Drug Development & Delivery

March 2020 Vol 20 No 2 www.drug-dev.com

Bioavailability & Solubility: Understand Your Molecule!

The science & business of drug development in specialty pharma, biotechnology, and drug delivery

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GRAHAM KELLY

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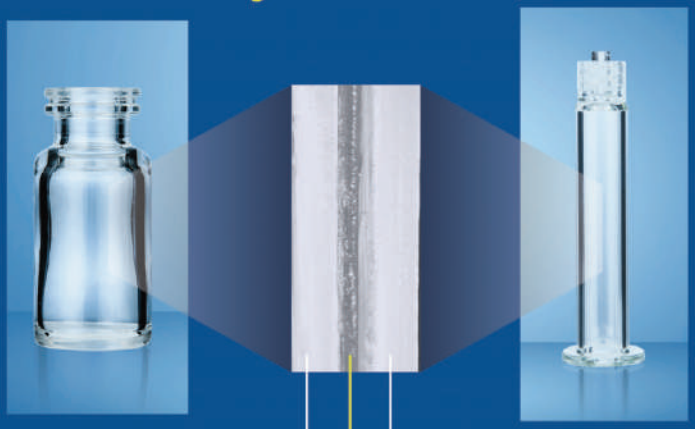

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Drug Development & Delivery

March 2020 Vol 20 No 2

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Understand Your Molecule

"Given that a large number of drugs fail to reach the market due to poor bioavailability, the industry is seeing various methods to mitigate this challenge while many choose to reformulate existing product candidates that exhibit poor bioavailability. Either way, the demand for novel bioavailability enhancement methods has grown significantly. To cater to this increasing demand, several contract manufacturers and technology developers have emerged."

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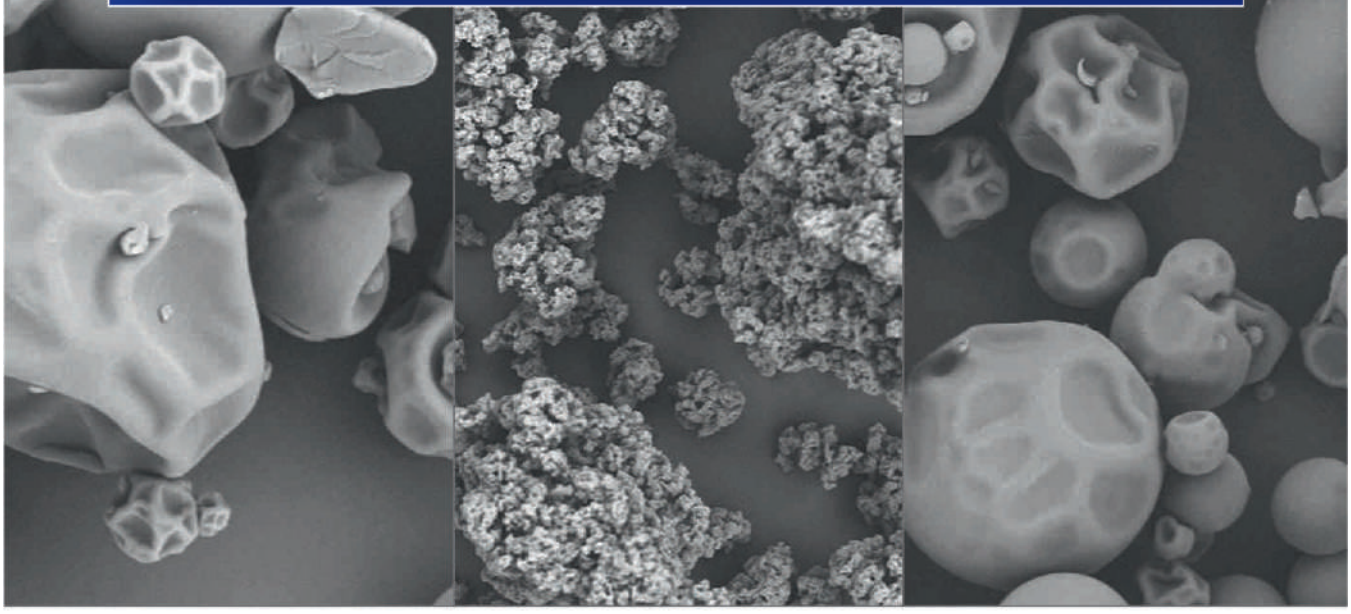
VIVAPHARM® Povidone Family



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Saama & Pfizer to Transform Work of Clinical Data Managers & Monitors With AI

Saama Technologies, Inc. recently announced it signed an agreement with Pfizer Inc. to develop and deploy an AI-powered analytics solution to reduce the challenges commonly experienced by clinical study data managers and monitors. Under this agreement, Saama's award-winning Life Science Analytics Cloud (LSAC) platform will aggregate, transform, analyze, model, and predict clinical data queries using deep learning techniques. Pfizer will provide the required ground truth clinical data and domain expertise to train Saama models to achieve the required accuracy.

"Saama is pioneering transformational changes to the way clinical study data is managed and understood by pharma, since current processes and systems are mostly manual and take a significant amount of time," said Sagar Anisingaraju, Chief Strategy Officer, Saama Technologies. "As part of this collaboration with Pfizer, the deep learning models of LSAC will be further trained and improved to provide augmented intelligence, empowering data managers to operate more efficiently and effectively. Saama appreciates the leadership role that Pfizer is taking to solve this industry-wide problem by providing valuable clinical data across therapeutic areas for training our smart data query solution."

"Historically, our industry has been limited to manual, inefficient data review processes to validate data from our clinical trials," said Demetris Zambas, Pfizer Vice President and Head of Data Monitoring and Management. "Through our strategic collaboration with Saama Technologies, we've identified efficiencies to improve processes and experiences for our clinical research partners."

Life Science Analytics Cloud (LSAC) is the leading AI-powered clinical analytics platform that seamlessly integrates, curates, and animates clinical trial data, delivering more actionable insights.

Saama is the number one AI clinical analytics platform company, enabling the life sciences industry to conduct faster and safer clinical development and regulatory programs. Ten of the top 20 pharmaceutical companies use Saama's award-winning Life Science Analytics Cloud (LSAC) platform. LSAC's rich applications facilitate an unprecedented, authoritative oversight of comprehensive clinical research data, enabling companies to file New Drug Applications (NDAs) more efficiently and bring drugs to market faster. Discover more at www.saama.com and follow Saama @SaamaTechInc.

TriSalus Life Sciences & Roger Williams Medical Center Announce Initiation of Phase 1 Clinical Trial for a Novel Delivery Technology

TriSalus Life Sciences recently announced the initiation of a new clinical trial assessing the safety and feasibility of an innovative new treatment that combines its intravascular, tumor-directed proprietary Pressure-Enabled Drug Delivery (PEDD) approach with standard of care systemic chemotherapy.

The goal of this clinical trial is to perform targeted delivery of the most toxic components of standard-of-care treatment regimen deep into pancreatic tumors using a novel approach that accesses the tumor via pancreatic veins. The chemotherapy involved is for the treatment of adults diagnosed with unresectable, pancreatic carcinoma. With the number of newly diagnosed patients with pancreatic cancer rising and fewer than 20% suitable for surgery, improved treatment options for pancreatic cancer are a critical health care need.

Traditional approaches for targeted therapeutic delivery to the pancreas rely on the use of the arterial system. The pancreatic arterial supply, however, poses unique anatomic challenges as the terminal pancreatic arteries are not large enough to accommodate delivery devices. This limits the ability for highly focused delivery of therapeutics to pancreatic tumors. TriSalus has developed a new retrograde venous proprietary approach using the simpler pancreatic venous system, making it far more suitable for PEDD.

The presence of highly dense tissue architecture and abnormal poor blood flow into solid tumors are critical barriers to drug delivery, resulting in less than 1% of systemic drug administration delivered into tumors with conventional therapies.

PEDD with SmartValve technology is a self-expanding, one-way micro-valve that enables optimal infusion pressures for deeper therapeutic penetration. Treatment is delivered directly into solid tumors with the goal to avoid healthy tissue while optimizing therapeutic effect. This pressurized delivery has the potential to open collapsed vessels in tumors and helps promote therapy delivery.

This study is designed to assess the technical success and safety of administering oxaliplatin through retrograde venous infusion (RVI) followed by systemic administration of FOLFIRI, a regimen containing folinic acid, fluorouracil, and irinotecan. Secondary measures of the study include local progression free survival, systemic progression free survival, overall survival, radiographic response rates, serologic response rates, and neurotoxicity from oxaliplatin. Exploratory measures include correlation of infusion pressures with treatment response, in addition to serum oxaliplatin pharmacokinetics following PEDD-RVI. Patients, who are new to treatment and have received first-line systemic therapy, are eligible for this trial.

The proprietary Pressure-Enabled Drug Delivery (PEDD) approach with SmartValve technology is FDA 510(k) cleared and features a self-expanding, nonocclusive, one-way valve, which infuses therapeutics into a solid tumor at a pressure higher than the baseline mean. This pressurized delivery opens collapsed vessels in tumors and enables perfusion and therapy delivery into hypoxic areas of solid tumors.

Alkahest Announces Initiation of Phase 2b Clinical Trial

Alkahest, Inc. recently announced the initiation of a Phase 2b clinical trial of its orally administered small molecule CCR3 inhibitor, AKST4290. The company has dosed the first subject in AKST4290-205 (PHTHALO), which will assess the effects of AKST4290 on visual acuity with loading doses of anti-VEGF in treatment-naïve neovascular age-related macular degeneration (AMD) patients.

"The initiation of this randomized phase 2b trial represents an important milestone for our clinical development program in age-related macular degeneration. While the current standard of care for neovascular AMD is effective, the high burden of therapy leads to significant undertreatment and sub-optimal outcomes," said Karoly Nikolich, PhD, Chief Executive Officer of Alkahest. "If safe and effective, adding a convenient oral agent to the treatment options for neovascular AMD would address a significant unmet patient and medical need."

AKST4290-205 (PHTHALO) is a multi-center, double-blind, placebo-controlled dose-ranging trial designed to evaluate the efficacy of AKST4290 in treatment-naïve neovascular AMD patients after three loading doses of anti-VEGF (aflibercept) therapy. Subjects will be randomized 1:1:1 to receive AKST4290 400 mg twice daily, AKST4290 800 mg twice daily, or placebo. The primary endpoint of the study is mean change in best corrected visual acuity (BCVA), per the Early Treatment Diabetic Retinopathy Study criteria. Key secondary endpoints include safety, time to PRN injection with anti-VEGF per defined criteria in the AKST4290 arms only, mean number of anti-VEGF injections, and the proportion of subjects with a BCVA change of ≥ 15 letters. Alkahest intends to enroll approximately 150 patients across 25 sites in multiple countries.

AKST4290 is an orally administered CCR3 inhibitor that blocks the action of eotaxin, an immunomodulatory protein that increases as humans age and with specific age-related diseases. By targeting eotaxin and its downstream effects, AKST4290 may reduce the hallmark inflammation and neovascularization of AMD while also acting more broadly to reduce inflammation associated with many other age-related diseases. The molecule is currently being tested in Parkinson's Disease with additional indications being explored.

Alkahest is a clinical stage biopharmaceutical company dedicated to discovering and developing treatments for neurodegenerative and age-related diseases with transformative therapies targeting the aging plasma proteome. The Alkahest pipeline includes multiple therapeutic candidates ranging from selected plasma fractions to protein-targeted interventions which aim to slow the detrimental biological processes of aging. Alkahest is developing novel plasma-based therapies in collaboration with Grifols, a global healthcare company and leading producer of plasma therapies. For more information, visit www.alkahest.com.

Credence MedSystems Receives Award for Best Innovation in Drug Delivery Devices

Credence MedSystems, an innovator in injectable drug delivery technology for the biopharmaceutical industry, has received the Pharmapack Award for its Connect™ Auto-Sensing Injection System. The Connect™ was voted by a panel of pharmaceutical industry executives to be the Best Innovation in Drug Delivery Devices at the Pharmapack conference February 5 and 6 in Paris.

The Credence Connect™ brings digital connectivity to any pre-filled syringe for the delivery of injectable medications. It incorporates automatic real-time monitoring and transmission of critical injection data into a reusable ergonomic finger grip. The Connect™ enables healthcare providers and self-injecting patients to automatically collect data and receive feedback on the success of the injection, while improving usability of the syringe. "The Connect™ can deliver value for clinical studies and commercial applications," states John A. Merhige, Credence's Chief Commercial Officer. "It can promote proper use and drive compliance, characterize patient use patterns, and facilitate important communication and other novel business opportunities in the healthcare ecosystem."

"This is another great honor for Credence," added Chief Operating Officer Jeff Tillack. "We thank Pharmapack for promoting and rewarding innovation. Credence is proud to have won this award again." Credence received the same honor at the 2015 Pharmapack conference for its Companion® Safety Syringe System. Credence is currently working with several pharmaceutical manufacturers towards implementation of the Companion® system for delivery of their innovative drug products.

Merhige continued, "Probably the fastest impact we can have is on improving the integrity of clinical trial data. By providing Pharma with actual use data, obtained via remote monitoring, the Connect™ supports informed arguments on data inclusion when determining safety and efficacy of new drugs. And it improves the economics of managing the studies." The Connect™ was first introduced at Pharmapack. "We look forward to discussing with our Pharma partners the most impactful implementation of this new technology."

Credence MedSystems is an innovator of drug delivery devices that solve unmet market needs. Credence's philosophy of Innovation Without Change allows our customers to impress and protect their end users while preserving their existing processes, sourcing strategies and preferred primary package components. The Companion® family of syringe systems includes proprietary needle retraction technology, syringe reuse prevention and other critical safety and usability features. The Dual Chamber Reconstitution platform offers single-step mixing and injection for drugs that require reconstitution at the time of delivery. Metered dose systems and other novel devices address the needs of specific therapeutic markets such as ocular therapies and cosmetic applications. For more information, visit www.CredenceMed.com or call +1-844-263-3797 (844-CMEDSYS).

Real World Challenges
in *Drug Delivery and Formulation*

The Objective

Need to understand the changing dynamics of clinical-stage pipelines by indication, molecule type and most advanced phase to present to senior management

The Challenge

How do I obtain this information in a format that will allow me to quickly evaluate overall trends in pharmaceutical development?

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Two Labs Acquires CEEK Enterprises

Two Labs recently announced it has acquired CEEK Enterprises, a management consultancy dedicated to supporting clients in the biopharma and MedTech industries with specialized expertise in corporate development, commercial strategy, clinical development, and medical affairs.

The union of Two Labs and CEEK significantly expands Two Labs' suite of integrated offerings, allowing the platform to better serve its broad base of clients across the life sciences industry. At its core, CEEK's ability to provide strategic guidance to clients early in the development process, as well as ongoing support through the product launch, enables Two Labs to enhance the value of its commercial pre-launch and launch capabilities. Joining forces with CEEK has expanded Two Labs' ability to support clients throughout the product lifecycle, from early product development through loss of exclusivity.

"As Two Labs continues on a path of growth, this partnership with CEEK makes sense from a client services standpoint, and from a values standpoint," said Howard Miller, General Manager at Two Labs. "At our core, we remain committed to the patient, and CEEK's unique Clinical Development and Medical Affairs capabilities, combined with their early stage Commercial and Corporate Strategy, enables our clients to better understand which products and indications are more likely to be successfully researched and commercialized. After learning about the tailored approach they use with their customers, we felt confident that CEEK was the perfect addition the Two Labs team."

"This new relationship with Two Labs affirms everything that CEEK has worked towards for the last 5 years," said Darius Naigamwalla, President at CEEK. "Above all, we are dedicated to delivering an exceptional customer experience while staying committed to our family of employees. I've admired the Two Labs organization for years, as they share our values and high standards of excellence. Moving forward, the combined organization will be able to create new and innovative solutions to address critical challenges facing the biopharma industry."

The transaction was completed as of Feb. 3, 2020. CEEK will continue operating out of their existing regional offices, including the headquarters in Boston. Terms of the agreement were not disclosed.

Two Labs is a leading pharmaceutical services company that provides a portfolio of market access, market intelligence and commercialization services to pharmaceutical manufacturers. Since its inception in 2003, Two Labs has led 200+ new product launches and more than 290 in-market projects from pre-launch to loss of exclusivity. For more information, visit www.TwoLabs.com.

CEEK is a specialized management consultancy focused on the biopharma and medical technology industries. With clients ranging from "Top 5" biopharma companies to start-up organizations seeking financing, our breadth and depth of expertise allows CEEK to help clients address critical corporate/commercial/clinical issues and drive value creation.

Pelican BioThermal Announces the Acquisition of NanoCool

Pelican BioThermal recently announced the acquisition of NanoCool, an Albuquerque, New Mexico-based manufacturer of temperature-controlled packaging solutions. This acquisition further increases the breadth of the Pelican BioThermal product portfolio, already the most comprehensive in the industry. The addition of NanoCool customers, market segments and product technologies will enable Pelican BioThermal to expand its access to patients, laboratories and other last-mile players in the distribution of life sciences materials and collection of patient laboratory samples.

"The core competency of Pelican BioThermal and NanoCool — innovative temperature-controlled packaging — is very much aligned, but there is little overlap between our market segments and product technologies," said David Williams, President of Pelican BioThermal. "Adding NanoCool's capabilities to our diverse product line will help fuel our efforts to expand our offerings and bring further innovation to growing sectors of the life sciences industry spanning the globe. We will continue to lead innovation in temperature-controlled packaging with the addition of NanoCool's customer-focused engineering approach — a methodology that both organizations fully embrace."

NanoCool's innovative evaporative cooling systems are the most convenient cold chain shipping containers available. With no need to refrigerate or pre-condition, NanoCool packaging can be stored at normal temperatures. A simple push of a button, engages the cooling technology and quickly conditions a payload space for shipping biological patient samples and other life science materials. These unique characteristics, and highly efficient volumetrics, make NanoCool ideal for markets including specialty couriers, diagnostic laboratories, clinical supply providers and gene and cell therapy organizations. The company also has a dry-ice friendly parcel shipper and a version of its cooling engine that patients can send in a shipping envelope from their homes. Combining companies opens the door for Pelican BioThermal to establish new customer relationships and further address cold chain challenges in these burgeoning markets.

"I'm thrilled to see NanoCool become part of the Pelican BioThermal family. The Pelican BioThermal brand is well known around the world for its temperature-controlled technology and we're excited that our products will gain access to their resources and best-in-class industry expertise," said Doug Smith, Founder of NanoCool. "Since we primarily serve customers in the US, we look forward to leveraging Pelican BioThermal's extensive global network to bring our innovative technology to more areas of the world – especially to areas where temperature-control is crucial."

Smith will continue with the business as a consultant to Pelican, and the NanoCool facility in New Mexico will continue to manufacture its products. Plans are underway to increase production at the facility to meet expected new sales following the acquisition. The approximately 60-person staff of NanoCool will be retained and new positions may be added to enhance operations and support sales growth.

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Cocrystal Pharma's Structure-Based Technology Demonstrated Broad Utility

Cocrystal Pharma, Inc. is a clinical-stage biotechnology company discovering and developing novel antiviral therapeutics using its proprietary structure-based drug discovery platform technology to create first-and best-in-class antiviral drugs for a wide variety of serious and/or chronic viral diseases.

Cocrystal's proprietary structure-based drug discovery platform (1) Provides direct visualization of how essential viral enzymes work, (2) Identifies attractive drug binding pockets on these enzymes, (3) Enables the design of compounds to block the function of these enzymes, thereby preventing viral production, and (4) Discovers novel broad spectrum antivirals with high barriers to drug resistance.

"Our proprietary drug discovery platform technology has enabled us to develop antiviral treatments that have generated positive data to date across our current pipeline of preclinical and clinical programs," said Dr. Gary Wilcox, Chairman and Chief Executive Officer of Cocrystal. "Based on the data we have generated and the demonstrated potential of our technology, we believe we have the capabilities to address shortcomings in the treatment of viruses with significant unmet needs, as well as develop safe and effective antiviral therapies for new viruses as they arise, such as the COVID-19 coronavirus. This is an opportunity to use our proprietary drug discovery platform and antiviral experience to participate in this worldwide health crisis and we have begun planning our coronavirus program."

Cocrystal's technology generates a 3-D structure of inhibitor complexes at near-atomic resolution providing the Company with the ability to identify novel binding sites and allow for a rapid turnaround of structural information through highly automated X-ray data processing and refinement. By utilizing this technology, Cocrystal is able to develop treatments that specifically target essential viral enzymes. The Company is currently leveraging its unique structure-based technologies to develop antiviral drugs for hepatitis C, influenza, and norovirus.

To date, Cocrystal's lead influenza molecule in development, CC-42344, has shown excellent antiviral activity against influenza A strains, including avian pandemic strains and Tamiflu-resistant strains, and a favorable pharmacokinetic and safety profile.

In addition, the company has an ongoing partnership with Merck Sharp & Dohme Corp. (Merck) to discover and develop a novel influenza drug for influenza A and B infections. The company expects the lead molecule will be selected for its influenza A/B program in the fourth quarter of 2020.

The company announced positive safety and preliminary efficacy data from its triple regimen, US Phase 2a study evaluating CC-31244 and Epclusa (sofosbuvir/velpatasvir) for the ultra-short treatment of HCV infected individuals. Planning is underway to initiate a Phase 2b study.

The company is working on a potential first-in-class non-nucleoside inhibitor (NNI) that will have both potent and broad-spectrum Noro polymerase inhibition. Work has also begun on a protease inhibitor. The technology platform has been completed and the structure-based lead discovery is ongoing in both programs.

Annovis Issued Patent for Method of Treating Parkinson's Disease & Other Lewy Body Diseases

Annovis Bio Inc. was recently issued a patent (US 10,383,851) in August 2019 for a method of treating Parkinson's disease, Lewy body dementia, and other Lewy body diseases in humans by administering its lead compound, ANVS401. The company expects multiple patents to be generated from this patent family, each targeting specific neurodegenerative diseases independently.

Maria Maccecchini, PhD, CEO of Annovis, said "Based on discussions with the patent office, we have filed additional patent applications for each individual neurodegenerative disease that our drug targets. We plan to provide further updates as we execute on this process."

ANVS401 improves axonal transport, the information highway of the nerve cell, by attacking multiple neurotoxic proteins simultaneously. ANVS401 is the lead compound in the company's ongoing Phase 2a clinical trial for Alzheimer's disease and in a planned Phase 2a trial for Parkinson's disease.

The company is planning a 50-patient Phase 2a study in Parkinson's disease with primary endpoints targeting a decrease in neurotoxic protein levels, increase in neurotransmitters and neurotrophic factors, lowering of inflammatory proteins, lowering of neurodegeneration markers, and positive cognitive and functional outcomes.

"We believe we have a novel solution to stop the course of Parkinson's disease and Alzheimer's disease, areas of unmet need valued in the multibillions of dollars and growing," continued Dr. Maccecchini. "The successful completion of our two Phase 2a studies will provide optimal information on target and pathway engagement in both diseases and allow us to move into pivotal studies."

Parkinson's disease affects an estimated 1 million people in the US and as many as 10 million globally. An estimated 5.8 million people in the US have Alzheimer's disease, and there are approximately 44 million people worldwide living with the disease.

Headquartered in Berwyn, PA, Annovis Bio, Inc. is a clinical-stage, drug platform company addressing neurodegeneration, such as Alzheimer's disease (AD), Parkinson's disease (PD), and Alzheimer's in Down Syndrome (AD-DS). We believe that we are the only company developing a drug for AD, PD, and AD-DS that inhibits more than one neurotoxic protein and, thereby, improves the information highway of the nerve cell, known as axonal transport. When this information flow is impaired, the nerve cell gets sick and dies. We expect our treatment to improve memory loss and dementia associated with AD and AD-DS, as well as body and brain function in PD. We have an ongoing Phase 2a study in AD patients and plan to commence a second Phase 2a study in PD patients. For more information, visit www.annovisbio.com.


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2019 Global Drug Delivery & Formulation REPORT

Part One of a Four-Part Series

Part 1: A Review of 2019 Product Approvals

Part 2: Notable Drug Delivery and Formulation Product Approvals of 2019

Part 3: Notable Drug Delivery and Formulation Transactions and Technologies of 2019

Part 4: The Drug Delivery and Formulation Pipeline

By: Kurt Sedo, VP of Operations, and Tugrul Kararli, PhD, President & Founder, PharmaCircle

Introduction

The topline pharmaceutical product approval figures are in for 2019, and they largely reflect in terms of number and product types what was reported for 2018. It's hard to judge whether or not this is a positive indicator for the sector. It's always comforting to see continuation, but there is the suspicion that the environment is changing, and the industry may not be properly prepared to address the accompanying opportunities and challenges.

Any number of reviews and reports discuss the number and nature of US FDA product approvals. This four-part series starts with a review of the 2019 approval numbers focused on technologies and dosage forms, essentially the nuts and bolts underpinning these products and their therapeutic benefits.

To better identify trends related to drug delivery and formulation, the Global Drug Delivery & Formulation Report focuses on "innovative" product approvals. This is a mixed group of products that incorporate a new molecular entity (NME), provide a new dosage form of an NME or Previously Approved Active (PAA), or represent a new combination of NME or PAA actives. Multisource products, generics, and biosimilars are excluded.

This first article summarizes the 2019 product approvals in the three major world markets, the United States (FDA), Japan (PMDA), and the European Union (EMA). From a technology perspective, this represents a historical review. Given that innovative products take on average 8 to 10 years[1] to get through clinical development and regulatory review, the technologies underpinning these products were developed at least a decade ago.

What about multisource approvals, generics, and biosimilars? These products represent ancient history. Approved in 2019, these products are essentially copies of products approved a decade or more ago based on technology and formulation decisions made two decades ago.

This report tries to connect the past with the present to suggest what the future will deliver from a product and technology perspective.

Note: This first article examines approvals in 2019[2] for the United States (FDA), Japan (PMDA), and the European Union (EMA). The European Medicines Agency (EMA) approvals represent a subset of all approvals in Europe but represent only pan-European approvals. In the case of Europe, product approvals made only at the country level (RMS, CMS, UK, other) are not included in the report figures. In all tables, the figures exclude multisource (generic) and biosimilars unless explicitly stated.

NDA and BLA approval numbers and types in 2019 were little changed versus 2018

Table 1. FDA Therapeutics Approval Numbers by Classification[3] (2019)

BLA (CDER*, CBER*)		**26**
CDER	Biologic, 351(a) & 351(k)	22
	- 351(a) (Innovator)	12
	- 351(k) (Biosimilar)	10
CBER	Biologic Therapeutics, 351(a)	4
NDA (CDER)		**117**
Type 1	New Molecular Entity	39
Type 2	New Active Ingredient	7
Type 3	New Dosage Form	26
Type 4	New Combination	8
Type 5	New Formulation or New Manufacturer	32
Type 7	Previously Marketed, Unapproved	1
Type 1/4	New Molecular Entity and New Combination	1
Medical Gas	Medical Gas	3
ANDA (CDER)	Abbreviated New Drug Approvals (Generic, Multisource)	**962**

Source: PharmaCircle Pipeline & Products Intelligence and FDA Products Modules

* CDER (Center for Drug Evaluation and Research), CBER (Center for Biologics Evaluation and Research)

- Total 2019 Biologic approvals, 351(a) and 351(k), fell short of 2018's 33 approvals.
- Biosimilar approvals in 2019 edged ahead of 2018, with 10 versus 9. Both years were well ahead of 2017's 5 approvals.
- 2019's 40 non-biologic novel drug approvals, including single active and combination products, fell just short of 2018's 41. Both were well above 2017's 34 approvals.
- New Dosage Form approvals (Type 3 and Type 3,4) totaled 26 in 2019, a little behind 2018's 28 approvals. These products incorporated previously approved actives (PAA) and generally offered improved convenience or addressed additional indications.
- New combination approvals incorporating PAA and novel actives totaled 9 in 2019. This fell well short of the 20 approvals in 2018.
- New Formulation or New Manufacturer (Type 5) approvals totaled 32 in 2019, a little short of 2018's 40 approvals. These approvals are often injectable multisource products not eligible for ANDA review.

Table notes: Multisource injectables are approved through the NDA rather than the ANDA regulatory process and can unintentionally skew the new drug approval figures. Type 5 approvals are not considered in the analyses presented on the following pages.

Injection route approvals largely matched oral route approvals in Japan and the EU

Table 2. 2019 Approvals by Administration Route

Route of Administration	FDA (n=105)	EMA (n=47)	PMDA (n=60)
Inhalation	**2**	**1**	**4**
Injection	**38**	**21**	**25**
Infusion, SCF	-	-	1
Infusion IM	-	2	-
Infusion IV	11	6	9
Infusion IV, SC	-	-	1
Infusion IV, Injectable IV	-	-	1
Injectable IM	4	2	3
Injectable IV	4	-	2
Injectable SC	14	8	8
Injectable IV, IM	1	-	-
Injectable IV, SC	1	1	-
Injectable IV, IM, SC	-	1	-
Injectable Intravitreal	2	-	-
Intralesional, Infusion IV	-	1	-
Implantation	**1**	**1**	-
Intrauterine	**1**	**-**	-
Nasal	**4**	**2**	**-**
Ophthalmic	**3**	**1**	**3**
Oral	**52**	**20**	**25**
Topical	**3**	**1**	**-**
Transdermal	**1**	**-**	**3**

Source: PharmaCircle Pipeline & Products Intelligence module

- As was the case in 2018, Oral products in 2019 represented the largest proportion (50%) of approvals in the U.S. followed by Injection products.
- Injection and Oral product approval numbers were almost balanced in the EU and Japan. In the case of the EU this largely reflects the EMA regulatory focus which only approves new products and dosage form improvements if they fall into a relatively limited range of therapeutic indications. Products that simply offer improved oral dosage forms are often approved through more localized regulatory pathways.
- Nasal products showed an upsurge in approvals in 2019, led by the high-profile approval in the U.S. of Janssen's Spravato (nasal ketamine).
- Transdermal approvals also experienced a bit of a bump in 2019, at least in the U.S. where Hisamitsu's Secuado (asenapine) daily patch was approved for the treatment of schizophrenia.
- 2019 saw the absence of sublingual approvals in the three territories following several years of multiple approvals.

Table notes: The figures above include all formulations approved for each product. In a few cases, two or more formulations were approved for a single product. The figures above do not include FDA Type 5 Approvals or Biosimilars (all). These excluded approvals, generally injectables, are not subject to ANDA regulations but still effectively represent generics in terms of drug delivery and formulation.

Industry interest in formulation enhanced products has waned with attention turning to devices

Table 3. 2019 Approvals by Drug Delivery Category

Route of Administration	FDA (n=105)	EMA (n=47)	PMDA (n=60)
Inhalation			
Devices (Integral)*	2	1	3
Formulations	2	1	4
Injection			
Device, Injection Systems (Integral)*	5	4	4
Device, Pre-Filled Syringes	6	5	2
Formulations			
Conjugates	4	2	2
Viral Vectors	1	-	-
None	21	10	14
Implantation			
Formulations	1	1	-
Intrauterine			
Formulations	1	-	-
Nasal			
Devices	4	1	-
Formulations	3	1	-
Ophthalmic			
Device, Pre-Filled Syringes	1	-	-
Formulation	3	1	3
Oral			
Formulations	15	6	4
None	37	14	21
Topical			
Formulations	2	-	-
None	1	1	-
Transdermal			
Formulations	1	-	3

Source: PharmaCircle Pipeline & Products Intelligence Module

* Integral refers to devices that are integrally associated with a product. Examples would include auto-injectors and dry powder inhalers.

- Formulation enhanced oral products represent a notable minority of approvals in all three territories suggesting the increasing development of molecule optimized therapeutics and the relative lack of opportunity for simple formulation enhanced next generation products.
- Injection systems, while an increasingly popular option to encourage the use of outpatient injectables, represent a small proportion of total Injectable approvals.
- For the second year in a row there were no approvals of abuse resistant modified release opioids in the U.S. This is doubtless a function of heightened regulatory scrutiny and increased potential liability.
- Nasal product approvals saw an increase in 2019, with the majority, 4/5, employing some sort of formulation technology.

Table notes: The figures above include all formulations approved for each product. In a few cases, two or more formulations were approved for a single product. The figures above do not include FDA Type 5 Approvals or Biosimilars (aff). These excluded approvals, generally injectables, are not subject to ANDA regulations but still effectively represent generics in terms of drug delivery and formulation.

Approvals continue to be associated with simpler dosage forms (Solutions & Tablets)

Table 4. 2019 Approvals by Dosage Form

Route of Administration	FDA (n=105)	EMA (n=47)	PMDA (n=60)
Inhalation			
Inhalation Powder	2	1	1
Inhalation Suspension	-	-	3
Injection			
Powder for Solution	1	-	
Solution	25	16	19
Suspension	4	1	1
Lipid Complex	-	-	1
Lyophilized Powder for Solution	7	4	3
Lyophilized Powder for Suspension	1	-	1
Nasal			
Powder	1	1	-
Solution	1	1	-
Spray Solution	2	-	-
Ophthalmic			
Ointment	1	-	-
Solution	2	1	3
Oral			
Bar	1	-	-
Capsule	9	3	4
Film	1	-	-
Pellet	2	-	-
Sachet, Granules	-	2	1
Soft Gel Capsules	3	-	-
Solution	3	3	-
Suspension	1	-	-
Tablet	32	12	20
Topical			
Cream	1	-	-
Foam	1	-	-
Lotion	1	-	-
Spray	-	1	-
Other			
Implant	1	1	-
Intrauterine Foam	1	-	-
Transdermal Patch	1	-	3

Source: PharmaCircle Pipeline & Products Intelligence module

- Oral Tablet and Capsule presentations, along with simple Injection Solution dosage forms, accounted for the majority, two thirds, of all dosage forms approved in 2019.
- Even Oral approvals, a longtime bellwether of dosage form innovation, saw only 30% of approvals associated with anything other than simple tablet and capsule presentations. A number of the non-tablet and capsule presentations were directed to pediatric applications.

Table notes: The figures above include all formulations approved for each product. In a few cases, two or more formulations were approved for a single product. The figures above do not include FDA Type 5 Approvals or Biosimilars (all). These excluded approvals, generally injectables, are not subject to ANDA regulations but still effectively represent generics in terms of drug delivery and formulation.

Approvals by Molecule Type were notably consistent across the major markets

Table 5. 2019 Approvals by Molecule Type

Molecule Type	FDA (n=105)	EMA (n=47)	PMDA (n=60)
Antibody	13	8	5
Carbohydrate	1	-	1
Cell Therapy	-	-	1
Gene Therapy	1	-	1
Oligonucleotide	-	1	1
Other (IgG)	-	-	1
Peptide	6	2	3
Polymeric	2	-	-
Protein	4	3	4
Protein Conjugate	1	3	2
SiRNA	-	-	1
Small Molecule	72	28	39
Stem Cell	-	1	-
Vaccine	4	1	1

Source: PharmaCircle Pipeline & Products Intelligence module

- Biologicals accounted for one third (71/212) of non-generic new product approvals in 2019, representing an insignificant change over the 2018 results.
- Antibody related approvals represent the largest proportion of biological approvals but seem on a downward trend in share, if not number, as newer molecule types are being developed and approved.

References

1. See Jan/Feb 2020 issue at www.drug-dev.com.
2. Summary reports of 2019 approvals in all three territories are available at www.pharmacircle.com/rc/.
3. NDA Classification Codes. https://www.fda.gov/media/94381/download.

Table notes: The figures above include all formulations approved for each product. In a few cases, two or more formulations were approved for a single product. The figures above do not include FDA Type 5 Approvals or Biosimilars (all). These excluded approvals, generally injectables, are not subject to ANDA regulations but still effectively represent generics in terms of drug delivery and formulation.

BIOSIMILAR DEVELOPMENT

Biosimilar Biological Products: Development & Applications

By: Kaiser J. Aziz, PhD

INTRODUCTION

The US Food and Drug Administration (FDA) is responsible for advancing the public health by helping to speed innovations that make medicines safer and more effective and by helping the public get the accurate, science-based information it needs to use medicines to maintain and improve public health. This publication provides an overview of biosimilar products development and evaluation criteria for FDA approval. The FDA provided a general guidance document for innovations, challenges, and solutions for new drug products that examine the critical path needed to bring therapeutic products to completion, and how the FDA can collaborate in the process, from laboratory to production to end use, to make medical breakthroughs available to those in need as quickly as possible.[1,2] In new drug clinical applications, a quality-by-design (QbD) approach is one of the most important features, while sponsor's drug product development team deals with the formulation, manufacturing processes, container closure features, and user instructions.[3-5] The FDA requires a biosimilar product to be similar, but not identical to the existing biologic medicine (referred to as a "reference product").[6-8] As more biosimilar products are developed, it is imperative that pharmaceutical companies develop strategies to comply with evolving regulations, mitigate risks, and implement requirements for their clinical applications. FDA guidances help sponsors of new biosimilar drug products in terms of providing organized data and appropriate labeling information in support of the new biosimilar drug's clinical use, development, and approval process.[8]

BIOLOGICS

Biological products are generally derived from living materials - human, animal, or microorganisms. Biological products are large complex molecules in comparison to chemically synthesized small molecular weight generic drugs. Section 351 of the PHS Act defines a "biological product as a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component, or derivative, allergenic product, or analogous product… applicable to the prevention, treatment, or cure of a disease or condition of human beings." Biological products subject to the PHS Act also meets the definition of drugs under the Federal Food, Drug, and Cosmetic Act (FD&C Act). In terms of structure differences, biologics are large molecules and cannot be described efficiently with a precise formula in contrast to chemically synthesized small molecular weight drugs, which have a well-defined structure and can be thoroughly characterized. Furthermore, changes in the manufacturing process, equipment, or facilities could result in changes in the biological product itself and sometimes require additional clinical studies to demonstrate the product's identity, purity, potency, and safety. In contrast, traditional drug products usually consist of pure chemical substances that are easily analyzed during manufacturing processes.[1-5] These fundamental differences in complexity and large-scale manufacturing are at the core of why biosimilars are not equal to generic drugs; therefore, these differences require biological products to follow the broad regulatory steps for approvals. There are preclinical and clinical studies, and finally appropriate manufacturing adjustments, using c-GMP requirements that require biologics to have an investigational new drug (IND).[5] The matrices of biological products are unique and

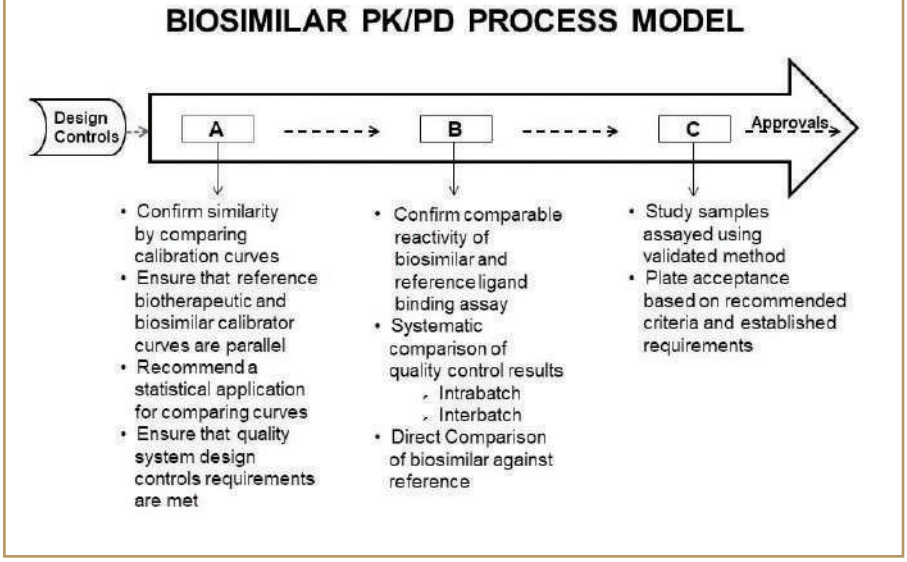
complex and; therefore, require a drug product development section of an NDA containing information on the development studies conducted to establish that the dosage form, formulation, manufacturing process, container closure system, microbiological attributes, and usage protocol are appropriate for the intended purpose specified in the NDA. Any parameters relevant to the performance characteristics or manufacturability (ie, active ingredients, release testing, stability, etc) are addressed in the NDA.[3,5] Biologics are unique and complex molecules. Biologics are produced in living cells with multistep processes, extracted and purified in comparison to small molecular generic drugs manufactured via chemical synthesis. In regard to these major structural and manufacturing differences, regulatory guidances have outlined robust data requirements to demonstrate similarity to reference biologics. Biosimilar applicant sponsors generally need to generate data from lab testing, non-clinical, and clinical data in order to show that the biosimilar they have developed will provide the same therapeutic benefit and risks to patients as the reference product.[2,7,8]

Biologics Approval Process

The sponsor of products of biological origin submits a biologics license application (BLA) under Title 21, CFR, Parts 314 & 601 [FDA forms 356(h)].The BLA consists of reports of all studies sponsored by the applicant, along with other pertinent information for the evaluation of the product's purity, potency, safety, and effectiveness. Even though the basic framework of chemical drug development applies to small drug molecules, it also applies to biological products, including blood-derived products, vaccines, in-vivo diagnostic allergenic products, immunoglobulin products, products containing cells or microorganisms, and most protein products. Biological products subject to PHS Act also meets the definition of drugs under FD&C Act. The development process approach for a biologic product is essentially the same as that for a traditional small molecular drug. This is based on a systematic approach to structure and function of the small drug molecule studies relative to expected clinical outcomes. In these situations, studies may be based on high throughput screening using enzyme immunoassays. For example, it may be cloning a specific antibody and demonstrating in-vitro studies as it binds to its ligand. In those situations where sufficient evidence exists, additional studies may be required. These studies, along with supporting manufacturing data, including process controls, analytical methods, nonclinical, and clinical data, are assembled into IND application.[4] Analytical methods may be referred to different types of in-vitro assays addressing characterization of the active drug molecule and *in-vivo* testing of drug levels and/or biological outcomes. For instance, a change in the fermentation process for the growth of production cells may lead to the introduction of new/modified species of the protein of interest (ie, a new glycoform). In these types of situations, a detailed analytical characterization of the new/modified process-derived materials could go undetected by routine release testing methodologies ending up in novel immunogens as end-products.[2,3] The regulatory requirements for chemistry, manufacturing, and controls (CMC) may address some of the aforementioned elements.[1-5]

The CMC manufacturing section requires biologics product's batch record representing drug's substances production process that provides information in two key areas: (1) In-process controls and (2) process validation. This includes a description of the methods used for in process controls (ie, those involved in fermentation, harvesting, and down-stream processing). For testing performed at significant critical control points (CCP) phases of production, criteria for accepting or rejecting is provided. In those situations where process is changed or scaled up for commercial production and this involves changes in the fermentation steps, a revalidation of cell line stability during growth is described and the data and results are provided. A description and documentation of the validation studies for the cell growth and harvesting process that identifies CCP parameters of process validation are provided.[4,5] Also, description and documentation of the validation of the purification process is included in the manufacturing process.[3,4] In those situations where reference standards are used (ie, WHO, USP), the sponsor of the biologics application is required to identify and submit the citation for the standard and a certificate of analysis. If an in-house working reference standard is used, a description of the source, preparation, characterization, specifications, testing protocol, and results are provided.[3,5] The specifications and tests to ensure the identity, purity, strength, potency, and the stability of the drug substance, as well as its lot-to-lot consistency, are provided in the application. The sponsor includes any impurities and analytical studies of the drug substance and information on container and closure system and its compatibility with the drug substance. This section includes information in regard to supply chain's profiles of tests, toxicity, and compatibility studies. This information

FIGURE 1



can be referenced in the drug master file (DMF). In regard to methods of manufacturing, a complete description of the process controls of the drug product's sterilization, aseptic and packaging procedures are described. This section includes a flow diagram indicating each CCP step.[1-5]

BIOSIMILARS

Biosimilar drug products are not considered chemically identical to their originator products because of structural differences of biosimilar molecules. For approvals of biosimilars, the sponsors of 351(k) applications must present analytical characterization, pharmacokinetic, and pharmacodynamic profiles, and comparative clinical studies to eliminate any residual uncertainty. In order to show that a proposed biosimilar is highly similar to a licensed reference product, the sponsor submits analytical studies demonstrating similarity to the reference product, animal studies (including toxicity assessment), and one or more studies in at least one clinical indication for use to demonstrate purity, potency, and safety of the proposed biosimilar (Figure 1).[7,8]

It is imperative for the proposed biosimilar to be tested for one of the intended clinical use described in the licensed reference product's labeling. The protocol requires a sponsor to describe the biosimilar candidate in a PK/PD study including healthy volunteers and clinical study comparing its safety, efficacy, and immunogenicity to that of the reference product in one of the clinical indications for use (Figure 2).

Biosimilar products are evaluated by demonstrating similarity to the reference product via Totality of Evidence (Figure 3). The FDA approval process consists of analytical comparison, biological characterization, preclinical, and clinical studies to evaluate PK/PD and safety data presented in the sponsor's 351(k) application (Table 1).

Biosimilars Approval Process

The biosimilar approval process provides a thorough characterization of the molecular structure related to safety and efficacy of the proposed biosimilar product and clinically meaningful data (Figures1-3). The most prominent development and application concepts are:

1. Design Controls, validation and verification studies (Analytical Similarity, Manufacturing and Effective CMC Strategy)
2. QbD approach to Biosimilar Development and Applications[2-8]
3. Statistical considerations for demonstration of analytical similarity[7]

FIGURE 2

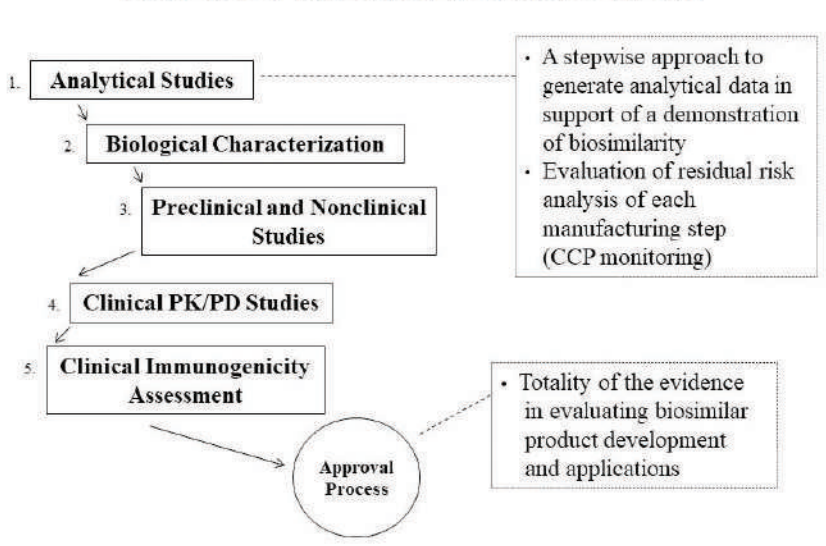
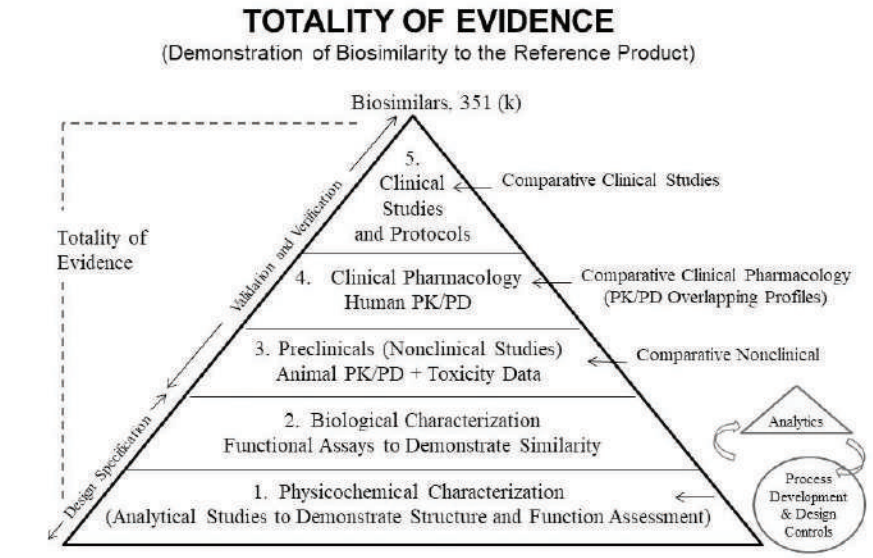


FIGURE 3



4. Clinical aspects of proposed biosimilar product (Design of studies, Immunogenicity Assessment, Extrapolations & Interchangeability)[2-12]
5. FDA Guidance on Biosimilar Labeling (Conformance with specific recommendations for labeling for interchangeable biological products)[8-12]

DISCUSSIONS

One of the most integral features of biosimilar development is the analytical characterization of significant lots of the innovator product and the proposed biosimilar product (Figures 1-3). These characterization studies show that primary amino acid sequence, tertiary structure specificity, and the mechanism of actions of biosimilar and innovator drugs are similar under Design Controls requirements of the FDA's CGMP/QbD guidances.[4,6] The International Conference on Harmonization (ICH) defines QbD as a systematic approach to development that incorporates the predefined objectives and emphasizes products's process controls based on quality risk management (ICH 2009).[6] The goal of this requirement is to ensure that built-in quality of the product from its design prototype phase through manufacturing and post-marketing surveillance is maintained.[6] The basic element of QbD requirement is Quality Attributes of Product Profile (QAPP). This entails quality characteristics of the biosimilar product which addresses the design of dosage form, strength, route of administration, intended clinical indication, safety, and efficacy. This element also includes the product's quality criteria for the intended clinical use in terms of purity, stability, potency, and safety. The QAPP is also known as critical quality attributes (CQAs). The CQA under ICH 2009 is also considered as a physical, chemical, biological, or microbiological characteristic feature of the output of the material including finished biosimilar drug product that should be within designed appropriate limits, range, or distribution for intended clinical use described in the labeling of the approved product.[6-10] Risk analysis and monitoring are described in ICH Q8 and Q10 documents.[4-6,10]

ICH Q8 (ICH 2009) describes the design space related to manufacturing process inputs, which includes both the CQA of the drug materials as well as CCPs design specifications, validation, and verification of biosimilar products (Figure 3). The design space is described as the relationship between CQA of the product and

TABLE 1

BIOSIMILAR ESSENTIALS FOR APPROVALS

	Regulatory Requirements	Applicant's Biosimilar Data Requirements
Regulatory Demonstration of Similarity	• Analytical studies	• Physicochemical & functional analytical data demonstrating that biosimilar product is highly similar to US licensed product
	• Nonclinical studies	• Animal studies (comparison and confirmation showing the pharmacologic and toxicological profiles of candidate biosimilar & reference product)
	• Clinical studies	• Clinical studies to evaluate PK, PD and safety studies
Clinical Demonstration of Similarity Based on Reference Biologic Studies	• Mechanism of action (Receptor binding assays)	• Selective binding to the G-CSF receptor and showing similarity across all indications for use described in the labeling
	• Route of administration (Dosage form and strength in comparison to US licensed reference product)	• Candidate biosimilar product dosage form and strength as US licensed reference product

process input/output. The design space for biosimilars is based on evaluation of the reference product, which is related to consistent quality improvement standards applicable to product quality (ICH 2009, 2012).[4,6,8] This quality control strategy is derived from current product and process controls monitoring through the implementation of process analytical technology (PAT) and HACCP Quality Monitoring System.[2-4,6] These quality control strategies help enhance the consistency and coordination of FDA's drug quality management programs. The ICH Q9 and Q10 were adopted by the US in 2009.[4-6] FDA guidance, Quality Systems Approach to Pharmaceutical cGMPs describes the main purpose to help sponsors of new medicines management tools to meet the requirements of the agency's cGMPs. The implementation of ICH Q10 throughout the total product life cycle (TPLC) strengthens the link between drug development and manufacturing processes (Figures 1-3).[6-8]

Extrapolation: One of the advantages under biosimilar 351(k) pathway is the term "extrapolation," which means that the sponsor need not conduct extensive clinical studies to cover every clinical indication for use described in the reference product labeling.[10] However, the sponsor usually conducts clinical evaluations in one or two indications for use described in the reference product's labeling and provides scientific rationale for extrapolating clinical data in support of biosimilarity.[7,8,11] The major concept of extrapolation is based on scientific rationale provided by the sponsor indicating that protein structure plays a key role in demonstrating the specificity of the protein structure related to performance characteristics of the biosimilar product and ultimately PK/PD, safety, and efficacy of the proposed biosimilar product (Figures 1-3 and Table 1).[10] Based on the scientific rationale, the key elements of extrapolation include (mitigation of residual uncertainty/acceptance of minimal functional differences between the proposed biosimilar and the reference products (Figures 1-3 and Table 1).[6-8] The sponsor of biosimilar product provides justification that mechanism of action in each indication does not produce any residual uncertainty or hazards giving any significant differences in clinical safety and efficacy due to extrapolation. This justification includes safety and immunogenicity profiles that clinical safety will not be affected by extrapolation (Figures 2-3 & Table 1).[2,6,11] It is important to clarify that extrapolation does not represent multiplicity of indications presented in the reference product's labeling, but instead this part of regulation represents structural-functional similarity and the scientific basis of how the biosimilar product's physical-chemical functional data represents structural-functional similarity to licensed reference product's mechanism(s) of action (MOAs) and the proposed biosimilar product represents highly similar to the reference product (Figures 1-3). According to FDA's guidance for industry the MOAs in each indication for use may include:

- The target receptor(s) for each relevant (activity/function) of the proposed biosimilar product (Figures 1-2)
- The receptor binding, dose-concentration response, and output signal(s)
- The mechanisms between biosimilar product's structure (target/receptor stereochemical interactions)
- The location and outputs of the target/receptors
- The PK and distribution of the biosimilar product's applications in different patient populations
- The immunogenicity assessment of the proposed biosimilar in different populations
- Comparative differences in toxicity profiles under each indication for use
- Factors that may affect the safety/efficacy of the proposed biosimilar in each indication for use

FDA guidance indicates that differences between conditions of use in regard to factors listed above do not necessarily preclude extrapolation. FDA requires "totality of evidence" in regard to extrapolation as long as it is based on scientific rationale and justifications. The guidance also recommends that proposed biosimilar sponsor conduct clinical studies in a condition of use that would be adequate to detect clinically meaningful differences between the candidate biosimilar and reference product.[8] The concept of extrapolation depends on the basis of biosimilar drug molecule being highly similar to the licensed reference product and the mechanisms of action in treatments are according to reference product's indications for use.

Interchangeability: The concept of interchangeability or switching is based on the criteria of switch from the reference product to the biosimilar. It is important to distinguish between the single switch and multiple switches between the reference product and a biosimilar. Section 351(k)(4) of the PHS Act determines the criteria for demonstrating interchangeability of the biosimilar with its referenceproduct.[12] In this guidance, it is stated that "biosimilar product can be expected to produce the

same clinical result as the reference product in any given patient." Section 351(i) of the PHS Act also indicates that "any biosimilar that meets the requirements described in this section for interchangeability may be substituted for the reference product." In order to be considered for the substitution, the FDA requires that candidate biosimilar must undergo additional testing and clinical studies (Figure 1 & Table 1). Additionally, the FDA requires the post-marketing vigilance data for the new biosimilars – particularly those with more complex molecular structures. It is expected that "stepwise evidence-based development" provides a more sensitive PK/PD information/data, on a case-by-case basis along with switching studies to demonstrate interchangeability (Figure 2).[6-12]

CONCLUSION

The FDA field investigators evaluate the biosimilar product's c-GMP risk-based requirements and make recommendations based on whether the manufacturer has the required checks and balances in place, and whether the manufacturer verifies and validates the implementation of critical quality attributes of the proposed biosimilar product. The FDA reviews clinical safety and efficacy of the biosimilar product, and it is essential that any residual risks and hazards are mitigated to acceptable levels. The FDA emphasizes the quality system approach to design and development studies by ensuring that organized data and appropriate labeling are presented in support of the new biosimilar's clinical use. The emphasis is placed on QbD approach to design of studies by providing guidances for analysis and expected clinical PK/PD data for the use of biosimilars in appropriate patient population studies. Biosimilar applications are approved based on totality of evidence described in US FDA guidance documents.◆

ACKNOWLEDGMENT

The views and opinions expressed in this article are those of the author and do not represent official views of the US Food and Drug Administration.

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BIOGRAPHY

Dr. Kaiser J. Aziz completed a 30-year career with the FDA as a clinical regulatory scientist and manager of drug and device evaluations, approvals, reengineering, standards, good manufacturing and quality system applications. He worked with individual and industry organizations in design and total product life cycle (TPLC) approaches to premarket applications for medical devices, pharmaceuticals, and combination products (510ks, NDAs, and PMAs). Prior to joining the FDA, he developed and implemented quality assurance standard operating procedures and protocols for medical diagnostic systems in hospitals, physicians' offices, and clinical reference laboratories. During his tenure at FDA, he served as an adjunct faculty in the Department of Medicine and Physiology, NIH Graduate School, where he developed and taught courses in Clinical Pharmacology, Toxicology, Therapeutic Drug Monitoring, and Clinical Laboratory Medicine. Currently, he serves as an adjunct faculty at Virginia Tech's Medical HACCP Alliance Program, where he teaches Quality Risk Management courses and workshops using HACCP principles for the pharmaceutical industry. He was an invited guest editor on Nanotechnology and Clinical Trials in the journal of Clinical Ligand Assay. He is the author of book chapters, textbooks, and over 70 publications in professional and trade journals. His expertise includes Quality System Approach to Medical Device and Pharmaceutical Premarket Applications.

Formulation Forum

Rational Design & Development of Long-Acting Injectable Dosage Forms

By: Jim Huang, PhD, Founder & CEO, Ascendia Pharmaceuticals

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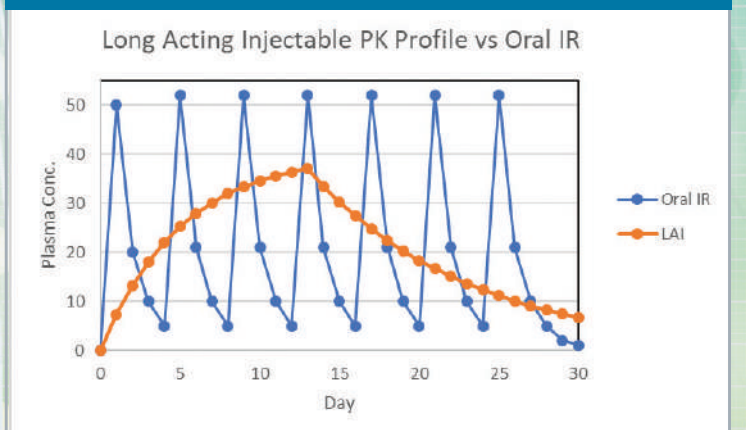
Due to the advantages of parenteral sustained-release drug delivery (also known as long-acting injectables, LAIs), such as reduced toxicity, longer body half-life, reduced dosing frequency, enhanced patient compliance, and overall reduction of medical care cost, different types of sustained-release injectable delivery systems have been introduced to markets, including injectable drug crystal suspensions, liposomes, polymeric microspheres, polymeric in situ gel systems, oil-based injections, implants, etc. The increasing prevalence of chronic disorders, such as schizophrenia, diabetes, cardiovascular diseases, and cancer, growing demand for self-administration and home healthcare, increasing focus on pediatric and geriatric patients, and the increasing demand for minimally invasive surgeries, have further fueled the growth of the LAI drug delivery market. Figure 1 (simulated PK profiles) illustrates the benefits of a LAIs by reducing dose frequency and plasm concentration fluctuation compared to a regular oral dosage form.

FIGURE 1



RATIONAL DESIGN & TECHNICAL FEASIBILITY

The ability to achieve the targeted pharmaceutical profiles of a therapeutic agent depends on dose, physicochemical/biopharmaceutical properties, pharmacokinetics, drug delivery technology, route of administration, and dosage form design. In designing an LAI delivery system, a defined clinical profile that addresses unmet medical needs and the physicochemical and biopharmaceutical characteristics of the compound must be considered in choosing a drug delivery technology and route of administration. Additionally, establishment of in vitro and in vivo correlation is beneficial to design and development of LAI dosage form. Figure 2 outlines the flow chart of a development process for LAI dosage forms.

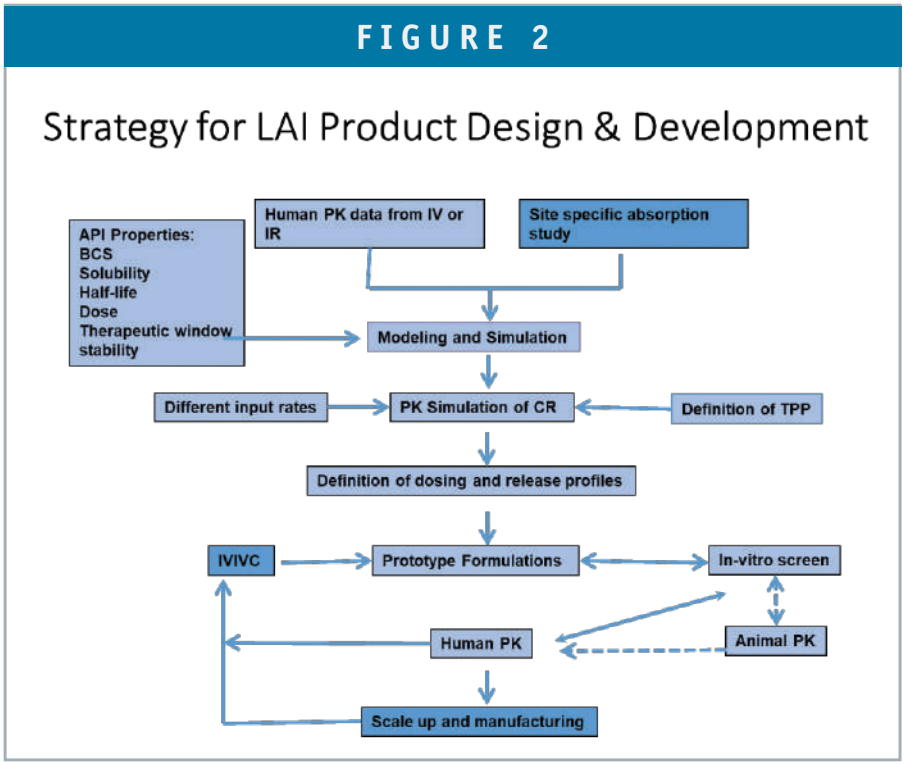
The main objective for an LAI product is to achieve optimal safety and efficacy and patient compliance via controlling drug input into the human body over a longer period of time. An essential part of developing LAI products is to establish a relationship between the pharmacodynamic and toxic response and the systemic exposure of the drug or active metabolite(s) in the human body. Design of the release characteristics for an LAI product should be based on the optimal drug pharmacokinetic profile defined by understanding of clinical pharmacology and toxicology, ie, drug therapeutic window: minimum effective concentration and minimum toxic concentration.

The most important task of parenteral sustained delivery systems is the formation of a carrier that prolongs drug release and circulation in the blood system or a depot or reservoir at the

injection site that results in prolonged release of drugs following drug administration. The most common routes of administration for LAI are intramuscular (IM), subcutaneous (SC), and less commonly, intravenous (IV), intraocular, implant, and intra-articular routes. SC has been frequently used for biological drug delivery due to advantages in ease of self-administration and better safety profile. The limitation of SC is that its dosing volume is limited to no more than 1-2 mL and potential issues in irritation and syringeability due to use of a smaller needle diameter. Whereas, a larger injection volume can be administered for IM (up to 2-5 mL) and IV (up to 100 mL).

In developing LAI dosage forms, formulation feasibility assessment is the first step toward the product design and development. It is essential to evaluate the physicochemical (solubility and stability) properties, dose requirement, physiological limitation of the injection site, and the drug clearance rate to determine the formulation feasibility. After the administration route, dosage form, and the target pharmaceutical product profile are determined, an in silico PK model is developed based on the pharmacokinetic parameters of an IV bolus or oral IR dosage form; and then the corresponding desired drug release kinetics and dose regimen can be determined by the pharmacokinetic simulation using the developed PK model, wherein the drug plasma levels should be controlled within the known therapeutic window. Emphasis should be placed on understanding absorption characteristics of the active drug in the injection site as well as the stability of the active drug during the dosing interval. The local absorption characteristics of a compound in the injection site and the duration of drug release are the most important parameters in assessing the feasibility of LAI dosage forms. Attention should be paid to the effect of a different injection site on absorption rate due to blood flow, pH, enzymes, macrophage uptake, and other factors. Drug absorption often differs in different regions of the human body. Once technology feasibility is determined, prototype formulations using appropriate LAI technology can be developed and evaluated by a physiological-relevant *in vitro* release method and by stability-indicating assay methods. Selection of an LAI technology should be based on dose, release duration, drug properties, drug release or absorption rate, IP landscape, and the commercial viability of the technology. Factors that affect the dosage form performance, such as drug loading, process parameters, release mechanism, polymer degradation, and drug stability, ideally need to be evaluated by a DOE design. Because drug-release testing is the most important among other characterization methods, development of *in vitro* release tests and its relationship with *in vivo* performance [*in vitro in vivo* relationship (IVIVR) or correlation (IVIVC)] is highly desirable for quality control of LAI dosage form during development, scale up, and technical transfer. An IVIVC can be established by correlation of the in vitro release rate of the prototype formulations of different release rates to *in vivo* bioavailability study, until a formulation with acceptable *in vivo* performance is identified.

FIGURE 2



LONG-ACTING INJECTABLE DOSAGE FORMS

Drug crystal suspensions, liposomes, and polymeric microparticles are the most commonly LAI dosage forms. Implants, oils suspensions, and in situ polymeric gels are also available in the market.

Drug Crystal Suspension

Nano/micro-crystals are composed of mainly hydrophobic drug with a small amount of excipient or surfactant, and different kinds of hydrophobic drugs can be formulated into crystals suspension with high-loading and encapsulation efficacy. Micronization and nanomilling is widely used as a common formulation method for sparingly soluble compounds. The saturation solubility of the nanocrystals is highly related to the particle

size, and solubility increases as particle size decreases due to the increased surface area, especially when the nanocrystals are below 300 nm. In these suspension formulations, the rate-limiting step for drug absorption is the speed for drug particle dissolution in the formulation or in the in vivo fluid surrounding the drug formulation.

To increase the half-life, it is a widely accepted way for long-acting formulations to be transferred into a long-chain fatty acid. The parent drugs are usually synthesized into prodrugs through esterification. Due to their extremely low water solubility, this fatty acid ester of a drug dissolves slowly at the injection site following IM injection. With the help of in vivo hydrolase, the prodrug is hydrolyzed into the parent drug and becomes available in the systemic circulation. Several other factors, such as injection site, injection volume, and surface properties of the crystal, can also affect the overall pharmacokinetic profile of the drug.

Regarding LAIs, the FDA has approved Invega® Sustenna® for schizophrenia and schizoaffective disorder treatment in 2009. Invega Sustenna is a good example of an LAI prodrug formulation, and paliperidone palmitate is the prodrug of paliperidone palmitoyl ester. This LAI formulation is indicated as an injection once every 28 days following an initial titration period. Olanzapine pamoate is another example of a poorly water-soluble salt form of olanzapine. Based on its extremely low water solubility, the drug dissolves slowly at the injection site following IM injection and is hydrolyzed to the parent drug. Once the ester is hydrolyzed intramuscularly, the parent drug becomes available in the systemic circulation.

Lipid-Based Nanoparticles

Lipid-based nanoparticles, such as liposomes as nano-pharmaceuticals are formed from phospholipids and cholesterol in aqueous medium. Liposomes have a spherical phospholipid liquid crystalline phase, and can be produced by dispersion of phospholipid in water by a mechanic energy, such as high-pressure homogenization or microfluidics. This results in the formation of multilayer structures consisting of several bilayers of lipids. After extrusion, these multilayer structures produce unilamellar structures that are referred to as vesicles. Liposomes can entrap both hydrophilic and hydrophobic drugs, and drug release can be targeted to specific sites. Biocompatibility, biodegradability, and low toxicity are the main advantages of liposomal delivery systems. Because injected liposomes can avoid uptake by the reticuloendothelial system (RES), the particles remain in circulation for a prolonged period of time. Typically, the particle sizes of liposomes range from 50 to 200 nm. To make liposomes suitable for therapeutic applications, their size distribution has to be controlled, which can be realized by passing them repeatedly, under elevated pressure, through membranes with defined pore size.

The concept of a liposomal drug delivery system has had a revolutionary effect on the pharmaceutical field, and its applications are now well-established in various areas, such as drug, biomolecules, and gene delivery. Due to extensive developments in liposome technology, a number of long-acting liposome-based drug formulations are available for human use, and many products are under clinical trials. Most commercially available liposomal drug formulations include Abelcet, AmBisome, DaunoXome, DepoCyt, DepoDur, Doxil, Inflexal, Marqibo, Mepact, Myocet, Onivyde, and Visudyne.

Two widely used liposome technologies include Stealth Liposome Technology and DepoFoam Technology. In Stealth liposome technology, a polymer (such as PEG) is incorporated into the liposome system that can improve the circulation of the dosage form inside the body. DepoFoam Technology encapsulates drugs in multivesicular liposomes. The multivesicular liposomes can sustain the release of drug(s) over the range of up to 30 days. Upon administration, DepoFoam particles undergo drug release, erosion, and reorganization of the lipid membranes.

Polymeric Nano/Microparticles

Polymeric nano/microparticles possess the advantage of both sustained release and improved stability – both in storage and *in vivo* application. For polymeric particles, the drug is entrapped within the polymer matrix, usually a biodegradable polymeric matrix. Polymer nano-medicines typically fall into one of two categories: (1) polymer-drug conjugates for increased drug body half-life and bioavailability, and (2) degradable polymer architectures for controlled-release applications.

Drug-polymer conjugate nanoparticles can be phagocytosed by the macrophages of the liver and spleen shortly following IV injection. The nanoparticle clearance is mediated by adsorption of blood components to the surface of the particles, namely opsonization. Their application has spanned the full nanomaterial size-scale, from single polymer chains up to large aggregates, depending on the required therapeutic outcome. To realize long-acting attributes, the polymeric nanoparticles can protect the drug from degradation, thus achieving prolonged drug delivery and a longer shelf-life. For therapeutic purposes, the most commonly used polymers include polyethylene glycol (PEG), poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), alginate, chitosan, and gelatin base. Commercially available injectable polymeric

TABLE 1

Product	Polymer	Active Drug
Risperdal Consta	PLGA	Risperidone
Lupron Depot, 3 months	PLA	Leuprolide acetate
Lupron Depot, 1 month	PLGA	Leuprolide acetate
Nutropin Depot	PLGA	Human growth hormone
Sandosatin Depot	PLGA-glucose	Octreotide
Trelstar Depot	PLGA	Triptorelin pamoate
Zoladex	PLA	Goserelin acetate

nanoparticle drug formulations include Adagen, Cimzia, Eligard, Genexol, Opaxio, and Zinostatin stimalamer.

Beyond just extending the circulation time of established drugs by drug-polymer conjugates, polymeric microspheres can be developed based on hydrophobic materials that facilitate controlled release of the therapeutic. This is achieved by using slowly degradation of microspheres polymer backbone that subsequently leads to kinetically driven release of the drug. Long-established polymer microspheres that have had significant success are based on incorporation of leuprolide (a testosterone inhibiting drug) into polylactide (PLA) and polylactide-co-glycolic acid (PLGA) microspheres.

Oil-Based IInjectable Suspensions/Solutions

Oil-based LAIs consist of lipophilic drugs in an oil carrier either as suspensions or as a solution. The duration of these long-acting formulations lasts from about 1 week to 1 month. Because the rate-limiting step for drug absorption is the dissolution or diffusion of drug in the formulation, controlling the viscosity of the oil carrier is used to prolong the absorption process. In many cases, prodrug of a drug is used to increase both hydrophobicity and lipid solubility of the compound in an oil-based parenteral solution, and the drug-release rate from oil solution is controlled by the drug partitioning between the oil vehicle and the fluid surrounding the injection site. Several other factors, such as injection site, injection volume, the extent of spreading of the depot at the injection site, and the absorption and distribution of the oil vehicle, will so affect the overall pharmacokinetic profile of the drug.

Pellet Implants

Pellet implants could be another LAI therapy that is easy to administer, provide reliable levels, and are affordable. For example, long-lasting testosterone pellets, Testopel, were approved by in 1972 to replace the IM injection suspension in the market. Testopel contains crystalline API and is formulated as 75-mg pellets. The pellets are surgically placed in the subcutaneous space, and the long-acting effect for up to 1-3 months is controlled by slow dissolution of the drug in the implant site.

SUMMARY

Due to the advantages of parenteral sustained-release drug delivery in enhanced patient compliance and overall reduction of medical care cost, LAI delivery systems have gained popularity in patients with chronic diseases. Moreover, these unique features in protecting compounds or biologicals from degradation and increasing the duration of drug release offer potential application of LAIs for use in the delivery of potent small-molecule compounds, peptides, RND/DNA, and proteins. ◆

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HIGH PURITY EXCIPIENTS

A Simple Solution to a Complex Problem

By: William Small, PhD, and Arsalan Khan, MS, MBA

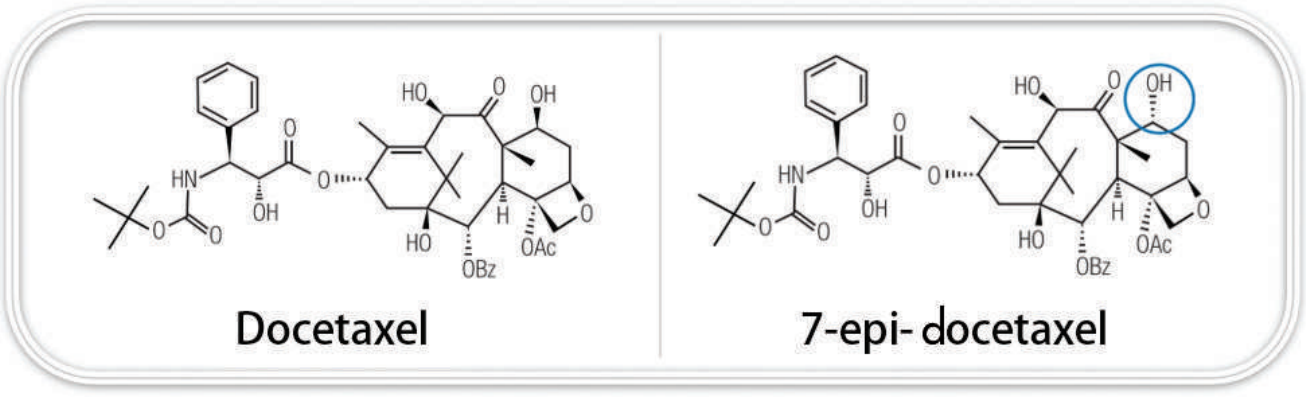
INTRODUCTION

It wouldn't come as a surprise to anyone that active pharmaceutical ingredients (APIs) come in a wide variety. Small molecule, large molecule, peptide, monoclonal antibody, innovative, generic; the list goes on. These molecules have the ability to cure or mitigate debilitating conditions that can change a person's life forever. It makes sense, then, that these ingredients are of primary importance in a formulation, and appropriate measures should be taken to maintain their stability and efficacy. As these APIs become more complex, they also become increasingly vulnerable to a series of different degradation pathways. Changes in pH environments can cause acidification and lead to breakdown. Exposure to moisture can initiate hydrolysis and subsequently lead to the formation of secondary byproducts. Residual catalyst that isn't removed from an excipient can trigger side reactions and perpetuate degradation of not just the API, but everything else in the formulation. To combat this, formulators will typically front-load their formulations to compensate for this anticipated loss. However, this does not end up being a practical solution, as the degradants are still forming, and becomes an even bigger concern when the cost of developing the formulation becomes even higher. As a result, the more practical solution is to ensure that the remaining ingredients in the formulation are of the highest quality and purity. This certifies the drug will not degrade, and that efficacy and longevity are maintained.

IMPROVED DOCETAXEL RECOVERY VIA HIGH PURITY

Docetaxel is a great example of where the importance of purity plays a meaningful role. This active, a member of the taxanes class of molecules, is used as a chemotherapy drug, primarily in the treatment of cancers, including breast, lung, prostate, and stomach. Figure 1 depicts the main degradation product for docetaxel, 7-epi-docetaxel. With the same molecular weight as docetaxel, 7-epi-docetaxel is an epimer – a structural stereoisomer

FIGURE 1



Structures of docetaxel and main degradation product, 7-epi-docetaxel.

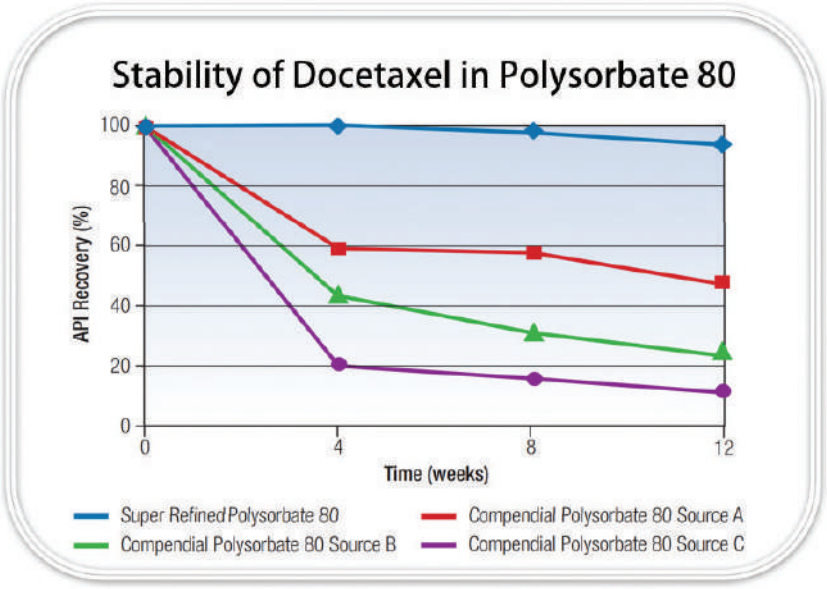
with the hydroxyl group at the C7 position ("flipping" position). Literature on the stability of the taxanes suggests that this is a common degradation product for docetaxel at that site, either through a retro aldol reaction or formation of an enolate intermediate.[1,2] The formation of 7-epi-docetaxel has been observed in basic and strongly acidic conditions and in the presence of electrophilic agents, though the epimerization can be inhibited in the presence of a metal salt.[3] 7-epi-docetaxel has been found to be less cytotoxic to leukemia cells compared to docetaxel, so the formation of this epimer could reduce the efficacy of the treatment.[4]

A study conducted on docetaxel comparing its stability in various grades of polysorbate 80 (Figure 2) showed that there is significantly improved (up to 80% higher) recovery after 12 weeks at 40°C, when using a high purity grade rather than a standard compendial grade. Additionally, the study showed that there is a much higher concentration of docetaxel degradants, including 7-epi-docetaxel, present after these same conditions when using a standard compendial grade. This enhanced profile of docetaxel when using a higher purity grade of polysorbate 80, both during standard and accelerated conditions, shows that there are significant benefits from selecting the right grade of excipient when formulating.

MINIMIZING IMPURITY FORMATION OF ETOPOSIDE

Another chemotherapy API that is heavily prone to degradation is etoposide. Used for treating testicular, lung, and ovarian cancer, there are more than 300 marketed products incorporating this sparingly water-soluble active, with the bulk of the formulations incorporating Polysorbate 80. In this instance, the main degradation product of concern is cis-etoposide, a stereoisomer of the active. Etoposide contains a trans-fused lactone ring that is under considerable strain, and will readily convert to the more thermodynamically stable cis-fused ring, known as epimerization. This altered structure can be seen in Figure 3. Literature suggests that cis-etoposide is biologically inactive in vitro, so any unwarranted conformation can have direct consequences on drug absorption and effectiveness.[5] As with docetaxel, a study was conducted with etoposide to look at its stability in various grades of excipients for 12 weeks at 40°C, and it was shown that significantly more cis-etoposide is formed when it is formulated with standard grade polysorbate 80, with API recovery varying anywhere from 17% - 85%. However, when formulated with the high-purity grade, little to no cis-etoposide is formed over the course of the 12 week study, with near 100% full etoposide recovery. The results (Figure 4) also show using higher purity excipients can promote analytical clarity from a data processing standpoint, as impurity formation can cause the appearance of additional peaks in a chromatogram, adding to the time it takes to complete analysis. This, ultimately, suggests that using higher purity ingredients is crucial to maintaining your desired API concentration in your formulation, both in the short-term and in the long-term.

FIGURE 2

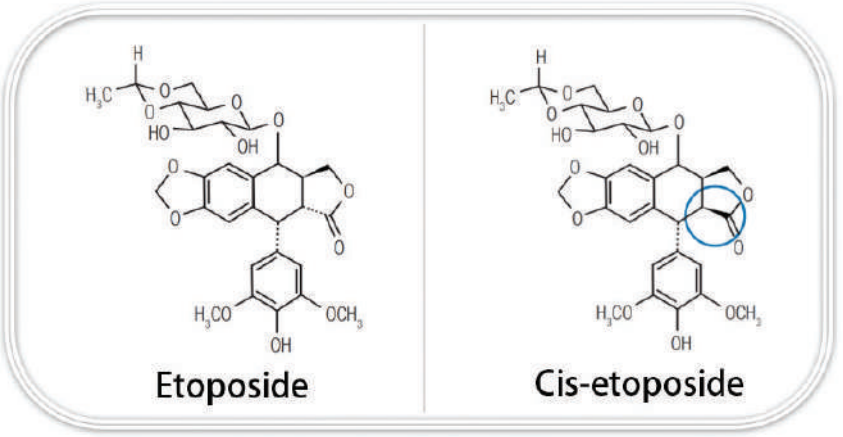


Stability of docetaxel in various grades of polysorbate 80. Using Super Refined™ Polysorbate 80 yields a significantly higher percent recovery after 12 weeks at 40°C than using standard compendial versions of polysorbate 80.

POLYSORBATES FOR BIOPHARMACEUTICALS

It is well documented that biopharmaceutical actives, such as proteins and nucleic acids, readily undergo breakdown when exposed to various external stresses, including, but not limited to, heat, pressure, purification and finishing processes, mixing, and exposure to atmospheric conditions. As a result, this causes unfavorable

FIGURE 3



Structures of etoposide and main degradation product, cis-etoposide.

interactions either within the protein structure or interactions with an external surface, ultimately leading to a decreased biologic efficacy. Additionally, these unfavorable interactions and product breakdown can be initiated through exposure to degradants found within the formulation.

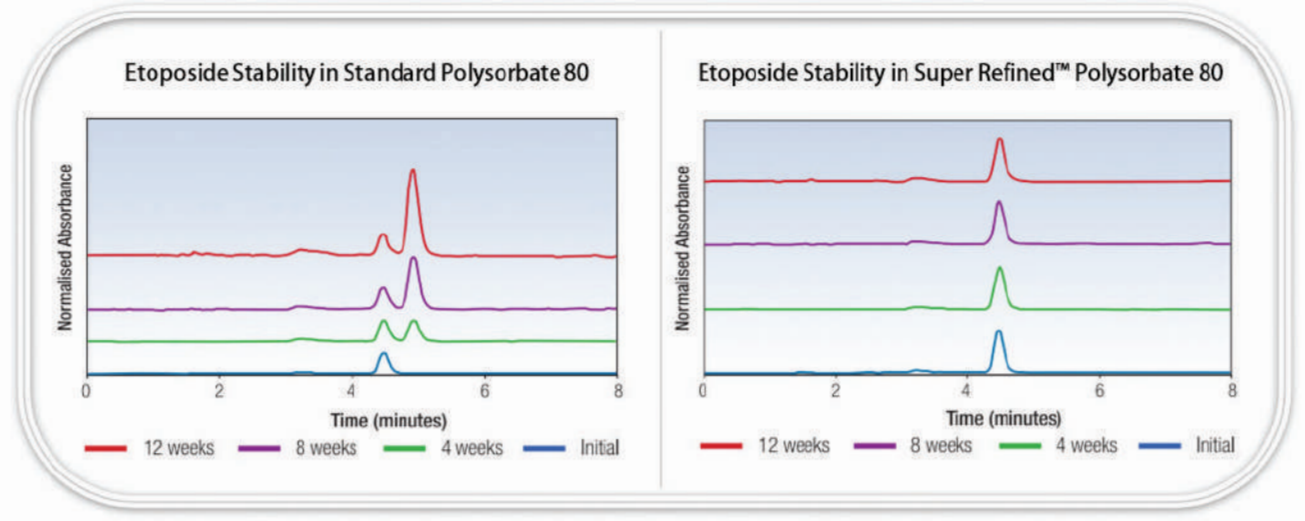
In this scenario, the culprit is the excipient that the therapeutic agent is formulated with. While in minute quantities, one of the key ingredients that these agents are formulated with are polysorbates, specifically polysorbate 20 and polysorbate 80. Polysorbates are used in a wide variety of applications, with one of their primary uses being as a stabilization and surface adsorption prevention agent for proteins. Its inherent biocompatibility and strong ability to maintain internal protein structure also makes it a favorable choice over other stabilizers, like human serum albumin (HSA) and disaccharides.[6] However, polysorbates are also notorious for undergoing auto-oxidation.

While the exact breakdown mechanism of these components is still unclear, it is theorized that the primary means are via acid or base-catalyzed hydrolysis or stress-initiated breakdown into aldehyde and acid subunits.[7] These subunits not only further propagate the breakdown of the polysorbate, but also interfere with stability of the active ingredient. For this reason, it is imperative that the highest purity ingredients are used in these kinds of sensitive applications. Croda's Super Refined™ Polysorbate 20 and Super Refined™ Polysorbate 80 has the low-impurity and high-stability profile that's required of these applications.

THE REAL BENEFITS OF PURITY

The main concern with oxidative impurities in excipients doesn't just pertain to active stability. Instability of the ingredient correlates to a number of concerns related to formulation and drug delivery. Chemical breakdown leads to the formation of species that can induce color, odor, and taste to an ingredient. Select impurities are known to be cellular irritants, inhibiting suf-

FIGURE 4



Chromatograms showing stability of etoposide in standard (left) and Super Refined™ (right) Polysorbate 80 over time. Etoposide appears at 4.4 minutes on the chromatograms, whereas cis-etoposide appears at approx. 5 minutes. Significant degradation can be seen in the standard version over the course of 12 weeks at 40°C, as indicated by the increasing impurity peak over time, whereas etoposide appears as one consistent peak over the course of the study.

ficient drug delivery and even inducing pain at the site of application. Additionally, small molecular weight impurities like formaldehyde can interfere with supplemental delivery vessels like gelatin capsules, altering or even preventing formulation release. These are normally common impurities that form as a result of poor control over the synthetic process, poor material handling and/or storage, or exposure of the material to undue stress. It is not just that a product should be synthesized with purity in mind, but also that the product should be handled with purity in mind. This isn't just the case with polysorbates, but with all ingredients used in the manufacturing of pharmaceuticals. Proper precautions, such as critically controlling the cleaning protocols of vessels and inerting packaging and filling environments are crucial to excipient stability and, ultimately, product performance.

SUMMARY

As conditions evolve, so do APIs. Complexity in design and structure lead to tailored and efficacious delivery for those who need it most. However, with that increasing complexity comes more concerns for breakdown, and that breakdown extends beyond the requirement for a higher active loading as a means of compensating. Drug degradation can have toxicological effects in many instances, and it is imperative that this mechanism be minimized as much as possible. The best solution to this is to ensure that appropriate ingredients, both high in quality and purity, are chosen and used throughout the entire drug product lifecycle. Purity plays a key role in all facets, from drug substance synthesis to final product formulation to maintaining drug product integrity during administration. It is what ensures that products can be efficiently made without waste, that reactions can yield desirable product, and that the product that is formulated at the manufacturing site is the same product that gets taken by the customer.

Croda's Super Refined™ range of excipients are a testament to the term purity. With a wide range of ingredients available across the globe, coupled with expertise in numerous formulation and drug delivery areas, Croda offers a complete line of solutions that helps bring innovative breakthrough therapies to market. Super Refined™ excipients are extensively purified to remove primary and secondary oxidation products, including aldehydes, hydroperoxides, and ketones, as well as residual catalyst from the synthetic process. This allows for a cleaner and clearer product that has a prolonged stability and shelf-life, as well as allows for better stability of any active ingredient that is solubilized in it. ◆

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BIOGRAPHIES

Dr. William Small joined Croda in 2008, working in product applications for several business areas before moving in to the Health Care business in 2014. He provides applications support for high purity pharmaceutical excipients in parenteral, topical, oral, and other dosage forms, understanding how the purity and properties of an excipient impacts customers, formulations, and active ingredients. Dr. Small earned his MS in Chemistry and his PhD in Physical Chemistry at the University of Hull, United Kingdom.

Arsalan Khan joined Croda in 2015, and is currently a Technical Marketing Coordinator for the Health Care business. He started off in R&D, working on both new product development for new and innovative high-purity excipients, as well as generating applications data to support the use of Super Refined™ ingredients. His current role involves helping to identify and serve customer needs through high-purity excipient solutions. He earned his BS and MS in Chemical Engineering from the New Jersey Institute of Technology, and his MBA from Temple University.

Drug Development
EXECUTIVE

Graham Kelly

Founder, Executive Chairman & CEO

Noxopharm

Noxopharm: Introducing a Novel & Potentially Transformative Drug Candidate in the Treatment of Cancer

Prostate cancer is one of the top five most-diagnosed cancers worldwide. Currently 360,000 men globally are estimated to die from prostate cancer each year;[1] 100,000-plus of those are in Australia, the United States, and Europe.[2,3] Treatments range from watchful surveillance to radical prostatectomy, aggressive radiation, and chemotherapy. Noxopharm, a publicly listed Australian clinical-stage drug development company, has identified an option that offers a novel approach to late-stage prostate cancer treatment. *Drug Development & Delivery* recently interviewed Graham Kelly, Founder, Executive Chairman, and CEO of Noxopharm, to discuss the company's innovative approach to cancer treatment.

Q: Can you provide our readers an overview of the company?

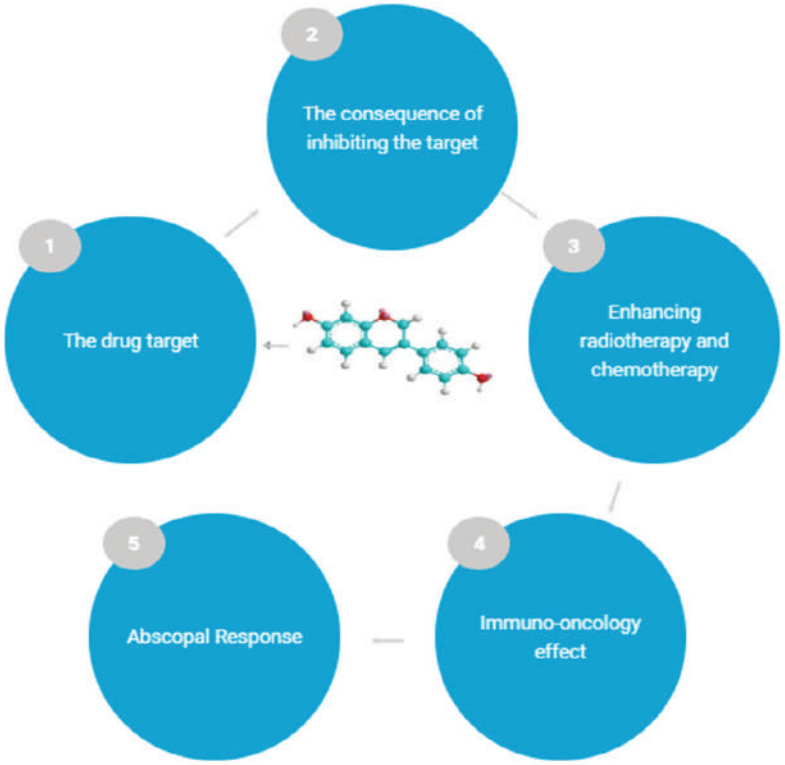
A: Noxopharm is a clinical-stage drug development company. The company's primary focus is on the development of clinical-stage drug candidate, Veyonda® (previously known as NOX-66).

Veyonda is a first-in-class, dual-acting cytotoxic and immuno-oncology drug candidate designed to enhance the effectiveness and safety of both chemotherapy and radiotherapy in solid cancers. The distinguishing feature of Veyonda is its aim of providing meaningful anti-cancer therapy (pain relief and survival prolongation) in a well-tolerated manner in late-stage disease, where palliative care for symptom relief is the current standard of care. Noxopharm is focusing initially on late-stage prostate cancer, in which patients have reached the end of their treatment journey and are eligible for palliative radiotherapy.

Q: How does Veyonda function?

A: Many cancers exploit our bodies' normal immune-dampening system by making very high levels of the bioactive sphingolipid metabolite, sphingosine-1-phosphate (S1P), effectively blocking the ability of the body to mount inflammatory and immune responses against cancer cell growth. S1P is produced in the plasma membrane of all cells and is a critical regulator that interacts with a variety of receptors within the cell and on the cell surface. Each of those receptors controls a different mechanism, such as cell growth or cell migration. In cancer cells, this "master switch" is over-expressed. Because S1P signaling inhibits cell death, this mechanism helps keep cancer cells growing.

For this reason, S1P is an obvious target for anti-cancer drugs. However, until now, researchers have been unable to inhibit it selectively in cancer cells. When healthy cells are also affected, these drugs are too toxic to be of use. Veyonda is the first and only drug that inhibits S1P only in cancer cells.



Q: Can you provide more information about your drug development status to date?

A: Direct & Abscopal Response to Radiotherapy (DARRT) is a combination of low-dose, external-beam radiotherapy and Veyonda intended to reset the body's immune system to attack and eliminate cancer cells, effectively immunizing the body against cancer. The success is the result of a combination of two actions:

First: Expose a small number (one or two) individual tumors to low-dose radiation. Low-dose is critical because the goal is to damage the tumor, not to destroy all cells including good cells such as those responsible for inflammation and immune responses — these cells need to be preserved. The key to DARRT is setting up an inflammatory response that serves as a trigger to an immune response.

Second: Irradiate the tumor in the presence of Veyonda to boost the modest, local immune response and turn it into a much stronger response, serving as a form of vaccination that will extend body-wide. Transforming a local immune response into a strong, all-of-body immune response is known as an abscopal response.

We took this drug through Phase 1 and are preparing for IND for Phase 2/Phase 3 DARRT clinical trials. The way we were using it was to restore sensitivity to chemotherapy. One of the things that S1P does is to promote DNA repair. In a normal cell, S1P repairs typical damage that's happening all the time. That's a normal survival mechanism. But in a cancer cell, this repair activity is increased to an enormous degree. So in a patient being treated with DNA-damaging chemotherapy and radiation, cancer cells can repair very quickly, whereas normal cells may take a day or two. That's one

of the reasons why tumors become resistant or have an inherent sensitivity to a lot of drugs — they're just able to repair themselves extremely efficiently.

We can remove that ability by depriving the tumor cell of S1P. By depriving it of its ability to repair DNA and then subjecting it to chemotherapy or radiotherapy, the cancer cell is unable to repair itself and dies.

Q: What's unique in the mechanism of action?

A: What distinguishes Veyonda as a cancer-fighting drug is its ability to work with, not against, the body's defenses against cancer. Chemotherapy and radiotherapy are destructive treatments that, while certainly inflicting damage on cancer cells, unfortunately also damage the defense mechanisms that the body relies on to fight the cancer.

Because the second outcome of S1P over-expression is lowered immune competence in tumors, Veyonda acts to overturn that effect, enhancing the ability of the body's immune system to fight the cancer throughout the body. This is achieved by initiating an inflammatory response that serves as a trigger to the immune response. When the drug is introduced in the next step, it boosts the pro-inflammatory effect of the radiation in the tumors while restoring local immune function, promoting an all-of-body immune response that leads to an anti-cancer effect in all tumors; the aforementioned abscopal response.

Therefore, instead of the body's immune defense being switched off by chemotherapy and radiotherapy, Veyonda ensures that it is switched on and primed to kill any cancer cells that survive the chemotherapy and radiotherapy.

Q: What is next for Veyonda?

A: Phase 1 clinical trial results of the DARRT study achieved durable anti-cancer response in a high proportion of late-stage prostate cancer patients. These were patients who had no other standard treatment options left, and 66% of them responded to the treatment at 6 months with stable disease or better. In addition, 62% had a major reduction in pain levels.

The DARRT treatment protocol has the potential to become standard of care for late-stage prostate cancer. Preparation for Phase 2/Phase 3 clinical trials is underway with our medical advisory board. We plan for a double-blind, control-arm, multi-national adaptive study design that we hope to be the final step to obtaining marketing approval.

DARRT-2/DARRT-3 will use six repeated cycles of treatment with Veyonda (there was a single treatment cycle in Phase I). This extended treatment could provide an additional anti-cancer effect, and with it, the potential for an increase in the survival endpoint.

Because of the results we've found against prostate cancer, we are anticipating the application of Veyonda will be very successful against a greater range of cancers, creating tremendous opportunity for patients who are battling this disease. ◆

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Special Feature

Improving Bioavailability & Solubility: Understand Your Molecule

By: Cindy H. Dubin, Contributor

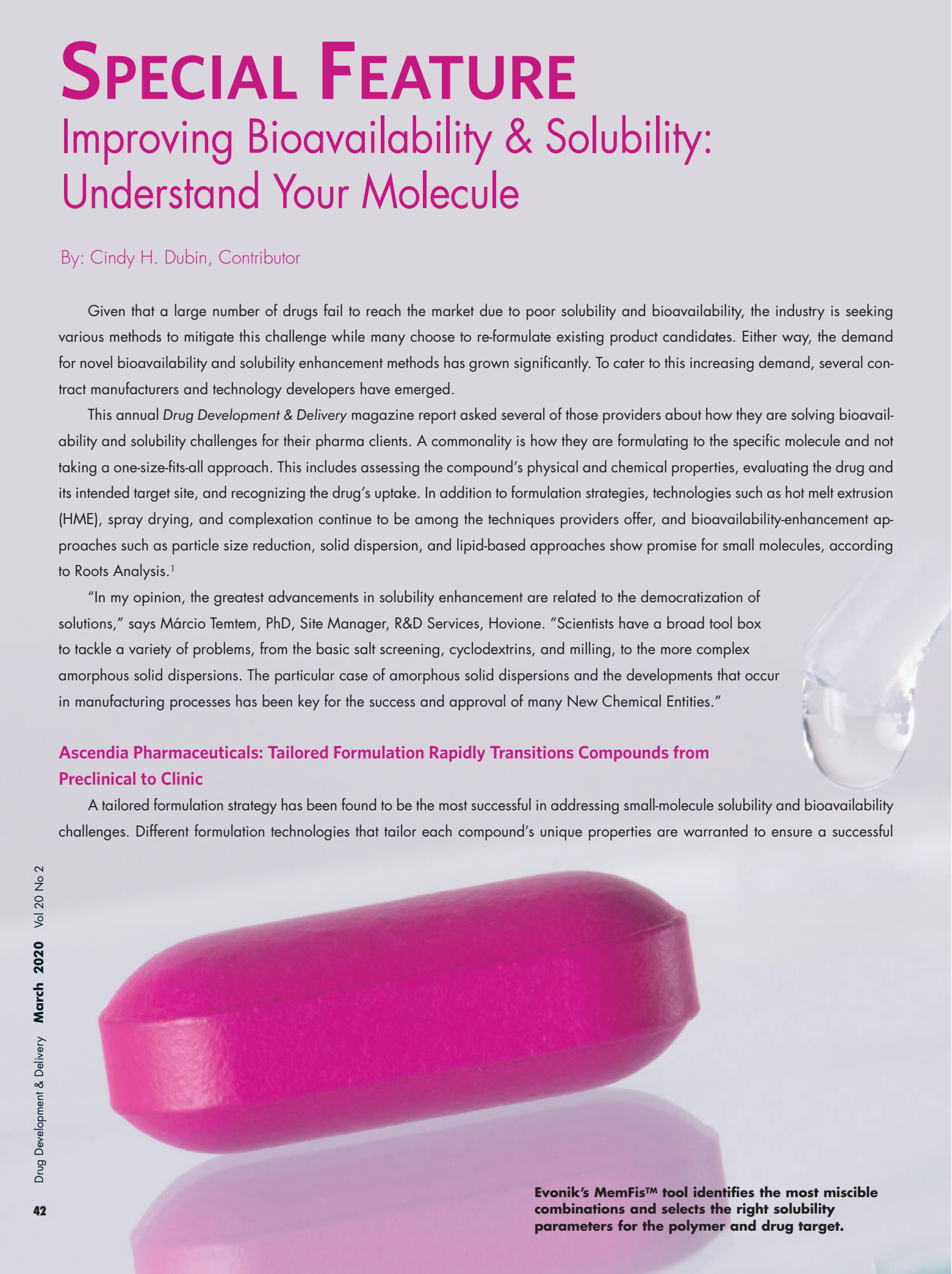
Given that a large number of drugs fail to reach the market due to poor solubility and bioavailability, the industry is seeking various methods to mitigate this challenge while many choose to re-formulate existing product candidates. Either way, the demand for novel bioavailability and solubility enhancement methods has grown significantly. To cater to this increasing demand, several contract manufacturers and technology developers have emerged.

This annual *Drug Development & Delivery* magazine report asked several of those providers about how they are solving bioavailability and solubility challenges for their pharma clients. A commonality is how they are formulating to the specific molecule and not taking a one-size-fits-all approach. This includes assessing the compound's physical and chemical properties, evaluating the drug and its intended target site, and recognizing the drug's uptake. In addition to formulation strategies, technologies such as hot melt extrusion (HME), spray drying, and complexation continue to be among the techniques providers offer, and bioavailability-enhancement approaches such as particle size reduction, solid dispersion, and lipid-based approaches show promise for small molecules, according to Roots Analysis.[1]

"In my opinion, the greatest advancements in solubility enhancement are related to the democratization of solutions," says Márcio Temtem, PhD, Site Manager, R&D Services, Hovione. "Scientists have a broad tool box to tackle a variety of problems, from the basic salt screening, cyclodextrins, and milling, to the more complex amorphous solid dispersions. The particular case of amorphous solid dispersions and the developments that occur in manufacturing processes has been key for the success and approval of many New Chemical Entities."

Ascendia Pharmaceuticals: Tailored Formulation Rapidly Transitions Compounds from Preclinical to Clinic

A tailored formulation strategy has been found to be the most successful in addressing small-molecule solubility and bioavailability challenges. Different formulation technologies that tailor each compound's unique properties are warranted to ensure a successful



Evonik's MemFis™ tool identifies the most miscible combinations and selects the right solubility parameters for the polymer and drug target.

outcome of the animal toxicity and human clinical trials for each compound.

"A specialty one-stop-shop CDMO that offers tailored formulation solutions will ensure a rapid, successful transition of compounds from preclinical to the clinic," says Jim Huang, PhD, Founder and CEO of Ascendia Pharmaceuticals. "A formulation partner that understands rational design of dosage forms based on compound properties, possesses different technologies to address varied compound challenges, and offers flexibility in terms of time and deliverables, will be an ideal partner."

To illustrate his point, he explains how one client worked with another CDMO without success to explore human formulation using a single technology. This particularly pharma client wanted to develop a human formulation for an insoluble small molecule and supply GMP CTM for human clinical trials within 4-5 months. This compound was classified as BCS II (low solubility and high permeability), which has no pKa, logP of ~5.6 and a melting point of ~130°C. Its aqueous solubility is extremely low, <0.2 micron/mL. As a result, its crystalline form's bioavailability in animal models is <4% and a significant food effect is observed.

"It was desirable to obtain a human formulation that has an enhanced bioavailability and a reduced food effect," says Dr. Huang.

Based on the assessment of the compound properties and a tight timeline, Ascendia's three most promising technologies for insoluble compounds – NanoSol (nanoparticles), Emulsol (nanoemulsion), and AmorSol (amorphous nano) – were simultaneously utilized for formulation screening and *in vitro* assessment. Three prototype formulations (one from each technology) were developed and tested in animal models within three months of project initiation that resulted in a 3-, 5-, and 10-fold enhancement in bioavailability that were respectively achieved with NanoSol, AmorSol, and EmulSol technologies, says Dr. Huang.

Ashland: Focused on Solid Dispersions & Complexation

Ashland's focus is on two technologies that utilize excipients for improving bioavailability and solubility: solid dispersions, both hot melt extrusion and spray drying; and complexation. Ashland offers three types of excipient chemistries and a variety of grades to improve the bioavailability and solubility of drug product formulations. These chemistries can be found in the inert ingredient list of approved pharmaceutical products. Copovidone, sold by Ashland under the brand name Plasdone S630, is an ingredient in several antiviral formulations for treating HIV and Hepatitis. Ashland claims it is the largest-volume excipient used in HME to improve bioavailability and solubility. "Ashland recently launched an improved grade that may significantly decrease HME and continuous processing manufacturing costs due to its improved processability," says Dean Ross, Global Business Manager, Pharmaceutical Specialties, Ashland.

For solid dispersion technologies, Ashland markets three grades of hydroxypropyl methyl cellulose acetate succinate (HPMC-AS), which is an effective excipient for improving bioavailability and solubility, and currently listed as an inert ingredient in many commercial pharmaceutical products produced by both spray drying and HME, says Mr. Ross. One study conducted at Ashland demonstrated the importance of evaluating all three grades of HPMC-AS (LG, MG, HG) in a proof-of-concept study to determine which grade provides the best possible increase in solubility. Each grade differs by acetate and succinoyl content and these differences impact solubility depending on the nature of the API being evaluated. "It's an important point because many formulators do not initially consider the differences and may evaluate one grade only," says Mr. Ross.

A second proven strategy for improving bioavailability and solubility is to complex the poorly soluble API with a cyclodextrin. These carbohydrate compounds have a bucket-like structure that encapsulates all or a portion of the lypophilic structure, leaving the hydrophilic component exposed and leading to improved solubility. "The great thing about cyclodextrins is their versatility in a variety of drug delivery systems, including oral solid dosage, oral liquid dosage, and parenteral systems (ophthalmic, IV, SC)," says Mr. Ross.

To support formulators, Ashland has six global R&D centers outfitted with spray driers or extruders to assist with proof-of-concept and/or process development. Mr. Ross says: "Recently, Ashland completed the development of a predictive solubilization model that can speed up development time by analyzing API characteristics with excipients to identify the most likely combination that will lead to improved solubility."

BASF Pharma Solutions: A Four-Tiered Approach to Poorly Water-Soluble Drugs

Dr. Nitin Swarnakar, Scientist III, Global Technical Marketing, BASF Pharma Solutions, says that successful products can be developed by careful evaluation of disease, drug, destiny (target site), and dosage form. Based on this approach, the formulator will know the class of drug and delivery route to determine suitable strategies that increase the bioavailability and solubility of a

Scientists at BASF Pharma Solutions evaluate drug, disease, target site, and dosage form to determine a successful strategy aimed at increasing bioavailability and solubility.

poorly water-soluble drug.

For instance, a parenteral formulation typically requires liquid solubilizers or other nanotechnology-based technologies that can improve solubility and bioavailability to the target site. "Specifically, Paclitaxel may be solubilized successfully in Kolliphor® ELP or encapsulated in a PEGylated liposomal," he says. "For the oral route, Amorphous Solid Dispersion (ASD) and Lipid-based Drug Delivery System (LBBDS) have been shown to be effective technologies for poorly water-soluble drugs, yet require special functional excipients such as Kollidon® VA64, Soluplus®, Kolliphor RH 40, Kolliphor EL, and Kollisolv® MCT 70 to be effective." He adds that the conventional approach of converting immediate-release to modified-release dosage forms can also increase the solubility and bioavailability of molecules.

One BASF solubilization project involved a poorly water-soluble and highly permeable drug. Dr. Swarnakar says the solubility of the drug was increased by selecting a suitable surfactant (based on the hydrophilic and lipophilic balance (HLB) value) and its respective concentration in the formulation. During *in vitro* and *in vivo* correlation, it was concluded that higher concentration of surfactant in the formulation demonstrated good solubilization, but negatively affected the flux of drug across the biological membrane leading to poor bioavailability. Therefore, a minimum required concentration of surfactant was recommended to overcome the drug problem.

BioDuro: A Strategy for Rapid Formulation Development with Minimal Material Use

Even though organic solvents are toxic and incompatible for clinical use, researchers often do preclinical studies in solvents, such as Dimethyl Sulfoxide, and wait until late in the development process to solve the bioavailability/solubility problem of drug formulation. The ability to address solubility challenges early saves costs, saves time, and rescues potentially life-saving compounds.

To improve a drug's kinetic solubility, amorphous dispersions (amorphous API in a polymer matrix) are commonly used. "Determining the right polymer to keep the API in a shelf-stable, non-crystalline form is traditionally a lengthy evaluation process that requires gram quantities of API," says Ruchit Trivedi, PhD, Associate Director, BioDuro. "BioDuro has developed a streamlined approach, called Solution Engine, to help our clients find the best formulation quickly – as early as lead optimization – with minimal material use. "We utilize small-scale studies that test multiple polymer matrices in parallel and only require milligram quantities of API. In evaluating candidate amorphous dispersions, we collaborate with in-house DMPK scientists to rapidly verify bioavailability in animal studies. We then scale up the best formulations for spray dry dispersions or HMEs. This approach can solve the most difficult solubility challenges, and typically shortens formulation development time for Phase 1 clinical supplies from 6 to 9 months to only 4 months."

One BioDuro client had an oral antibacterial drug candidate with the goal to develop an immediate-release tablet for Phase 1 clinical trials. This particular compound was extremely hydrophobic and formed a strong crystal structure that was hard to dissolve even in organic solvents, which Dr. Trivedi says is rare. "BioDuro used Solution Engine, its proprietary technique for solving API bioavailability/solubility issues, to identify the best solubilization technology and the optimal formulation to scale-up and produce clinical materials," he says.

"We started with micro-evaporation studies to efficiently determine the polymer matrix that best enhances solubility," he explains. "This innovative small-scale screen requires only milligrams of API, and allows parallel evaluation of multiple approaches, including different excipients, proportions, and concentrations. We characterized kinetic solubility of the micro-evaporative dispersions *in vitro* using non-sink dissolution in simulated intestinal fluid as an indicator of opportunity for intestinal drug absorption. Quickly coordinating *in vivo* pharmacokinetic studies gave insights to bioavailability of the candidate API formu-

lations. We found that micro-evaporative dispersions are a good predictor for spray-dried dispersion, and leveraged these results for downstream development of the right formulation. We scaled it up for larger animal toxicology studies and successfully manufactured tablets for Phase 1 clinical trials BioDuro moved forward successfully and expeditiously with this small-molecule API as a viable clinical candidate and it's now in the clinic."

Catalent: Different Approaches are Critical to the Success of Small Molecules

It is important to realize that the premise of a one-size-fits-all approach to improve oral bioavailability and solubility challenges is flawed because it assumes that all small molecules behave in the same way, believes William Wei Lim Chin, PhD, Manager, Global Scientific Affairs, Catalent. To successfully formulate a small molecule, the question of whether the molecule is dissolution-rate limited or solubility-limited for it to become systematically bioavailable must be addressed. To answer this question, the total dose, the solubility in biorelevant media, and the human intestinal permeability of the molecule should be known.

"The determination of these three critical parameters forms the basis for the Developability Classification System (DCS)," he says. "Catalent takes the approach that particle-size reduction technologies or formation of high-energy crystal forms would be the preferred choice of technology for DCS IIa molecules, whereas solid amorphous dispersions or lipid-based formulations would be recommended for DCS IIb molecules. For DCS III molecules that have permeability challenges, formulation with permeation-enhancing excipients would be recommended."

In cases where bioavailability is caused by pre-systemic metabolism, Dr. Chin advises that it is important to recognize that formulation approaches may not necessarily overcome intrinsic metabolic effects, although it has been documented that formulation methods that leverage high solubility, at high doses, may saturate certain metabolic enzymes and thus improve the bioavailability of the drug.

At the structural modification level, a prodrug approach is also typically used to mitigate high first-pass metabolism. Prodrugs can be used for injectable products to improve the solubility and stability of the solution formulation. Catalent previously worked with a client that was developing a prodrug as an orphan drug for a rare disease. The prodrug was only partially successful in increasing the solubility and bioavailability of the parent compound to the desired level for clinical studies, Dr. Chin explains.

"By understanding the limitation of this prodrug, Catalent's formulation experts successfully screened three formulation technologies and provided four formulation prototypes, in only 12 weeks, through a parallel technology screening platform," he says. "In three of the four prototypes, the bioavailability of the molecule was enhanced substantially. Based on the assessment of physical and chemical properties, processability, and DCS classification, a co-micronized formulation was identified as the best prototype to bring forward in the clinic. The implication of this was significant to the pharma company as it was able to progress to the next clinical milestone."

Croda Inc.: Understand the Nature of Every Molecule

Small-molecule pharma is a complex balance between optimizing characteristics of the drug and optimizing the components of the final formulation. "Small doesn't necessarily correlate to straightforward and every molecule is slightly different, so the first step to ensuring drug success is to understand the nature of the molecule, advises Arsalan Khan, Technical Marketing Coordinator, Croda Inc. "This isn't just understanding the basic chemistry behind it, but also understanding its mechanism of breakdown, the way it behaves in different temperature and pH conditions, and in what sorts of environments the molecule's uptake is most enhanced."

The next step is determining what is in the formulation. Mr. Khan says this involves selecting the appropriate ingredient, and if it will be used as a solubilizer, a delivery agent, a stabilizer, or anything else. This is key to ensuring that the drug remains solubilized and stable.

Impurity profile also plays a key role, as various impurities can cause the drug to break down or destabilize the formulation. This means the drug and excipients in the formulation must be free of various oxidative impurities, he explains.

Additionally, a focus needs to be put on the actual uptake of the drug. "There are a host of options to maximize drug uptake, but the key here, again, is to understand its core mechanism and look at the best option," says Mr. Khan. "Consider the effect of decreasing particle size of the active, using a delivery-enhancing ingredient, or encapsulating into a multi-component micro- or nanoparticle that can improve drug absorption through the various cell membranes that the drug will encounter upon administration, whether that be the skin, gut lining, or blood-brain barrier."

Supply chain should also be held to a paramount importance throughout the development process. "From the formulator's per-

spective, it's important to work with your suppliers to look at all options available that will make preclinical development either very straightforward or very difficult," says Mr. Khan. "The decision of choosing one or multiple suppliers is another serious consideration. This can be tricky because while it makes sense to consolidate to one partner for the sake of convenience and ease of tracking, it also poses a risk for the same reason. Additionally, one supplier may not necessarily provide every ingredient or may not have expertise on every material that is needed. In that case, expectations need to be maintained."

With that in mind, Mr. Khan says all partners must be in agreement when proceeding on formulation and development, including preclinical development, ingredient selection, processing, analytical characterization and testing, and trial protocols.

Evonik: Stabilized ASDs Can Result in Higher Bioavailability

In order to make any active bioavailable, keep in mind that attaining some level of aqueous solubility is essential, and that insoluble compounds have virtually no bioavailability. On the other hand, high solubility is not always a guarantee of achieving high bioavailability, as this will depend upon the inherent permeability of the drug. The physical modification of small molecules, such as through particle engineering, salt, and polymorph screening, have proven to be largely ineffective in enhancing the solubility of poorly soluble actives, says Dr. Firouz Asgarzadeh, Director of Technical Marketing, Evonik Health Care.

"We have found that stabilized amorphous solid dispersions (ASDs) are the most effective and commonly used method of solubility enhancement that can result in higher bioavailability, especially when permeability is not the limiting factor," he says. "ASD formulations are typically either prepared from active and polymer solutions in organic solvents using film casting, precipitation, or spray-drying technologies, or from polymer-drug high temperature mixtures cooled down to room temperature, or below, using co-melting, differential scanning calorimetry or hot-melt extrusion."

To identify the most miscible combinations and select the right solubility parameters for the polymer and drug target, Evonik utilizes the Melt Extrusion Modeling and Formulation Information System (MemFisTM) tool. "We've found that the most reliable combinations are then screened using spray drying and/or hot-melt extrusion," says Dr. Asgarzadeh. "Because MemFis includes all pharmaceutical polymers, including EUDRAGIT®, Cellulosic, Povidones, and others, these screening studies can identify the best formulations to optimize solubility enhancement outcomes."

Dr. Asgarzadeh explains how one client previously developed an ASD with only a slight increase in solubility for its poorly soluble active. Limited screening was conducted using two pre-selected polymers with no consideration for polymer drug physical bond interactions and miscibility. "By using MemFis, we were able to screen all pharmaceutical polymers and identify attractive new combinations that were not included in the original development program," he says. "The client measured the solubility of these new ASDs *in vitro*, and identified significantly improved solubility outcomes. This led to a change of direction in upcoming animal studies and the selection of a superior product for further clinical studies."

Additionally, Dr. Asgarzadeh says that ASD and other solubility-enhancement technologies can be incorporated in pharmaceutical 3D printing substrate powders and filaments during the printing process.

Gattefossé Corp., USA: The Advantages of LBDDS vs. Polymeric ASD

"Lipid-based drug delivery systems (LBDDS) are among the most effective approaches to development and delivery of poorly soluble, poorly absorbed actives," says Jasmine Musakhanian, Scientific and Marketing Director, Gattefossé Corp., USA. "This discipline takes into account drug solubilization/dissolution in the dose, dissolution behavior in relevant media, and the biopharmaceutical role of the excipients (formulation), which impact the *in vivo* performance of the dosage form."

The biopharmaceutics of LBDDS involves digestion, permeation at the enterocytes, and the path of absorption (hepatic vs. lymphatic). When assembled appropriately, LBDDS offer safety, biocompatibility, low intra/inter subject variability, and speedy path to market, she adds. "A lipid formulation developed in the early preclinical phase can be carried to late-stage human clinical stages with little or no modification, shaving 1.5 to 3 years off the development timelines." LBDDS offer several advantages over polymer-based amorphous solid dispersion (ASD) technologies, she says. Table 1 shows % PK variability and food effect associated with drugs formulated with LBDDS are significantly lower than those with polymeric ASD.

To address the unique challenges of a drug, Ms. Musakhanian says that Gattefossé applies a systematic approach to the selection of the excipient(s) followed by the

TABLE 1

Drug Product	Technology	PK (%) Variability	Food Effect
Paricalcitol	LBDD	<30	No significant effect
Enzalutamide	LBDD	<30	No significant effect
Isotretinoin	LBDD	<30	1.5-fold increase
Dutasteride	LBDD	<30	No significant effect
Norethindrone acetate /ethinyl estradiol	LBDD	?	No significant effect
Nintedanib*	LBDD-MCT	30-70	20 % increase*
Ivacaftor	Spray Drying	30-50	2.5 to 4-fold increase with food
Etravirine	Spray Drying	40-60	1.5-fold increase with food
Itraconazole	Melt Extrusion	44-66	2-fold increase with food
Vemarafenib	Co-precipitation	>66	5-fold increase AUC with food
Ledipasvir/sofosbuvir	Spray Drying	?	2-fold increase AUC
Lopinavir/ritonavir	Melt Extrusion	?	Can be taken with/without food

Comparing PK variability and food effect: lipid-based drug delivery systems vs. amorphous solid dispersions (Gattefossé).

assembly of the drug delivery system. "This includes sophisticated solubility screening in liquid and solid excipients, evaluating compatibility/stability of two or more components in the system within days of preparation, and assessing the formulation performance (lipolysis testing) in biorelevant media to predict the impact of digestion on drug dissolution *in vivo*," she says.

For high-LogP/highly lipophilic actives, for example, she recommends screening of Gattefossé glycerides like Maisine®, Peceol®, Labrafac®, or Labrafil®. For API that are poorly soluble in both hydrophilic and lipophilic media, she proposes self-emulsifying lipid formulations (SELF), commonly known as SEDDS, SMEDDS, or SNEDDS. Gattefossé excipients for SELF include Plurol®, Labrasol®, Labrafil, and Gelucire® series. "Combined, the SELF act as a carrier for the solubilized/suspended drug active in the dosage, but then form fine dispersions in the aqueous media of the gut, maintaining drug solubility *in vivo* to accommodate absorption."

HERMES PHARMA: User-Friendly Dosage Forms Are Well-Suited to Small Molecules

User-friendly dosage forms – such as effervescent tablets, chewable tablets, orally disintegrating granules (ODGs) and instant (hot) drinks – are ideally suited to improving the bioavailability and solubility of small molecules. All these dosage forms are already dissolved or dispersed when administered, and so can result in a faster onset of action, says Dr. Martin Koeberle, Head of Analytical Development & Stability Testing, HERMES PHARMA.

As user-friendly dosage forms are not swallowed whole, relatively large amounts of API(s) and excipients can be incorporated in a single dose (sometimes as much as 5g). "Compared with conventional tablets and capsules, this affords more freedom to fine-tune the quantities of excipients for optimization of pH and solubility," he says.

User-friendly dosage forms may be worth considering when the target patient population takes numerous tablets per day, which can lead to altered disintegration and dissolution characteristics. Likewise, if patients take medication for acid reflux, and therefore have an increased stomach pH, the solubility of tablets can be affected. "User-friendly dosage forms eliminate problems associated with disintegration and dissolution as the API is already dispersed when it is swallowed," he says.

3D-printing brings exciting possibilities for pharmaceutical manufacturing, particularly in user-friendly dosage forms. Dr. Koeberle explains that user-friendly dosage forms, such as orally disintegrating granules, sometimes require a very narrow particle size distribution. With 3D-printing, particle size distribution can be adjusted and controlled very precisely. For difficult APIs with narrow therapeutic or small absorption window, 3D-printing may be the solution because almost any geometric shape, which determines dissolution, is possible. In addition, it may be easier to achieve certain dissolution characteristics, such as pulsatile release. However, like in other industries, 3D-printing is best suited to short-run and bespoke manufacturing – such as for personalized medicine and clinical trials – rather than larger-scale manufacture.

Relying on computer-aided formulation development is challenging because evaluating the functionality of any formulation is a complex process, he says. "Aside from physico-chemical properties, the morphological characteristics of API and excipients need to be considered, including how these may change during manufacture."

Drug developers also need to explore the impact of scaling effects and how impurities in the APIs and constituents may affect the formulation's functionality. "Nevertheless, research into computer-aided formulations is a worthwhile en-

deavor since it will help us better understand certain aspects of a formulation's functionality and interactions," says Dr. Koeberle. "It would not replace, but could reduce, the amount of trial and error required by starting from a stronger, more informed position."

Idifarma: Spray Drying Turned Injectable Drug into Oral Dosage Form

Idifarma is an independent, privately-owned pharmaceutical CDMO specializing in highly potent drugs. Throughout its experience in improving bioavailability and solubility in small molecules, Idifarma has used different strategies, such as surfactants, reducing particle size in low-solubility active ingredients — excipients that increase the solubility of the APIs — amorphizing active ingredients through the use of spray drying technology, and working with solid dispersions by choosing suitable polymers to increase solubility.

"One of the great successes achieved by Idifarma has been with solid dispersions and using spray drying technology," says Iñaki Bueno, Formulation and Manufacturing Manager at Idifarma. "We were able to develop a product that can be administered in oral solid dosage form, which due to its low bioavailability, was only formulated in injectables. The change in the form of administration is an advantage for the patient and results in better compliance with the dosage schedule."

Prodrugs are also a strategy aimed at improving bioavailability of oncological BCS class III, IV products that usually have been formulated as injectable, and with this strategy have been formulated by oral dosages and once they achieve the system circulation are metabolized by the organism in an active compound. "This strategy is mainly used for innovative products that achieve higher solubility in aqueous media and higher permeability throughout biological membranes to improve the solubility and bioavailability of active ingredients, which Idifarma has used on several occasions," he says.

Lonza: Two Technologies for a Range of Molecules

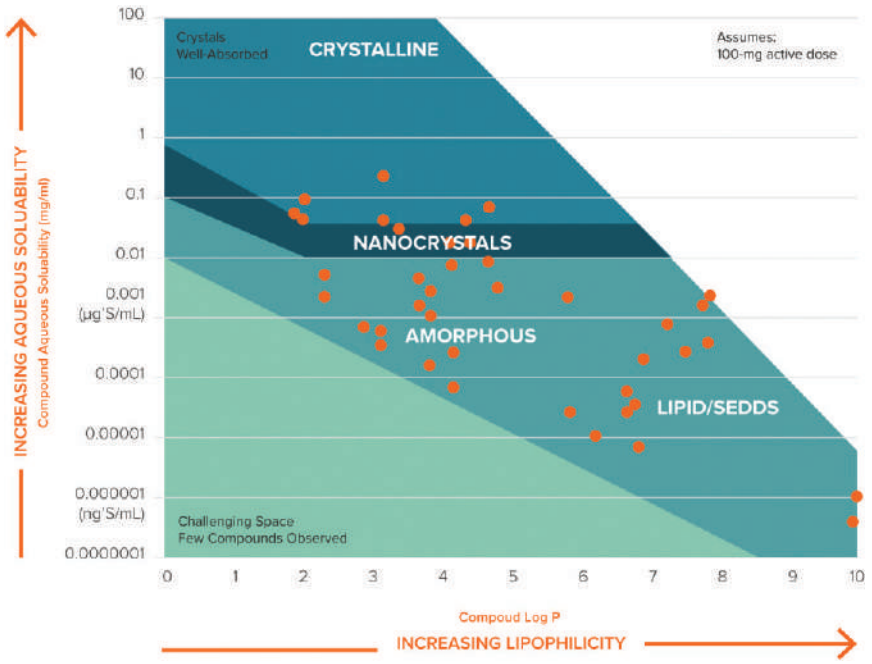
Two bioavailability- and solubility-enhancing technologies found successful and used in many marketed drug products are amorphous solid dispersions (ASD) and lipid-based formulations (LBF). But bioavailability enhancement is not one-size-fits-all. "ASD and LBF technologies are appropriate in different scenarios and with different molecules, depending on a range of physicochemical properties," says David Lyon, PhD, Senior Fellow, Research, Lonza.

An ASD formulation renders compounds amorphous and high energy, resulting in supersaturation of the molecules once they are in the GI tract. Typical approaches for developing an ASD incorporate hot-melt extrusion or spray-drying technology. "ASDs are solid forms, which allows for molecules to be readily developed into conventional dosage forms such as tablets, which are typically preferred in most drug development programs," he says.

LBFs center on getting a bioavailability-challenged compound to dissolve in a lipid. This technology is most appropriate for lipophilic compounds with a lower melting point. Dr. Lyon says the end result tends to be amenable to soft-gel and liquid-filled hard capsule dosage forms.

Lonza's SimpliFiH™ Solutions is an integrated first-in-human service specifically designed to accelerate bioavailability-challenged molecules to Phase I and on to commercialization. This service offering leverages Lonza's experience across multiple enabling technologies and processing techniques for ASD and LBF, as well as par-

TABLE 2



Lonza uses a concept technology guidance map based on compound physicochemical properties at a fixed dose to help select the most appropriate bioavailability-enhancing technology for a given compound.

ticle size reduction.

Dr. Lyon shares two examples based on ASD in which Lonza teams worked with customers to enhance bioavailability and move drug products through the development process toward patients. First, a customer was developing a protease inhibitor for HIV treatment. In its crystalline form, the molecule's bioavailability was extremely low, at around 1%. "After we worked to reformulate the molecule in an ASD form, we were able to achieve a high-loading tablet – 400mg/tablet – with close to 95-100% bioavailability," he explains.

Second, Lonza helped formulate a compound for a cardiovascular indication. The original form of the API was an oil, with a logP of 9.5-10 and solubility of about 1 nanogram/mL. He says: "After formulating the compound as an ASD with some processing additives, we achieved a stable formulation with a dose-linear exposure up to 2 grams active in humans (60-70% bioavailability) that we could produce in tablet form."

Lubrizol Life Science Health: Nanomilling Enhances Dissolution Rates

Manipulating particle size/morphology is a proving successful in improving solubility. Reducing particle size, most commonly through nanomilling, increases specific surface area, leading to enhanced dissolution rate. "Lubrizol Life Science (LLS) Health has found nanomilling to be an effective, scalable, and reproducible process," says Robert W. Lee, PhD, President, CDMO Division, LLS Health. "We are the only CDMO capable of performing nanomilling under aseptic conditions and can take our clients into commercial production. Traditional milling equipment is not set up for aseptic processing, but LLS Health's SteriMill™ was specifically designed for this purpose."

LLS Health's SteriMill™ was designed for aseptic processing.

Lubrizol's proprietary SteriMill technology employs high energy media milling (nanomilling) to reduce particle size and increase the dissolution rate of poorly water-soluble APIs. The technology uses Lubrizol-developed equipment that enables aseptic production of nanosuspensions from R&D through commercial scale.

One LLS Health client was seeking to match the pharmacokinetic profile of a rectally administered gel, containing a DEA-schedule IV API, with a nasal spray formulation. "We were able to formulate the poorly water-soluble API (aqueous solubility of 50µg /mL), along with a proprietary permeation enhancer in a solution formulation with equivalent bioavailability when dosed intranasally," explains Dr. Lee.

LLS Health has also used computer modeling to predict the flux of an API out of a non-bioerodible drug eluting device. "With knowledge of the API's solubility in the polymer and its molecular diffusivity, the elution rate of the API can be accurately calculated," he explains. "LLS Health also has models to predict stability of electrostatically-stabilized colloidal suspensions as a function of ionic strength. As long as the technologies expedite the drug development process and provide a better outcome, they are useful and warrant consideration."

Metrics Contract Services: Two Projects Illustrate Experience with Amorphous Material

To improve solubility and bioavailability of API, Metrics Contract Services offers clients the ability to manufacture spray-dried material or to micronize the API through jet milling. The resulting material will be formulated as a capsule or a tablet. "These technologies fit well within our scientists' skill sets as they have a keen understanding of amorphous material and nanoparticles," says Brad Gold, PhD, Vice President, Pharmaceutical Development, Metrics Contract Services.

This experience was put to the test when one of Metrics' clients had a clinical candidate that demonstrated variable pharmacokinetic data using a Phase I formulation of API in a commercially available one-size-fits-all aqueous vehicle with sweetener, suspending agent, and preser-

vative. Metrics scientists reformulated the Phase I formulation to simply incorporate the API in a dispersant consisting of a low molecular weight amphiphilic solvent, says Dr. Gold. "The dispersed API then was added to the client's original off-the-shelf vehicle to provide a well-dispersed final product. The new formulation not only provided increased bioavailability, it also removed variability previously observed in *in vivo* performance."

In another example, a poorly water-soluble and highly permeable molecule (BCS class IV) was provided by a client for reformulation. Initial Phase I studies on a simple capsule (API and lactose anhydrous) formulation showed poor oral bioavailability. Several solubility enhancement approaches — such as particle size reduction, inclusion complex (using HP B-CD), surfactant (sodium lauryl sulfate with dry granulation process, polysorbate 80 with wet granulation process), hot melt granulation, hot melt extrusion — were evaluated to improve solubility. Hot melt extrusion with copovidone as carrier and sorbitan monolaurate as surfactant/plasticizer showed improved dissolution in water, 0.1 N HCl, and pH 4.5 buffer, explains Dr. Gold. Batches with different levels of polymer and surfactant were manufactured to identify the optimum ratio of drug, polymer, and surfactant. Clinical trial material batches were manufactured for Phase I study using the optimized formulation.

Formulation methods such as micronization, amorphous solid dispersion, nanocrystals, and nanoparticle — all of which Metrics offers — are commonly used for solubility enhancement. Dr. Gold says that although these approaches have shown positive results for many drugs, there are some APIs that need further formulation to increase solubility. ◆

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CONTAINER CLOSURE INTEGRITY

Mitigating Risk in Pharmaceutical Manufacturing With Visually Inspected Components

By: Olga Laskina, PhD

ABSTRACT

Final drug products are 100% visually inspected for particulate matter and defects. The aim of visual inspection is to remove defected units. Prevention of these defects should also be an important consideration. The use of visually inspected container closure components can significantly decrease the number of end-of-line rejects associated with these defects, improving the yield and ultimately patient safety. Visible particles and manufacturing defects of the packaging components are discussed here as well as the impact these defects can have on container closure integrity and functional characteristics.

INTRODUCTION

Final parenteral drug products (DP) are required to be essentially free of visible particles; as such they are subject to 100% visual inspection. However, no regulatory requirements are currently applied to the level of particles in primary container closure components.1 Primary container closures must: (a) adequately protect and be compatible with the DP; (b) utilize materials that are safe for use with the DP and the route of administration; and (c) function properly. The primary container closure plays an essential role in the quality of the final DP. The earlier the primary container closure is selected in the drug development process, the easier it is to ensure that DP will not have packaging compatibility issues in the future. Manufacturing defects in container closure components and loose or embedded visible particles can lead to sterility failures and loss of container closure integrity (CCI). In prefilled syringes and cartridges, these defects might also affect functionality. The use of visually inspected container closure components can decrease the risk of a defective final parenteral DP being administered to a patient. Moreover, the overall quality of the final DP will be improved as the final product can only be as good as its components.

Rejection of defective parts is the primary goal of visual inspection. Adoption of automated inspection, at both container closure component manufacturer and DP manufacturer, enables 100% visual inspection, the goal of which is, of course, zero defects. Use of automated visual inspection also enables process control optimization; this enables continuous feedback to the manufacturing process with the result of reduced reject rates.

United States Pharmacopeia (USP), European Pharmacopoeia (EP), and Japanese Pharmacopoeia (JP) require that final parenteral DP should be free from readily seen visible particles. Visible particles are a common cause of audit observations and findings and one of the leading reasons for parenteral DP recalls. Almost one half of the recalls in sterile DP in 2010-2017 were due to the presence of visible particles.[1,2] The use of visually inspected components adds to the control strategy for preventing visible particles. DP recalls put patients at risk and cause shortages. They also impair the financial situation of the company and its position in the marketplace. These recalls can be minimized by placing proper controls on processes, equipment, and procedures. Defects in the primary container closure components can range from critical to minor; classification is based on their effect on CCI and ultimately impact to patient safety. Defects can include, but are not limited to, presence of particles and fibers, cosmetic issues, intermixing (ie, presence of wrong product), and manufacturing defects (eg, issue with product forming or inade-

TABLE 1

Scope	USP	EP	JP
Therapeutic Protein Injections	<787> Subvisible particle matter in therapeutic protein injections[9]		6.17 Insoluble particle matter test for therapeutic protein injections[10]
All Injections	**<788> Particle matter in injections[11]**	**2.9.19 Particle contamination: sub-visible particles[12]**	**6.07 Insoluble particulate matter test for injections[13]**
Ophthalmic Solutions	<789> Particle matter in ophthalmic solutions[14]		6.08 Insoluble particulate matter test for ophthalmic solutions[15]
All Injections (Visible Particle Only)	<790> Visible particles in injections[8]	2.9.20 Particle contamination: visible particles[16]	6.06 Foreign insoluble matter test for injections[17]

Pharmacopoeia chapters related to particles in different DP. Harmonized chapters are in bold.

quate compounding).

Nonconformities in elastomeric components and aluminum seals are detailed in the Parenteral Drug Association (PDA) Technical Report No. 76.[3] Nonconformities in glass vials, cartridges, syringes, and ampoules are detailed in the PDA Technical Report No. 43.[4] Both PDA reports serve as excellent guides on defects for which visual inspection should be made. Defects that can negatively impact CCI are considered critical. Their impact depends on both the defect severity and location. Defects on areas responsible for sealing (on vials, syringes, or cartridges and elastomers) have a higher probability to lead to sterility breach and exchange of the vial (or syringe or cartridge) headspace with air and water. Incomplete film coverage on drug contact area of elastomeric component can adversely affect compatibility with the DP.

Some defects can be detected readily during visual inspection and are therefore eliminated at the end of the production line. Other defects cannot be detected readily; they might be located on areas not visible in the final sealed container closure. Others might not be readily detected due to the container closure type (eg, amber or non-transparent containers) or due to the nature of the DP (eg, suspensions or colored liquids).

The following discusses particles and container closure defects, as well as the risks these defects pose to patient safety, CCI, and functionality.

PARTICLES

Particles can compromise the quality and safety of parenteral DP and lead to sterility failures. The impact of particles is currently not well correlated to patient harm.[5] However, there are requirements for final DP in the USP.[6] Chapter USP <1> Injections and Implanted Drug Products (Parenterals) – Product Quality Tests requires that every lot of parenteral DP must be essentially free from visible particles, as defined in USP <790> Visible Particles in Injections.[7,8] Subvisible particles are also regulated. Table 1 outlines pharmacopoeia chapters related to particles in different DP.

Particles can be extrinsic (foreign to the manufacturing process, eg, hair, non-process related fibers, etc); intrinsic (from processing or primary packaging materials, eg, stainless steel components, gaskets, packaging glass, and rubber components, fluid transport tubing, etc); or inherent (associated with specific DP formulations, such as suspensions, aggregates, etc) to the final DP. They can be of various sizes and morphologies and can appear in final DP at various concentrations. They can appear during manufacturing, or over time as a result of storage and handling. In particular, they can result from extrinsic sources such as container closure components (for example caused by loose or adhered materials resulting from abrasion/tumbling).

Quality attributes related to safety, efficacy, potency, and immunogenicity can be affected by particles.[18] The identification, classification of size, enumeration, and characterization of particles from all sources are essential for assessing both quality of parenteral DP and impact to patient safety.

While it is important to realize the potential contribution of particles from individual components, the critical particle profile to establish is that of the primary container closure. This can be done only with the final parenteral DP and knowledge of the manufacturing, storage, and shipping conditions. There are well-established container closures for many parenteral DP. However, these can be challenged by specific needs of biologic and cell therapies. For example, the presence of either extrinsic or intrinsic particles

FIGURE 1

Fiber on a Stopper

in a protein-based biologic DP can lead to formation of protein particles by providing a nucleation site for aggregation. These protein particles can lead to immunogenic responses in patients.[18]

CONTAINER CLOSURE DEFECTS

Expectations of regulatory agencies is not only that 100% visual inspection will be performed on final DP for the identification and removal of defected products. Since it is well realized that even 100% visual inspection cannot guarantee removal of 100% of defected units (eg, DP with particles present); prevention of defects is important. It is likewise an expectation of regulatory agencies that prevention is pursued. Prevention can be achieved by adopting an inspection life cycle approach. Inspection lifecycle provides a framework for continuous process improvement. It involves multiple elements such as qualification, maintenance, training, and categorization of defects. It also includes testing of components to specific quality attributes and evaluation processes for component preparation and DP filling procedures.[19,20] Adoption of 100% visually inspected components helps ensure the prevention of defects and particles appearing in final DP.

CONTAINER CLOSURE INTEGRITY

An integral container closure, ie, one with good CCI, prevents microbial ingress, entry of gases and debris, and loss of contents. Quality of container closure components is critical to good CCI. CCI can be negatively impacted by the presence of defects in components, such as cracks, holes, splits, tears, and particles or fibers. An example of a fiber that can negatively impact CCI is shown in Figure 1.

Figure 2 shows a photo of a glass syringe that has a fiber trapped between the plunger and the syringe wall. Tracer gas leak detection with helium was performed on this system - a value of 2.11*10-3 std*cc/sec was obtained. This is three orders of magnitude higher than the acceptance criteria for microbial ingress that has been reported by Kirsch, et al.[21] This is a clear illustration of the CCI problem that can be caused by a particle.

PERFORMANCE

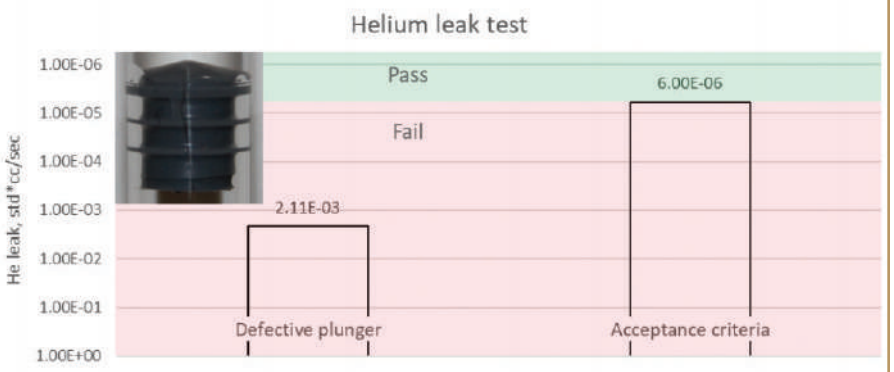
Defects in syringe and cartridge plungers can cause performance issues, specifically related to functionality and sterility (ie, leakage). Break loose and extrusion forces can increase and become inconsistent, causing administration challenges and negative patient experiences. For autoinjectors and other automated delivery devices, it can cause incomplete dose delivery, or a complete failure if the device cannot overcome increased break loose and extrusion forces. Leakages can cause a breach of sterility and CCI failures. The following performance tests can be used to observe the impact of defects:

- ISO 11040-8 Break Loose and Extrusion Forces and Liquid Leakage Beyond Plunger[22]
- ISO 13926-2 Freedom from Leakage and Initiating and Sustaining Forces[23]
- ISO 7886-1 Freedom from Air and Liquid Leakage Past Plunger Stopper and Force to Operate the Piston[24]

CONCLUSION

Quality of the final parenteral DP depends upon the quality of components, ie,

FIGURE 2



Effect of a Fiber on a Plunger on CCI

both DP and container closure system. Defective components can result in issues with leakage, contamination, sterility, compatibility with DP, functionality, and machinability. These all pose risk to patient safety. For the final DP, rejection resulting from end-of-line visual inspection may result in drug shortages, along with lower product yields, lost revenue, brand damage, and enhanced regulatory scrutiny. The use of visually inspected container closure components decreases these risks. ◆

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BIOGRAPHY

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DEVELOPMENT TIMELINES

Drug Development Times, What it Takes - Part 2

By: Josef Bossart, PhD

INTRODUCTION

In Part 1 of this series (see Jan/Feb 2020 issue at www.drug-dev.com), I outlined the overall scope of the analysis and identified the need to appropriately segment approvals by Approval Type in the hope of gaining an understanding of the realities surrounding the Development and Review times for pharmaceutical products approved by the Drug Division of the FDA. In Part 2, I review the Development and Review Times associated with new molecular entity (NME) approvals throughout the 2010 to 2018 period. Readers are encouraged to refer to Part 1 in the series for an explanation of the terms and the limitations of the analysis.

THE BIG PICTURE

The product development requirements for NME product approvals by the FDA are reasonably consistent. A company hoping to gain approval for a new product needs to provide sufficient information that establishes the safety and efficacy of the product for the intended application.

A total of 340 products incorporating an NME that received approval in the 2010 to 2018 period are available for analysis in terms of Development and Review Times. Development Time for the purpose of this analysis is the period of time calculated from the earlier of the start of clinical trials, a Pre-IND meeting, or the filing of an IND application, and the date the application for approval is filed with the FDA. Review Time is the period of time between the first filing of a drug approval application with the FDA and its first approval.

OVERALL NME DEVELOPMENT & REVIEW TIMES

NME-approved products include New Drug Applications (NDAs) and Biologic License Applications (BLAs). The mean average Development and Review Time for the 340 products included in this analysis was 10 years. The mean average Review Time was 1.3 years, and the Development time was 8.8 years. This is longer than the mean averages of 8.2, 1.5, and 6.7 years found with the larger group NDA and BLA approvals (n=802), including NMEs and Previously Approved Actives (PAAs).

NDA DEVELOPMENT & REVIEW TIMES

Development and Review Times for the 257 NDA approvals, non-biologics, involving NMEs is presented in Table 1. This group includes both Single Entity, Type 1, and Combination, Type 1,4 approvals.

As a group, the NME Type 1 and Type 1,4 mean average

TABLE 1

	Development Time Mean Average (Median)	Review Time Mean Average (Median)	Development + Review Time Mean Average (Median)
All Type 1 & Type 1,4 (n=257)	**8.8 (7.7) Years**	**1.3 (0.8) Years**	**10.1 (8.9) Years**
All NME (n=340)	8.8 (7.6) Years	1.3 (0.8) Years	10.0 (8.9) Years
All Approvals (n=802)	6.7 (5.6) Years	1.5 (0.9) Years	8.2 (7.2) Years

Type 1 & Type 1,4 NDA Development & Review Times, Overall

"While there is seemingly a limit to how short a development and review process can be, there is no limit on how long it can take. It may be helpful to look at products found at the extremes of the development and review continuum to see if there are any obvious lessons."

Development and Review Times are on par for the larger set of NME products that include BLA approvals, but longer than All Approvals, +2.1 years, despite having slightly shorter Review Times, -0.2 years. Table 2 summarizes the Development and Review Times for Type 1 and Type 1,4 products as a whole and for Orphan- and Priority-designated products.

In general, Single Entity Type 1 products took a little longer than the average of all NME approvals. Development Times were a little longer in terms of the mean average for Orphan- and Priority-designated products, although the medians were much lower. The longer mean average times for Type 1 NMEs are accounted for by a few products that took decades from first clinical trials to approval. These products were often tried for one or more indications early on, put on a shelf for one reason or another, and later dusted off and developed for the same or a new indication. Some other products experienced substantial delays after being "passed around" between companies because of portfolio or financial considerations. The median Development and Review Times perhaps provide a more realistic picture. Review Times were shorter for both Orphan and Priority products with a difference between the mean and median values accounted for by a few products that had delays associated with their initial regulatory filings.

The smaller cohort of 20 Combination Products were developed in a shorter period of time, 7.2 years, about 1 to 1.5 years quicker than other NME NDA approvals in terms of median and mean averages. These products as their name suggests combined an NME with another agent, generally a previously approved active. Often, these products addressed reasonably well-understood indications and incorporated an NME that was a second or third in class agent that was combined with a well-validated previously approved active. Examples include Hepatitis C and HIV products in which a new NME was either added to, or replaced a component of, a previously approved combination product. A very few of these approvals were for single-agent actives that were approved for use only in combination with another agent, for example, Braftovi and Mektovi.

BLA DEVELOPMENT & REVIEW TIMES

BLAs represent a separate approval group from both a regulatory and legal perspective. Molecularly, they are large molecules derived from biological systems that are at best poorly characterized in terms of their secondary and tertiary structures and manufacturing processes. Despite these differences, their Development and Review Times are strikingly similar to that for small molecule NME products approved through the NDA process. There are currently no approved combination BLA products as defined by the FDA. In some cases, BLA products are used in combination with other agents but not as co-formulated products.

Biosimilars are approved as BLA products through the 351(k) regulatory pathway rather than the 351(a) pathway used for the more familiar originator BLA

TABLE 2

	Development Time Mean Average (Median)	Review Time Mean Average (Median)	Development + Review Time Mean Average (Median)
Single Entity (Type 1)			
All (n=237)	8.9 (10.0) Years	1.3 (1.1) Years	10.3 (11.3) Years
Orphan (n=92)	9.2 (7.8) Years	1.1 (0.7) Years	10.2 (8.9) Years
Non-Orphan (n=145)	8.8 (7.7) Years	1.5 (1.0) Years	10.4 (9.3) Years
Priority (n=134)	9.2 (7.8) Years	1.1 (0.7) Years	10.3 (8.8) Years
Combination (Type 1,4)			
All (n=20)	7.2 (6.5) Years	1.0 (0.8) Years	8.2 (7.8) Years
All NDA and BLA NME (n=340)	8.8 (7.6) Years	1.3 (0.8) Years	10.0 (8.9) Years
All Approvals (n=802)	6.7 (5.6) Years	1.5 (0.9) Years	8.2 (7.2) Years

Type 1 & Type 1,4 NDA Development & Review Times

TABLE 3

	Development Time Mean Average (Median)	Review Time Mean Average (Median)	Development + Review Time Mean Average (Median)
Innovator - 351(a)			
All (n=84)	8.6 (7.6) Years	1.1 (0.9) Years	9.7 (9.0) Years
Orphan (n=45)	8.6 (7.4) Years	1.1 (0.8) Years	9.8 (8.8) Years
Non-Orphan (n=39)	8.5 (7.9) Years	1.0 (0.9) Years	9.5 (9.0) Years
Priority (n=56)	7.6 (7.4) Years	0.9 (0.7) Years	8.5 (8.4) Years
Biosimilar - 351(k)			
All (n=14)	5.3 (5.0) Years	1.5 (1.1) Years	6.8 (6.2) Years
NDA NME Single Entity	**8.8 (7.7) Years**	**1.3 (0.8) Years**	**10.1 (8.9) Years**
All Approvals (n=802)	**6.7 (5.6) Years**	**1.5 (0.9) Years**	**8.2 (7.2) Years**

BLA Innovator & Biosimilar Development & Review Times

products. The Innovator and Biosimilar Development and Review Times are summarized in Table 3.

As a group, Innovator BLA approvals had mean average Development, Review, and combined Development and Review Times of 8.6, 1.1, and 9.7 years, respectively. This differed little from the Development and Review Times for NME approvals for NME small molecule NDA products in either the mean or medians. Innovator BLA products that qualified for Priority Review were developed and approved about 1 year more quickly than their non-Priority peers. Most of the saved time came during development, 1 year less, rather than during FDA review, -0.2 years.

Biosimilar BLA products were approved in a much shorter time than Innovator BLA products, about 3 years less. The time saved was typically seen in development rather during the review process, which was a bit longer, +0.2 years. The difference is accounted for by the more limited requirements for the approval of Biosimilars, albeit much more than what is required for small molecule generics.

DEVELOPMENT & REVIEW TIME COMPARISON

When plotted on a single chart, some sense of a comparison becomes apparent between the Development and Review Times for all NDA and BLA approvals and the times for NME products, both BLA and NDA.

Figure 1 presents the number of All NDA/BLA approvals in the period 2010 to 2018, the NDA NME approvals, and the BLA NME approvals. Each column on the x-axis shows the number of products developed and approved in that number of years. For example, the Year 7.5 represents the number of products approved in more than 7 years and less than or equal to 8 years.

The number of NDA NME approvals peak in 8 to 9 years, while BLA NME approvals peak a bit later in the 8- to 10-year period. This is at odds with the means and medians seen earlier in which the NDA and BLA NME approvals were similar.

Notable is the large number of products that required more than 20 years for development and review. These outliers represent 4% and 2.5% of all NDA NME and BLA NME approvals, respectively.

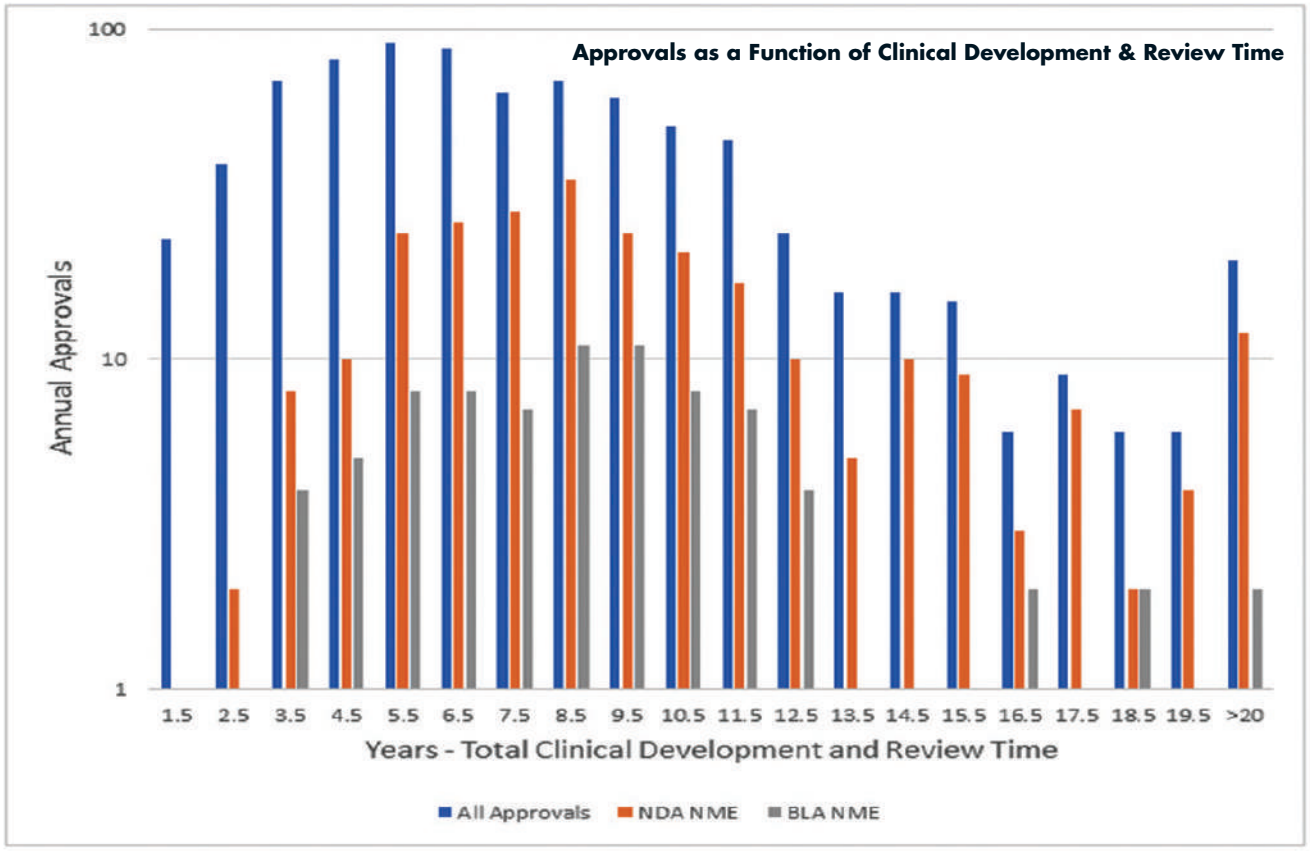
A look at Review Times revealed that 31% of BLA NME approvals experienced some sort of regulatory delay compared with only 22% of NDA NME approvals. For the full set of 802 approvals, 33% of products experienced some sort of delay in the review process.

OUTLIERS

While there is seemingly a limit to how short a development and review process can be, there is no limit on how long it can take. It may be helpful to look at products found at the extremes of the development and review continuum to see if there are any obvious lessons.

Among all NME approvals, the shortest Development and Review times was recorded by Wellstat Therapeutics' Xuriden, uridine acetate, an NDA NME for the ultra-rare indication of uridine replacement therapy. It clocked in at 2.1 years from Pre-IND meeting to approval. This was after the FDA approached the company to develop the product because of perceived medical need. The company was granted a Pediatric Rare Disease Voucher, and the product received Orphan Product and Breakthrough Product designation along with Priority Review. The development program primarily involved a small Phase 3 trial. Development took 1.4 years, and

FIGURE 1



regulatory review was 0.7 years.

Ultomiris recorded the shortest BLA NME Development and Review Times of 3.1 years. Alexion developed the product for the ultra-rare condition Paroxysmal Nocturnal Hemoglobinuria (PNH). The first human trial for the product began in November 2015 in Australia followed by FDA approval in December 2018. Given that there must have been some sort of earlier correspondence with the Australian regulatory authorities, it might be reasonable to add on another quarter year to normalize the overall review and approval time. Even then, development to approval would have been accomplished in 3.5 years, a remarkable feat aided by a 6-month FDA review. Close behind was BioMarin's Brineura, which moved from first development to approval in 3.5 years for another orphan indication, Neuronal Ceroid Lipofuscinosis Type 2.

At the very long end is Jazz Pharmaceuticals' Erwinaze, asparaginase Erwinia chrysanthemi, clocking in at 43.6 years. A BLA NME, Erwinaze is approved for the treatment of Acute Lymphoblastic Leukemia in patients allergic to the previously approved E. coli-derived asparaginase. The product bounced around between companies for decades. The original IND was filed by Ipsen in April 1968 and transferred to OPi SA in 2006, which was acquired by EUSA Pharma in 2007, followed by approval in 2011.

In general, NME approvals with Development and Review Times of more than 30 years were the victim of general indifference and were developed reasonably quickly once the appropriate resources were applied. Synribo (omacetaxine mepesuccinate) for example was the subject of a National Cancer Institute IND in 1981, with institutional trials starting in earnest in 1994. After sitting on a shelf, ChemGenex began development in 2001 with NDA submission in 2009 and approval in 2012. There is a similar story with Solosec (secnidazole), which was first approved in France in 1976. After seemingly being ignored for the US market for decades, the necessary work for FDA approval was quickly put together starting in 2013 with approval in 2017.

LESSONS LEARNED

What conclusions can we draw from these numbers? What is a reasonable benchmark for the Development and Review Times for a product incorporating a new molecule entity?

The answer probably isn't found in the means or the medians. The medians do suggest that once the switch is flipped to

start clinical development, it is reasonable to expect it will take 9 to 10 years until FDA approval is received.

It may be more helpful to look at the shape of the distribution of Development and Review Times as presented in Figure 1. For NDA NME products, the Development and Review Times peak at between 8 and 9 years, less than the mean and median values. This is probably a reasonable starting point for estimating a target timeline. There are any number of products that took between 5 and 8 years.

For BLA NME products, the means and medians are just a little greater than the peak of Development and Review Times seen in Figure 1. Any number of BLA products were approved in the 4- to 8-year range, again, suggesting that it would be appropriate to understand what led to these relatively quick development and approval programs.

Figure 1 also shows a number of products with Development and Review Times in the 1- to 5-year range. These are for the most part products approved using previously approved actives and the subject of Part 3 of these articles. This is a very heterogeneous group that used a number of different paths through development and approval.◆

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BIOGRAPHY

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April 30 - May 1, 2020

INTRATUMORAL DELIVERY

Combining Local & Systemic Treatments: Could Immuno-Oncology Finally Enable Local Intratumoral Delivery?

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INTRODUCTION

Tip O'Neill, former US Speaker of the House, is associated with the phrase "all politics is local." Like politics, all tumors are local. However, visible tumors may only be part of one's cancer; so unlike politics, cancer can be both local and systemic.

Surgery, often with chemotherapy, is the main treatment method for solid tumors. Immunotherapy, also referred to as immune-oncology or IO, is a new approach generating much excitement. IO harnesses the immune system and offers patients the potential for long-term remission. Many oncologists are now using the term "cure," which was previously unheard of in relation to cancer.

Unfortunately, recent clinical data have clouded the blue sky promise of IO. Data suggests that the benefits of immunotherapy may be limited to "immunologic" or "hot" cancers, ie, those types in which immune cells can recognize the cancer. Yet, even in those cancers, immunotherapy treatment for many patients is inadequate. Could coupling IO with new local treatments, such as intratumoral drug administration, overcome IO's current limitations? Are there intratumorally delivered products that could turn "cold" tumors "hot"? Let's explore the long arc of cancer treatment and review the exciting potential of novel local approaches coupled with modern immunotherapy.

CANCER IN HISTORY

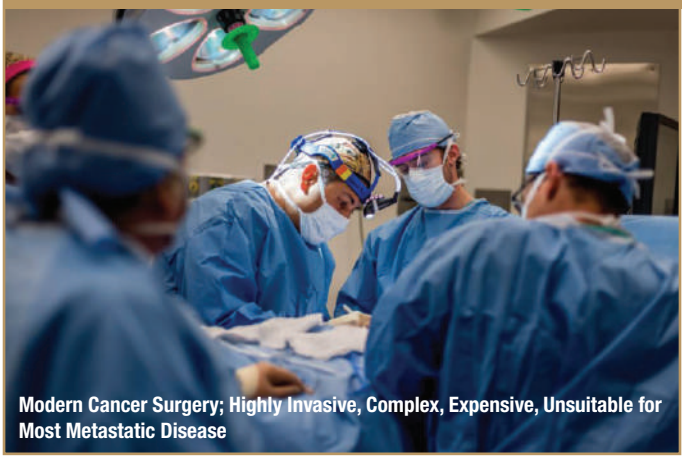
The human record of cancer is nearly as old as written language. A papyrus scroll from ancient Egypt (~1600 BCE) describes a process to remove tumors of the breast by cauterization.[1] Throughout the centuries, many theories were put forward about the origins of cancer. At the beginning of the enlightenment, physicians began to seek the causes of cancer in a scientific manner.

LOCAL APPROACHES

Cut-It-Out: Surgery

Initially, the local nature of cancer dominated thought. In the mid-1700s, John Hunter began the era of modern surgery. Hunter saw that cancer was moveable and operated to remove tumors. The use of the microscope to study tissue also began during this period. Rudolf Virchow developed the concept of "pathological processes." His application of cell theory explained the effects of disease in the organs and tissues of the body.[2] This knowledge led to the modern concept that surgery is most effective if the cancer is caught early and has not spread. Finally, scientists began to think of cancer as both a local and systemic disease.

FIGURE 1



Modern Cancer Surgery; Highly Invasive, Complex, Expensive, Unsuitable for Most Metastatic Disease

Beam-It-Out: Radiation

Wilhelm Conrad Röntgen discovered X-rays in 1895.[3] One year later, those powerful beams were used by Emil Herman Grubbe to treat a patient with breast cancer.[4] Again, a new local treatment idea took hold. Radiotherapy (RT), also known as radiation therapy, is a local treatment that uses high-energy rays or radioactive substances to damage tumoral cells to halt their growth and division. RT is now quite common with about two-thirds of all cancer patients receiving the therapy as a unique treatment or as part of a more complex therapeutic protocol.[5] Unfortunately, during RT, normal cells, especially those that divide frequently, may also be damaged and killed. Radiation is not an effective treatment modality in metastatic settings for many tumor types, especially when tumors are large and deep in the body.

Melt or Freeze Away: Ablation

Ablation is a minimally invasive local treatment method for solid cancers. Various methods of imaging are used to guide and position a probe into the tumor. This requires only a tiny hole to reach the cancer. A generator attached to a probe within the cancer "burns" or "freezes" the tumor. The effectiveness of ablation technique in treating cancer depends on two things: the size of the tumor and its accessibility. In general, for tumors three centimeters or less and easily accessible, the technique can work well.[6] There are only a limited number of tumors that can be treated, and there is no systemic component for ablation techniques. The approach is mainly used in treating small liver lesions.

SYSTEMIC APPROACHES

Poison Potions: Chemotherapy, Targeted Therapy, Antibodies

When the cancer is beyond the local environment, even if only a few cells are found in the neighboring lymph nodes, systemic therapies are often added to local methods or used alone. At the start of the 20th century, Paul Ehrlich began developing drugs to treat infectious diseases. Ehrlich first used the term "chemotherapy" and defined the word as the use of chemicals to treat disease.[7] One of the first chemicals tested against cancer was a derivative of an agent used to kill soldiers in World War I. Today's molecular arsenal includes hundreds of compounds that, once inside the cancer cell, disrupt various processes to kill the cells. The problem is that healthy fast-dividing cells, such as those in the scalp or gut, also absorb these agents, resulting in severe toxicities. Targeted agents acting like a guided missile are highly specific to various tumor types and have shown great promise. Unfortunately, there are not many cancers for which patients have the correct molecular profile for these agents to work. When the agents do work, they work well, almost miraculously. Though often, the tumor mutates and the drugs lose effectiveness. Despite tremendous funding and initial enthusiasm about molecular targeting drugs, such as kinases or inhibitors of growth factor receptors, long-term patient outcomes are frequently disappointing.[8] Often a patient will suffer multiple lines of drug therapy with severe side effects and diminishing rates of return. Once a patient with metastatic disease fails two or more lines of drug therapy, their odds of long-term survival are significantly reduced.

Harness the Defenses: Immunotherapy

In October 2018, Dr. James Allison and Dr. Tasuku Honjo were awarded the Nobel Prize in Physiology or Medicine for their groundbreaking cancer research. Allison studied a protein on the surface of T cells called CTLA-4, discovering that it inhibits immune cells. Honjo and his colleagues were studying another T-cell protein called PD-1, or programmed cell death protein-1, which they identified in 1992.[9] The antibody products that affect these immune cell proteins have become blockbuster drugs and today are the basis for the majority of clinical cancer research. The idea of using the immune system to fight cancer is not new. Willian Bradley Coley in the early 1900s began to experiment with using a mixture of killed bacteria as a treatment for cancer. Even further back in 2600 BCE, the Pharaoh Imhotep deliberately infected his tumors to attack his cancer. Modern medicine has now come full circle back to the Egyptians. One of the biggest challenges of IO is recognition by the immune system. Cancer is derived from a patient's healthy tissue. Essentially the immune system cannot easily distinguish cancer from healthy cells. Because the immune system is programmed not to attack a person's tissue, the cancer can grow unimpeded. Some tumor biomarkers such as the percent expression of PD-L1 protein or a tumor's mutational burden (TMB) values are indicative of who will respond. Patients fortunate enough to have tumors recognizable to the immune system are those most likely to benefit. Despite their promise and hype, drugs that act on the immune system currently only benefit a fraction of cancer types and patients.

REGIONAL ADMINISTRATION

Surgery and chemotherapy remain the leading workhorses of cancer treatment. If cytotoxic agents can kill cancer but cause systemic side effects, why not administer these drugs locally? Local delivery could kill the tumors, leave healthy tissue unharmed, minimize off-target toxicities, and be less invasive than surgery. Even though there may not be a systemic benefit of having "surgery in a bottle," for cancers confined in a region or for single tumors local administration should be of benefit. This win-win idea is old and has been proposed since the discovery of these killing agents; however, success has only been marginal.

There are two main concepts of local drug delivery to treat cancer. The first is delivery solely to the specific affected organ or part of the body, ie, regional delivery. Physicians currently use regional delivery in settings such as the liver, limbs, peritoneum, localized areas of the skin, and even in some central nervous system (CNS) settings. One of the most common modalities is in the liver and is known as trans-arterial chemo-embolization (TACE). The second approach is to be more precise by administering the drug directly into the tumors, ie, intratumoral delivery. Both regional and intratumoral delivery spare the majority of the body of the ill effects of chemotherapeutic agents.

The Challenges of Intratumoral Delivery

There are many cancers that originate deep in the body. To treat these tumors requires the aid of a visualization technique to determine where to place the injection needle. Fortunately, the recent development of computer aided tomography (CT) and easy-to-use ultrasound devices have made image guidance much more economical, precise, and practical.

Aside from imaging requirements, there are other problems that need to be solved for effective intratumoral delivery. The first is how to disperse drug throughout the tumor. Most potent agents are given systemically, and the drugs have thus been designed or formulated for the blood stream, which is an aqueous fluid. In general, cytotoxic drugs are hydrophilic and lipophilic compounds are challenging to formulate. Yet tumors often contain a high percentage of lipids, with some types as high as 30%.[10] Aqueous formulations are not well absorbed into these tumors. If there is chemical incompatibility of the drug with the tumor, then thorough dispersion and good absorption may be difficult.

The second key issue is for penetration of the potent agents into the cancer cells. There are three main cell internalization routes a molecule can take; via a receptor, by endocytosis of a vacuole, or by diffusion. Receptor-based transport is mostly genetically determined. Without a sufficient number of receptors, internalization is limited. Additionally, endocytosis is inherently slow. Finally, if the agent is water-loving, it will be incompatible with the cancer cell membrane, and diffusion will be poor.

Throughout the years, there have been several attempts at delivering cytotoxic agents intratumorally. These technologies include delivery in nanoparticle formulations, use of retentive gels, vasoconstrictors, microwaves, electroporation, and many other schemes.[11-14] None of these approaches adequately solved the dispersion and diffusion problems, and intratumoral dosing often failed to show benefit over systemic administration coupled with the local treatment.

Immunotherapies Revive the Potential of Intratumoral Delivery

With the advent of immunotherapy, intratumoral delivery has recaptured the interest of the biotech industry. In October 2015, the FDA approved Amgen's Imlygic® (talimogene laherparepvec) for the treatment of localized melanoma.[15] Also known as T-Vec, the drug is a modified form of the herpes virus dosed by direct intratumoral injection. Unfortunately, efficacy is not strong and sales of this drug are quite low. Several other companies have initiated clinical programs to test the intratumoral delivery of agents that can cause an immunological inflammation in the tumor microenvironment. These programs include intratumoral delivery of RIG-1, STING, and TLR9.[16-18]

Though the idea for intratumoral delivery to provide inflammation and antigen release is intriguing, these agents still need to be absorbed, retained, and dispersed in the tumor to be effective. Chemical compatibility between the drug formulation and the tumor is paramount.

A New Approach for Intratumoral Delivery

A new technology that can increase dispersion and diffusion of drugs in the tumor microenvironment is being tested in the clinic.[19] The drug, INT230-6, contains cisplatin and vinblastine co-formulated with an amphiphilic agent that improves tumor dispersion and cancer cell penetration. A recent paper indicates the drug induces direct cancer cell death as well as immune activation. INT230-6 is also quite effective when combined with immunotherapies.[20] The ability to attenuate the tumor *in situ* without damaging the cancer cell membranes may mean that INT230-6 has the potential to turn "cold" tumors "hot", ie, increase immune cell recognition, which

could solve a major challenge of immunotherapy. Early clinical results are promising.

DISCUSSION

There are now multiple weapons against cancer, including modern surgery; high-tech radiation; sophisticated ablative techniques; novel compounds comprising small molecules, peptides, oligonucleotides, or proteins; and immunotherapies. Despite these armaments, over 606,000 Americans are expected to die from cancer in 2019.[21] There is hope as the 5-year survival rates from 1975-1977 to 2008-2014 have gone from 49% to 69%. While there has been progress over the past 45 years, medicine is still a long way away from a cure for most cancers, especially late-stage disease.

CONCLUSIONS

There is often a long arc to fighting illnesses. Infectious diseases, such as bubonic plague, smallpox, and polio, killed or disabled hundreds of millions of people over the millennia. Today, in advanced countries, many of these dreaded diseases have been eradicated. Cancer too has a long and ancient history. We now understand that cancer is a local and systemic disease. New forms of local treatment, such as intratumoral dosing coupled with systemic immunotherapy, are being explored. If humanity is to win the fight against the Emperor of all Maladies a significant shift in treatment approaches beyond surgery with systemic chemo will be required.[22] Whether replacing cutting and poisoning by local delivery and immune activation can be achieved, only time will tell. One thing is certain, given the perseverance and dedication of scientists and our exponentional growth in understanding the complexities of cancers, someday this disease too shall be tossed into the dustbin of history. Hopefully that day is near.◆

FIGURE 2

Depiction of Intratumoral Delivery of INT230-6

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BIOGRAPHY

Lewis H. Bender is Founder and CEO of Intensity Therapeutics, a clinical-stage biotechnology company pioneering a novel, immune-based approach to treat solid tumor cancers through direct injection of the company's proprietary therapeutic agents. He has more than 26 years of leadership in the biopharmaceutical industry, taking products leveraging novel drug delivery techniques from discovery through Phase 3 development and partnering with major pharmaceutical and biotechnology companies. Previously, he was the CEO of Interleukin Genetics (IG) and held numerous positions at Emisphere Technologies, Inc., including CEO and VP of Business Development & Manufacturing. He earned his SB and SM in Chemical Engineering from the Massachusetts Institute of Technology (MIT), his MBA from the Wharton School of the University of Pennsylvania (UPenn), and his MA in International Studies, also from UPenn.

CLINICAL TRIALS

Leaning Into Investigator Sponsored Trials

By: Martin Lehr, MA

INTRODUCTION

Investigator Sponsored Trials (ISTs) elicit visceral reactions from both start-up and established pharmaceutical companies. When properly implemented, ISTs can identify new uses for marketed drugs, advance the scientific understanding of a drug that is in development, or provide a therapeutic outlet for patients who have limited treatment options. ISTs can also be a source of frustration for pharmaceutical companies as timelines can be longer than anticipated, there may be limited access to study data, and publication of trial data is at the discretion of the Investigator. By understanding the challenges associated with ISTs, stakeholders can utilize ISTs to deliver high-contrast clinical data on underserved patients.

ISTs are defined by the FDA as unsolicited, independent research in which the investigator or the institution (academic, private governmental) serves as the Sponsor and the pharmaceutical company provides support in the form of study drug, protocol development assistance, or financial support. ISTs are equally important for approved and investigational products. For established products, ISTs can be utilized to identify new diseases or patient populations that will lead to label expansions. For emerging products, ITSs can help define preliminary efficacy and safety to de-risk the product ahead of late-phase development studies.

IST SUCCESSES

Successful ISTs have provided the foundation that ultimately led to the approval of numerous notable medicines (Table 1). Prior to the initiation of ISTs, GLEEVEC®, IBRANCE®, and Nolvadex were sitting on the shelves of large pharmaceutical companies. In each case, an intrepid Investigator – Brian Druker, MD, Oregon Health & Science University (GLEEVEC), Dennis Slamon, MD, PhD, University of California, Los Angeles (IBRANCE), and V. Craig Jordan, CMG, OBE, FMedSci, University of Leeds (Nolvadex) – identified a key mechanistic insight and then spent years lobbying CIBA (and later Novartis), Pfizer, and ICI Pharmaceuticals, respectively, for access to the drugs to test their hypothesis. Through their perseverance, the investigators each won over the pharmaceutical companies and initiated their respective ISTs.

Conducting ISTs within a large academic research hospital

TABLE 1

Generic Name	Brand Name	Mechanism	Institution	Partner	Indication
Bevacizumab[1]	Avastin®	Anti-VEGF	Moorfields Eye Hospital NHS Foundation Trust	Genentech	Neovascular AMD
Brentuximab vedotin[2]	ADCETRIS®	CD30 ADC	Stanford University	Seattle Genetics	*CTCL*
Gefitinib[3]	IRESSA®	EGFR inhibitor	Aichi Cancer Center Hospital (Japan)	AstraZeneca	*NSCLC*
Imatinib[4]	GLEEVEC®	*abl*, c-Kit, PDGFR	Oregon Health & Science University	CIBA/Novartis	*CML*
Infliximab[5]	REMICADE®	Anti-TNFα	Gent University	Centocor	*Ankylosing Spondylitis*
Infliximab[6]	REMICADE®	Anti-TNFα	University of Chicago	Centocor	Plaque Psoriasis
Obeticholic Acid[7]	OCALIVA®	FXR Agonist	National Institutes of Health	Intercept Pharma	NASH
Palbociclib[8]	IBRANCE®	CDK4/6 Inhibitor	University of California, Los Angeles	Pfizer	HR+/HER2- Breast Cancer
Tagraxofusp-erzs[9]	ELZONRIS®	CD123 ADC	University of Texas Southwestern Medical Center	Stemline Therapeutics	Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)
Tamoxifen[10]	Nolvadex	Estrogen Receptor	University of Leeds	ICI Pharmaceuticals	HR+/HER2- Breast Cancer
Trastuzumab[11]	Herceptin®	HER2	University of California, Los Angeles	Genentech	HER2+ Breast Cancer

ISTs That Led to Commercial Products or Expanded Labels

afforded Drs. Druker, Slamon, and Jordan a distinct advantage over pharmaceutical companies. These researchers work at the intersection of patients, basic researchers, and translational researchers, all of whom were committed to finding novel medicines to treat diseases. The passion and drive of these academic researchers to explore the unknown would be hard to replicate within a pharmaceutical company, which are large, matrixed organizations that are generally risk averse.

The success of Drs. Druker, Slamon, and Jordan fundamentally changed the course of treatment for patients with chronic myelogenous leukemia and hormone receptor-positive breast cancer. Since then, there have been numerous other success stories wherein the insight of an Investigator led to the initiation of an IST and ultimately the approval of a drug.

IST CONSIDERATIONS

In most cases, the trajectory for the success of an IST can be determined before the first patient is enrolled. There are common issues to each IST that when constructively discussed between the Investigator and the pharmaceutical partner can be addressed to ensure that the trial meets both parties' expectations. A summary of common issues and potential mitigation steps are provided in Table 2.

IST BENEFITS

Pharma Perspective

Large pharmaceutical companies are increasingly embracing the power of ISTs. In particular, ISTs have been most often utilized to explore new uses of late-stage development or marketed products.

Even the largest multinational pharmaceutical companies operate within a constrained budget and cannot fund every trial they would ideally want to initiate. ISTs play a key role for large pharmaceutical companies that want to expand the clinical footprint of their drugs. With ISTs, the pharmaceutical company can tap an external pipeline of idea generators to identify new patient settings or patient subsets distinct from internal programs.

Despite considerable interest by large pharmaceutical companies in ISTs, it is no small feat for an Investigator to get his or her IST supported by a pharmaceutical company. Large pharmaceutical companies receive hundreds of IST requests per year. Given the sheer number of submissions, only a small fraction will ultimately get supported. This supply and demand constraint gives pharmaceutical companies considerable leverage when reviewing IST submissions so they tend to gravitate toward funding submissions from top research institutions and well-known Investigators.

Start-Up Company Perspective

Despite the potential benefit of data generated from ISTs, many start-up biotechnology companies choose not to partner with Investigators. Risk aversion or general lack of experience with ISTs are the primary reasons start-ups often prefer to manage their own studies. For those start-up companies that leverage an IST strategy, the benefits that can be realized are: short timelines to data; a broader pipeline; and external validation by key opinion leaders.

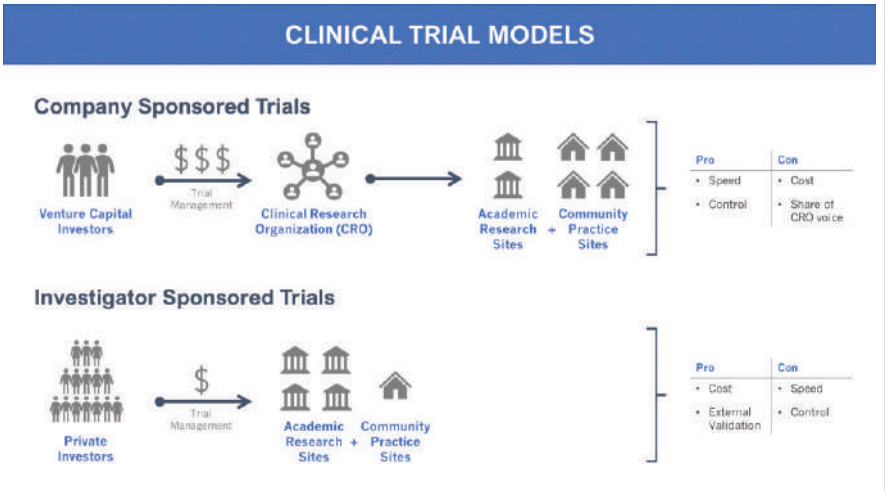
There is also a general assumption that ISTs are slower than CRO-supported trials. Investors often believe that Investigators, particularly academic investigators,

TABLE 2

Issue	Risk	Mitigation
Bias	-IST results unlikely to be replicated in larger study	-Open multiple sites that are geographically distributed -Co-Investigators
Communication	-Unmet expectations -One-sided interaction -Publication of data	-Regular communication and full transparency -Support of Department and participating Investigators -Pharma company to provide updates on other trials and insights on the product being evaluated -Yearly off-site retreat to review studies, data and generate positive morale
Data	-Ownership -Completeness	-Partner receives license to data -Data tracking in industry-standard software
Project Management	-Lack of infrastructure -Timely FDA reporting -Quality control	-Define project team and responsibilities -Investigator provides partner with Annual Report within 30 days of reporting period -Access to site, pharmacy and laboratories for audits
Impropriety	-Investigator kick-back or incentive to work with pharma in the future -Off-label promotion	-Potential use of RFAs so that applicants know scientific focus and max award size -Fair Market Value (FMV) should be established for the Investigator's service plus the indirect costs of the institution where the trial is being held -Qualify investigators and monitors (CVs, 1572, financial disclosures) -Clearly state in all public disclosures that the trial is "Investigator-Sponsored"
Patient Enrollment	-Slow recruitment -Poor quality of patients	-Strong institutional support for trial -Staggered payments based upon recruitment thresholds and report submission (interim, final)

Common IST Issues & Solutions

FIGURE 1



Company vs. Investigator Sponsored Trials (Source: Context Therapeutics)

do not understand industry timelines. This is ironic, given that CROs would contract with those same Investigators in a Company-Sponsored trial. A 2015 survey by the Association of Clinical Research Professionals (ACRP) found that the average time to IST completion was 2 to 3 years and about 75% of those trials ultimately finish, which is consistent with broader industry averages.[12]

For capital-constrained start-up companies, ISTs can provide an attractive path to product validation and de-risking (Figure 1). Most start-up companies can afford only one well-designed Phase 2 trial. Due to their lower cost, ISTs enable start-ups to initiate multiple trials to broaden their pipelines and reduce binary risk – something that should be highly attractive to investors. For example, recent Phase 2 clinical collaborations with Memorial Sloan Kettering, Wisconsin Oncology Network, Jefferson Health and Grupo SOLTI have helped our small company, Context Therapeutics, advance our lead candidate Onapristone ER into multiple trials across several different cancer types that we would otherwise not have been able to fund had the trials all been Company Sponsored.

Another often overlooked benefit is the gravitas an Investigator brings to a start-up. The Lead Investigator of a trial allocates 2 to 3 years of their career to the trial, which is a significant commitment that is not lost on their peers or investors. This external validation may lead to additional ISTs, investment, or pharmaceutical partnering interest. Further, the Investigator is the face of the trial, so partnering with a charismatic Investigator who is respected by their peers, invited to give presentations at major conferences, and is known to investors can boost the perception of a drug and positively impact its development trajectory.

Investigator Perspective

ISTs are an essential component of the academic mission of research hospitals and institutions. These studies provide a forum for Investigators to explore new science that may provide therapeutic benefit to patients, which is critical to both the success of the institution and the Investigator. For the institution, ISTs are a semi-exclusive relationship with a pharmaceutical company to provide patients with free access promising drugs. Institutional competition for patients is fierce, so offering patients a multitude of unique clinical trial options is a differentiator that helps with institutional rankings, patient recruitment and retention, and the overall growth and financial health of the institution.

For the Investigator, ISTs provide an opportunity for career advancement. In academic medicine, career advancement is determined by the discovery of novel science, publications, and leadership. In an era of tight budgets and stagnant National Institutes of Health funding, financial support of clinical trials for career advancement can be challenging. Conducting ISTs enables Investigators to tap external funding and resources to ensure that they are publishing. ISTs also provide critical leadership opportunities for Investigators who get to wear multiple hats (scientific, operational, logistic) during the IST that reveal the breadth of their skills. The Investigator is also the presenter of data at major conferences, which provides a venue for the Investigator to introduce themselves to a large and diverse audience of their peers. In success, the Investigator will become forever tied to the drug, which in turn, may help advance or even define their career, much like Drs. Druker, Slamon, and Jordan.

Despite the positive aspects of being an Investigator-Sponsor, it is not for the faint of heart. As previously described, there are numerous issues that could derail an IST. A good Investigator is someone who understands the potential challenges and is prepared to weather the ups and downs of the trial process. To navigate uneasy seas, it is essential that the Investigator has strong communication skills and robust institutional support for the trial, particularly within the Investigator's department. Alignment between the Investigator

and their department helps mitigate the risk that competing trials will be initiated and ensure that qualified patients will be referred to the Investigator's trial.

Often overlooked is the fact that Investigators and their Institution assume legal responsibility for the trial. This includes not only the protection of patients, but also protection from improper incentives provided by the company to the Investigator. If the pharmaceutical company is only providing drug supply, they should request the Investigator to provide a Fair Market Value for the trial, including both the direct Investigator costs and the indirect costs to the institution, so that it can be properly accounted. All participating Investigators should also provide CVs and 1572 and financial disclosure submissions to the FDA as part of the study startup process.

LOOKING TO THE FUTURE

Given the capital and intellectual capacity constraints within large pharmaceutical companies and start-ups, ISTs provide an important path to unlocking the therapeutic value of developmental and marketed drugs. By better understanding the risks associated with ISTs and identifying mitigation steps, ISTs have a greater probability of delivering meaningful data in a timely manner that is beneficial to patients, Investigators, and companies alike. ◆

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BIOGRAPHY

Martin Lehr is the Co-founder and CEO of Context Therapeutics. In addition, Mr. Lehr is a member of the Scientific Advisory Board of Integral Molecular, Board Member of CureDuchenne, and Editorial Advisory Board of Life Science Leader magazine. Previously, he was part of the founding team at Osage University Partners, a venture capital fund focused on academic spin-outs from leading research institutions. At Osage, Mr. Lehr focused on early stage oncology and rare disease opportunities. Prior to Osage, he conducted research at the Sloan Kettering Institute in DNA repair and at the Children's Hospital of Philadelphia in thrombosis and hemostasis. Mr. Lehr is a Director of BioBreak, a biotech executive peer networking group with over 2,500 active members across the US. He earned his MA in Biotechnology from Columbia University and his BA in Economics from the University of Pennsylvania.

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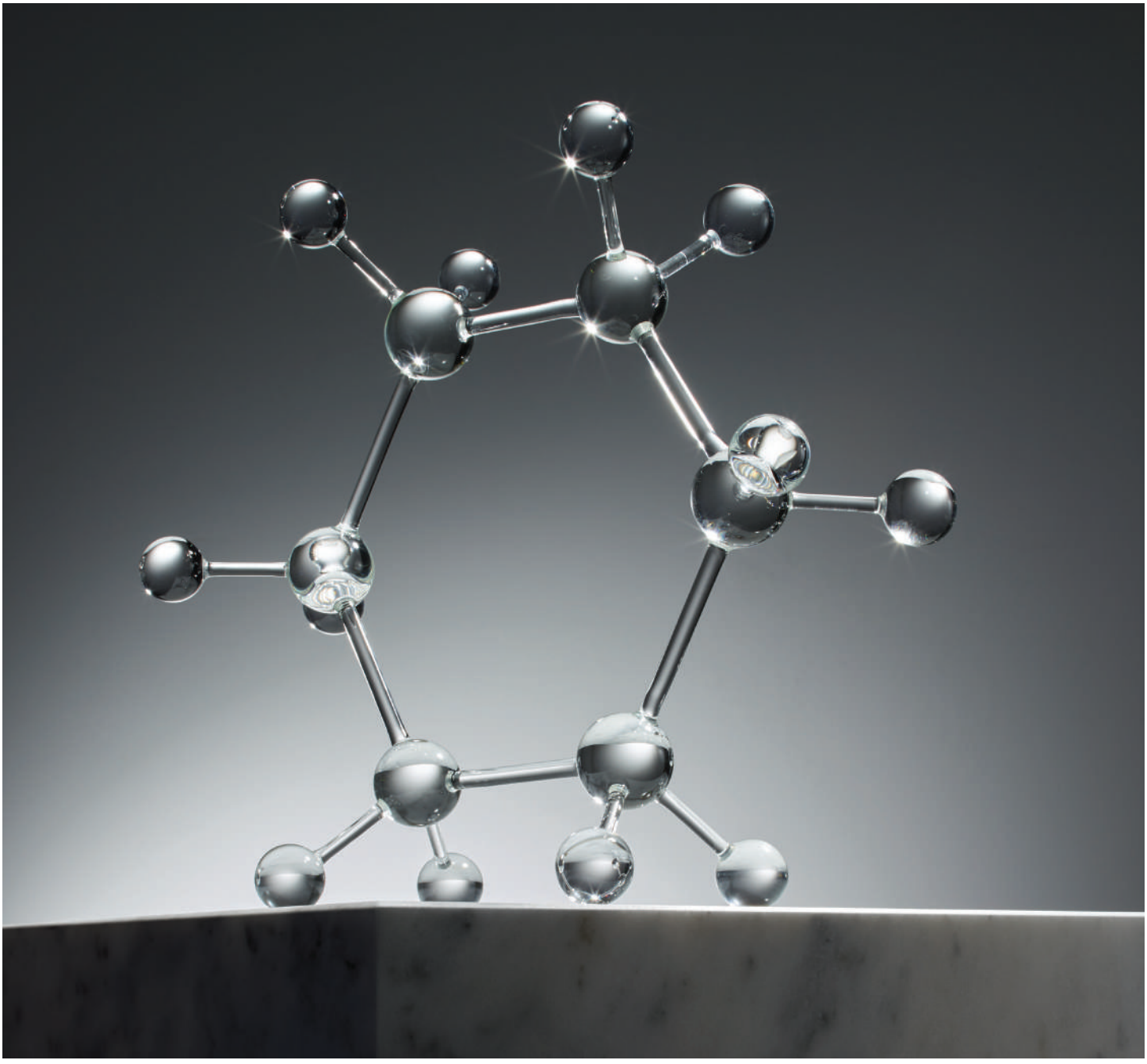

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