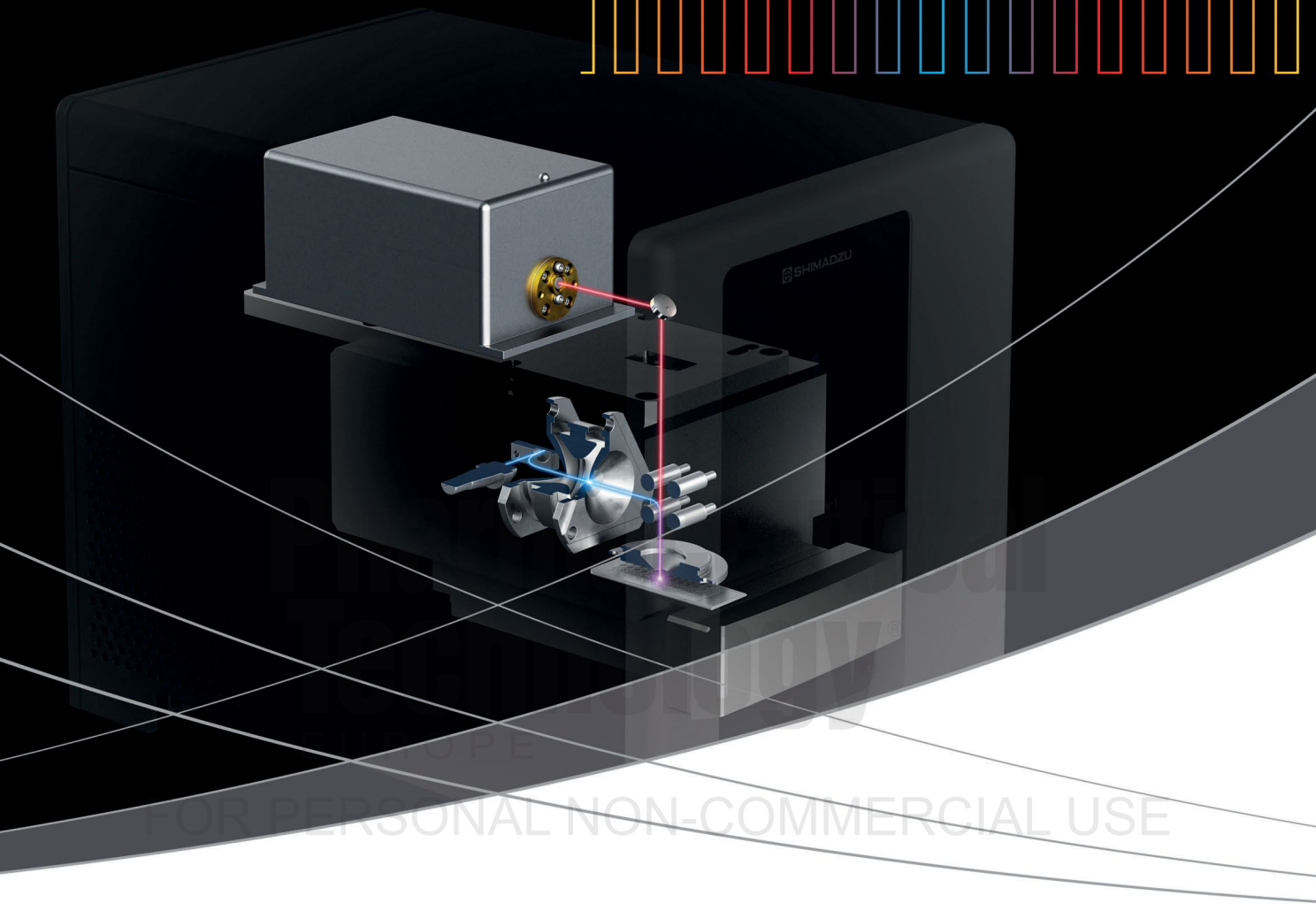
In addition, the guideline also recommends that, "If the demand for MNPs cannot be met by the measures described above, manufacturers can consider reducing activities that are more directly connected with batch manufacturing or a product accept/reject decision provided that they have a documented rationale or risk assessment to show that the proposed changes will not unacceptably reduce assurance of product quality. Examples include:

- "Not requiring second-person verification of activities for less critical steps (though we recommend a self-check of work)
- "Reducing the number of samples for labour-intensive laboratory testing
- "Forgoing an in-process test to assure adequacy of mix, particularly when making successive batches, where the risk is judged to be low in terms of drug safety and efficacy
- "Delaying completion of deviation investigations of minor events.

Contin. on page 41

SHIMADZU
Excellence in Science

50th MS anniversary 1970-2020



Entering the digital age in MS

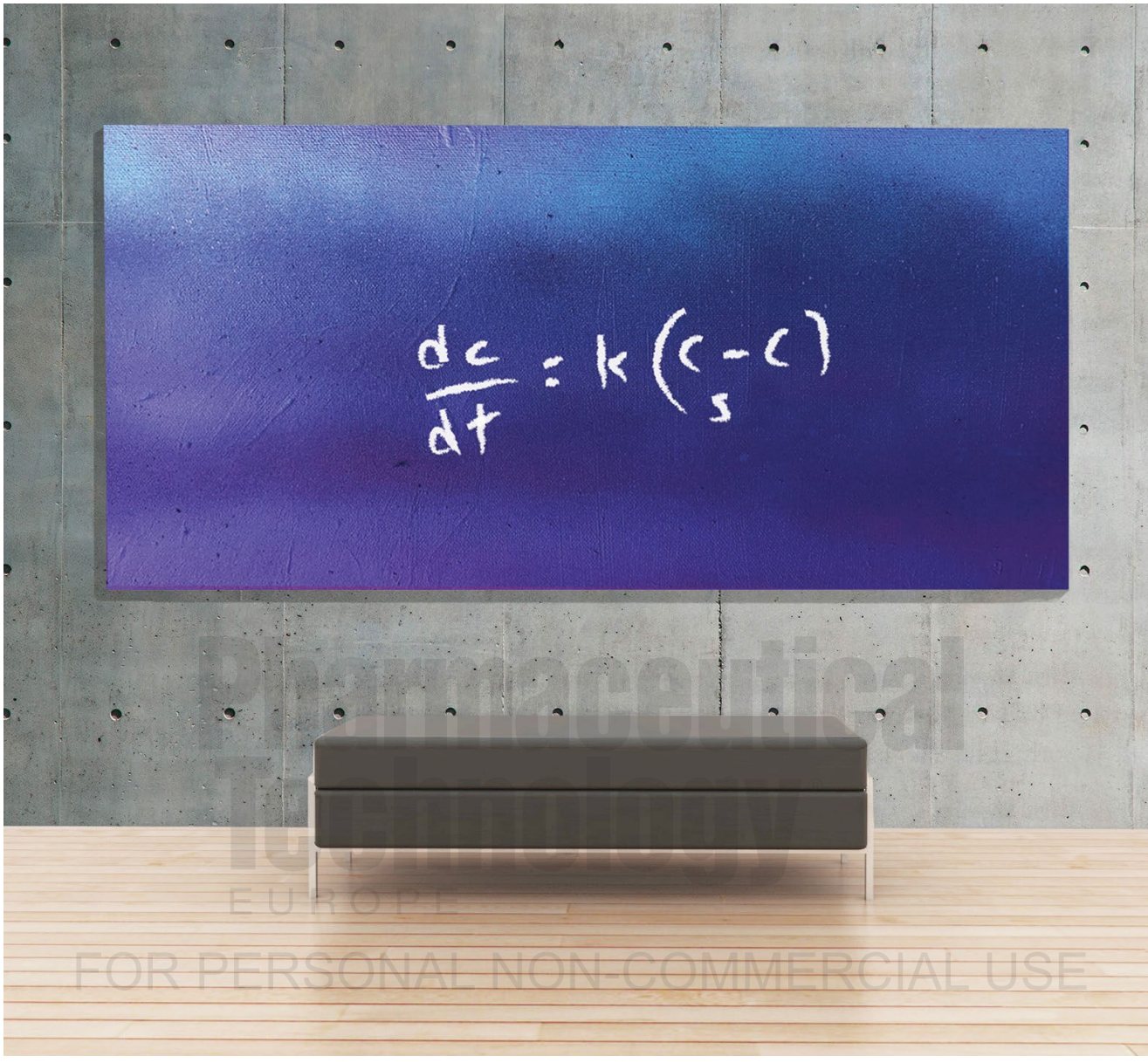
Introducing the MALDImini-1 digital ion trap mass spectrometer

Shimadzu's first-of-its-kind MALDImini-1 digital ion trap mass spectrometer fits in a space the size of a piece of paper, allowing installation in places where mass spectrometers could not previously fit. It enables ion trapping up to 70,000 Da and the MS/MS and MS^3 functionality of the digital ion trap allows researchers to carry out comprehensive structural analyses with ease.

- **Fast, simple setup allows for a more convenient workflow**
- **Software allows switching quickly and easily between MS, MS/MS and MS^3 modes for seamless analysis**
- **Only device capable of MALDI-MS^n in this compact size**
- **Space-saving lightweight design fits anywhere**

MALDImini-1

www.shimadzu.eu/maldi-dit



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) **EUR** 00800 8855 6178 catalent.com/solubility