Investments Inject Growth in Cell and Gene Therapies

Development
Combo Drug Formulation
Minimizing Toxicity

Manufacturing
Scaling Up Topical Drugs
Process Development

Quality/Regulations
GMPs for Gene Therapies

Analytics
Stability Testing

Operations
Sustainable Facilities

Peer-Review Research
Algorithm for Retrospective Process Monitoring
Here’s Why the Right Size Matters

Every project has a specific set of needs. When choosing a CDMO, bigger often isn’t better. You need the right mix of size and experience to complete your project on time, on budget, and within specifications.

At TEDOR, we help customers meet their development and commercial launch timelines, achieve regulatory approvals, and solve complex formulation challenges. We offer a full range of oral solid dose services, including formulation development, analytical methods, and Phase I-III clinical trial material manufacturing through to full-scale commercial manufacturing.

No matter what stage your product is in, our experienced development and manufacturing teams can help ensure a smooth and successful outcome.

Meet to discuss your unique formulation challenges with our experts. Visit our website to schedule a meeting during DCAT Week, March 23–26.
At Contec, we understand that you have choices when it comes to your disinfectant needs. But, why look anywhere else? Especially now that we have CyQuanol, a NEW Intermediate disinfectant with a 1-minute contact time.

Going to Interphex? Visit us at Booth 3259 to learn more about CyQuanol and other exciting new products!
EDITORIAL

Editorial Director Rita Peters rpeterson@mjhlifesciences.com
Senior Editor Agnes Shanley ashanley@mjhlifesciences.com
Managing Editor Susan Haigney shaigney@mjhlifesciences.com
European Editor Felicity Thomas fthomas@mjhlifesciences.com
Manufacturing Editor Jennifer Markarian jmarkarian@mjhlifesciences.com
Science Editor Feliza Mirasol fmirasol@mjhlifesciences.com
Assistant Editor Lauren Lavelle llavelle@mjhlifesciences.com
Senior Art Director Marie Maresco Graphic Designer Maria Reyes
Contributing Editors Jill Wechsler jillwechsler@gmail.com
Hallie Forcinito editorial@cs.com,
Susan J. Schniepp sue.schniepp@mac.com; Eric Langer info@bioplanassociates.com; and Cynthia A. Challener, PhD challener@vtlink.net

Correspondent Sean Milmo (Europe, smilmo@btconnect.com)

485 Route One South, Building F, Second Floor, Iselin, NJ 08830, USA
Tel. 732.596.0276, Fax 732.647.1235, PharmTech.com

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 should be sent directly to the managing editor. Below is a partial list of the Pharmaceutical Technology brand editorial advisory members. The full board, which includes advisory members from Pharmaceutical Technology Europe, can be found online at PharmTech.com.

James P. Agapito
President
Agapito & Associates
Larry L. Augburger, PhD
Professor Emeritus
Pharmacy, Rutgers University
David H. Bergstrom, PhD
Senior Vice-President, Pharmaceutical Development & Corporate Quality Assurance
Antares Pharma, Inc.
Phil Borman, DSc
Director
Product Development & Supply
Lachman Consultants
Phil Borman, DSc
Director
Pharmaceutical Sciences
Lachman Consultants
Eveline Brennan
International Technical Marketing
Manager, Pharmaceutical Division
IMCD Ireland
Rory Buddhinadja
Lachman Consultants
Motin Celik, PhD
President
Pharmaceutical Technologies International
Zak T. Chowhan, PhD
Consultant, Pharmaceutical Development
Sugiy S. Chral, PhD
President and CEO
Chral Associates, Inc.
Roger Dabbah, PhD
Principal Consultant, Tri-Intersect Solutions
Robert Dream
Managing Director
HDR Company
Tim Freeman
Managing Director
Fremont Technology
Sanjay Garg, PhD
Professor and Director
Center for Pharmaceutical Innovation and Development
University of South Australia
R. Gary Hollenbeck, PhD
Research Faculty
University of Maryland
School of Pharmacy
Rory-Ching (Richard) Hwang, PhD
Senior Director
Pharmaceutical Sciences,
Pfizer Global R&D
Mark W. Jenitz
President
G-CON Manufacturing Inc.
Manos S. Khan, PhD
Professor
IIMA Lepa’s Angil College of Pharmacy,
Texas A&M Health Science Center
Russell E. Madsen
President
The Williamsburg Group, LLC
Heidi M. Mansour, PhD
Assistant Professor
University of Arizona-Tucson
Jim Miller
Founder and Former President
PharmGuard, A Global Data Company
Colin Minchin
Senior Director Pharmaceutical Sciences,
Merck Pharmaceuticals
R. Christian Morten, PhD
Partner
Firmenich Consulting
Fernando J. Muzzio, PhD
Director,
NIST Engineering Research Center on Structural Organic Particulate Systems,
Dept. of Chemical and Biochemical Engineering,
Rutgers University
Mehdy M. Nass, PhD
Principal
Nass Pharma Regulatory Consulting
Garret E. Peck, PhD
Professor Emeritus of Industrial Pharmacy,
Pharmacy, Purdue University
Wendy Saffett-Gemmer
Director,
Research, Baxter Healthcare
Gurvinder Singh Rehki, PhD
Department of Pharmaceutical and Biomedical Sciences,
The University of Georgia College of Pharmacy
Susan J. Schniepp
Executive Vice-President
Post-approval Pharmaceuticals and Distinguished Fellow
Regulatory Compliance Associates
David R. Schonker
Director of Global Regulatory Affairs,
Colson
Alaka Srinivasan
VP Regulatory
Lachman Consultants
Read board members’ biographies online at PharmTech.com/pharmtech-editorial-advisory-board.

SALES

Publisher Mike Tracey mtracey@mjhlifesciences.com
East Coast Sales Manager Joel Korn jkorn@mjhlifesciences.com
Mid West, West Coast Sales Manager BJ Ghiiglione bghiiglione@mjhlifesciences.com
European Sales Manager Linda Hewitt lhewitt@mjhlifesciences.com
European Senior Sales Executive Stephen Cleland scleland@mjhlifesciences.com
C.A.T. Data and List Information Michael Kushner mkushner@mjhlifesciences.com
VP/Managing Director, Pharm/Science Group Dave Esoia

ADDRESS

485 Route One South, Building F, Second Floor, Iselin, NJ 08830, USA
Tel. 732.596.0276, Fax 732.647.1235
PharmTech.com

Permissions Alexa Rockenstein, arockenstein@mjhlifesciences.com
Audience Development Research Director
Christine Shappell cshappell@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
Senior Vice President, Content Silas Inman
Senior Vice President, I.T. & Enterprise Systems John Morcone
Senior Vice President, Audience Generation & Product Fulfillment Jay Puzzo
Vice President, Human Resources & Administration Shari Lundenberg
Vice President, Business Intelligence Chris Hennessy
Vice President, Marketing Amy Erdman
Executive Creative Director, Creative Services Jeff Brown

© 2020 Multimedia Pharma Sciences LLC All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical including by photography, recording, or information storage and retrieval without permission in writing from the publisher. Authorization to photocopy text for internal/educational or personal use, or the internal/educational or personal use of specific clients is granted by Multimedia Pharma Sciences LLC for libraries and other users registered with the Copyright Clearance Center, 222 Rosewood Dr., Danvers, MA 01923, 978-750-8400 fax 978-646-8700 or visit http://www.copyright.com. For uses beyond those listed above, please write your request to Permissions Dept. or email: mmhinfo@mmhgroup.com

Multimedia Pharma Sciences LLC provides certain customer contact data (such as customers’ name, address, phone number, and e-mail address) to third parties which wish to promote relevant products, services, and other opportunities that may be of interest to you. If you do not want Multimedia Pharma Sciences LLC to make your contact information available to third parties for marketing purposes, simply email mmhinfo@mmhgroup.com and a customer service representative will assist you in removing your name from Multimedia Pharma Sciences LLC lists.

Pharmaceutical Technology does not verify any claims or other information appearing in any of the advertisements contained in the publication, and cannot take responsibility for any losses or other damages incurred by readers in reliance of such content. Pharmaceutical Technology welcomes unsolicited articles, manuscripts, photographs, illustrations, and other materials but cannot be held responsible for their safekeeping or return.

Reprints: Contact Mike Tracey, mtracey@mjhlifesciences.com. Display, Web, Classified, and Recruitment Advertising Contact, tel. 732.346.3027. Permissions: Contact Alexa Rockenstein, tel. 732.346.3007, arockenstein@mjhlifesciences.com

To subscribe: mmhinfo@mmhgroup.com

Editorial Advisory Board

The International Advisory Board is comprised of experts in the fields of pharmaceutical science, technology, and development. The board provides guidance and strategic direction to the editorial team, ensuring the publication’s content remains relevant and valuable to its readers. The list of advisors is intended to be a representative sample and not exhaustive. For a complete list of the editorial advisory board, please visit the PhromTech.com website.
**MOVE PRODUCTS NOT CONTAMINATION**

**ELIMINATE CART WHEEL DISINFECTION**

- 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.

Cart top slides onto a new, clean base.

Cart base ready to move products going to a GRADE A area.

For more information visit: sterile.com/cart2core
Pharmaceutical Technology 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.

COVER STORY

16 **Investments Inject Growth in Cell and Gene Therapies**
The growing interest in developing cell and gene therapies has prompted industry investment to grow manufacturing capacity.

Cover Design by Maria Reyes
Images: Mopic - Stock.adobe.com

FEATURES

DEVELOPMENT

22 **Characterizing APIs is Essential for Combo Drug Formulations**
Formulating fixed-dose combination drugs proves more complex than simply adding one ingredient to another.

26 **Keeping Toxicity to a Minimum**
Assays can provide a useful tool in determining the potential toxicity of drugs throughout the development cycle.

MANUFACTURING

30 **Challenges in Clinical Manufacturing for Topical Drugs**
Understanding of scale-up parameters and use of process analytical technology are important to meet demand for larger batch sizes.

32 **Optimizing Process Development for Emerging Therapies**
Tackling process development early on can better optimize manufacturing processes for emerging therapies.

ANALYTICS

40 **Stability Testing: The Crucial Development Step**
As compounds become more complex in nature and biological ingredients are more widely used, stability testing approaches must follow suit and provide flexibility for developers.

QUALITY/REGULATIONS

44 **Navigating GMPs for Gene Therapies**
While new industry guidance documents issued by FDA speak to the agency’s efforts to promote the development of new gene therapies, certain hurdles remain to challenge stakeholders.

OPERATIONS

50 **Improving Efficiency for Sustainable Pharmaceutical Facilities**
New technologies and best practices improve sustainability.

OUTSOURCING

52 **Fast vs. Formulated?**
Can investing in early formulation studies drive a new therapy successfully across the commercialization finish line?

PEER-REVIEW RESEARCH

PEER-REVIEW RESEARCH

34 **Implementation of Autocorners Algorithm for Retrospective Process Monitoring**
The authors present a simple-to-use Microsoft Excel-based statistical tool that uses cumulative sum techniques to aid retrospective understanding of data trends.

Continued on page 8
Our problem-solving team leverages a diverse excipient and film coatings portfolio to provide comprehensive solutions that ensure the integrity and usability of your oral solid, liquid and parenteral formulations. Partner with Ashland for solutions to today’s formulation and drug delivery challenges.


ashland.com/dcat1
NEWS & ANALYSIS

FROM THE EDITOR

10 Coronavirus Response: Reaction or New Reality?
Emergency action to protect patients and the drug supply may have long-term implications.

REGULATION & COMPLIANCE

REGULATORY WATCH

14 Drug Production Draws Multiple Contenders
States, hospitals, and insurers support manufacturing arrangements to ensure access to affordable medicines.

ASK THE EXPERT

62 Embracing Change Management
No matter why change may be needed, it is important to comply with all the relevant regulatory requirements, says Siegfried Schmitt, PhD, vice-president, technical, Parexel Consulting.

DEPARTMENTS/PRODUCTS

12 Product Spotlight
58 Spring Show Guide 2020
60 Marketplace
60 Ad Index

Pharmaceutical Technology is selectively abstracted or indexed in:

» Biological Sciences Database
  (Cambridge Scientific Abstracts)

» Biotechnology and Bioengineering Database
  (Cambridge Scientific Abstracts)

» Business and Management Practices (RDSI)

» Chemical Abstracts (CAS)

» Current Packaging Abstracts

» DECHEMA

» Derwent Biotechnology Abstracts
  (Derwent Information, Ltd.)

» Excerpta Medica (Elsevier)

» International Pharmaceutical Abstracts (ASHP)

» Science Citation Index (Thomson)

Pharmaceutical Technology is proud to be a member of IPEC and PDA.
Now That’s Brilliant!

The Ross HSM 100LCI-t Laboratory Mixer delivers POWER, PRECISION and VERSATILITY. Variable speed up to 10,000 rpm, constant torque operation and HMI touchscreen controls ensure optimal results in critical formulations. Record information in 20-second increments with an optional Data Station. Take on virtually any mixing challenge with interchangeable High Shear Rotor/Stator, Disperser, Inline and Micro mixing assemblies.

Batch volumes from 50mL to 15L. Call or buy online. Ask about our Trial/Rental Program.

Try our free online Knowledge Base & Product Selector web app at mixers.com/web-app.
Coronavirus Response: Reaction or New Reality?

Rita Peters

Emergency action to protect patients and the drug supply may have long-term implications.

The rapid spread of the novel coronavirus, COVID-19, in China and beyond prompted the World Health Organization to declare a Public Health Emergency of International Concern on Jan. 30, 2020, and pushed regulatory organizations to evaluate needed response, researchers to accelerate studies of potential treatments and vaccines, and pharma companies to examine supply chain and business disruptions.

For an industry accustomed to long development and approval times, stringent regulatory oversight, and a not-so-transparent supply chain, the coming months may test bio/pharma’s ability to react, adapt, and change.

Confidence in drug quality

In a February 2020 report (1), FDA’s Office of Pharmaceutical Quality noted that nearly half of the physicians responding to a 2019 survey said drugs manufactured abroad were of lower quality than those manufactured in the United States. In light of the volume of APIs manufactured offshore, consumer confidence in drug quality may further erode with FDA’s suspension of facility inspections in China, in accordance with a State Department warning against travel in the region.

The agency said its regular risk-based surveillance testing of imported products will continue, however. In lieu of inspections, the agency will use alternate measures, include import screening, import alerts, a firm’s previous compliance history, and information from foreign governments as part of mutual recognition agreements. The agency said it also will request records from firms “in advance or in lieu of” drug surveillance inspections in China to assess possible quality threats (2).

R&D shifts to high gear

A number of pharma companies and organizations are accelerating the investigation of treatments and vaccines. For example, in late February, the National Institute of Allergy and Infectious Diseases initiated the first US clinical trial to evaluate the safety and efficacy of remdesivir (Gilead Sciences) on a volunteer patient diagnosed with COVID-19 who was quarantined on a cruise ship in Japan and repatriated to the United States.

The investigational broad-spectrum antiviral treatment was previously tested in humans with Ebola virus disease and has shown promise in animal models for treating other coronaviruses (3).

FDA stated that the agency is providing regulatory advice, guidance, and technical assistance to sponsors developing medical countermeasures to emerging threats. These efforts include the review of development proposals including the design and set-up of clinical trials. The agency also noted that under Emergency Use Authorization authority, the agency may allow unapproved medical products or unapproved uses of approved medical products to be used in an emergency when clinical circumstances warrant (2).

Supply chain in question

As US manufacturers rely on manufacturers in China for a significant portion of APIs and other raw materials, the potential for supply disruptions and drug shortages is likely. FDA noted that the agency is “proactively reaching out to manufacturers as part of our vigilant and forward-leaning approach to identifying potential disruptions or shortages” and is adding resources to monitor potential vulnerabilities. In the event of a potential shortage or disruption, FDA says it will work with manufacturers to expedite review of alternate supplies to prevent shortages (2).

FDA also is taking action to protect the nation’s supply of blood, human cell, tissue, and cellular/tissue-based products. And, the agency is also monitoring for fraudulent products claiming to prevent, treat, or cure COVID-19 and its effects.

Whether a disruption in the pharma ingredients supply chain is incentive for US-based manufacturers to seek alternate suppliers in the West will be just one factor to watch.

References

2020 PDA Advanced Therapy Medicinal Products Conference

Cell and Gene Therapy – From Promise to Cure

Join us for another two-day Conference offering an in-depth examination into the latest advances in the rapidly evolving field of cell and gene therapy. This year, we are drawing on the expertise of industry insiders, regulatory authorities, and a diverse group of bio/pharmaceutical professionals to provide insight into this innovative area of medicine.

Sessions will examine topics, including:

- The quality of raw materials
- Technology transfer
- Testing
- Registration of ATMPS
- Clinical development
- Bringing product to market

Get a global perspective! Select sessions will be simulcast with the PDA Europe Conference on Advanced Therapy Medicinal Products. We invite you to participate in one of the industry’s most recognized meetings on this topic!

To learn more and register, visit pda.org/2020ATMPs
Double Planetary Mixer
The Double Planetary Mixer from Ross is scalable through 1000-gallon production models and is offered in a sanitary turnkey configuration that features a stainless-steel workbench for the mixer and discharge system.

The sanitary four-gallon Double Planetary Mixer & Discharge System Model DPM/DS-4S (pictured) includes type 316 stainless steel on the interior and exterior, electropolished to a 150-grit (#4) finish. The mixer’s jacketed mixing vessel and high viscosity blades are equipped to produce thick gels, pastes, putties, and other semi-solids at precise temperatures. The sealed gearbox and stirrer shafts guarantee complete cleanability and eliminate cross-contamination between batches.

Charles Ross & Son Company
www.mixers.com

Double Clamshell Barrel Continuous Processor
Readco Kurimoto introduced a continuous processor with a double clamshell barrel design that provides full access to the paddle and screw assembly to enable thorough cleaning and inspection processes while allowing for easy adjustments to the configuration.

The barrel top and bottom of the processor can be easily opened and closed with the push of a button, and the barrel is automatically locked in the open position for cleaning and maintenance, which eliminates the need for the cranes and hoists traditionally used to maintain the barrel. Additionally, the clamshell design reduces the potential of cross-contamination and offers flexible options for processors interested in constructing multiple product formulations with powders, liquids, and viscous materials on a single unit.

Readco Kurimoto
www.readco.com

Isolator Head for Microbial Air Sampling
The SAS Tri-Clover Isolator Head from Cherwell Laboratories allows for precise and flexible monitoring of isolator cabinets and filling lines in cleanroom, isolator, and other controlled areas. The device uses bespoke stainless-steel sampling heads with tri-clover fittings and is permanently placed inside isolator cabinets and connected to an external control unit to reduce contamination risk.

Used alongside a SAS Super isolator, the device is equipped for confined spaces and can be easily removed for maintenance or calibration. It can also be provided for contact plates or petri dishes based on customer requirements.

Cherwell Laboratories
www.cherwell-labs.co.uk

Compressor-Free Plate Sealer
Thermo Fisher Scientific launched the ALPS 5000 Plate Sealer to simplify the plate sealing process and provide enhanced dependability and productivity for stand-alone and integrated robotic projects.

Operated via a touchscreen, the plate sealer enables control over sealing parameters to guarantee repeatability while integrating programming parameters into automation or robotic workflows. The device is designed for tool-free foil loading that can function without the use of adapters to change between different plates and offers fast sealing times and a compact footprint to save bench space.

Additionally, the device is equipped for various process customization capabilities including polymerase chain reaction, high-performance liquid chromatography, next-generation sequencing, compound storage, and flow cytometry. Users have the ability to program sealing time, temperature, and pressure parameters and can select the most appropriate sealing foil length.

Thermo Fisher Scientific
www.thermofisher.com
LOOKING FOR A CMO TO COVER ALL YOUR DEVELOPMENT, MANUFACTURING AND ANALYTICAL NEEDS FOR A PARENTERAL PRODUCT?

A RELIABLE CMO PARTNER FOR INJECTABLES FROM DEVELOPMENT TO COMMERCIAL MANUFACTURING

We are here to help

With 30-years of experience working with injectable pharmaceuticals, PYRAMID offers a broad range of services that span from preclinical development to commercial manufacturing and distribution of liquid vials, lyophilized products and pre-filled syringes. Small molecule, biologic or a drug-delivery vehicle, we will fulfill your project with maximum quality and efficiency.

+1-714-435-9800  pyramidlabs.com  info@pyramidlabs.com
Drug Production Draws Multiple Contenders

Jill Wechsler

States, hospitals, and insurers support manufacturing arrangements to ensure access to affordable medicines.

Building on the efforts of CivicaRx, a number of organizations and political leaders are mapping strategies for producing drugs and biologics that they believe will be faster, more reliable, and less costly. The stated aims are to prevent or remedy drug shortages quickly, while also expanding patient access to less expensive medicines, primarily sterile injectables. The many challenges in producing drugs to meet quality standards, however, could undermine these undertakings.

The issue has surfaced among Democratic presidential candidates as part of the debate over strategies for cutting drug prices. Sen. Elizabeth Warren (D-Mass) has proposed that Congress empower the federal government to manufacture drugs, an approach she said would lower the price of insulin and HIV treatments, as well as EpiPens and top-selling biotech therapies. And if Congress fails to act, Warren said she would do this administratively as a first initiative after becoming president.

Local governments are eyeing similar activities, as seen in the January announcement of California Governor Gavin Newsom’s plan for the state to establish its own generic drug label to gain access to cheaper medicines (1). The state’s strategy is to use its buying power to contract with existing generic-drug manufacturers for low prices on certain products, with a state purchasing list and prices to come. And the state could extend the program to brand products by allowing all drug purchasers in California—public plans, private insurers, self-insured employers—to combine purchasing power to negotiate a lowest price for all.

A move to ensure supplies and reduce costs of cutting-edge gene therapies is the goal of an initiative by a leading research hospital to expand an existing small-scale operation that provides clinical supplies for early-stage gene therapy trials into broader production to handle anticipated growth in studies of gene-based treatments. The Columbus, Ohio-based Nationwide Children’s Hospital’s Abigail Wexner Research Institute (AWRI) aims to establish Andelyn Biosciences as a for-profit operation to support the production and advancement of novel gene therapies for rare diseases. Initially, Nationwide will extend current production from early research to supplies for more advanced clinical studies, and eventually gear up for commercial production of gene therapies (2).

Civica takes lead

California officials acknowledged in announcing their drug production plan that it was modeling its program on that established by the CivicaRx nonprofit formed in 2018 by a large group of hospitals and healthcare systems to create and produce more affordable generic drugs. The stated aim was to overcome chronic shortages in vital therapies for emergency care and hospital procedures (3). Led by Intermountain Healthcare, HCA Healthcare, Mayo Clinic, and several others, the group obtained funding from major philanthropies and engaged former Amgen Chief Quality Officer Martin VanTrieste as CEO.

Civica began supplying drugs to its hospital members in 2019, based on an initial production contract with the Danish company, Xellia, to provide certain anti-infectives. In July 2019, Civica signed a five-year agreement with Hikma Pharmaceuticals to manufacture and supply 14 sterile injectable medications to the organization, with Civica serving as a private label distributor and using its own drug code. Then in January 2020, Civica announced an agreement with Thermo Fisher Scientific to develop its own medicines for member hospitals, starting with nine drugs used in critical or emergency care that have experienced supply problems (4). By providing a guaranteed market for these contract manufacturers, Civica aims to obtain the agreed-on medicines at lower, set prices. Ultimately Civica hopes to establish its own manufacturing facilities to produce more of its own generic drugs.

Similarly, the hospital service firm Premier Inc.’s Provide Gx program negotiated a contract with Exela Pharma Sciences to produce certain sterile injectables experiencing long-term shortages for hundreds of hospitals in its network. The initiative started in October 2019 by resolving shortages of several drugs, including cysteine hydrochloride injection for parenteral nutrition (5).

Meanwhile, Civica took an important step to expand its customer base by forming a partnership with the Blue Cross Blue Shield Association (BCBS) to create a subsidiary to manufacture generic drugs for health plans serving some 40 million pa-
Regulatory Watch

patients. BCBS invested $55 million in the new venture, which aims to start with production by 2022 of 7–10 products lacking competition (6). Analysts expect that insulin will be a main target.

In addition to addressing shortages and affordability of vital medicines, VanTrieste emphasized the larger goal of providing high-quality medicines that are always available at a public meeting on drug quality sponsored by FDA and the Duke Margolis Center for Health Policy in Washington, DC in February 2020. Convened to address stakeholder concerns about drug access and threats to quality from an expanding global supply chain, officials from the Center for Drug Evaluation and Research described efforts to encourage manufacturers to invest in advanced manufacturing and innovative technology to support drug quality systems able to avoid shortages. In lamenting the uncertain quality of drugs made in China and India, VanTrieste said his program would disclose where the drug is made and the origin of active ingredients. Manufacturing costs may be higher for Civica products made in the United States, he acknowledged, but this non-profit organization will maintain low prices. VanTrieste further supported FDA proposals for some kind of quality system score card, which would help companies that excel to expand, and those that fall short to see where to fix problems.

Civica’s strategy of working with established contract manufacturers appears appropriate, given the difficulties hospitals and health agencies often have with in-house production of drugs that meet FDA standards for quality and safety. Several years ago, the National Institutes of Health (NIH) had to shut down a clinical supplies production unit at its main Clinical Center due to contamination and sterility issues identified in FDA inspections. A report on the program issued in 2016 documented the challenges in producing sterile injectables at even such a prominent health center and advised NIH not to rebuild the pharmaceutical production unit, but to tap commercial sources for sterile products (7). The report concluded by noting that manufacturing novel drugs for clinical trial use is “a high-risk process” that requires attention to quality, extensive staff training, and clearly defined standards.

References
7. NIH, Reducing Risk and Promoting Patient Safety for NIH Intramural Clinical Research, Final Report, April 2016. PT
Investments Inject Growth in Cell and Gene Therapies

Feliza Mirasol

The growing interest in developing cell and gene therapies has prompted industry investment to grow manufacturing capacity.

With the hard-fought road to commercialization won by cell and gene therapies in the past few years, biopharmaceutical companies have stepped up their interests in developing these emerging therapies. Some biopharma companies are also building capacity by investing in expansions and/or new facilities. In anticipation of growing demand for capacity and services, contract manufacturing organizations (CMOs) and contract development and manufacturing organizations (CDMOs) have also been investing in expanding manufacturing capacity and capabilities for cell and gene therapies.

Building capacity now and for the future
One such example is biopharmaceutical company Gilead Sciences, which acquired Kite Pharma in October 2017 for approximately $11.9 billion. That same month, Kite’s cell therapy product, Yescarta (axicabtagene ciloleucel) for large B-cell lymphoma, was approved by FDA. Through Kite, Gilead has established a global manufacturing network to meet patients’ needs for cell therapies today and in the future. “Outside of California, key investments include the opening of a manufacturing site in Amsterdam later this year [2020] and ongoing construction of our newest automated facility in Frederick County, MD, that will significantly expand our ability to manufacture a variety of chimeric antigen receptor T (CAR T) therapies, and our new clinical manufacturing facility in Gaithersburg, MD will produce investigational T-cell receptor (TCR) cell therapies being evaluated in solid tumors,” says Charles Calderaro, Kite’s global head of Technical Operations.

In addition, in July 2019 the company announced the development of a new facility in Oceanside, CA (1) that will be dedicated to the development and manufacturing of viral vectors. Viral vectors are a critical starting material in the production of cell therapies, Calderaro notes.

Also looking to leverage itself with capacity for now and in the future, Orchard Therapeutics, a London-headquartered biopharmaceutical company, has been organizing its CDMO network as well as its in-house capabilities. “In anticipation of a potential launch, we will be leveraging our existing CDMO infrastructure to produce the required vector and drug product. At the same time, we understand that we must invest in our own, in-house manufacturing capabilities given the depth of our clinical-stage pipeline,” says Ran Zheng, chief technical officer, Orchard Therapeutics. “We are beginning construction of a manufacturing facility in Fremont, CA, in order to meet the
PFANSTIEHL LAUNCHES NEW HIGH PURITY, LOW ENDOTOXIN, LOW METAL HISTIDINE

- Trehalose
- Sucrose
- Histidine
- Mannitol
- Arginine

- Galactose
- Mannose
- Maltose
- Sodium Succinate

Quality • Consistency • Commitment

- HIGH PURITY • LOW ENDOTOXIN • LOW METAL
- MULTICOMPENDIAL • cGMP PRODUCTION
- ICH Q7 COMPLIANCE • USA MANUFACTURING
- ICH Q3D COMPLIANCE ON SPECIFICATIONS
- ACTIVE DMF PROGRAM • GRAM to MT QUANTITIES

www.pfanstiehl.com

Pfanstiehl, Inc.: 1219 Glen Rock Avenue, Waukegan, Illinois 60085
USA Telephone: 1.847.623.0370 • Toll Free Telephone: 1.800.383.0126 • Fax: 1.847.623.9173
International Telephone: +41 41 755 40 54 • Email: cs@pfanstiehl.com
Companies are also making strategic investments to support advancing product candidates through the pipeline.

need for greater capacity, and expect it to be operational in 2021. In addition to vector and drug product manufacturing, the Fremont facility will house process development, quality control, and other support functions. Meanwhile, CDMO Catalent made a significant investment with its $1.2-billion acquisition in May 2019 of Paragon Bioservices, a CDMO specializing in viral vector development and manufacturing for gene therapies (2). Paragon had just opened its second good manufacturing practices (GMP) gene therapy manufacturing facility in Harman’s, MD, in April 2019, notes Colleen Floreck, senior director of Marketing and Communications at Catalent’s Paragon Gene Therapy. “The 425,000-ft² facility offers individualized manufacturing suites specially designed to handle the unique needs of gene therapy products,” Floreck says.

Soon after the acquisition, Catalent Biologics and Novavax partnered in a strategic deal under which Paragon Gene Therapy would assume the leases to two of Novavax’s product development and manufacturing facilities in Gaithersburg and Rockville, MD. The deal gave Paragon immediate access to state-of-the-art manufacturing equipment and a further 54,000 ft² of current good manufacturing practice (CGMP) space that the company needs to grow its gene therapy development and manufacturing business. One hundred of Novavax’s employees transferred to Paragon.

“Each of these announcements included commitments from customers for dedicated capacity for their programs, but also provides additional capacity for technology expansion and new development customers. Since then, Catalent’s Paragon Gene Therapy business has announced further collaborations, validating its proactive investment strategy,” Floreck says.

Investments beyond capacity
In addition to building up capacity for cell and gene therapies, companies are also making strategic investments to support advancing product candidates through the pipeline. “We are investing across a number of areas to support the advancement of our investigational ex vivo autologous gene therapy programs for rare, inherited diseases,” says Zheng.

Orchard Therapeutics’ additional investments include research and development for new indications; technological innovations, such as stable cell lines for vector production and hematopoietic stem cell transduction enhancers; automated cell processing; and initiatives to identify metachromatic leukodystrophy (MLD) patients, including diagnostic testing and newborn screening pilot programs. “We view all of these activities as crucial to our long-term success,” Zheng emphasizes.

Catalent’s additional investments include its February 2020 acquisition of MaSTherCell Global, a cell therapy CDMO, for $315 million. “This creates an industry-leading platform spanning both cell and gene therapy and complementing Catalent’s cell line, analytical, and biologics fill/finish capabilities,” Floreck says.

MaSTherCell has a 25,000-ft² facility in Gosselies, Belgium, that provides clinical services and a 32,000-ft² facility in Houston, TX, which is currently undergoing validation activities to undertake development-scale projects before the end of 2020, Floreck explains. “Like Paragon, MaSTherCell already has expansion plans in progress and construction is underway on a dedicated 60,000-ft² commercial-scale production and fill/finish facility adjacent to its existing Belgian facility, which is scheduled to open in the fall of 2021. MaSTherCell adds a unique portfolio of capabilities and technologies to Catalent that include the development and manufacture of autologous and allogeneic cell therapies and related analytical services,” Floreck adds.

MaSTherCell’s expertise includes therapies based on CAR-T cells, TCR, tumor-infiltrating lymphocytes (TIL), and mesenchymal stem cells (MSC).

Gilead’s investments beyond building capacity is based on Kite’s commitment to continuous innovation in platform services and logistics support, both necessary to improve the cell therapy experience for patients and healthcare professionals. “We have a customized program, Kite Konnect, which is designed to help enable rapid and reliable delivery of Yescarta to treatment centers. Kite Konnect uses an integrated technology platform to provide real-time status updates to patients and doctors throughout treatment,” explains Calderaro.

Market capacity dynamics
The increased focus on developing cell and gene therapies and the significant number of product candidates in the clinical pipeline means that there is need for capacity upgrades on the market. “With so many cell and gene therapy companies looking to bring products through clinical trials to the market, capacity is tight,” Zheng concurs. “We’re increasingly seeing companies adjusting to this dynamic by securing supply agreements with CDMOs, building internal manufacturing capabilities, and improving manufacturing processes and efficiency by exploring new technologies.”

In gene therapy manufacturing, Catalent focuses on growing with its clients. “It is critical that we can sup-
We are a domestic source of ultra high purity chemical salts with exceptionally low levels of elemental impurities.

With 35 years of experience, Jost manufactures high purity USP/EP/ACS chemical salts in cGMP-compliant, FDA-registered facilities. Our products are free-flowing, fully reacted, consistent from lot-to-lot and meet all customer requirements. Jost’s team of scientists provide particle size options, custom product development and technical support.

Visit jostchemical.com
US +1 314 428 4300   EU +32 85 552 655
The successes of winning regulatory approval from FDA and further approvals in Europe have sparked an increase in the further development of new cell and gene therapies, many of which aim to treat difficult-to-treat or previously untreated diseases. As a result of a growing clinical pipeline for these therapies, manufacturing capacity on the market is tight. Biopharmaceutical companies, contract manufacturing organizations (CMOs), and contract development and manufacturing organizations (CDMOs) have turned an interested eye toward boosting manufacturing capacity. A summary of some of the manufacturing investments made during 2019 and up to the present in the cell and gene therapy fields follows.

**Fujifilm.** In January 2019, Fujifilm announced that it will add current good manufacturing practices (CGMP) aseptic filling of recombinant proteins to its existing fill/finish services at its Fujifilm Diosynth Biotechnologies (FDB) facility at College Station, TX, by March 2021 (1). The services will also apply to gene therapy fill/finish. The company previously announced that it would start offering gene therapy fill/finish services. Fujifilm followed this up with a $55-million investment to establish a new gene therapy innovation center adjacent to its FDB CDMO’s existing gene therapy manufacturing facility at College Station (2). The new 60,000-ft² innovation center will house state-of-the-art upstream, downstream, and analytical development technologies, the company announced in November 2019. The facility will be operational in autumn 2021.

**GE Healthcare.** GE Healthcare Life Sciences commercially launched a KUBio box in October 2019 intended to accelerate the production of viral-vector-based gene therapies and increase capacity in the viral vector space (3). The new KUBio box features a Germfree biosafety level 2 modular bioprocessing environment and is equipped with the FlexFactory single-use biomanufacturing platform, which has been tailored specifically for the production of viral vectors, according to the company.

**Hitachi Chemical.** Hitachi Chemical Advanced Therapeutics Solutions (HCATS), a subsidiary of Hitachi Chemical and the North America representative of Hitachi Chemical’s Regenerative Medicine Business Sector, opened a new commercial-scale cell and gene therapy manufacturing facility in Allendale, NJ, in late January 2020 (4). The facility houses six classified environment rooms and has the capability to add more rooms that can be specifically configured according to need. The facility includes manufacturing and development labs as well as quality control and microbiology labs.

**Nationwide Children’s Hospital.** Nationwide Children’s Hospital, based in Columbus, OH, in conjunction with key partners created an affiliate company named Andelyn Biosciences in January 2020 to manufacture gene therapy products. The new company is scheduled to begin operations in 2023 (5). The new startup will establish the first commercial-scale CGMP clinical manufacturing facility in Ohio devoted to gene therapies, according to Nationwide Children’s Hospital. The new company will be the result of the hospital’s clinical manufacturing success and work with gene therapy via its Abigail Wexner Research Institute (AWRI). AWRI has operated a small-scale CGMP gene therapy manufacturing facility on-site for several years focused on early-stage gene therapy products for Phase I and II clinical trials. Beginning in summer 2020, the current facility will manufacture products compliant with Phase III clinical trial regulations while the new commercial-scale manufacturing site under Andelyn Biosciences is being built and validated.

**Novartis.** Novartis opened its new cell and gene therapies manufacturing facility in Stein, Switzerland, in November 2019 following on the heels of the company’s first successfully completed clinical production of a cell and gene therapy batch at Stein in September 2019 (6). The new facility houses manufacturing areas for novel chimeric antigen receptor T cell (CAR-T) cell therapies in addition to hosting production of innovative, difficult-to-manufacture solid dosage forms.

**Pfizer.** In August 2019, Pfizer announced that it is investing $500 million to construct a new gene therapy manufacturing facility in Sanford, NC (7). The facility is expected to support Pfizer’s ongoing investment in gene therapy R&D. The facility would increase Pfizer’s ability to supply both clinical- and commercial-scale quantities of gene therapies, specifically, highly specialized, potentially one-time gene therapies that use custom-made recombinant aden-associated virus (rAAV) vectors.

**The Discovery Labs.** The Discovery Labs, an MLP Venture company and provider of CGMP manufacturing, turnkey laboratory solutions, critical materials, and office space, formed a new CDMO and specialty investment company in January 2020 in partnership with Deerfield Management, a healthcare investment management firm. Under the new CDMO, named The Center for Breakthrough Medicines, The Discovery Labs and Deerfield will invest $51.1 billion to build a manufacturing facility for cell and gene therapies in King of Prussia, PA, which is expected to provide instant capacity to the market (8). The new CDMO will provide manufacturing from preclinical- through to commercial-scale of cell therapies, gene therapies, and component raw materials. It will also offer process development, plasmid DNA, viral vectors, cell banking, cell processing, and support testing capabilities, all housed under one roof. Renovations are also underway at the King of Prussia site to construct a total of 86 plasmid, viral-vector production, universal cell processing, CGMP testing, process development, and cell banking suites.

**Thermo Fisher Scientific.** Thermo Fisher Scientific opened its new $90-million viral vector CDMO site in Lexington, MA, in December 2019 (9). The 50,000-ft² facility will support development, testing, and manufacture of viral vectors for gene and cell therapies. The new facility adds much-needed capacity for viral vector development and manufacturing, which has been a bottleneck area for biotech companies, according to Thermo Fisher, which has noted that the demand for new gene therapies has outpaced capacity. The investment is expected to accelerate commercialization of new cell and gene therapies by providing a range of services—from drug development through clinical trials to commercial manufacturing.

**References**

port our customers’ pipelines and increasing asset portfolio with GMP viral facilities,” says Floreck.

With the number of gene therapy clinical trials on the increase and many gene therapy programs carrying expedited status, it is additionally important to Catalent that the company offers not only dedicated space for clinical trial and commercial production, but also scale-up expertise to support increased manufacturing efficiency, Floreck explains.

“It should be the goal of any successful gene therapy CDMO to offer an end-to-end solution for its customers. From the raw materials through to development, scale-up, manufacturing, and fill/finish, we want to be able to guide our customers through the process and increase their chances of final approval and patient material. At Catalent, we are committed to expanding capacity to meet industry demand; however, without the viral vector expertise, it is just empty space. Early phase clients need to lock-in early with manufacturing partners, to not only secure the production suite but also to have the necessary technical expertise in place to optimize their program,” Floreck stresses.

On the cell therapy front, the constraint isn’t so much about capacity but more about getting into the field early. Floreck points out that the barrier to entry in the cell therapy field is low, but the real challenge involves the people and expertise. “There are many manufacturers who can build upstream and downstream cell culture suites, especially without the challenges of virus production, but it takes a minimum of six months to effectively train personnel across various platforms,” say says.

“Additionally, you are so close to the end user (i.e., the patient) that the cell production and the need to lock down a process early is even more critical. Knowledge and expertise across a variety of cell types and modalities are important to offer customers the speed they need to get to the clinic faster. Many cell therapy indications and products are similar, making speed to market of paramount importance to customers,” Floreck says.

In the field of autologous cell therapy, in particular, there is no option but to build out. “Since you are treating one patient at a time, clients often do not even know how many patients they will have during each month of the trial. With enrollment being the biggest unknown, the numbers also challenge the affordability of the treatment,” Floreck explains.

In comparison, for allogeneic cell therapy, it is not known yet what the final bioproduction process will be. “At Catalent’s most recent acquisition, MaSTherCell, we are designing the processes, including stirred-tank reactors all the way through to fill and finish. We are working with clinically advanced companies like CRISPR Therapeutics and Servier as they navigate the defining of the allogeneic production process,” Floreck says.

Furthermore, unlike traditional biomanufacturing, current CAR T therapies require a complex and carefully controlled, multi-step process that can be difficult to optimize, adds Calderaro. “Manufacturing speed and quality in cell therapy is critical because people waiting for these medicines are typically very ill and have the potential for rapid disease progression. In addition to our global, industry-leading manufacturing network, Kite continues to explore ways to optimize the quality of manufacturing and has currently set the bar for the industry with a rapid and reliable median 16-day turnaround time in the United States,” Calderaro states.

Calderaro goes on to say that the progress of cell therapy is closely tied to innovation in manufacturing and technical operations. “In addition to our US and European locations, we are investing in other areas around the globe to ensure our operational footprint allows us to meet the needs of potential patients worldwide. We are actively advancing cell therapy technology across all aspects of the manufacturing process, including technologies such as next-generation autologous and allogeneic development platforms.”

What drives the future

Because Kite’s singular focus is cell therapy, it’s strategic drive into the future is also very focused. Today, the company is exploring cell therapies in more than 10 cancers, including hematologic malignancies and solid tumors, and is also exploring varied technologies. “As we advance our industry-leading cell therapy pipeline, expanding and investing in our capabilities is essential to ensuring we are able to improve outcomes for people with cancer now and in the future,” says Calderaro.

Catalent is taking its cue from its customers and intends to build a future with them. “It is critical for Catalent to grow with its customers. We are committed to developing the capacity needed to support their programs as they grow and expand,” Floreck says.

Meanwhile, Orchard Therapeutics is considering several factors looking toward the future as it develops and executes its manufacturing strategy. “Our first consideration is about patients and our ability to produce and deliver products to them reliably. With the construction of our facility in Freemont, we will work to ensure increased manufacturing capacity to make products for these patients. Given the nature of our investigational products—ex-vivo autologous gene therapies, which use a gene-corrected version of a patient’s own cells—reliable supply chain management is also necessary to ensure quality and timely delivery of our products. We are committed to working closely with regulators in the European Union, the US, and globally to ensure compliance and efficient product approvals,” Zheng says.

References


Characterizing APIs is Essential for Combo Drug Formulations

Cynthia A. Challener

Formulating fixed-dose combination drugs proves more complex than simply adding one ingredient to another.

Fixed-dose combination (FDC) drugs offer a number of benefits to drug manufacturers, patients, and caregivers. These medicines contain two or more active ingredients in a defined composition or fixed ratio. The greater focus on patient centricity and improving patient medication adherence has led to a growing interest in FDC formulations.

In the past five years, approximately 43 fixed-dose combinations were approved in the United States, according to Anil Kane, global head of scientific and technical affairs at Thermo Fisher Scientific. The majority were treatments for cardiovascular, metabolic disorder (including diabetes), and infectious diseases (including HIV). Most are solid, orally delivered drugs.

Benefits of FDCs include:

- **Benefiting patients and industry**: FDC medicines, because they contain multiple APIs, provide advantages for patients and opportunities for manufacturers. From a patient perspective, according to Torkel Gren, senior director and science and technology officer at Recipharm AB, FDC products can be consumed quickly and easily because fewer tablets need to be taken. “By altering and controlling API release rates through the combination of multiple drug products into a single carrier, treatment is ultimately more efficient and straightforward for patients,” he says. “To this end, FDCs have helped to improve patient compliance and by extension the overall treatment of diseases.” Gren adds. FDCs also have the potential to offer patients increased efficacy and synergistic effects that may enable the need for lower doses, according to Kane.

- **Stability, dosage, and other challenges**

Developing an FDC formulation that offers these benefits and challenges can be difficult, however. Because many active ingredients are incompatible—meaning they are less stable in the presence of each other—selecting excipients and processes that reduce the degradation rate of the active ingredients and afford the optimal composition and process parameters increases in difficulty as the number of active ingredients increases, Gren notes. In fact, the main challenge to fixed-dose combination development usually involves product formulation and manufacturing strategy to address stability, dose differential, and analytical method development issues, according to Kane.

The APIs in an FDC must be physically and chemically compatible with one another and all of the excipients used in the formulation and not generate any new impurities or raise any new drug-drug interactions. “The physicochemical properties and stability of each of the APIs in...”
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
an FDC will define the formulation approaches to maintain stability during the shelf life of the combined drug product. As an example, the hygroscopicity of one active drug substance can influence the stability of the other drug in a combination product unless they are completely separated by way of multiple techniques,” explains Kane.

Dosage size is another challenge experienced during pharmaceutical development, according to Gren. For example, if several high-dosage drugs are combined, the resulting target may be too large to be consumed by the patient. Differentials in individual drug doses are another issue. “The particle size distribution of a low-dose drug and the distribution of a second high-dose drug can impact the content uniformity of the former and the flow and processability of the latter in a single two-layer tablet,” Kane observes.

From an analytical chemistry standpoint, it may be challenging to develop an analytical method that can quantitate all of the active ingredients and their degradation products, according to Gren. New analytical methodologies are often required to be developed for these innovative formulation strategies to accurately assess the product potency of multiple ingredients, as well as potential degradation products and their quality parameters, Kane agrees. “One alternative,” says Gren, “is to apply several analytical methods. However, the employment of multiple analytical methods will increase quality control costs and subsequently impact the cost of goods,” he notes.

Finally, Kane observes that the packaging of a fixed-dose combination product may need to be re-considered based on the criticality of the multiple actives and their stability profiles in combination.

**Start with understanding each drug**

The best way to overcome these challenges, Kane asserts, is for formulators to fully evaluate/understand the individual drugs that need to be combined in FDC products with respect to the API characteristics, forced degradation and stability profiles, site of absorption and pharmacokinetics, potential for drug-drug interactions and chemical compatibility, and the individual doses required to have an optimal therapeutic effect. “A thorough pre-formulation assessment of the combination and generation of critical data is the key to a successful formulation development strategy,” he concludes.

Clarity around the stability of the APIs to be formulated into an FDC product can be gained through retrieved literature data and experimental work, notes Gren. “Gathering information and knowledge around the specific patient population and other market conditions, combined with an understanding of stability issues, will allow for a clear development strategy to be outlined and implemented,” he states.

**Managing incompatibilities**

Where the APIs in FDCs are known to be incompatible in the presence of each other, formulation in a single pill can be achieved using a number of different options. Kane identifies multilayer tablets, compression-coated tablets, multi-particles in capsules, and combinations of coated and uncoated beads and pellets of one active placed with a powder of another active as common technologies.

A suitable way to manage incompatibilities is by separating the different active ingredients with multilayer tablets or by including one of the drug substances in the coating and another at the core of the tablet, Gren notes. Formulation of different actives into separate pellets that can then be mixed into a capsule or tablet can make it easier to vary the doses of each API, he adds. For modified-release formulations, the pellets are typically coated.

It is important to note, however, that although pellet technology has broad applications in oral FDCs, it is not a universal tool. “While some drug substances can be readily combined in a conventional tablet without any problems occurring, liquid or semi-solid formulations are often required for some indications and administration routes,” Gren comments.

In general, therefore, the strategy for developing FDCs is entirely dependent on the individual active ingredients in the combination, their dose, stability profile, target release profile, sight of release, and other factors, Kane asserts.

**Potential of 3D printing**

Looking to the future, 3D printing has recently been introduced as a manufacturing method for pharmaceutical products and may enable contract development and manufacturing organizations to effectively customize combination drugs for individual patients, according to Gren. He notes that it could also potentially facilitate the separation of different drug substances to reduce incompatibility issues.

The first approval of a product manufactured using 3D printing (Appecia Pharmaceuticals’ Spritam) was granted by FDA in 2015. “There are, however, several quality assurance and regulatory issues that need to be solved before this technology can be employed across the industry on a larger scale,” Gren says. **PT**

---

### Bovine heparin meets acceptable impurity levels

A recent study demonstrated that bovine heparin can be produced to meet acceptable impurity levels, as defined by the US Pharmacopeia (USP), supporting the use of bovine-derived heparin as an alternative to porcine heparin (1).

In 2018, FDA encouraged the reintroduction of bovine-sourced heparin, as a proactive approach to address possible shortages. USP worked with independent laboratories to analyze, test, and control samples for impurities and evaluate whether the tests and limits for impurities—including oversulfated chondroitin sulfate—in the USP heparin standard could be applied to bovine heparin. Test results for bovine heparin were comparable to porcine heparin with respect to impurity levels, with both falling within acceptable ranges. In 2007–2008, the intentional contamination of batches of porcine heparin resulted in side effects for patients and nearly 100 deaths.

### Reference


—Pharmaceutical Technology Editors
The Drug Supply Chain Security Act (DSCSA) mandates serialization be in place by November 2017 and unit level traceability by 2023. At Mikart, we’re way ahead of schedule. We’ve been running full 2023-compliant packaging since September 2015. In fact, we’ve successfully run serialization “from bottle to pallet” for millions of tablets. Mikart also offers a broad range of other CDMO services, including pharmaceutical development; clinical trial manufacturing and packaging; regulatory submissions; commercial scale manufacturing; and packaging solutions.

Call 1-888-4MIKART today to learn more about our wealth of industry-leading solutions.
Adverse drug reactions (ADRs) are reportedly the fourth to sixth highest cause of death in the United States and are estimated as being responsible for 5–10% of hospital admissions within Europe (1). Therefore, ADRs are considered to be a cause of considerable economic and clinical burden (2).

All pharmaceuticals have the potential to produce ADRs that can be related to the drug dose (i.e., dose-dependent), or can be dose-independent, which includes an allergic reaction to the API or other ingredient used in the formulation, or idiosyncratic reactions (3). As has been previously reported, the timely identification of ADRs can not only have a beneficial impact on the patient population but can also help to improve the efficiency and robustness of drug development pipelines (4).

Drug toxicity and drug development
According to research, drug toxicity is a significant causative factor of drug candidate attrition and, if unrecognized until late in the development cycle or during post-marketing, it can contribute to high costs (5). The potential impact of drug toxicity on drug development could be exacerbated as a result of the increasing frequency of more potent compounds entering the pipeline, such as cancer therapeutics.

Screening for a form of drug toxicity to the hematopoietic system (hematotoxicity) has been previously reported to have the potential to effectively improve drug development (6), particularly in light of the changing viewpoint that through using biological and physiological information while developing drugs toxicity can be minimized.

“Certain drug classes, such as tyrosine kinase inhibitors, antibody drug conjugates (ADCs), histone deacetylase (HDAC) inhibitors, and antivirals, are known to cause hematotoxicity, which includes neutropenia (reduction of white blood cells), thrombocytopenia (reduction in megakaryocytes that produce platelets), severe anemia (reduction in red blood cells), and lymphotoxicity (reduction in immune cells),” explains Dr. Emer Clarke, chief scientific officer, ReachBio. “Additionally, certain classes of drugs can also initiate cytokine storm events through hyperstimulation of the autoimmune system, causing damage to normal cells.”

Drug toxicity is a significant causative factor of drug candidate attrition and, if unrecognized until late in the development cycle or during post-marketing, it can contribute to high costs.

In-vitro assays, such as colony-forming cell (CFC) assays, are useful tools for the detection of drug-induced toxicity to the hematopoietic system and have garnered significant support from the European Center for the Validation of Alternative Methods (ECVAM) (6). Using the platform of assays (CellPrism) available as an example, Clarke highlights that it is possible to determine whether compounds induce a cell lineage-specific or broader toxicity profile. “The assays involve culturing primary blood or bone mar-

Keeping Toxicity to a Minimum
Felicity Thomas

Assays can provide a useful tool in determining the potential toxicity of drugs throughout the development cycle.
Discover why we’re the small molecule company, with end-to-end capabilities and experts you’ll enjoy working with.

- **DCAT Week, March 23-26**
  Lotte NY Palace, New York
- **CPhI North America, May 5-7**
  Booth 901, Philadelphia
row cells and testing these with drug compounds preclinically to evaluate read-outs that include the reduction of red blood cells, white blood cells, and platelets or the release of deleterious cytokines into cell cultures,” she says.

As safety is always a concern for industry, when advancing a new drug compound clinically, there is heightened interest from drug development agencies in drug assay platforms that can effectively predict unexpected “off-target” toxicities, explains Rob Chaney, chief operating officer, ReachBio. “Because some blood cells have very short half-lives, drugs that affect the cells could have a rapid and deleterious effect on patients,” he adds. “Some of the assays in the CellPrism platform, for example, have been validated by ECVAM, and drug development agencies (e.g., FDA) have recommended the **in-vitro assays, such as colony-forming cell (CFC) assays, are useful tools for the detection of drug-induced toxicity to the hematopoietic system.**

**Noteworthy historical cases of adverse drug reactions**

**Thalidomide**
Thalidomide, which was released in the late 1950s, is probably the most publicized and well-known medicine that caused significant adverse reactions and has been identified as a major factor in changing the way drugs are tested (1). Originally marketed as a sedative by Chemie-Grunenthal, thalidomide was discovered to have effective anti-emetic properties and, as such, was used for the treatment of morning sickness in pregnant women (2).

Reports about the development of peripheral neuropathy in patients taking thalidomide started occurring shortly after the drug’s release, along with reports of birth defects—although these were not initially linked to the drug. In 1961, two clinicians—one from Australia (3) and one from Germany (4)—confirmed the link between thalidomide and severe birth defects in huge numbers of children. After confirmation of the link between thalidomide and the occurrence of severe birth defects, the drug was withdrawn from markets, however, it had never gained approval in the United States due to concerns raised by Frances Kelsey, a physician with the Food and Drug Administration, over the drug’s safety (1).

As a result of the incidence of birth defects linked with thalidomide, the inter-species variances that can occur with the use of drugs was demonstrated and, as such, has led to changes in drug screening policies, including the requirement of in-vitro testing (1). Additionally, the thalidomide case raised awareness on the importance of enantiomeric purity of drug compounds and their metabolites in terms of desired pharmaceutical effect (5) and also highlighted the importance of post-marketing surveillance.

Nowadays, thalidomide is approved for use in two conditions—skin lesions caused by leprosy and multiple myeloma—and research into the drug’s uses in other conditions is ongoing.

**Bromfenac**
The non-steroidal anti-inflammatory drug (NSAID), bromfenac (Duract, Wyeth Ayerst Laboratories), was withdrawn from the market around a year after it was introduced as a result of multiple incidences of liver failure and mortality (6). Despite the drug’s efficacy in pain relief and the pre-marketing safety profile being deemed acceptable, a lack of patient adherence to the recommended use, as specified on the label, led to several deaths and the requirement of multiple patients to have liver transplants due to hepatotoxicity.

This case highlights the difficulty in determining toxic effects of drugs reliably prior to marketing due to the patient populations that are studied being much smaller than the anticipated post-marketing population (7). Additionally, it underlines the importance of adherence to the recommended and specified drug regimen, as well as the use of reporting systems by regulatory bodies (6).

**Rofecoxib**
Rofecoxib (Vioxx, Merck) was voluntarily recalled from the market in 2004 as a result of a clinical trial in which concerns were raised that the drug increased the risk of cardiovascular events (8). The NSAID, which is part of a larger family of anti-inflammatory called COX-2 inhibitors, was approved in 1999 for the treatment of arthritis, acute pain in adults, and menstrual pain.

The decision to recall the drug was made after a trial aimed at evaluating the efficacy of the drug to prevent the recurrence of colon polyps was stopped early due to the observed increased risk of cardiovascular events with chronic use of the drug (9). Although the recall was not initiated by regulatory bodies, there was agreement that it was the best course of action for the drug (10,11).

**References**

—*Felicitas Thomas*
Clarke continues to explain that the cleavage of the linker is believed to be a consequence of natural neutrophil degradation systemically, whereby enzymes in circulation indiscriminately cleave these linkers. “This [cleavage] results in a toxic payload that normally would be targeting certain cancer cells (via the antibody) but instead damages healthy circulating blood cells,” she says.

Two assay platforms, specifically designed for ADCs, have been developed by ReachBio as a result of increasing demand by industry for ways to assess the potential toxicity of these innovative therapies, Clarke reports. “The first one looks at off-target effects on white blood cells, red blood cells, and platelets. The second assay platform involves the incubation of the ADC drug with cultured neutrophils that release enzymes and cleave the ADC linker, thus causing systemic toxicity by virtue of unbound toxic payload in circulation,” she adds. “These assays have helped stratify the potency of the ADC and the stability of various linker constructs.”

Streamlining selection
Predicting toxicity based on a drug’s chemical structure can prove a difficult task; as a result of the difficulties encountered, drug developers aim to eliminate certain compounds early in the drug screening process using a series of assays, Chaney specifies. “As drug development companies streamline compound selection throughout the drug development process and towards clinical trials, the assays implemented for toxicity testing are better defined and provide more clinical relevance,” he summarizes.

References

In a recently published study, in Frontiers in Neurology, the author reports finding the potential risk of persistent visual side-effects, including light sensitivity and color vision impairment, in male patients who have taken the highest recommended dose of sildenafil (1). The patients, who attended a hospital in Turkey, had suffered from numerous visual disturbances after taking sildenafil for the first time.

The retrospective report describes the cases of 17 men, who were identified as being in good health and who experienced visual disturbances that were persistent for at least a 24-hour period after taking the highest dose of sildenafil. Although side effects are expected with sildenafil, the duration of side effects usually only last around 3–5 hours, which makes the persistence of the visual disturbances in the reported cases notable, particularly in light of the fact that all the patients who were affected had taken the maximum dose of the drug.

As sildenafil is a phosphodiesterase (PDE) inhibitor, the author noted that there may be vulnerability in certain patients to metabolize drugs in this class, and the case series highlighted the need for awareness of rare heightened sensitivity to PDE inhibitors. Additionally, the author concludes that the findings of the study support the practice of initiating a modest dose of sildenafil and only reserving higher doses for cases where heightened sensitivity to the drug is not seen.

Reference

The editors of Pharmaceutical Technology

For continuous processing... EXPERIENCE COUNTS!

**Twin screw extruders & systems**
- nano-scale and production twin screw extruders
- Foamed, multi-layer & specialty dosage forms
- Pharmaceutical extrusion seminars
- Validation documentation and services
- Fully equipped process development laboratory

**Twin Screw Seminar**
**June 17-18, 2020**
**Call 908/685-2333 ext. 614 for seminar details (ask for May Zaw)**

Melt extrusion + Granulation + Dosage Forms + Transdermals

sales@leistritz-extrusion.com // www.leistritz-extrusion.com
Challenges in Clinical Manufacturing for Topical Drugs

Jennifer Markarian

Understanding of scale-up parameters and use of process analytical technology are important to meet demand for larger batch sizes.

Topical drug products have unique characteristics compared to other dosage forms, including particular challenges in development and clinical manufacturing. Pharmaceutical Technology spoke with Jason Carbol, Chemistry, Manufacturing, and Controls manager and senior formulator with Dow Development Labs (DDL), a contract development and manufacturing organization (CDMO) in California that specializes in the development, manufacture, fill, and release of topical drug products, about recent trends in topical drug development and manufacturing.

Trends

PharmTech: What do you see as the most significant changes affecting product development and clinical trial manufacturing and packaging in the past few years?

Carbol (DDL): For topical product development and manufacturing, one of the big challenges is scale up. There seems to be a shift to move to bigger batch sizes more quickly than ever before. Good laboratory practice (GLP) animal studies are requiring larger amounts of material than in the past, partly due to changes in FDA guidance and requirements for GLP repeat-dose cumulative toxicity studies in minipigs. Studies that used to require 5–10 kg of material are now requiring 30–50 kg. Additionally, sponsors are trying to accomplish more in single studies rather than in multiple studies, which necessitates more material for the study. These larger batch sizes are challenging for benchtop R&D development work, as the formulation and process development is very quickly being transitioned from small scale to medium or large scale. Scale-up engineering was a relatively small part of the formulator’s job in the past; however, it is now becoming a larger part. Another challenge is identifying contract manufacturing organizations that are capable of large-scale batch manufacturing and filling of topical products, as there are a limited number of large-scale/commercial contract manufacturers with experience with semi-solid products.

Scale up

PharmTech: What are some of the technical challenges of scale-up and how can these be addressed?

Carbol (DDL): A key challenge in scaling up is retaining the product’s desired cosmetic elegance, viscosity, and physical stability. Topical products are fundamentally difficult to scale up due to the vast changes in physical forces seen at the bench scale vs commercial scale. At a larger scale, mixers tend to be more powerful, but mixing efficiency tends to decrease. One option for increasing mixing efficiency is to mix for a longer duration, but the product may then be subjected to forces never experienced at the bench scale during development. Additionally, it is very difficult to heat and cool at the benchtop scale similar to what will be done at the commercial scale. The effect of the time and temperature during heating and cooling during commercial-scale processing can often result in unexpected physical product changes, such as changes to viscosity. Lastly, the mass of the commercial amount of product manufactured is significant; the product on the bottom of the vessel is experiencing pressures never developed with a benchtop process. Understanding all these forces is critical to a successful scaleup.

Predictive formulation and process work at small scale that can help with scale up is increasingly important. Developing new tools to identify pitfalls early and then develop solutions is key. Some of the interesting technologies are real-time data tools used during processing. Good work is being done to integrate mixers that will measure viscosity (and as a result, torque) during processing. This
information can then be used to map out a product and its characteristics over time and/or temperature.

In addition, FDA is showing an increasing interest over the past few years in evaluating what are referred to as the Q3 properties of semi-solid products. These are the formulation microstructure properties (e.g., crystalline habit, effects of sheer on viscosity, particle size) and they must be studied and assessed during the scale-up manufacturing of these products. Scale, equipment, and manufacturing process can all greatly affect the product microstructure, particularly droplet size and viscosity. Special care needs to be taken to be sure all the microstructure characteristics developed on the bench-scale product are maintained throughout scale-up development.

Topical semi-solid products are becoming more complicated. With the wider acceptance of screening tools, such as in-vitro permeation testing, the resulting data has pushed some drugs into complicated delivery systems that sometimes include high solvent loads and/or high surfactant loads. Previously, these formulations would have been discarded as potentially irritating; however, these delivery systems are more often being pursued due primarily to superior skin penetration screening data. These products can be difficult to manufacture and scale up for a variety of reasons. For example, some of these products have high alcohol content or other flammable material content and some have high levels of surfactants. High alcohol products have flammability considerations when manufactured (explosion-proof-rated manufacturing suites are required). High surfactant systems can have compatibility challenges with other ingredients and/or with packaging, and they can present foaming concerns as well.

Clinical trial manufacturing

PharmTech: What are some of the key challenges for small-scale manufacturing, such as for clinical trials, and what are some best practices in this area?

Carbol (DDL): A big challenge in small-scale manufacturing is associated with cleaning. Cleaning validations are expensive and time consuming, yet the small clinical batches may only be made once. Disposable or single-use equipment is becoming more of an option, but using disposable equipment becomes increasing difficult when the scale is moving from small (1–10 kg) to medium-sized (10–50 kg) batches.

“Scale, equipment, and manufacturing process can all greatly affect the product microstructure.” —Jason Carbol, Dow Development Labs

Developing unique, cost-effective solutions for fully custom, one-time-use, dedicated equipment is a key challenge. In contrast to single-use systems for biologics (aqueous solutions at room temperature), for example, topical semi-solid products may require processing that includes temperature cycling. The ability to heat and melt waxes (in what would be mainly plastic-based systems for biologics) is of concern with respect to integrity of the plastic and leads to leachable/extractables issues. Additionally, ingredients that are used in topical semi-solid products are not always water-based and thus compatibility issues come into play. In addition, the need for high-speed and high-shear mixing in a one-time use system is not yet well-addressed for semi-solid products. Mixing dynamics is critical, and therefore, there is a need for a good single-use high efficiency mixing system.

Another challenge is with respect to the use of digital technology as it relates to manufacturing small-scale clinical materials. For small-scale GMP manufacturing, many systems are still easier to accomplish via pen and paper. Many new electronic tools exist for the pharmaceutical industry, but being strategic about which ones to incorporate into small manufacturing processes is difficult. Many systems are difficult to justify on a cost-benefit basis and may be needlessly complicated.

PharmTech: What are some of the key challenges in packaging for clinical trials?

Carbol (DDL): Packaging topical drug products into tubes, jars, sachets, applicators etc. is always challenging. For small clinical batches, filling tubes in a fully manual filling process used to be the norm. Now, with larger batch sizes, manual filling is becoming cumbersome. However, large fill lines are not practical, and cleaning validations are again an issue. Developing fast, accurate, cheap, one-time use filling equipment is ideal. Filling can be accomplished at times with small semi-automated equipment, but when more unique packagings are desired, such as applicator pens, syringes, single dose applicators, or sachets, creative solutions are needed.

Another packaging trend we have noticed is that some of our clients would like to have the product in a representative final packaging, even during early clinical trials. Historically, final packaging was decided much later, closer to phase III/commercial stage. With tube manufacturers having minimum order quantities of approximately 10,000 units, orders for small clinical trials can be impractical.

Topical products in clinical trials can be uniquely challenging due to the potential for variability of dosing. How much to provide (package) to each study subject requires thought and planning. When the indication is a fixed site (the face, for example) it is easier to estimate use than for psoriatic subjects when anywhere from 5% to 20% body surface area may be involved. Sometimes dosing cards or cups that provide a guide for the amount to dose are used, but most often a description of the amount to express from a tube (e.g., pea size) is all that is provided. Having additional packaged product ready and available for dispensing to subjects may be an important aspect to clinical trials involving topical products, depending on the product and study design.
An early start on process development helps optimize biomanufacturing processes, shorten time to market, potentially cut costs, and keep product in line with current good manufacturing practices. While the approach to process development for emerging therapies (e.g., gene therapies and cell therapies) is similar to the approach used for more traditional biologic medicines (e.g., monoclonal antibodies [mAbs]), the nature of emerging therapies means there are further nuances to consider in optimizing their manufacturing processes.

**Gene therapy challenges**

“Many of the general bioproduction concepts for gene therapies are similar to the more mature protein therapeutic market; however, there are many nuances in raw material costs, supply chain, technologies, regulatory standards, and overall scale that make gene therapy production a more dynamic process,” says George Buchman, vice-president of Pre-Clinical and Process Development at Catalent’s Paragon Gene Therapy.

Viral vector manufacturing, for example, is a complex process, Buchman notes. Add to that the influx of various and ever-evolving enabling technologies and growth platforms, and viral vector manufacturing becomes even more dynamic. “For example, the supply chain process for standard biologics is more mature and optimized, offering a relatively clear path for manufacturers to follow. However, due to the exponential growth being experienced with increasing numbers of gene therapy molecules with regulatory agency fast-track status, and a large influx of gene therapy assets in the clinical pipeline, raw material supply can be outpaced,” Buchman says. “Additionally, the cost of gene therapy raw materials is generally higher and more varied than what is seen in traditional biologics. Therefore, it is critical to plan ahead and have a risk mitigation strategy for secure supply and cost management.”

Process modeling is also critical to any good development and scale-up process, Buchman points out. Various scale-down approaches can replicate large-scale conditions at small scale, and this is a relatively inexpensive modeling method. It is often highly predictable at large scale for both upstream and downstream processes.

However, there are cases in which process modeling is not very predictive, Buchman notes. “A good example is when a given platform may not scale linearly. However, if you focus on the relative data rather than the absolute data, side-by-side comparison rather than the actual numbers, it is still somewhat effective. All of these modeling approaches take time and deep gene therapy production expertise to develop a trustworthy and predictive model,” he says.

**Optimizing gene therapy processes**

For viral vector manufacturing, yield and recovery are key factors considered when optimizing processes. A good deal of focus is on developing a process that creates more full capsids versus empty ones and optimizes the percentage of material that can be recovered from the total production, Buchman explains. Optimization can also occur in the downstream development process by removing the empty capsids while decreasing the full ones that are removed at the same time, he continues.

“Additionally, we are always focused on vector safety (making sure non-vector components are removed) and vector function (making sure the vector not only is properly isolated but also transduces correctly). For lentivirus production, a key factor is reducing stability issues during viral recovery,” Buchman says.
“For gene therapy manufacturing, material costs (virus and plasmids) are actually higher than the cost to manufacture the product, so reducing material costs is essential for economical production. Of course, creating an optimized manufacturing process to achieve an economy of scale is the goal for the industry, but with so many changes and new technologies and platforms, this will need to evolve over time. We are in a great position as a focused development and manufacturer because we have experience and exposure to a variety of biologic entities, platforms, and processes,” Buchman adds.

**Cell therapy challenges**

Cell therapies have their own set of process development challenges. Cell therapies can be either autologous (one individual is both the source and the recipient of the therapy) or allogeneic (a donor is the source of cells used for the therapy, which can be administered to a number of recipients). In both approaches, it is critical that the therapeutic cell be characterized to define which properties of the cell determine that it has been produced to acceptable standards and quality. This characterization is necessary to ensure that the risk of incorporating anomalies or shifts in cell function have been minimized, because such discrepancies may compromise the safety or efficacy of the therapeutic cell (1).

To be successful from a clinical or commercial standpoint, cell therapy manufacturing processes must create a consistent, safe, and effective cell therapy product, regardless of the cell type or the application for which it is used. Process development for a cell therapy must therefore apply to all elements of the manufacturing cycle—cell isolation, cell characterization, cell culture media, scale-up, and removal of impurities.

Process development for a cell therapy, whether autologous or allogeneic, must address at least the basic questions about how the therapeutic cells will be expanded and manufactured in ways that will retain their potency. Process development should additionally consider what characteristics must be monitored that define the particular cell product of interest. Further, what assays should be used to measure these desirable cell characteristics? The process development approach (1) must also consider how the cell therapy product will be stored and administered as well as take into account the lot size dictated by the market for that specific product.

**Lessons from mAbs**

Monoclonal antibodies have had decades to establish robust and economical commercial biomanufacturing processes and are today considered the leading modality for biotherapeutics (2). Blockbuster success with some mAb therapeutics has also encouraged refinement and innovation in bioprocessing steps, making the manufacture of mAbs further efficient and more productive while retaining safety and efficacy.

Lessons learned during the growing pains of mAb process development may also benefit cell and gene therapies.

*Lessons learned during the growing pains of mAb process development may also benefit cell and gene therapies.*
Process variability must be assessed over time to ensure that pharmaceutical product quality is maintained. While the application of prospective statistical process control has been widely published, much less emphasis has been given to retrospective statistical analysis and associated methods and approaches. The authors present a simple-to-use Microsoft Excel-based statistical tool that uses cumulative sum techniques to aid retrospective understanding of data trends. Practical recommendations and experience of applying the tool from a pharmaceutical manufacturing context are also provided, including the teamwork needed to fully exploit these approaches through combining input from multiple disciplines.

Implementation of Autocorners Algorithm for Retrospective Process Monitoring

Robert Shaw and Marie South

In pharmaceutical development and manufacturing, scientists are often involved in assessing process variability over time. For example, having developed a new analytical method, the analyst needs to review data to ensure that the method continues to perform adequately over time; or scientists responsible for manufacturing processes need to demonstrate that product quality is maintained and that there is no evidence of systematic or special cause variability in processes. It can be misleading to apply traditional prospective techniques when analyzing data retrospectively (see below), and a useful alternative is cumulative sum techniques.

The tool presented in this paper incorporates such cumulative sum techniques and furthermore uses the Autocorners algorithm to automatically identify statistical changes in the average over time, which can aid problem-solving and process improvement.

Retrospective vs prospective monitoring

The techniques and approaches described in this paper apply to any process where data are gathered in time-ordered sequence and one wishes to understand the process to ensure statistical control and variability within acceptable limits. For many processes, Shewhart control charts work well for prospective monitoring. The implementation of effective Shewhart charts involves a set-up phase prior to the subsequent run phase. The set-up phase includes capturing data over a pre-defined period of time exhibiting statistical control (absent of special cause variability) and calculating control limits based on the mean and standard deviation. These summary statistics are then applied to calculate control limits to be used subsequently in the run phase. Often, analysts want to review data retrospectively (e.g., in manufacturing, analyze data from previous batches of product to assess process robustness or to identify a root cause of a problem). In these cases, the traditional Shewhart chart does not apply in the conventional way. In particular, care needs to be taken in constructing a Shewhart chart from historical data where the limits applied are based on the same data being analyzed. In this case, the limits might be derived from data exhibiting special cause variability, which would inflate the limits calculated. An effective alternative to Shewhart charts in the
Who We Are
Chemic Laboratories, Inc. is a full service cGMP/GLP contract analytical chemistry laboratory. Chemic provides an array of R&D and cGMP contract testing services including; Extractables/Leachables analysis, CMC Method Development & Validation, Quality Control analysis, Release testing, Raw Materials analysis, Compendial testing, Organic Synthesis/Formulation Development & ICH Stability testing. Chemic continually strives to exceed the requirements and expectations of our sponsors. We are committed to providing quality services to our clients in support of their product development needs.

Major Markets
Chemic Laboratories, Inc. is located in Canton, Massachusetts and provides cost-effective outsourcing solutions to a broad spectrum of global clients in the pharmaceutical, medical device and biopharmaceutical industries. We are committed to developing long term strategic alliances with our clients. Chemic offers the ideal blend of expertise and experience that is critical to our clients’ success.

Services Offered
Chemic Laboratories, Inc. offers a wide array of cGMP/GLP contract testing services including:

- Quality Control Testing of raw materials, API's and finished products
- Monograph Testing (USP, EP, BP and JP)
- CMC Method Development & Validation
- Degradate Quantitation
- Extractables and Leachables Analysis
- Container Closure Assessment
- ICH Storage and Accelerated Stability Studies
- GMP/GLP Method Development and Validation
- Organic Synthesis and Formulation Development
situation of retrospective data analysis is CuSum charts and the Autocorners algorithm described in this paper.

Cumulative sum (CuSum) charts and Autocorners can be applied both in prospective and retrospective situations. Many texts (1–7) describe the improved sensitivity in identifying small shifts in the average or variance when using CuSum techniques compared with Shewhart methods. Table I distinguishes the benefits of Shewhart charts for prospective monitoring versus CuSums/Autocorners analysis.

**Overview of CuSum chart construction**

In constructing a CuSum chart, the data are first suitably ordered (e.g., by manufacturing date) and the following steps applied.

Suppose there is a set of results in sequence, denoted by \( x_1, x_2, \ldots, x_n \). The differences of each result from a target or reference value, \( T \), are calculated, so the ith difference = \( x_i - T \). The cumulative sum (CuSum) chart is produced using the overall mean as reference value. CuSums are formed using the overall mean as reference value.

The effect of the CuSum is to produce a smoother picture of changes in data over time—a shift up or down in the raw data will appear as a change in slope in the CuSum.

Having plotted the CuSum data as a chart, it may be useful to assess whether an observed change in slope demonstrates a genuine signal (special or assignable cause) or whether it represents typical noise in the process (common cause variation). Several approaches to making this assessment are described by Taylor et al. (8).

The Autocorners algorithm identifies where statistical changes in slope occur in the CuSum chart. These change points are highlighted in a plot of the original raw data by splitting the data into stages and plotting the average per stage.

**Autocorners algorithm description**

In the retrospective analysis of process data, Woodward and Goldsmith describe several approaches that can be applied to decide whether a change in the slope of a CuSum chart is real or due to noise. These include two manual approaches (the “span” method and the decision interval method) and one automatic search by computer. It is this latter approach, called “Autocorners”, that has been programmed into the Manhattan tool. The data in Figures 1–3 are used to illustrate the approach described as follows:

1. The first step is to inspect the data for unusual observations that may be individual outliers. These are identified by testing whether an observation differs from both of its neighbors by more than 4.12 times the mean range (4.12 is the appropriate 0.1% significance point—see Weatherill et al. (1) Table 5.2). If any are found, then they are replaced in subsequent calculations by the average of the two adjacent values in the series. It is important to note that these unusual values are not excluded from the final interpretation and are represented in the output plot; however, outliers should not overly distort the CuSum chart or skew the overall trends and associated calculations.

2. The overall mean of the data series is calculated, and CuSums are formed using the overall mean as reference value.

3. A forward search is carried out through the data series starting at the first point as follows: a chord is joined from each CuSum back to zero, and the maximum difference between the chord and corresponding CuSums is found (see Figure 1): a. The position of this largest difference is used to split the intervening original observations into two groups, and a t-test is carried out between the mean values of the two groups.

b. When the value of t is not significant, the program moves to the next CuSum and repeats the process. When the value of t becomes significant, the program, subject to further tests, declares this position to represent a significant changepoint (called a “corner”).

4. A forward search is carried out through the data series from each corner as follows: a chord is joined from each CuSum back to the last corner, and the maximum difference between the chord and corresponding CuSums is found (see Figure 2). The same criteria a. and b. are applied as in 3 above.

5. When this forward search is completed, the program re-

---

**Table I: Comparison of Shewhart and CuSum charts.**

<table>
<thead>
<tr>
<th>Shewhart Charts</th>
<th>CuSum Chart/Autocorners</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Primary goal: Identifying special cause variation at the time it occurs to facilitate understanding the causes and hence reduce the frequency in future.</td>
<td>• Primary goal: Visualising, understanding and reducing the frequency of step changes (in mean or variation).</td>
</tr>
<tr>
<td>• Ideal for prospective analyses.</td>
<td>• Able to pick up subtle step changes and able to identify any step change more quickly.</td>
</tr>
<tr>
<td>• Suitable when process is predominantly stable.</td>
<td>• Ideal for retrospective analyses.</td>
</tr>
<tr>
<td></td>
<td>• Flexible in dealing with unstable processes with frequent step changes (in mean or variation).</td>
</tr>
</tbody>
</table>

---

The tool has been applied successfully in a variety of different pharmaceutical applications, including:

- Monitoring stability of in-vitro assays in research
- Assessing animal model performance by monitoring control groups over time
- Aiding understanding of variability in critical quality attributes and processing parameters in manufacturing processes.

---

**PharmTech.com**

**36  Pharmaceutical Technology MARCH 2020**
verses the order and does a backward search.

6. Finally, the two lists of change points are amalgamated, and a list of significant change points made.

In the above steps, numerous tests of differences between adjacent segments are made. The overall significance level (α) has been explored by varying between 1, 5, and 10%, so that the algorithm would find increasing numbers of corners with higher α. In the authors’ experience, applying a 1% significance level works well for most of the data sets, and this is used as the default setting in the tool. The overall adjustment is applied for multiple comparisons described in BS 5703: Part 2. This standard has been superseded by BS ISO 7870–4 (3); however, this more recent version does not include the multiple comparisons details; two alternative references (9,10) have been provided for readers without access to the original standard.

As explained in the references (4,9,10), for retrospective analysis using CuSum charts, the individual tests should have significance level \( \alpha / \sqrt{m} / 2N \), where \( m \) = length of segment, \( N \) = total number of observations. The \( t \)-test with an ad hoc adjustment has significance level given by Lewis et al. (9), \( \alpha / (2\sqrt{m}) \). Where multiple tests are carried out in a series of total length \( N \), the adjustment described by Osanaive et al. (10) also applies: \( (m/N)\alpha \). This leads to a combined adjustment of \( \alpha (m/N)/(2\sqrt{m}) = \alpha / \sqrt{m} / 2N \).

Having identified points of change or corners in the raw data, then a convenient representation of the data is provided in Figure 3. The raw data are shown as green triangles and connected with a blue line. (In situations where an unusual value has been identified, as in step 1 described previously, then such a point is connected to its neighbors with a green rather than blue line, such as shown in Figure 4.) In Figures 3, 4, and 5, the black line shows the CuSum plot. The red line shows the means across the regions between the break points, and shifts in this line indicate where the significant change points occur. This plot is called the Manhattan plot as it can look like the skyline of Manhattan. The changepoints in the Manhattan plot coincide with where the slope changes in the CuSum plot.

Using the tool

The Autocorners functionality described in this paper has been written into the Excel tool using VBA.

Data entry and tool output. Raw data are entered into the spreadsheet. There is some additional functionality that is available including the ability to refresh the spreadsheet by deleting existing data. The tool is flexible to handling different numbers of response variables.

When the analysis is run, for each variable, two new worksheets are produced:

- One sheet consists of a plot of the raw data with the Manhattan plot overlaid, together with the CuSum chart (if selected).
- The other sheet provides statistical summary statistics and details of the different stages.

The choice of whether to include the CuSum chart or not depends on the nature and amount of data entered. In the following example, the CuSum is particularly helpful to visualize alongside the Manhattan plot to help confirm the key change points in the data. When viewing the Manhattan plot, some pragmatic interpretation is required (e.g., it is crucial to take account of the scale of the \( y \)-axis and to avoid over-in-
interpreting changes which are not of practical importance). If changes are made to the data entry sheet and the analysis re-run, then the new sheets produced will over-write the previous ones.

**Example of application—capsule dissolution investigation.** The dissolution test for this product involves taking a random sample of six capsules from a batch and submitting them to the dissolution test. The dissolution test gives the percent dissolved at 90, 300, and 480 minutes, from which the rate of change between 300 and 480 is calculated. The average dissolution rate for the six capsules across multiple time-ordered batches has been recorded and analyzed using this tool. See Figure 4 for an example of the graphical output with the following features:

- There is one value deemed to be an unusual value—batch 84. This one value is connected to the ones either side by a green line. The algorithm automatically identified this point (see point 1 in Autocorners Algorithm Description) and replaced it in calculations by the average of the two adjacent values.
- The CuSum plot shows an important change in slope at batch 315. Prior to this point, the slope is predominantly negative, while subsequently the slope is consistently positive.
- The change in slope of the CuSum corresponds to an upward shift in the raw data and an upward step-change in the Manhattan plot.

There are some other changes that can be seen in Figure 4 between batches 40 and 63, and around batch 275; however, these are more subtle and not sustained over a long time.

Various other processing factors were also recorded for these batches. These were examined to assess their variability and to seek a possible link with dissolution. One such variable is spray time, which has been analyzed and presented in Figure 5. It is notable how similar the pattern in the CuSum is for spray time compared to dissolution. This provides a plausible hypothesis for a causal relationship which could be further investigated in a designed experiment.

**Practical considerations**

From practical experience, the following recommendations are made to fully exploit the tool and approaches:

- Ensure appropriate staff are involved in the review process, including both technical staff and, depending on the nature of the problem, operators as they are closest to the day-to-day running of the process.
- Statisticians should be involved in the data review and interpretation. They should also take responsibility to raise awareness of the techniques and skill level of scientists and engineers in basic data manipulation, visualization, and statistical analysis. In-house statistical training should be provided to scientists and engineers including understanding variability, statistical process control, and retrospective data analysis including CuSums.
- While the tool operates in an automated fashion, it is important to not treat it as a black box, but to make practical interpretation of the trends in the raw data and change-points identified, for example:
  - A corner identified using the automated algorithm may represent an unimportant change, scientifically.
  - While step-changes are common in manufacturing processes (e.g., due to switch of batch of raw material, change in operator, change to procedure), other types of change can occur (e.g., drift or cycling)—these may not adequately be picked up by this tool.
- Further statistical analysis may be required in some situations (e.g., more in-depth data visualization and multivariate data analysis).

**Conclusion**

The tool presented in this paper provides an automated approach to retrospective data analysis and interpretation. The tool is user-friendly and accessible, only requiring the user to paste in data and click a button to run the analysis. The
output is easy to interpret comprising a CuSum plot, identification of significant change points and subsequent visualization using the Manhattan plot, and summary statistics of each stage between adjacent change points.

Important areas of application include manufacturing and engineering where some insightful applications of the tool have been delivered, particularly regarding trends in critical quality attributes (responses) and relating these to in-process parameters.

**Access to tool.** The tool can be downloaded from Box here: http://goto.az/manhattan. (Click the “Download” button to open in Excel or save the file. As it opens in Excel, click the button “Enable Content” and “Enable Editing” to proceed. Data can be entered to the worksheet “Data for Monitoring” following the instructions in the Help tab.)

**Editor’s Note:** The link is provided by the author, and Pharmaceutical Technology does not assume any liability for the contents of the linked file.

**Acknowledgments**
The authors wish to thank Linda McKinnon for her instrumental delivery of Excel VBA code.

**References**


*To whom all correspondence should be addressed.
According to market research, the global pharmaceutical analytical testing outsourcing market is projected to have strong growth from 2020 to 2027 (1). Drivers of this growth include an increase in demand for biopharmaceuticals, biosimilars, and analytical drugs, in addition to a general requirement for bio/pharma companies to streamline operations and reduce costs.

To learn more about the criticality of stability testing throughout drug development, potential differences with small versus large molecules, regulatory requirements, and future trends, Pharmaceutical Technology spoke with Ramesh Jagadeesan, senior director of analytical development, Recipharm; and Karin Kottig, manager contract service analytics, Vetter Development Services.

As compounds become more complex in nature and biological ingredients are more widely used, stability testing approaches must follow suit and provide flexibility for developers.

An essential part of drug development

PharmTech: Could you elaborate on the importance of stability testing throughout the various development steps of drug products?

Jagadeesan (Recipharm): Stability testing is one of the most crucial steps in the development of new drug products. By performing a series of analyses, testing programs can determine how long a product will maintain the properties and characteristics it possessed at the time of manufacture. The effect of environmental factors (such as temperature, light, and humidity) on a formulation’s purity, efficacy, and structure is evaluated over time to define both its shelf-life and the necessary storage conditions. This information is vital for the regulatory approval of a new medicine.

Stability studies are conducted during all phases of drug development. They typically start at the preclinical stage of drug development and continue through Phase I–Phase III clinical trials to support formulation development, and to satisfy the regulatory requirements for clinical trials. However, the purpose of the studies and regulatory requirements vary depending on the product type, the phase of the program, and the intended markets.

The first stage of stability testing usually takes the form of forced-degradation studies. These studies help to identify the ideal formulation from a host of different candidates to take forward for further testing. The aim of this is to understand the primary degradation products of a molecule and aid analysts in selecting the best methods for further stability tests, which mimic real-life storage in different global regions. Long-term stability studies will subsequently be initiated and validated on both the API and the drug product.

In short, the aim of the stability testing process is to produce data that demonstrates whether any physical, chemical, or microbiological changes affect the efficiency and integrity of a pharmaceutical product. This helps to ensure medicines are safe and effective, irrespective of where in the world they are supplied.

Kottig (Vetter): Stability studies are an essential and vital part of drug development. They are necessary throughout all phases with stringent timelines for analytical testing. The purpose of the studies is to prove how the quality of an API or drug product changes over the course of time while under the influence of environmental conditions such as temperature, humidity, or light. Stability studies also support the determination of the re-test date of the active ingredient, shelf-life of the drug product, suitable packaging materials, and recommended storage conditions.

With respect to new drug applications, submissions for approval by regulatory authorities are required to
Lonza Capsugel® – The Right Partner for Your Next Drug Development Project

ON-DEMAND WEBCAST: Aired Thursday, March 12, 2020

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

Event Overview
Building on a history of innovation in polymer science and capsule engineering, the Capsugel® brand, now part of Lonza, offers a product and services portfolio beneficial for Pharmaceutical and OTC customers alike. Capsugel® is the global leader in capsules, encapsulation technology, and designs. Their unique combination of science, engineering, formulation, and capsule expertise enables customers to optimize the bioavailability, targeted delivery, and overall performance of their products and services. Learn more about the benefits of partnering with Lonza Capsugel® and their full offerings by joining this informative webcast.

Key Learning Objectives
• The importance of choosing the right capsule during the development phase
• Discover new tools to help choose the right capsule during the development phase
• Explore value-added services aimed at cost reduction and improved efficiency
• Discover encapsulation tools that can help make the process to commercialization faster, easier and more successful

Who Should Attend
• R&D, early-stage drug developers, formulators, product development, formulation scientists, purchasing, regulatory, quality managers, quality engineers, compliance, pharma project managers, procurement, research chemists, production managers, operations managers

For questions or concerns, email mdevia@mmhgroup.com

Presenters
Julien Lamps
Product Manager, Capsule Delivery Solutions
Lonza Pharma & Biotech

Mary Ellen Johnson
Product Manager, Capsule Delivery Solutions
Lonza Pharma & Biotech

Amber Lowry
Senior Editor
Special Projects

Sponsored by
Lonza
Pharma & Biotech

Presented by
Pharmaceutical Technology
contain data from stability studies conducted on both the drug substance and the drug product. During drug development, this assessment is performed with the help of a variety of well-designed stability studies in the different development phases. During early development, stability studies are performed on technical batches as well as on clinical samples. These include, for example, stress and accelerated studies of the drug substance and product to support setup of formulation, selection of primary packaging, and production process. In later phases, transport and cycling studies as well as long-term and accelerated studies with registration batches are realized. All data are compiled to generate the expiration date of the drug and, finally, to obtain the market authorization.

After product launch, follow-up stability studies of market batches are conducted on a regular basis. The studies are also necessary after post-approval changes. In this way, they significantly influence the entire lifecycle of a product. Ultimately, they are essential to provide a drug and thus the health of the patient by supplying a stable product with consistent quality.

Small versus large molecule

PharmTech: Are there specific differences in terms of stability testing for small-molecule versus large-molecule products?

Kottig (Vetter): From complex and highly sensitive substances to vaccines and biotechnologically produced proteins, the manufacturing of drug products demands a high degree of expertise and flexibility to perform all the necessary and product-specific processes prior to the independent completion of the final product. Thus, stability testing required for ensuring a product is fit for use are adapted on a case-by-case basis.

The increasing number of biologics in clinical development has had a significant impact on analytical methods and has brought forth new scientific challenges. When it comes to injectables, biologics are placed into a small volume of liquid that often requires a very high concentration. This leads to unique stability issues related to aggregation, viscosity, and thermal degradation. And, while still relatively complex, it is usually a straightforward process to demonstrate the identity, correct content, and purity of small-molecule drugs and the correlated products. The evaluation of the quality of a biological, large-molecule product requires much more complex analytical and bioanalytical methods.

“The increasing number of biologics in clinical development has had a significant impact on analytical methods and has brought forth new scientific challenges.”
—Karin Kottig, Vetter

From my point of view, the increased focus on particulate matter is also correlated to large-molecule products as they are often very sensitive. Aggregation, as well as interactions with other components such as excipients and packaging material, for example, could lead to increased particulate matter formation. These particulates will then be analyzed with different analytical methods.

Jagadeesan (Recipharm): The development of an appropriate stability testing program typically considers the specific nature of the product being evaluated. Based upon the constituent compounds and knowledge of how they are impacted by storage and environmental conditions, the degradation dynamics of small-molecule products are predictable. The rise of newer, large-molecule drugs developed using biotechnology has brought new scientific challenges for stability testing.

The greater complexity of large-molecule products, combined with more batch-to-batch variance and specialized storage conditions, makes typical stability study conditions unsuitable. To this end, bespoke stability testing programs need to be designed for each product. Biopharmaceuticals are generally highly concentrated and/or less soluble, which increases the likelihood that the API will precipitate during stability studies. Clear, quality data surrounding this process are essential to ensuring regulatory compliance.

In addition, small-molecule degradation pathways are more predictable and shelf-life specifications are set based on the toxicological studies. Whereas, with biopharmaceuticals, degradation pathways are much more unpredictable, and they differ for different proteins. For example, some parenteral biologics administered for patients are highly concentrated, so they may precipitate during the stability studies.

Biopharmaceuticals are often only stable over a very limited temperature range, meaning that excursions/temperature deviations outside the optimum storage conditions can have a significant impact on stability. To this end, they should be stored within an extremely narrow temperature range to avoid an impact on biological activity. Testing the stability of such sensitive products in a range of temperatures needs to be carefully planned to take actual storage conditions into consideration. Additionally, the stability of proteins often calls for other analytical methods other than the liquid chromatography that is frequently used for small organic molecules.

Regulatory expectations

PharmTech: What are the regulatory expectations for stability testing?

Jagadeesan (Recipharm): The International Council for Harmonization of Technical Requirements for Pharma-
As a result, testing programs should be conducted with relative humidity up to 75%. The European Medicines Agency (EMA) and the FDA for its abbreviated new drug applications pathway.

There are, however, marked differences in the specific stability data required by authorities in each market. As a result, testing programs should be developed with the specific market in mind. For example, despite authorities in the United States and European Union adopting the same standards, they set different microbiological limits for stability tests. In addition, some assessments that can be omitted in the US are mandatory in the EU and vice versa.

Stability testing of pharmaceutical products is mandatory for regulatory approvals. If a product fails to meet the standards prescribed by the ICH, as well as those defined by the World Health Organization, the product will not be granted approval for commercialization. Planning, execution, and completion of studies in given timelines plays a major role in securing approval and ensuring a product reaches patients.

**Kottig (Vetter):** Drug stability is not simply a requirement of the regulations. Rather, stability testing operations are a ‘window’ for the development program of the product and the assurance of quality. Practically all regulatory requirements for drug stability testing are clearly described in [good manufacturing practices] GMP guidelines. Today, stability plans include far more than just the determination of an expiration date for a pharmaceutical product. They also require a written stability testing program that specifies sample sizes and test intervals, controlled storage conditions, validated and specific test methods, and specifications. Furthermore, requirements stipulate that an adequate number of drug production batches are tested. In addition, it is mandatory to perform stability testing of the product in its marketed container or closure system.

“A great challenge in product development is the time it takes to ensure stability.”

—Ramesh Jagadeesan, Recipharm

There has been considerable harmonization of regulatory guidelines, with the ICH pharmaceutical stability guidelines now recognized as the globally accepted industry standard. ICH provides practical guidance on the amount and type of drug substance and drug product stability data needed to support marketing applications. The included quality guidelines Q1A–Q1F have made a major contribution to increasing the quality of pharmaceuticals and are applicable for small molecules. Generally speaking, they apply to large-molecule products as well. ICH Q5C takes into consideration the specific characteristics of biotechnological/biological products. These large-molecule products are typically more sensitive than small-molecule products and require complex analytical methods to demonstrate that their molecular conformation is maintained during shelf life. For example, a potency assay is required to prove biological activity is maintained. Usually, more than one analytical method is needed to prove purity of the product.

**Future trends**

**PharmTech:** As molecules in development become more complex and difficult to deal with, what trends do you predict may impact the industry over the next 5–10 years in the area of stability testing?

**Jagadeesan (Recipharm):** As the demand for biopharmaceuticals increase, even more efficient methods will need to be in place for the assessment of protein activity. This makes it necessary to have access to more analytical technology compared to when handling small molecules, where liquid chromatography can fulfill most analytical needs.

A great challenge in product development is the time it takes to ensure stability. There is a significant need for methods that enable the prediction of the stability of a formulation at an early stage as this will allow companies to shorten development timelines and reduce the risk of unforeseen timelines later on in stability studies.

While APIs are growing in complexity, there is also a trend towards more complex formulations, such as nanoparticles, microemulsions, and amorphous formulations to give acceptable solubility and bioavailability. For these formulations, physical-chemical characteristics, in particular solid-state characteristics, are very important; hence, this leads to the need for more physical-chemical characterization during stability studies.

**Kottig (Vetter):** When addressing the challenges of increased complexity of molecules in development in combination with even shorter timeframes for drug development and smaller batch sizes, the pharmaceutical and biotech industry should collaborate with regulatory bodies to generate meaningful risk-based guidance. Holistic approaches will require good data management and integrated systems to collect, manage, and process data to effectively support stability analyses in the future.

**Reference**

Navigating GMPs for Gene Therapies

Feliza Mirasol

While new industry guidance documents issued by FDA speak to the agency’s efforts to promote the development of new gene therapies, certain hurdles remain to challenge stakeholders.

The focus on developing emerging therapies, especially cell and gene therapies, has intensified, making the need for good manufacturing practices (GMP) guidance more imperative. In its specific efforts to promote the development of novel gene therapies, FDA published six final guidance documents on gene therapy manufacturing and clinical development and released a draft guidance on gene therapy products under orphan drug regulations in January 2020. To date, the agency has approved four gene therapy products (1).

Guidance challenges

The Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) (2) guidance provides a comprehensive framework to guide the development of a broad range of products, says Karen Magers, head of Regulatory Affairs Cell and Gene Therapy Technologies, Lonza. The guidance document provides many recommendations that help to clarify the expectations for product development, characterization, manufacturing, and testing of these products, she points out.

“Stakeholders, including Lonza, submitted comments [to FDA] requesting clarification on the information to be submitted prior to a first-in-human clinical study and information to be submitted in a phased approach, as more manufacturing experience is obtained during product clinical development. FDA acknowledged in the final document that ‘information may be limited in the early phases of development and recommends that sponsors provide additional information and updates as product development proceeds,’” she states.

However, because limited specific recommendations and examples were provided in the guidance, there are remaining challenges in determining the requirements for first-in-human studies and subsequent clinical studies, she continues.

The challenges to gene therapy development and manufacturing are what they have always been. “I don’t think there is anything unexpected in the final CMC guidance,” says James Blackwell, PhD, principal consultant and president of The Windshire Group, a Boston, MA-based biopharmaceutical consulting group. “The challenges are what they have always been. However, there are numerous challenges posed in the guidance for developers.”

Blackwell narrows down challenges his group has experienced, which will likely be the same experiences that other stakeholders in gene therapy development will also experience. First, for any combination product or potential combination gene therapy product, developers should carefully assess the available guidance and make early assessments in the program because the regulatory and documentation requirements can vary significantly for various components. “For areas of doubt, one should engage the Health Authorities early. This can be a challenging area for emerging technologies,” Blackwell says.

Blackwell also points out that there is a higher burden, compared to traditional products, for gene therapies to understand critical attributes and parameters earlier in the development cycle while trying to establish as robust of a process as early as possible. This burden stems from the complexity of a gene therapy product. “The benefits of doing so are dual. First, you minimize the need for change later and, if change is needed, you have a more solid basis for rationalizing and approaching it to minimize impact to development timelines. The latter point is always important but will be a key consideration for many of these programs,” Blackwell states.

“Containers used for drug substance and drug product need to be closely scrutinized for products that can’t be filtered,” he continues. “The level of particulates may not be controlled as closely as needed during the manufacture of these components, and the particulates will end up in..."
Introducing the New Portable XRF Analyzer for Identity Testing of Pharmaceutical Ionic Salts

ON-DEMAND WEBCAST: Aired Wednesday, March 11, 2020

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

Event Overview

This webcast explores the use of a portable x-ray fluorescence (XRF) instrument, the Thermo Scientific™ IonicX™, and explains how it can identify ionic salts in seconds and replace traditional time-consuming and resource-intensive wet chemistry and benchtop methods.

In pharmaceutical manufacturing, handheld Raman and near-infrared spectroscopy (NIR) analyzers are widely accepted for material verification of excipients and APIs. Complementary to the use of these portable instruments for raw material ID is the new IonicX portable XRF analyzer for identity testing of pharmaceutical ionic salts. Built for biopharmaceutical manufacturing, IonicX is 21 CFR Part 11 compliant and employs a patented algorithm C-value that allows ionic salts to be identified in seconds using portable x-ray fluorescence.

Key Learning Objectives

- Learn what materials can be identified using portable XRF
- Understand how to measure ionic salts quickly with the IonicX
- Be able to make the decision if portable technologies will help you

For questions or concerns, email mdevia@mmhgroup.com.
your product if not controlled or removed in advance. For some of these suppliers, a gene therapy developer represents such a small part of their overall business that the supplier will not accommodate changes deemed necessary by the developer. Particulates and their potential to cause adverse events have been the subject of increasing regulatory scrutiny.

**Guidance benefits**

The bottom line to having these gene therapy guidance documents is to facilitate not only the development and current good manufacturing practice (CGMP) compliance of gene therapies, but also the regulatory pathway to drug approval.

The two guidance documents (2,3) that include CMC-specific recommendations also provide clarity on many aspects related to the manufacturing and testing requirements for gene therapy products, Magers asserts. “[These] documents provide both general guidelines and specific recommendations. As an example of a general guideline, FDA provided information supporting the classification of viral vectors. Comments on the draft Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) document sought this clarification. In the final version, FDA cited regulation to confirm their position that a vector ‘used to transduce cells *ex vivo* and which furnishes a pharmacological activity for the treatment of disease is a critical component. Without the vector, the resulting cell product would not have the same pharmacological activity. Similarly, a vector in its final formulation for administration of the genetic material is generally considered a DP [drug product],” Magers cites.

She notes that FDA gave examples of specific vector recommendations, which include replication competent retrovirus (RCR) testing of cell banks, vector-harvested material, and *ex-vivo* transduced cells. FDA had also given an example of the derivation in its recommendation for an appropriate test volume for RCR detection.

**Moving forward past the hurdles**

At present, there are still hurdles to overcome in the manufacturing of gene therapies, and a number of biopharmaceutical companies as well as contract manufacturing organizations/contract development and manufacturing organizations are tackling these challenges.

For one, gene therapy (and cell therapy) manufacturing is still a highly manual aseptic manufacturing process, which poses several challenges, says Magers. It is important to consider the correct and functional layout of cleanrooms and the number of trained operators needed for those cleanrooms, she points out. She also emphasizes the high importance of ensuring the qualification of sterile consumables and raw materials because, often, only research-grade material is available and there is no GMP material available to replace them when manufacturing is scaled up.

“We are also observing a high investment in infrastructure and facilities in contrast to low throughput areas (personalized medicine, small batch sizes—down to one batch per patient), as well as unclear expectations for concurrent manufacturing of several batches and product segregation strategies,” Magers notes.

Navigating the regulatory landscape and complying with regulations can be difficult as an international manufacturer, Magers also observes. “There are three main regulatory systems: European Union (EU) GMP regulations, United States (US) GMP regulations, and Pharmaceutical Inspection Co-operation Scheme (PIC/S) regulations,” she states. “The new Good Manufacturing Practice Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products (EU GMP part IV) (4) does not provide the most straightforward guidance and expectations. Moreover, it refers to risk management, which is not easy to navigate, as the perception of risk is subjective to a certain extent.”

Magers also points out that these new EU guidelines exclude the link and reference to GMPs for other pharmaceuti- cals, including in Annex I, Manufacture of Sterile Medicinal Products (Corrected Version) (5). “However, the PIC/S and the US will not adapt to this move. Therefore, the ‘classical’ pharmaceutical regulations apply to products that will be licensed in those regions. Furthermore, many countries are part of more than one of these regulatory systems (e.g., EU GMP and PIC/S, US regulations and PIC/S); navigating through expectations from different regulatory bodies will soon arise and need to be complied with,” she adds.

“I think one of the biggest challenges will be the complexity of the supply chain demands, both on the front end (starting with supply of materials or patient samples) and back-end (delivery to the patient),” observes Blackwell.

“Some of these products and technologies use relatively novel materials, and the suppliers are not mature from the standpoint of their manufacturing processes and quality systems. In some cases, the sponsor will need to help the supplier and improve and reduce risk. The bar keeps getting raised as the products enter Phase III and commercial manufacturing. So how these critical components will be sourced in a compliant manner needs to be assessed early in development and planned for with risk-reduction strategies,” Blackwell adds.

Further, the definition of the “control space” around the product is becoming another hurdle. For traditional products the “control space” has entailed batch manufacturing, batch area clearance, and various room checks to limit the risk of cross contamination and product mixups. For many of the newer technologies, Blackwell asserts, the traditional manufacturing model simply won’t be economical.

“The control space around the product will need to shrink to accommodate simultaneous and parallel manufacturing on the same production floor. Again, the interplay of data technologies (e.g., radio frequency identification, wireless, mobile, barcode, manufacturing execution system) and engineered controls (e.g., electronic batch records) to ensure compliance and the safety, identity, strength, purity, and quality (SISPQ) of the product will be essential. These systems will need to interact with the quality system in real time and be validated to support release by exception. Unexpected events will need to be investigated immediately.
and alerted by the electronic process monitoring systems,” Blackwell explains.

**Best practices are needed**
Gene therapy stakeholders would do well to have a set of best practices that will help keep the development of a novel gene therapy in compliance with new regulatory guidelines. Early and frequent use of risk assessments is a good practice that can greatly enhance process understanding and focus efforts, for instance. Gene therapy, as well as other emerging therapy products, required a broad and deep understanding of the science behind them in order to do proper risk assessments, Blackwell says. “This will often entail close collaboration between R&D scientists, process scientists, and quality control, especially early in the development program before little process data and manufacturing history has been garnered,” he adds.

Blackwell considers that stakeholders for a number of these products will seek expedited approval pathways, which will compound the challenges with CMC because of the shortened timelines. He notes that it is always challenging to keep CMC off the critical pathway under any circumstance, and when these pathways get expedited, the pressures on CMC activities are enormous. Unfortunately, there will be no relief from FDA in terms of meeting the expectations and spirit of the guidance documents. “Again, strategic and project planning that links to the data and technical reports requirement and regulatory expectations is clearly a best practice,” Blackwell says.

Blackwell believes it is helpful to always keep the end-goal (i.e., commercialization) in mind. “Is a change really needed now, or can it wait until after approval and commercial launch? But, having the end-in-mind is not enough. Starting early with a strategic and project plan focused on regulatory requirements and guidance pays tremendous dividends. It helps to make sure things are not overlooked, and helps the team make appropriate adjustments quickly when things don’t go as planned. They almost never do,” he says.

Another best practice Blackwell recommends, though on a different tact, relates to process, equipment, and facility validation. “Many of these processes will need to scale up on parallel and not in scale like traditional products. Thus, the master validation plan should accommodate this by simplifying the level of qualification needed for new product lines and suites,” Blackwell says.

He also advocates using quality-by-design and product lifecycle approaches, which are the best ways to meet all these challenges. “For example, the target product profile is one of the few tools in an organization that brings most of the key stakeholders together, including commercial, medical, CMC, regulatory, and quality; keeps everyone on the same page; and focuses efforts. Start early with it since it becomes a living document that has the end-in-mind,” Blackwell states.

**Guidelines still needed**
Meanwhile, although the new gene therapy guidelines issued by FDA are a significant step forward in moving new gene therapies through the regulatory process toward approval, some note that further GMP guidelines are still needed. Magers points out that although GMP requirements have been issued that are specific to gene therapy products, FDA has not yet issued a guidance document that contains detailed GMP recommendations.

The EC’s GMP guidelines for advanced medicinal products (4) that went into effect in May 2018 contain detailed recommendations, Magers observes. “Some of these recommendations were included in the PIC/S GMP Guide Annex 2A Manufacture of Advanced Therapy Medicinal Products for Human Use (6), which was issued for public comment from September to December 2019. FDA is providing recommendations to address specific topics (e.g., recommendations for multiproduct cell and gene therapy manufacturing facilities) in public forums, however, no guidelines have been issued,” Magers states.

“In addition, it would be beneficial if FDA would update some CMC guidance documents to reflect their current thinking. Guidelines that should be updated include the Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs), issued April 2008, and the Potency Tests for Cellular and Gene Therapy Products Final Guidance for Industry, issued January 2011. Further, a guideline addressing comparability approaches for cell and gene therapy products is needed, as changes are often made during the development of these products that require an assessment of comparability,” Magers adds.

Blackwell points to an area where future guidance will likely be needed, and that is in “bedside manufacturing” and “distributed manufacturing” in non-GMP environments. “The CGMPs, guidelines, and technology will be pushed to its limits to ensure the SISPQ of the product is ensured. Guidelines that will be particularly useful will be on process analytic technology (PAT), CFR [Code of Federal Regulations] Part 11, and risk assessment, but I expect new guidance that tie these together in conjunction with these types of technologies will be needed. For example, how will the quality unit oversee and interact with these technologies? What will be deemed acceptable? Appropriate engineering controls; analytics, testing, and release; validation; data integrity; handling unexpected events; handling and control over the manufacturing equipment will be especially challenging,” he concludes.

**References**
4. EC, Guidelines on Good Manufacturing Practice Specific to Advanced Therapy Medicinal Products (Nov. 22, 2017).
5. EC, Annex 1, Manufacture of Sterile Medicinal Products (Corrected Version) (Nov. 25, 2008).
Discover Lonza Engine™

The Lonza Engine™ equipment portfolio supports bioavailability enhancement of molecules, encapsulation, and early-phase clinical development technologies.

The Lonza Engine™ equipment portfolio offers state-of-the-art machines, including micronization, capsule filling and sealing, and powder microdosing equipment. The portfolio is designed to address the needs of customers throughout the entire small-molecule drug development process.

Pharmaceutical Technology sat down with Mattia Wiedemeier, Sales Manager of Engineering at Lonza, to discuss the Lonza Engine™ portfolio, Lonza’s contract manufacturing organization (CMO) services, the benefits of micronization and market trends, and the advantages of microdosing in early-phase new drug development.

PharmTech: What does the Lonza Engine™ portfolio include and when was the equipment launched?

Wiedemeier: The Lonza Engine™ portfolio is a comprehensive equipment offering for the drug development and manufacturing process. The portfolio includes the equipment offering of the legacy Capsugel® and Micro-Macinazione companies, which includes the Xcelodose® powder microdosing system, CFS (Capsule Filling and Sealing) machines, and micronization and containment equipment. Lonza is an integrated solutions provider that creates value along the Healthcare Continuum® and with the launch of Lonza Engine™ in June 2019 Lonza continues to help customers achieve their goals.

PharmTech: How does the sale of equipment combine with the service?

Wiedemeier: The Lonza Engine™ portfolio offers equipment backed by outstanding technical service. As a solutions provider, offering equipment and engineers who specialize in that equipment go hand-in-hand. Some customers prefer to outsource, whereas others prefer to insource. Most customers combine outsourcing and insourcing as a strategy. Therefore, being able to serve customers on both sides is crucial to letting them be flexible in their outsourcing strategy. Indeed, it is easier for a company to outsource if its CMO partner has the same equipment. Moreover, with Lonza’s CMO service, equipment can be improved upon for the market, which is especially valuable for very innovative projects.

PharmTech: What trends do you see in the micronization market, and what are the latest developments in micronization technology?

Wiedemeier: There is a big increase in demand for micronization because it is one of the main ways to improve the bioavailability of an API. For the most part, new chemical entities are poorly soluble and have poor bioavailability. That is why the market demand for micronization is increasing.

The demand for CMO services is also increasing. In the last few years, the potency of compounds has also been increasing while batch sizes have been reduced.
**PharmTech: What kind of products can be micronized, and what benefit does jet milling give to these types of products?**

**Wiedemeier:** In principle, any dry powder can be micronized. The first benefit of jet milling is that it reduces the particle size, which increases a product’s bioavailability and suitability. For instance, particle reduction can serve different purposes; in the case of inhalation compounds, particle size can be reduced to a powder that is fine enough to enter the lungs.

**PharmTech: How do you micronize highly potent APIs?**

**Wiedemeier:** We need to select the right containment system, which could be, for example, closing the whole line from loading to unloading. It could also be a system with flexible isolators or with rigid isolators, or a system with rigid isolators with special inlet and outlet solutions depending on the operational exposure limit (OEL) of the compound.

**PharmTech: What is microdosing, and to which APIs is it applicable?**

**Wiedemeier:** Microdosing is the process of dispensing a precise amount of API into a container for use in early-phase human studies. In the capsule world, microdosing means being able to fit as little as 100 mg of powder—at least in our case—in a single capsule without the use of excipients. In the Lonza Engine™ portfolio, Xcelodose® microdosing units are used for these applications.

In principle, microdosing is applicable to any API and is highly recommended for dry powder inhalers because only the API is dispensed into the capsule, which allows customers to eliminate excipient compatibility screening and streamline product development. The Xcelodose® can precisely dispense powders, granules, and beads in amounts as low as 100 μg and up to 100 mg and beyond. The system also has the ability to handle moisture-sensitive compounds, as filling can be performed at < 5% RH.

**PharmTech: What are some potential effects of microdosing in first-in-human studies?**

**Wiedemeier:** Microdosing can save up to six months of development time because it eliminates the need for excipient compatibility screening, as the capsule can be filled with the API only. Accelerating the development time of a new drug to first-in-human studies is critical in streamlining product development. Microdosing also reduces cost in drug development, as it is not necessary to buy the excipient nor to combine it with the API. This allows for cost-effective product development in conjunction with reducing waste of material and simplifying stability evaluations.

**PharmTech: Does Lonza Engine™ include any after-sales or installation support other than the equipment itself?**

**Wiedemeier:** Lonza has a global technical service engineering team that provides solutions for customers’ capsule filing and equipment needs. These engineers consult on equipment purchases, assist with equipment repairs, provide component(s) ordering support, training on the equipment, and consult on equipment upgrading.

Additionally, the team helps with reduction of risk as it pertains to capsule filling and equipment challenges. This includes being experts in capsules, formulas, and equipment as well as the corresponding interaction between the three. The technical service engineers also help with customer operational excellence goals, which include but are not limited to reduction in downtime and increased machine output. These engineering services are provided worldwide, therefore customers can both request on-site training and support and/or visit one of the CFM training centers within Lonza’s global network.
The energy efficiency of technologies for bio/pharmaceutical manufacturing facilities is changing quickly, and manufacturers can take advantage of these improvements for both old and new facilities, says Keith Beattie, executive director at Energy Efficiency Consultancy EECO2. Pharmaceutical Technology spoke with Beattie about trends and best practices in sustainable pharmaceutical facility design.

**Trends**

**PharmTech:** What are the key trends in sustainability in bio/pharma facility design?

**Beattie (EECO2):** There are several trends in equipment use and facility design that will improve efficiency and sustainability. The trend towards use of isolators for improving sterility assurance, for one, also leads to the use of lower cleanroom class background environments, which require less energy to maintain.

Single-use technology in biopharma manufacturing is being promoted as a more sustainable solution to large fixed vessels. It is reasoned that these allow smaller batches and therefore smaller facilities house them, with a subsequently lower HVAC [heating, ventilation, and air conditioning] energy demand. In addition, water use is lower because the systems are disposed of rather than washed.

Although I wouldn’t yet say it is a trend, there are some examples of companies taking a more holistic design approach, in which they consider and implement sustainability design from an early stage. Good examples include the winners of the International Society for Pharmaceutical Engineering Facility of the Year Award (ISPE FOYA) for sustainability, such as the Pfizer Consumer Health manufacturing facility in Suzhou, China, in 2018.

I know of one company that is changing their HVAC design standard to mandate design of low (40–45 °C) temperature heating coils in HVAC systems, which would enable them to use waste heat from processes. There is a lot of wasted heat in pharma plants, but often temperature is not high enough to be useful. HVAC is a good use for this heat, but only if coils are sized appropriately. Retrofitting is almost impossible. Design from day one gives you possibilities for the future—so designing flexibility in is a good thing to do.

A definite trend I have noticed over the past 18 months is that sustainability (in particular addressing climate change) is getting serious C-level attention, with many organizations making public commitments to going further to tackle this business issue, declaring aims to be carbon neutral or even carbon negative. This is significant. A range of solutions will be needed to achieve this, with increasing efficiency being a key one—simply offsetting emissions is not going to cut it with an increasingly aware stakeholder base.

**Best practices**

**PharmTech:** What are the biggest areas of waste in pharmaceutical manufacturing facilities? What are some examples of best practices in tackling these areas?

**Beattie (EECO2):** The most surprising thing is that most facilities don’t know where their waste is, because they don’t have an effective metering and monitoring system or do not review the data that are available to them. From our experience, one of the biggest areas of waste is energy, especially consumption related to HVAC.

We find many opportunities for energy savings here on almost every site we go to. For example; inefficient, faulty, or inappropriate control systems, configured for GMP compliance only, with little account of efficiency is one of the simplest things to solve. It is possible to be compliant and efficient! Another is over-processing of air: larger flow rates than necessary, over-cooling, over-dehumidifying, simultaneous heating and cooling—all preventable with no product quality impact.

Another area of waste is water. It’s generally a cheap resource, so paybacks on project initiatives to reduce water use are not often prioritized over energy savings. However, because its cheap, few manage it effectively, and there are often many low...
to no-cost opportunities to uncover. We often find savings opportunities in quality water systems (water for injection [WFI] and purified water), where the treatment processes make the water a more expensive resource. Opportunities include the recovery and reuse of WFI drain water or of water from reverse osmosis regeneration; often these can be used in lower grade uses such as cooling tower makeup or boiler makeup.

PharmTech: What are some best practices for refurbishing older manufacturing facilities for energy efficiency?

Beattie (EECO2): You should always review any space where use has changed to ensure the HVAC system particularly is not over-designed for its new use. Look for the best available technology; do your research, because technology development in energy efficiency is moving fast. Rising energy prices and falling technology costs do change efficiency project return on investment (ROI) dramatically, so an opportunity rejected for low ROI a few years ago, may now have become economic to do.

For example, HVAC fan technologies have improved enormously over the last five to 10 years. Electronically commutated (brushless direct current) motors/fans, for example, can be installed in arrays (a group of fans) rather than one single fan. The array adds the benefit of redundancy, and retrofit is easier. Many older facilities have much larger fans running slowly, as the facility may have already done an air-change rate reduction. These large fans are now very inefficient, so changing to a correctly sized fan array can demonstrate great savings. In older facilities, fans are often at or past end-of-life, so the business case is good for replacement. Replacement offers benefits such as energy saving, reliability, quality improvement, and less maintenance.

PharmTech: What are some best practices for new facility design?

Beattie (EECO2): Companies should consider sustainability early in the design stage (pre-concept design) and carry it on all the way through. There is always a pressure to ‘value engineer out’ non-essential features, including sustainability features, but this is a very short-term view that is becoming increasingly unacceptable. It takes a strong company leader with a clear vision to ensure the right things are kept in.

Dynamic modeling and simulation of lifecycle cost and energy and water use is an evolving technology that helps designers make informed choices. Building information modeling (BIM) for commercial buildings, such as offices or hotels, has been around a long time, but BIM is more complex in a pharma plant. Where it has been found useful is to model the interaction of different technologies and the synergies to maximize the ‘system’ efficiency, rather than simply the efficiency or contribution of discrete technologies evaluated in isolation.

The new ISO 14644-16 (energy efficiency in cleanrooms) (1) and the soon to be published, updated ISO 14644-4 (design, construction, and startup of cleanrooms) (2) have excellent guidance on new thinking about cleanroom design. The basic philosophy behind these standards is that you should design your cleanroom with efficiency in mind and with the ability to tune it during its service life to match the real performance needed and to minimize energy.

PharmTech: Do new technologies for artificial intelligence (AI), such as predictive maintenance, help?

Beattie (EECO2): I have seen some examples of AI/machine learning in building controls to identify inefficiencies and flag these to users for action. One example I saw a few years ago was a client who was very proud of the long (170 items) list of issues to address on his control system that would improve efficiency. But he still struggled to get anything fixed; every month the same items would flag on the report. The point is that there are new technologies emerging that show promise, but there are well-established, proven technologies available today that are not being fully exploited.

Dynamic control of cleanrooms based on real-time measurement of particulate concentration and microbiological contamination to assure quality and deliver huge energy benefits is a reality now. I believe this technology will start to be adopted at scale over the next two to three years. For example, the EECO2 ICCS [Intelligent Cleanroom Control System] uses advanced predictive control to enable response to changing conditions in the cleanroom.

References
In an automobile race, a vehicle must be well designed, highly tuned, and have the proper fuel to outperform the other competitors. If corners are cut on any of these elements, the car may stall or be forced out of the race. In the traditional drug development race to get a molecule to clinic, drug companies sometimes look for shortcuts. Questions about manufacturability and drug performance may not be answered until formulation steps are initiated after the filing of the investigational new drug application. As a result, the commercialization finish line may be farther away, or never reached.

The traditional approach works if APIs that are easy-to-formulate, are water-soluble, and have a conventional route of administration (e.g., oral dosage forms) are used, says Robert W. Lee, president, Lubrizol Life Science Health’s CDMO division, “but this level of ease is no longer the reality in drug development.” The complex and poorly soluble molecules that are typical of many novel drug candidates in research phases are prompting drug developers to consider more factors about a drug earlier in the development cycle.

The drug formulation process requires time, money, specialized expertise, and resources that may not be available to small drug companies in early research phases. Development-phase companies anxious to get to clinic may seek to gain an advantage by postponing early stage formulation development. Instead, they place priority on activities traditionally considered to have the largest impact, such as optimizing potency and determining efficacy determination, says Darren Matthews, research leader, pharmaceutical sciences at Charles River.

“The biggest disadvantage to delaying formulation activities is that the inherent risk is significantly increased, resulting in a potentially poor candidate being nominated,” Matthews explains. “Consequently, any challenges relating to bioavailability post-candidate nomination must be solved using formulation strategies alone, whereas prior to candidate nomination a different molecule could have been selected or the medicinal chemistry optimized further.”

“For Developability Classification System (DCS) I compounds (1), this is a low-risk approach, because the formulation is not likely to have much impact on drug performance,” says Meredith Perry, director of pharmaceutics, Catalent Pharma Solutions, San Diego. “But for all other DCS class compounds, understanding the bioavailability in various preclinical species is critical.”

Newer drugs present new formulation challenges

Unfortunately, most new molecular entities have low aqueous solubility; if preformulation or formulation studies are not conducted to solve this issue, it may not be possible to deliver the drug to its target. “Without investigating advanced drug delivery technologies at this early stage, you’re not creating the best chance of success and may end up eliminating a good molecule. Formulation groundwork should be done up front to at the very least identify a viable candidate,” says Lee.

“Not addressing solubility challenges through formulation prior to conducting clinical studies can render the clinical data meaningless and potentially ‘kill’ good molecules that would become good drugs if formulated correctly,” states Lisa Caralli, director of science and technology, pharmaceutics, Catalent Pharma Solutions, San Diego. Physicochemical characterization, preformulation, and drug metabolism and pharmacokinetics (DMPK) analyses are needed to identify hurdles to bioavailability that an enabled formu-
Complex Liquid Formulations: Solutions for Scale-Up Challenges

ON-DEMAND WEBCAST: Aired Tuesday, March 17, 2020

Register for this free webcast at: http://www.pharmtech.com/pt_p/complex
All attendees will receive a free executive summary of the webcast

Event Overview
Scaling-up liquid formulations can present a number of challenges and headaches. This is especially true for complex solutions, suspensions and emulsions as well as biologics, sterile products, potent compounds and sensitive APIs. In this webcast, learn about potential formulation and filling issues when transitioning a liquid formulation from feasibility through commercialization.

Product development experts share insights on a variety of formulation issues including mixing, solubility, microfluidization, viscosity, filtration and special API handling, with discussed solutions based on Catalent’s expertise in complex formulation. Equipment for liquid-filling and scale-up will be discussed with a focus on potential applications of advanced aseptic Blow-Fill-Seal (BFS) technology.

Register early and submit your question for the Q&A discussion.

Key Learning Objectives
- How to manage challenges associated with typical liquid formulations, as well as unique issues for complex solutions, suspensions, and emulsions
- Special considerations for biologics, as well as potent or sensitive APIs
- Challenges when transitioning from small- to large-scale, and solutions made possible by Blow-Fill-Seal technology

Who Should Attend
- Manager, director, vice-president level and senior scientists for pharma and biotech companies (large to small)

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

An understanding of how a drug may behave in vivo is predicated on initial in-vitro studies, as well as an understanding of basic drug substance physicochemical characteristics, says Stuart Madden, vice-president, drug development and consulting, ICON. “Lacking knowledge of key aspects of a drug product’s characteristics may hinder an understanding of in-vivo data related to the product’s performance,” he explains. “So, although initiation of a clinical program may be quicker and cheaper, in the longer term it may be more difficult to make rationale choices for formulation and process development for any follow-on clinical program.”

Evaluating strategic approaches
Using a drug substance for dosing patients in small, early-phase clinical trials saves the cost of developing, manufacturing, and testing a product for a compound that may be discontinued, says Eugene McNally, vice president, consulting, PPD. “The disadvantage is, not all drugs are candidates for such ‘powder in bottle’ dosing.”

Getting quickly to clinical studies using API in capsule or powder in a bottle is an advantage, agrees Sanjay Konagurthu, senior director, Thermo Fisher Scientific—Pharma Services Group. “Based on outcomes, a formulated drug product might have to be developed in a short time,” he explains. For fast track and breakthrough therapies, developing a formulated, commercial dosage form is advantageous, he says.

Managing expectations and the amount of available API also must be considered. “Companies desiring to sell early stage assets should consider that buyers expect to see formulation and manufacturing process development results that demonstrate the product can be commercialized,” says McNally. And, Perry notes, “Determining whether formulation enhancement is feasible can decrease the doses needed for efficacy, which decreases the risk of side effects and reduces the quantity of API needed throughout the program.”

Preformulation factors
Formulation and manufacturing process development is driven by the route of delivery and the anticipated human dose, says McNally. For small-molecule drugs—typically oral doses—knowledge about a compound’s solubility and permeability is crucial.

For oral solid-dosage drugs, the DCS can be an effective predictive tool to determine risks associated with a compound’s bioavailability by classifying a drug into one of five different categories. “Classifying a potential drug using the DCS provides the formulator with an appropriate strategy for maximizing bioavailability, especially for sparingly soluble drugs,” Matthews says. “The DCS provides a simple approach, by using solubility and permeability data, to understand and predict a complicated subject (e.g., bioavailability of a potential drug).”

Charles River uses DCS for hit-to-lead and lead optimization stages, and Matthews sees the hit-to-lead stage as an early opportunity to understand potential development risks associated with a chemical series. “Determination of the DCS risk number at this stage empowers the medicinal chemists to choose an appropriate series to take forward to determine a suitable development pathway during lead optimization,” he says.

Understanding the molecular properties of the drug is crucial. “Bioavailability can be impacted by the fraction absorbed, which is dependent on the drug’s solubility and permeability,” says Caralli. “But it can also be impacted by gut wall and hepatic metabolism. If the source is the former, it can be addressed through formulation. If the issue is metabolism, the basic molecular structure of the candidate may need to be reconsidered.”

Detailed preformulation studies can help drug developers understand a molecule’s physicochemical characteristics, solid-state characteristics, and dissolution rate, says Lee. “This will indicate whether the use of enabling technologies like nanomilling will be needed to help formulate the molecule.” Other factors to consider include the molecule’s stability in water, acid/base, oxidation, heat, and light; excipient compatibility; potential for polymorphic transformation; particle size distribution and powder flow; and hygroscopicity.

Typically, biologic drugs require extensive preformulation studies because they are more complex with aggregation and degradation of special concern as they are much more sensitive to stresses from manufacturing and environmental conditions, says Madden.

“For large molecules, it’s not just the sequence of the monomers (i.e., amino acids or nucleotides) that is a concern but also the three-dimensional structure,” says Lee. “During formulation development, it’s important to track this 3D structure as this may be key to its biological activity, and this may very well be impacted by the formulation.”

An indication of solution stability, and whether a lyophilized, or dried, formulation will be needed to maintain stability, is typically the starting point for development of large molecules, adds McNally.

Predicting potential and problems
Advances in screening and characterization have enabled more rapid and accurate analysis of molecules, providing support for formulation steps. “Materials science-based characterization of the drug substance using modern compaction simulators, Raman spectroscopy, electron microscopy, chromatography, crystallography, thermal characterization, and dissolution and absorption technologies can help in the characterization,” explains Konagurthu.

“Physical characterization of each API lot requires very small amounts of API (milligram quantities),” says Perry. “It is worthwhile to use the sensitive, API-sparing tools that are now available, such as differential scanning calorimetry, thermogravimetric analysis, powder X-ray diffraction, and scanning electron microscopy.” In addition, she notes, the use of software modeling, in addition to actual characterization, can help expedite the process. “Predictions for solubility,
Cultivating powerful connections in the world’s most vital pharma marketplace

Over the last three years, CPhI North America has brought together more than 15,000 industry professionals across the entire pharmaceutical supply chain, including: custom chemicals, ingredients and manufacturing, contract services, finished dosage and formulations, machinery, technology, and packaging.

Join us in 2020: cphinorthamerica.com
permeability, and DMPK performance are all helpful tools,” she says.

Tools developed in the past 20 years are allowing formulation scientists to do more, says Matthews. For example, biorelevant dissolution media allow the formulation scientist to predict the solubility and dissolution behavior of sparingly soluble drugs in vivo. When coupled with small-scale dissolution equipment with in-situ measurement by fiber optics, automated pH adjustment, or automated media addition, these systems can mimic the in vivo environment. And, in silico prediction tools that consider formulation, polymorphic, and particle sizes effects on in vivo performance can be powerful tools for the formulator. “Such a method can be used to triage potential approaches to enhancing bioavailability without the need for expensive animal studies,” he says.

Madden also notes the importance of software to aid development, ranging from programs to calculate basic physicochemical parameters for drug substances to bioavailability development toolkits and excipient interactions software. “There are also strategies developed by contract research organizations that allow the rapid in-vivo screening of numerous formulation prototypes to aid rapid formulation selection prior to the start of any formal clinical program,” he states.

Employing multiple toolsets
Physiologically based pharmacokinetic modeling is essential to ensure that the correct delivery route and dosage form is pursued for a molecule, says Caralli. “These in silico models can incorporate both in vivo data from animal models, and in vitro data from biphasic dissolution studies, to predict the performance of a formulated API in human clinical studies.”

Konagurthu notes that predictive models are of great benefit in early development, citing Thermo Fisher’s Quadrant 2 platform as an example. “Implementation of in silico predictive models are being used to guide formulation,” he says, citing materials science and characterization (e.g., compaction simulation), accelerated stability assessment, discrete element modeling, computational fluid dynamics, and pharmacokinetics and pharmacodynamics models. “An ensemble approach can help developing quantitative models that relate product structure to performance,” he says.

Predictive pharmacokinetic and pharmacodynamic modeling certainly helps to inform the ‘best’ dose and dose frequency, formulation, and route of administration to take forward into clinical trials, says Scott Dove, vice president, early development, PPD.

A decision to divert limited resources from early formulation studies may come back to haunt many drug developers.

While models can help direct studies, they do not necessarily replace laboratory analysis. “Computational models can give you an idea of the molecular characteristics in silico and predict solubility and a host of other properties. Some are particularly effective and can guide your lab work, but they are not a substitute for actual lab work—this must still be carried out,” Lee says. “If you are looking at several different molecules to synthesize in early development, then using predictive models to do a computer screen of potential structures can help direct your work and narrow your choices.”

Using predictive models as a substitute for experimental data in the early stages of drug development can save time and money, allowing the development program to move to wet chemistry more quickly, says Madden. “For example, screening a series of analogues to determine bioavailability, solubility, or even potential genotoxicity signals by quantitative structure-activity relationship can be of tremendous value in early development and accelerate lead optimization efforts enabling faster development.”

Balancing priorities to maximize resources
A decision to divert limited resources from early formulation studies may come back to haunt many drug developers, especially when the solubility or other issues associated with a compound are revealed in clinical trial stages. However, notes Perry, “Formulation screening at small scale is significantly less expensive than a failed clinical trial.”

The consequence of not gaining insight early in development can result in batch failures that lead to delays or cancellations of trials due to a lack of understanding of the root causes of these failures, say McNally.

“It is critical for companies to understand that investing in formulation and process development during the early phases can yield dividends in the long run,” says Konagurthu. “The company should obtain a mechanistic understanding of the formulation and process.”

“Companies must have a viable formulation for in vitro studies and beyond, so it’s important to invest effort and resources in the most effective formulation,” says Lee. “At the same time, it’s a balancing act, and it’s not cost effective to waste resources on the wrong technologies.”

“Scientists must often justify their chosen scientific path to management, who may have limited understanding of the underlying science. For low-solubility molecules, this inability to translate the ‘why’ can lead to decisions being made for purely financial reasons,” says Caralli. “Using a visual tool like the DCS, solubility, permeability, and dose can be plotted to demonstrate the need for an enabled formulation to ensure a successful clinical trial outcome.”

Reference
The drug and healthcare product market continues to evolve. You must stay informed of the latest trends, compliance requirements and innovations to survive.

NO OTHER EVENT covers vital excipients like Excipient World.

• More technical education on formulation and R&D, global supply chain, biologics, new excipient solutions and emerging technologies
• More exhibitors and new companies to learn about and source excipients and manufacturing services
• Critical regulation updates from FDA, IPEC-Americas and other groups
• More networking events to meet peers and suppliers while having fun
• More attendees and suppliers to connect with via the new ExcipientConnect appointment scheduling system
• Hear from investigative journalist / author of Bottle of Lies, Katherine Eban, Dr. Thomas Hartung, professor at Johns Hopkins, and Sam Raney at FDA (invited)

SAVE $100 off conference registration from Pharmaceutical Technology with code: PT100
REGISTER TODAY @ www.ExcipientWorld.org

*Discount valid on Attendee (buyer) registration rates only.
2020 Spring Show Guide

DCAT Week
March 23–26; New York, NY
PDA Annual Meeting
March 30–April 1; Raleigh, NC

VISIT US AT THE PDA ANNUAL MEETING

PDA is the leading global provider of science, technology, regulatory information, and education for the bio/pharmaceutical community. For nearly 75 years, PDA has developed sound, practical technical information and resources to advance science and regulation through the expertise of our more than 10,000 members worldwide. We promote dialogue on new technology and regulations to ensure high-quality pharmaceutical production.

Parenteral Drug Association (PDA) • 4350 East West Hwy, Suite 600 Bethesda, MD 20814 • info@pda.org - pda.org • tel. 301.656.5900

VISIT US AT DCAT WEEK

Next-Generation Biopharmaceutical Development Services
Catalent Biologics is a global leader in biopharmaceutical development services, bringing next-generation therapies to the market. Its recent acquisitions of Paragon Bioservices and MaSTherCell have expanded its service portfolio to include development and manufacturing of cell and gene therapies, alongside new biological entities, biosimilars, sterile injectables, and antibody-drug conjugates.

Catalent Pharma Solutions • 14 Schoolhouse Rd, Somerset, NJ 08873, USA • tel. +1.888.765.8846 • solutions@catalent.com • www.catalent.com/biologics

Over nearly two decades, TEDOR has helped customers meet their project timelines, achieve regulatory approvals, and solve formulation challenges. TEDOR offers services ranging from formulation development, clinical trial manufacturing, scale-up and full-scale commercial manufacturing, tech transfer, stability studies, and product life cycle management with patented FLEXITAB™ technology.

TEDOR • 400 Highland Corporate Dr, Cumberland, RI 02864 • tel. 401.658.5219 • www.tedorpharma.com

At Lonza Pharma & Biotech, we provide contract development and manufacturing services that enable biotech and pharma companies to bring large and small-molecule medicines to patients in need. From drug substance to the final drug product, our solutions feature concept to commercial capabilities to simplify your outsourcing experience and to provide a reliable outcome when you expect it. Together, we can bring your next medicine to life.

Lonza Pharma & Biotech • Muechensteinstrasse 38 4002 Basel, Switzerland • tel. +41.61.316.8111 • solutions@lonzapharma.com - pharma@lonza.com

CordenPharma is your full-service CDMO partner for APIs, Drug Products, and Packaging Services. Through a network of cGMP facilities across Europe and the US organized under five technology platforms—Peptides, Lipids & Carbohydrates, Injectables, Highly Potent & Oncology, Small Molecules, Antibiotics—CordenPharma experts translate complex ideas and projects at any stage of development into high-value pharmaceutical production.

CordenPharma International GmbH • Otto-Hahn-Strasse, 68723 Plankstadt, Germany • www.cordenpharma.com • www.cordenpharma.com/contact-us/DCAT Week 2020 Sponsors — March 23-26, NYC
Thermo Fisher Scientific

Thermo Fisher Scientific provides end-to-end development and manufacturing solutions to customers through Patheon and Fisher Clinical Services. With more than 40 locations around the world, the company has extensive capabilities including drug substance, and product development, viral vector services, clinical trials, and commercial-scale manufacturing. Thermo Fisher Scientific • 4815 Emperor Blvd. Suite 110, Durham, NC 27703 • tel. 919.226.3200 • pharmaservices@thermofisher.com • www.thermofisher.com/patheon

Mikart, Inc.

Mikart specializes in the development, manufacturing, and packaging of solid-dose and liquid-oral dose products. The company’s services include formulation development; analytical, manufacturing, packaging, and regulatory services; and complete project management. Mikart offers clients more than 40 years of experience, a responsive working relationship, and the ability to take products from formulation development through full-scale commercial production.
Mikart, Inc. • www.mikart.com • tel. 404.351.4510

Enabling the efficacy, integrity and usability of pharmaceutical formulations.

At Ashland, our goal is to help you apply pharmaceutical polymers to develop your formulations. Our molecular scientists, chemists, formulators, and process engineers can help advance complex oral solid-dosage formulations. Our problem-solving team leverages a diverse polymer excipient and film coatings portfolio to provide comprehensive solutions, so when you’re ready to formulate, we’re ready to help.
Ashland • 500 Hercules Road, DE 19808 • www.ashland.com

Chemic Laboratories, Inc.

Chemic Laboratories, Inc. is a full service cGMP/GLP contract analytical chemistry laboratory. Chemic provides an array of R&D and cGMP contract testing services including: Extractables/Leachables analysis, CMC Method Development & Validation, Quality Control analysis, Release testing, Raw Materials analysis, Compendial testing, Organic Synthesis/Formula Development & ICH Stability testing.
Chemic Laboratories, Inc. • 480 Neponset St., Building 7, Canton, MA 02021 • www.chemiclabs.com • fcw@chemiclabs.com • tel. 781.821.5600 • fax 781.821.5651

Contec, Inc.

Contec, Inc. • 525 Locust Grove Spartanburg, SC 29303 • www.contecinc.com • info@contecinc.com

PYRAMID Laboratories, Inc.

PYRAMID Laboratories, Inc. is a CMO focused on parenteral drug products, offering a comprehensive pipeline of services. Established in 1988 in Southern California, we offer aseptic vial and syringe filling, as well as lyophilization capabilities, for both Clinical and Commercial products, supported by full array of Analytical services.
PYRAMID Laboratories, Inc. • 3598 Cadillac Ave., Costa Mesa, CA 92626 • tel. +1.714.435.9800 • info@pyramidlabs.com • www.pyramidlabs.com

Steramist by Tomi

SteraMist® achieves rapid, effective disinfection/decontamination with high efficacy against a wide range of organisms throughout life-science facilities including: pharmaceutical, biotechnology, research, vivarium laboratories, etc.
Steramist® is easy to implement into any facility and offers iHP® service with its sole active ingredient of 7.8% Hydrogen Peroxide. TOMI Environmental Solutions is a global disinfection/decontamination company committed to Innovating for a Safer World®.
Steramist by Tomi • www.tomimist.com

Advancing quality in biopharmaceuticals

USP is an independent scientific organization that collaborates with the world’s top experts in health and science to develop quality standards for medicines, dietary supplements, and food ingredients. Through our standards, advocacy, and education, USP helps increase the availability of quality medicines, supplements and food for billions of people worldwide.
USP • www.usp.org
## MARKETPLACE

### MANUFACTURING/PROCESSING EQUIPMENT

**Mixing/Blending/Drying**

---

### Ad Index

<table>
<thead>
<tr>
<th>COMPANY</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashland Specialty Ingredients G.P.</td>
<td>7</td>
</tr>
<tr>
<td>BIO International Convention</td>
<td>61</td>
</tr>
<tr>
<td>Cambrex</td>
<td>27</td>
</tr>
<tr>
<td>Catalent Pharma Solutions</td>
<td>53,64</td>
</tr>
<tr>
<td>Chemic Labs</td>
<td>35</td>
</tr>
<tr>
<td>Chemspec Europe</td>
<td>39</td>
</tr>
<tr>
<td>Contec, Inc.</td>
<td>3</td>
</tr>
<tr>
<td>CPhI North America</td>
<td>55</td>
</tr>
<tr>
<td>ExcipientWorld</td>
<td>57</td>
</tr>
<tr>
<td>INTERPHEX 2020 (Reed Exhibitions)</td>
<td>63</td>
</tr>
<tr>
<td>Jost Chemical</td>
<td>19</td>
</tr>
<tr>
<td>Leistritz</td>
<td>29</td>
</tr>
<tr>
<td>Ligand</td>
<td>23</td>
</tr>
<tr>
<td>Lonza</td>
<td>41, 48–49</td>
</tr>
<tr>
<td>Mikart</td>
<td>25</td>
</tr>
<tr>
<td>PDA</td>
<td>11</td>
</tr>
<tr>
<td>Pfanstiehl</td>
<td>17</td>
</tr>
<tr>
<td>PYRAMID Labs</td>
<td>13</td>
</tr>
<tr>
<td>ROSS Mixers</td>
<td>9, 60</td>
</tr>
<tr>
<td>Syntegon Technology GmbH</td>
<td>15</td>
</tr>
<tr>
<td>TEDOR Pharma</td>
<td>2</td>
</tr>
<tr>
<td>Thermo Fisher Scientific</td>
<td>45</td>
</tr>
<tr>
<td>TOMI/STERAMIST</td>
<td>51</td>
</tr>
<tr>
<td>Veltek Associates, Inc.</td>
<td>5</td>
</tr>
</tbody>
</table>

FOR PERSONAL NON COMMERCIAL USE

---

**SANITARY RIBBON BLENDERS**

1-800-243-ROSS  
www.ribbonblenders.com

**HIGH SHEAR MIXERS**

World’s Widest Selection, Single Stage to Ultra-High Shear!

1-800-243-ROSS  
www.HighShearMixers.com

Scan to learn more.  
Try our mobile app: mixers.com/web-app

---

Register for our mobile app to keep up-to-date with the latest news and events in the pharmaceutical industry. Download from the App Store or Google Play.
GO BEYOND AT
BIO 2020
San Diego, California
JUNE 8-11, 2020

The World’s Largest
Biotechnology Partnering Event
is Coming to California

REGISTRATION NOW OPEN

Early Bird Registration
Discounts End April 16
Take your business BEYOND expectations
with 48,500+ BIO One-on-One Partnering™
meetings at the world’s largest
biotechnology partnering event.

Visit bio.org/convention to register today
Embracing Change Management

No matter why change may be needed, it is important to comply with all the relevant regulatory requirements, says Siegfried Schmitt, PhD, vice-president, technical, Parexel Consulting.

Q. I work in my company’s quality department. What are some best practices for handling process or product changes?

A. In December 2019, the Pharmaceutical Inspection Co-operation Scheme (PIC/S) published a recommendation, ‘How to Evaluate/Demonstrate the Effectiveness of a Pharmaceutical Quality System in relation to Risk-based Change Management’ (1) and a Concept Note on this Recommendation document (2). This action highlights two critical aspects, namely the importance of change management within the realm of quality and the necessity to apply a risk-based approach.

Nothing stands still; therefore, change is inevitable. Though the PIC/S document covers all relevant steps in the change management process—from change proposal, change assessment, change planning and implementation, through to change review and effectiveness checks—it does not detail categories of change. It merely states, ‘Change categorizations are appropriate and based on the level of risk’ (1).

In practice, the following are three typical categories of change:

- Planned changes: Someone wishes to make a change for whatever reason and applies to make this change. This change, if approved, will be implemented, its effectiveness verified, and it becomes permanent.

- Temporary changes: Sometimes, someone wishes to make changes for a defined period of time followed by a return to the previous state. This could be because there is the need for some building work, or because of staff shortages, or other reasons. Again, it is known that someone wants to make this change. If approved, it will be implemented for the desired period and then all goes back to as it was before. Some companies use the term ‘planned deviations,’ which is synonymous with ‘temporary changes.’

- Emergency changes: Rarely, an organization may have to implement emergency changes. Here, nobody knew that this change would be required, so there is no planning. Perhaps there is not even time for approval before the change is being implemented. Almost always, this type of change is triggered by an event that endangers environment, health, or safety. In short, an emergency change is triggered by a deviation. Perhaps a gas pipe develops a leak; the line must be immediately shut down and work perhaps continues with gas cylinders. As soon as possible, the change needs to be properly assessed and a decision must be made; this will either become a temporary change or a permanent change. To emphasise, the only difference here is that you cannot plan for it.

Looking at these scenarios, one finds that the starting point can differ (either a change request or a deviation). The end point may also differ; one may end up in a new state (permanent change) or back where it all started from (temporary change). The pathways for these change categories are shown in the flow chart (Figure 1). This flow chart needs to be amended as necessary, to reflect the specific processes and procedures within each company. Just make sure, you comply with all the relevant requirements in the regulations, as summarized in the PIC/S document.

References


MAXIMIZE EFFICIENCY
You’ll find the solutions here.

NEW TECHNOLOGIES
You’ll see innovation here.

LEARN FROM EXPERTS
You’ll learn from subject matter experts here.

ACCELERATE TO MARKET
You’ll find everything you need, from science through commercialization, to cost effectively develop and manufacture product here.

Experience science through commercialization

SAVE THE DATE
APRIL 28-30, 2020
JAVITS CENTER, NYC

NEED TO ATTEND? NEED TO EXHIBIT?
Register to attend OR submit to exhibit: INTERPHEX.COM
Your one integrated biologics partner.

For Biologics and Gene Therapy, we have the passion to help you accelerate, simplify and de-risk from development and biomanufacturing, to fill/finish, analytical, clinical supply and commercial launch.

- 25+ commercially approved products through fill/finish
- 600+ antibodies & 80+ recombinant proteins developed
- 5000+ clinical trials supplied
- 12 marketed products using Gpex® technology
- 60+ gene therapy programs
- 120+ clinical trials using Gpex® cell lines

Catalent has acquired Masthercell, a global leader in cell therapy.