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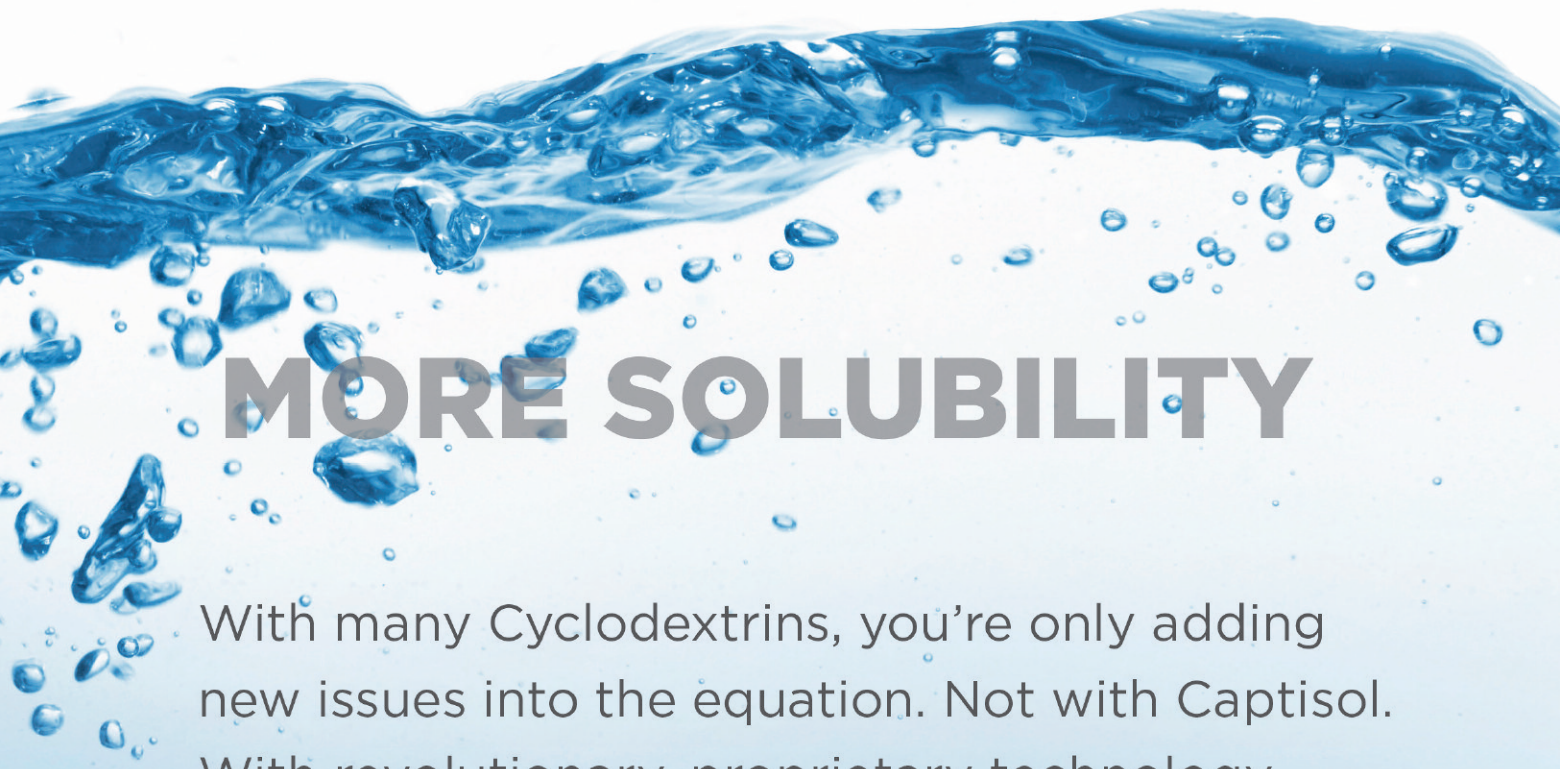

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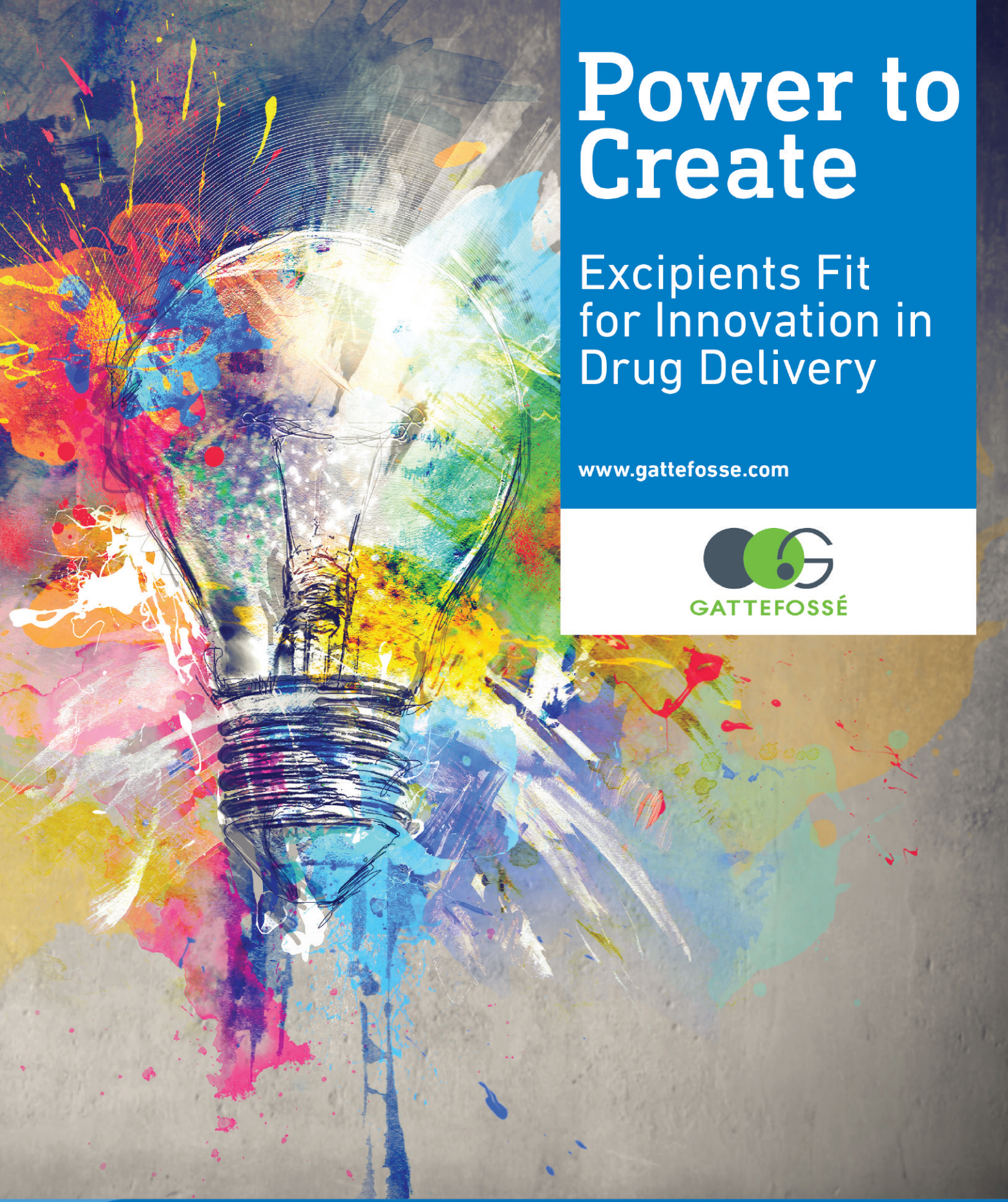

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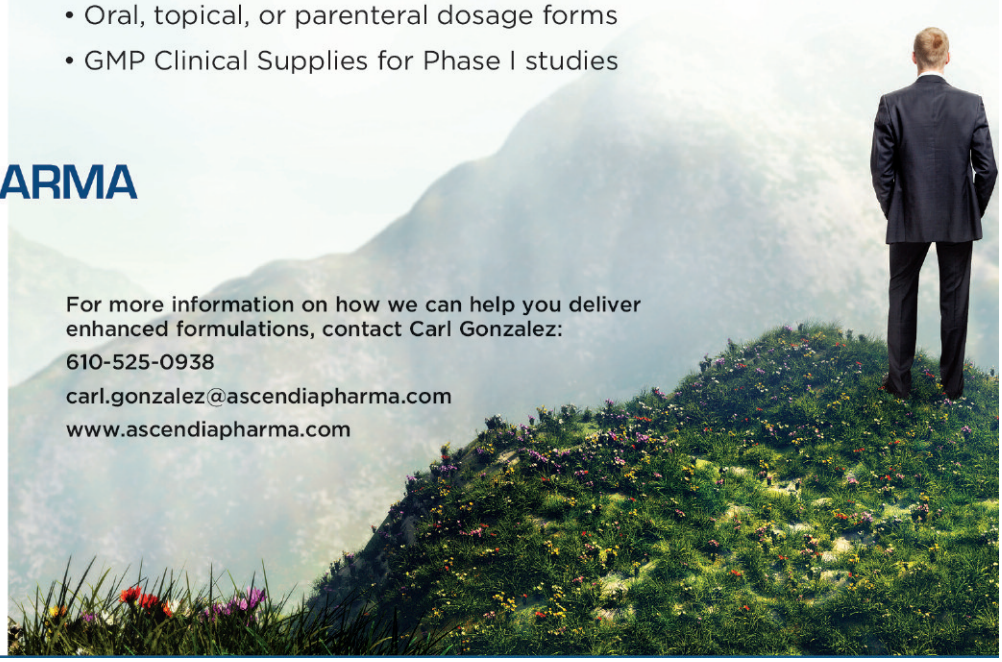

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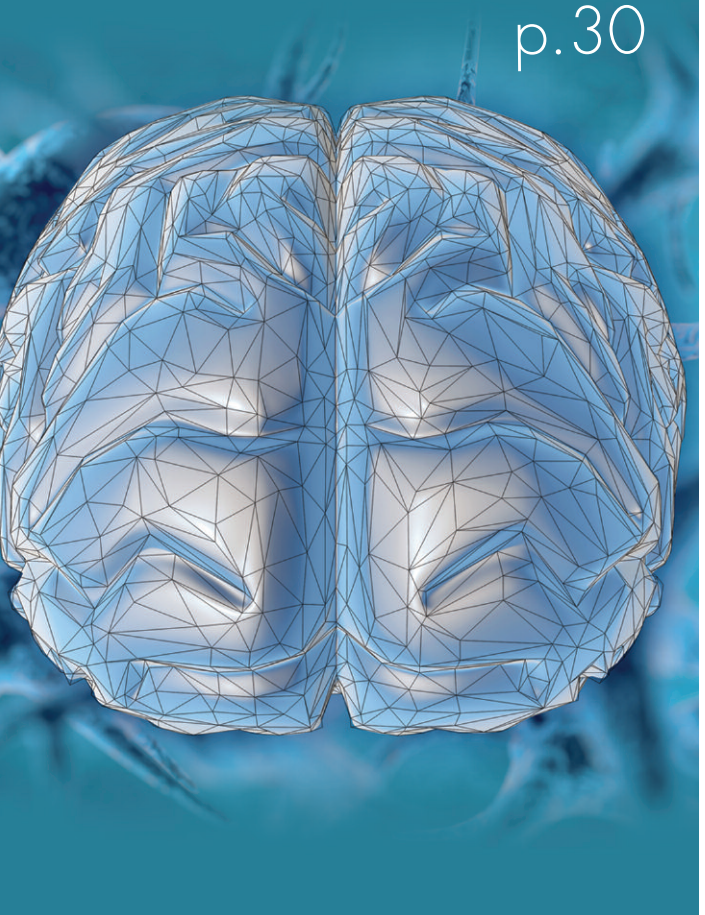

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What do you *really* know about end users of drug delivery technologies?

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Bioavailability & Solubility

"From a technical standpoint, the solubility and permeability of many new chemical entities are key issues for the development of new drug formulations. As a result, the industry is in urgent need of new approaches to drug development and specifically to tailored drug delivery."

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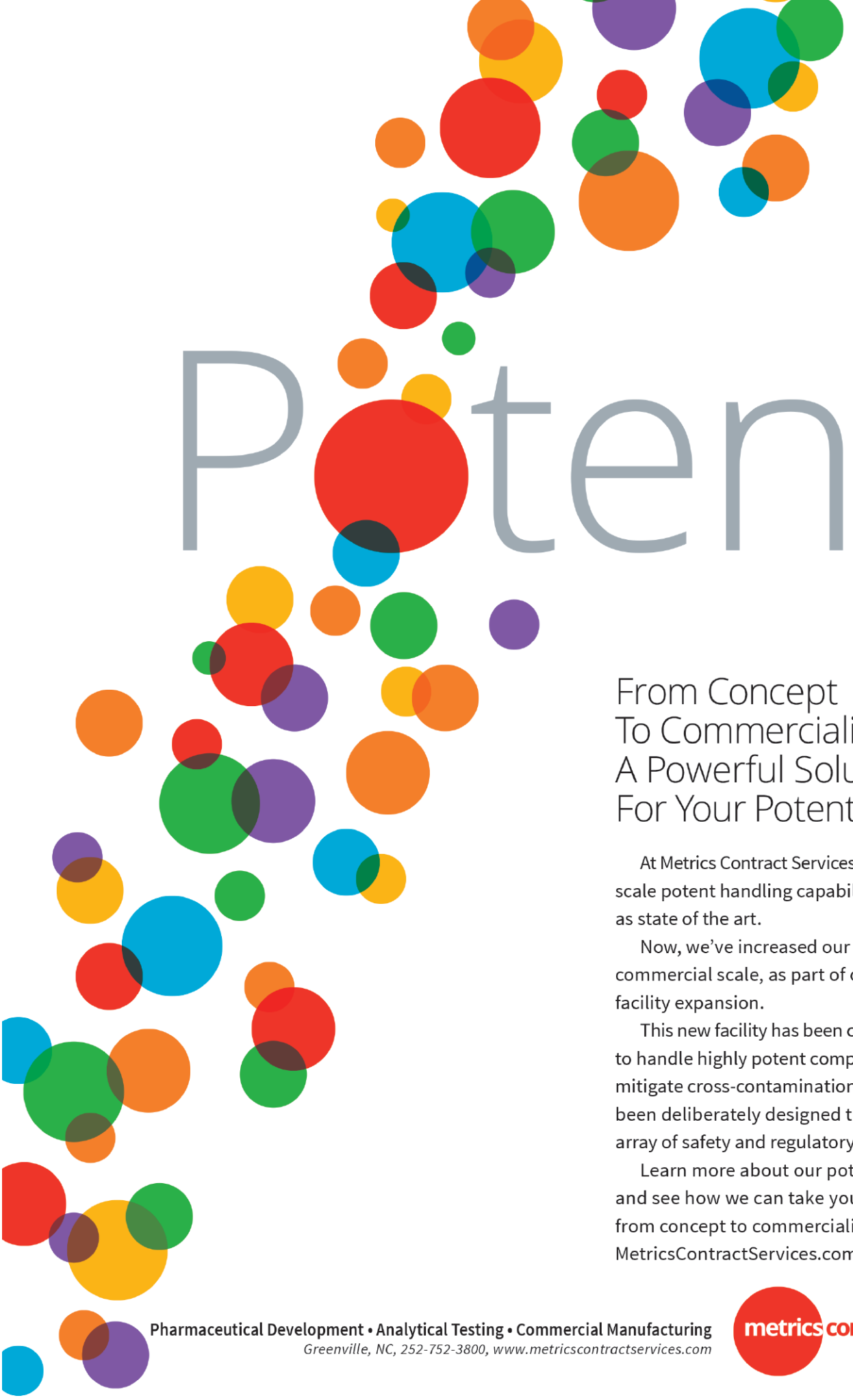

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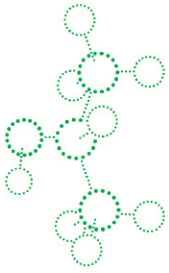

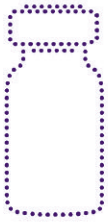

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2017

Global Drug Delivery & Formulation REPORT

A Global Review

Part 1 of a 4-Part Series

Part 1: A Global Review

Part 2: Notable Product Approvals of 2017

Part 3: Notable Transactions and Technologies of 2017

Part 4: The Drug Delivery and Formulation Pipeline

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

Introduction

With the books closed for 2017, we can take a closer look at pharmaceutical product approvals for the year. In a series of articles through the next four issues, we will review 2017 with an emphasis on pharmaceutical products, technologies, transactions, and a look forward to 2018 and beyond with a review of the current clinical pipeline. The overall focus of this article series will be on drug delivery and formulation technologies and products, plus a peek at what is unfolding in the field of gene and cell therapy. In this first installment, we look at the macro aspects of the 2017 product approvals.

Considerable attention is placed on new molecular product approvals, with too little time spent on repurposed versions of previously approved actives. A closer look at dose-modified products often provides a better sense of what the future holds. There is much less risk associated with applying a novel technology to a previously approved active; one less variable to juggle. Once validated, it becomes much easier to rationalize applying a next-generation technology, with next-generation benefits, to a novel molecular entity.

Product Approvals in the USA

The US FDA provides a variety of approval types for pharmaceuticals and medical devices. These range from New Drug Approvals (NDAs) to Abbreviated New Drug Approvals (ANDAs) to Biologic License Approvals (BLAs) to Premarket Approvals (PMAs) to 510(k) approvals. This last group, 510(k) approvals, are new products approved on the basis of their functionally similarity to products approved prior to 1976. These 510(k) approvals along with PMA and ANDA approvals are ignored in this review. BLAs include well characterized therapeutic agents from both the Drugs and the Vaccines, Biologics & Blood Divisions.

Within the NDA classification, there are a variety of Types of approvals. Most attention is placed on Type-1 approvals that apply to new molecular entity (NME) products. Often overlooked are the Type-3 New Dosage Form, and Type-4 New Combination Approvals. These approvals often point to new pharmaceutical approaches in terms of drug delivery, formulation, and therapeutic treatment strategies. While Type-5 approvals at times embody interesting formulation approaches, they often represent approvals for new products with little or no novelty. This is particularly the case with multisource generic injectable approvals, which are required to use the NDA 505(b)(2) rather than the ANDA pathway for approval. For the purpose of this article, multisource injectable 505(b)(2) Type-5 approvals have been excluded from the analysis.

Another wrinkle concerns the approval of Supplemental NDAs and BLAs that do not qualify as a new product but can represent a new dosage form. These products have been selectively included in the analysis where they represent important new dosage forms. For consistency, PMA and 510(k) approvals, largely device approvals, have been ignored even though they may at times include a drug component.

Based on the aforementioned defined criteria, a total of 134 products were included in this review of 2017 FDA approvals. These approvals covered the Drugs, Vaccines, Biologics & Blood Divisions of the FDA. Of this total, 64 approvals represent NMEs. The remaining 70 approvals represent new formulations of previously approved products, new combinations of previously approved products, or some other category as noted in Table 1.

Table 1. FDA Approvals by Classification

	Classification	Number
BLA & Related		**25**
BLA	New Biological (Drugs Division)	15
sBLA	Supplemental BLA (Drug Division)	1
Biologic	New Biological (Vaccine, Blood & Biologics Division)	9
NDA		**109**
Type-1	New Molecular Entity	34
Type-2	New Active Ingredient	2
Type-3	New Dosage Form	22
Type-4	New Combination	8
Type-5	New Formulation or Other Differences	29
Type-7	Previously Marketed but Without an Approved NDA	2
Type-10	New Indication or Claim, Drug to be Marketed Under Type 10 NDA After Approval	1
Type-1/4	New Molecular Entity, and New Combination	6
Type-3/4	New Dosage Form, New Combination	1
sNDA	Supplemental NDA	4

Product Approvals in the European Union

Properly analyzing product approvals in Europe is trickier. While the US has a single regulatory body covering the sale of pharmaceuticals to some 320 million people, the European Union (EU) boasts more than 500 million people and a variety of regulatory bodies approving products at a pan-European and individual country basis. For the purpose of this review, products approved by the European Medicines Agency (EMA) were included in the analysis. This analysis may overlook some notable products approved at the country level but deciding which should and shouldn't be included would result in an unreasonably biased dataset. The dataset used for the 2017 EU approvals was drawn from the PharmaCircle Pipeline & Products Intelligence module and cross referenced with the PharmaCircle EMA module. Using the PharmaCircle dataset provides important benefits, most notably an expanded and consistent set of individual product characteristics. The EMA and FDA provide datasets with limited individual product information that the PharmaCircle analysts expand upon by analyzing individual products to tease out additional information that ranges from product formulation details, to molecule type, to dosage form, to injection route.

The EMA dataset does not provide the same detail as the FDA dataset in terms of approval types. Despite this shortcoming, it is possible to do a detailed analysis of EMA product approvals by examining individual product characteristics. A total of 62 product approvals are included in the analysis and represent new molecular entities as well as novel formulations of previously approved actives approved by the European Medicines agency.

2017 Approvals by Administration Route, FDA & EMA

A summary of product approvals by Administration Route is presented in Table 2. The distribution is largely consistent between the EMA and FDA approvals. Oral delivery accounted for about 40% of approvals in both territories. Summed together, Injection-based delivery accounted for almost the same number of approvals. The remaining delivery routes, Inhalation, Nasal, and Topical accounted for no more than a low single-digit percentage of all approvals.

Table 2. 2017 Approvals by Administration Route

Delivery Route	FDA	EMA
Injection	**59**	**29**
-Infusion IV	24	9
-Infusion SC	1	0
-Injectable IA	1	1
-Injectable ICV	1	1
-Injectable IM	4	2
-Injectable IT	1	1
-Injectable IV	5	2
-Injectable SC	19	13
-Unspecified	3	0
Instillation/Implantation	**1**	**0**
Inhalation	**5**	**2**
Nasal	**4**	**2**
Ophthalmic	**3**	**2**
Oral	**61**	**25**
Sublingual	**0**	**1**
Topical	**5**	**2**

2017 Approvals by Drug Delivery Category, FDA & EMA

This is a PharmaCircle-defined series of pharmaceutical product designations that help define and categorize products in terms of their essential drug delivery characteristics. Table 3 is an abridged version of the full list of 70 or so separate categories. Perhaps the most notable point is that formulation enhanced oral products represented a surprisingly small proportion of all approved oral products in 2017, certainly in comparison to a decade ago. Have we moved past "peak oral formulation"? Is the reduced interest in enhanced versions of multisource actives a result of fewer new product ideas or the relatively low period of exclusivity available in the absence of strong technology or molecule patents? Another interesting point not obvious in Table 3 is that 2017 went by without another transdermal new product approval.

Table 3. 2017 Approvals by Drug Delivery Category

Drug Delivery Category	FDA	EMA
Adeno-Associated Virus Vectors	**1**	**0**
Biodegradable - All	**2**	**0**
Inhalation	**4**	**1**
-Dry Powder Inhalers	2	0
-Liquid Inhalers/Nebulizers	1	0
-Metered Dose Inhalers	1	1
Injection – Device Related	**15**	**12**
-Autoinjectors	4	2
-Pens	5	5
-Prefilled Syringes	6	5
Injection Other	**29**	**9**
-Nanoparticle Emulsion	1	0
-None	28	9
Instillation/Implantation	**1**	**0**
Nasal - Formulation & Devices	**4**	**2**
Ocular - All	**4**	**2**
Oral	**58**	**21**
-Formulation Enhanced	10	1
-Abuse Resistant Modified Release	1	0
-Other / None	47	20
Prodrugs - All	**2**	**4**
Topical - All	**4**	**2**
Other - All	**10**	**7**

2017 Approvals by Dosage Form, FDA & EMA

The relationship between Administration Route, Drug Delivery Category, and Dosage become more obvious as one looks at the data. Products administered by Inhalation or Injection, for example, are composed of a variety of different dosage forms using different drug delivery technologies. Examining approvals, and the development pipeline, can provide insights into where the industry is headed and where opportunities exist for drug delivery and formulation enhanced therapeutics.

It's worth noting that in the case of Injection, while there is considerable attention being placed on patient-friendly subcutaneous drug-device pairings, less attention is being placed on dosage form and drug delivery technology enhancements, with most products using simple Injection Solution approaches. The most common oral dosage form continues to be the Oral Tablet, with only a smaller proportion incorporating any type of drug delivery technology.

Table 4. 2017 Approvals by Dosage Form

Dosage Form	FDA	EMA
Implant	1	1
Inhalation	5	2
-Inhalation Powder	3	1
-Inhalation Pressurized, Solution	1	-
-Inhalation Solution	1	1
Injection	55	27
-Injection Emulsion	2	-
-Injection Lyophilized Powder for Solution	9	6
-Injection Lyophilized Powder for Suspension	2	-
-Injection Powder for Suspension	1	-
-Injection Solution	38	20
-Injection Suspension	3	1
Nasal	3	2
-Nasal Solution	1	-
-Nasal Spray	-	1
-Nasal Spray Metered	1	1
-Nasal Spray metered, Suspension	1	-
Ophthalmic Solution	4	2
Oral	63	25
-Oral Capsule	8	6
-Oral Powder for Solution	2	-
-Oral Powder for Suspension	1	1
-Oral Soft Gel Capsules	1	1
-Oral Solution	3	1
-Oral Suspension	4	-
-Oral Tablet	38	16
-Oral Tablet for Suspension	1	-
-Pellet	1	-
-Powder, Metered	1	-
-Sachet/Granules	3	1
Topical	4	2
-Topical Cream	3	-
-Topical Gel	-	1
-Topical Solution	1	1

2017 Approvals by Molecule Type, FDA & EMA

Once again, small molecule therapeutic approvals in 2017 represented the largest number of product approvals followed by antibody therapeutics moving up the ranks in terms of total approvals. It's hard to remember that 3 decades ago, antibodies were considered to be a major disappointment in terms of therapeutic products. Perhaps the situation is repeating itself as we witness the approval of an emergence of gene and cell therapy therapeutics following their apparent crash and burn 2 decades ago. Oligonucleotide and carbohydrate therapeutics meanwhile continue to try and find a meaningful role.

Combination products, beyond the traditional antihypertensive and diuretic and more recently antidiabetic and metformin pairings, have increased in terms of numbers and variety. The intended benefits of these products range from improved convenience to improved efficacy, especially with anti-infective and respiratory products.

Table 5. 2017 Approvals by Molecule Type

Type	FDA	EMA
Single Active	**116**	**53**
Antibody	14	12
Carbohydrate	0	1
Cell Therapy	2	1
Gene Therapy	1	0
Small Molecule	80	26
Oligonucleotide	0	1
Peptide	8	2
Polymeric	0	1
Protein	11	9
Multi Active	**18**	**9**
Protein, Peptide	0	1
Protein, Protein	0	2
Small Molecules (2)	12	2
Small Molecules (3)	4	3
Small Molecules (4)	2	1

2017 Approvals — Reflections

From a macro perspective, 2017 was in many ways a repeat of 2016 in terms of total approvals and approval types. There was an overall increase in NME approvals, in part a result of more orphan product approvals, and of course cancer product approvals. Surprisingly perhaps, infectious disease products were in second place in terms of the number of FDA product approvals, behind cancer products. The cardiovascular product approval numbers were on par with endocrinology products, largely treatments for diabetes.

The emergence of gene and cell therapy products as meaningful therapeutic options for the treatment of poorly managed medical conditions was perhaps the most notable trend of 2017, if not yet reflected in the approval numbers.

There was activity in the area of respiratory therapeutics with the introduction of new dry powder devices being applied to previously approved therapeutics, some of which provided the convenience of three medications in a single device.

One therapeutic area that saw a relative drop in approvals was oral opioids. With the public scrutiny of opioid prescribing, the industry came to understand that abuse-deterrent properties, as evidenced by Opana ER, were not a hedge against misuse and censure.

But opportunity is often revealed by studying the details. In the next installment, we look at individual product approvals to see what is revealed by examining the 2017 approvals at the micro level.

INTRADERMAL DELIVERY

New Technology Brings Simplicity & Scalability to Intradermal Drug Delivery

By: Boris Stoeber, PhD, Sahan Ranamukha, PhD, and Rory St. Clair

ABSTRACT

Intradermal drug delivery is increasingly recognized as a potential solution to many of the challenges faced by new and existing medicines. Intradermal dosing provides the opportunity to more effectively administer agents such as small molecules, biologics, and vaccines, allowing for improved bioavailability. Nonetheless, the widespread use of this route of administration continues to be limited by technical challenges in the performing of intradermal injections, which requires specialized training and has poor reproducibility.

Microneedles are a rapidly growing technology developed to solve issues surrounding intradermal drug administration. While many microneedle platforms have been developed over nearly 2 decades, the issues and concerns remain largely the same. A simple, robust, reproducible platform that can be scaled for widespread use has not been achieved. Some of the existing microneedle products have addressed one or more of the limiting hurdles in development, but no single platform has yet addressed them all. Microdermics' needles are novel, hollow, metallic microneedles, which offer all the benefits of intradermal drug delivery in a simple design that is completely manufacturable. The following describes the Microdermics technology and its improvements over the conventional subcutaneous route of administration.

INTRODUCTION

Intradermal dosing has been recognized as a route of administration that would be beneficial for small molecules, biologics, and vaccines. The dose sparing effects have been well described; these would reduce the amount of drug required for injection and reduce costs.[1] Additionally, intradermal injection of vaccines shows improved efficacy when compared to subcutaneous and intramuscular injections. Biologics, such as insulin and human growth hormones, are given subcutaneously as they cannot be administered orally due to poor absorption and/or instability in the gastrointestinal tract.[2] Intradermal delivery would provide an advantage over current methods because of faster absorption from the skin and improved or equivalent bioavailability. These results suggest that intradermal injection would be an improved method of drug delivery for many agents. So the question remains: why haven't we seen more intradermal injection products?

The method for intradermal injection requires highly trained, specialized staff, which increases the cost associated with this route. For life-saving drugs like insulin this method may not be desired, as patients typically need to inject themselves multiple times daily. Microneedle devices with a low efficiency – those that cause a wasted dose due to difficult administration, leakage, or dead volume in the injection system – can also diminish the benefits of a higher bioavailability and result in a greater waste of resources. Thus, while intradermal administration provides improvements over the current approaches, the lack of reproducibility and technical difficulty have made it difficult to adopt widespread intradermal injection.[3]

MICRONEEDLES

Microneedles are needle-like structures that have been produced at the micron-scale. While traditional hypodermic needles are large in comparison, allowing them to reach deep into the body beyond the skin, microneedles were developed to penetrate the skin's top most layer and deliver drugs into the dermis. Because of their size, microneedles do not behave in the same way as traditional hypodermic needles in that they allow for intradermal dosing, whereas other needle systems are typically used for dosing via intravenous, intramuscular, and subcutaneous routes.

Microneedle devices could allow for the intradermal route of administration to become a widespread method for both healthcare professionals and patients. As noted by the World Health Organization in regard to microneedle devices: a simple, reliable, and reproducible technology is required to make this method viable.[4] While many devices are in development, the cost of large-scale manufacturing and commercialization of these devices may become the limiting factor in their routine inclusion in the healthcare setting.

The two types of existing microneedles, solid and hollow, are discussed in the following sections. Solid microneedles are faced with the challenge of requiring reformulation of many drugs and vaccines. On the other hand, hollow microneedles are more amenable to use with liquid formulations and thus, in many cases, require no reformulation.

SOLID MICRONEEDLES

Solid microneedles were among the first to be developed. They are solid structures that puncture the skin while the drug is applied to the site of the puncture as a topical cream. This delivery method is simple and does not require significant training, thus simplifying the process for patients, but placing the burden of manufacturing and reformulation on pharmaceutical companies, as most injectable drugs would have to be recreated (and possibly re-approved by health agencies) as a cream or other topical solution. There are also drawbacks in delivering large doses of drugs to patients and sufficiently controlling the amount of the drug that is absorbed. Given these issues, this would lead to high and unnecessary costs for drugs already on the market, but may prove useful for new candidate drugs designed for this system.

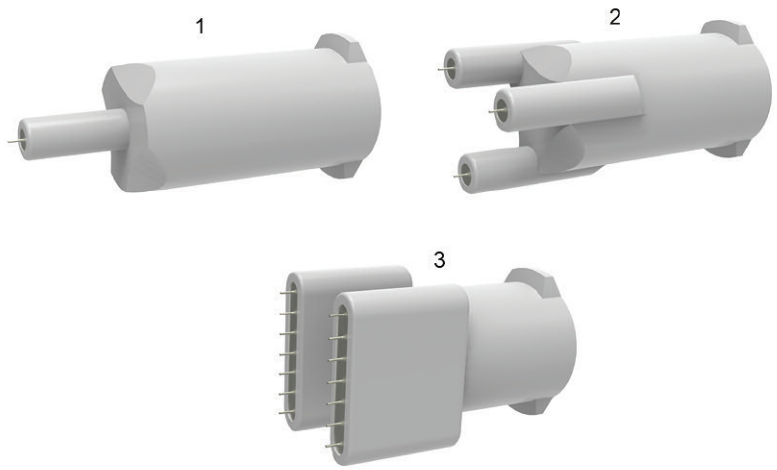
Coated and dissolvable microneedles are among the newest types of solid microneedles. They deliver the drug directly into the targeted area of the skin as a dissolvable polymer matrix microneedle releases the drug it carries. Although these microneedles would allow for the delivery for a more precise dose of drug compared to that of the topical cream, coated and dissolvable microneedles still face important limitations. The amount of drug that can be contained in the dissolvable matrix of a microneedle device that is the size of a household adhesive bandage may be too low to treat a given condition or have the desired effect, and a patch with a fixed size means that the dosage is also fixed and cannot be customized by the administrator in the way that a conventional syringe can. While there may be utility in these systems, solid microneedles are not versatile enough for widespread use over many different drug classes.

HOLLOW MICRONEEDLES

Hollow microneedles function in much the same way as traditional hypodermic needles: through the distribution of an injectable drug through the needle and into the targeted tissue; however, in the case of microneedles, the drug is injected into the dermis rather than subcutaneous tissue or muscle. Hollow microneedles mitigate the need for drug reformulation, which means they can readily be used with most existing drugs and vaccines approved for the intradermal route of administration. These approved drugs will see a rapid path to commercial adoption of hollow microneedle-based injection systems. Drugs that are suitable, but not yet approved, for intradermal delivery, such as insulin, will require a combination product clinical trial before completely adopting hollow microneedle-based injection systems.

After work in the early 1990s on individual microneedles and individual rows of microneedles, the first two-dimensional hollow microneedle array was made from metal using a costly, non-reusable silicon mold. Most early microneedle devices were manufactured in silicon through technologies such as microelectromechanical systems (MEMS) manufacturing methods, including deep reactive ion etching (DRIE) and lithography. The goal was to create high aspect ratio, hollow core microneedles structures. The challenge in this manufacturing system lies primarily in the high cost of infrastructure and maintenance of the silicon manufacturing tools. Many of the microneedles that are currently being commercialized come from this costly manufacturing process, leading to difficulty in scaling and adoption. However, these structures are valuable tools in demonstrating the potential of microneedle technol-

FIGURE 1



Microneedle configurations are customizable on an application-by-application basis, including: (1) single-projection devices for small dose administration; (2) multiple projections reduce pain while increasing volume; (3) large custom array designed for application-specific administration.

ogy and are largely still in use for research studies.

MICRODERMICS MICRONEEDLE TECHNOLOGY

Microdermics, a medical device company, understands the pharmaceutical potential of intradermal drug delivery. The Microdermics team has focused on the development of a microneedle platform that can address the limitations that have hindered other devices, and is committed to establishing a viable, useful microneedle solution that can be adopted by pharmaceutical companies and for general use.

Those working with microneedle technologies must balance the relative complexity of design and manufacturing with how it affects the complexity of adoption and use for biopharmaceutical companies. Where previous microneedle manufacturing solutions have opted for simpler processes and designs – leaving the complexity to the pharmaceutical companies or other contract manufacturers in drug reformulation – the team at Microdermics has chosen to take on most of the complexity in manufacturing through its engineering, design, and manufacturing process. This reduces the need for reformulation and thus shortens the approval process timelines at a reduced cost. Inverting complexity by focusing on the manufacturing process rather than the pharmaceutical process saves the biopharmaceutical company time and money by providing optimally dosed, effective products to market more efficiently, as well as opening up the possibility for more high-cost, highly specialized biologics.

Microdermics has also developed multiple microneedle arrays for specific drugs and targeted areas of the body to increase efficacy for the delivery of certain drugs. The second array shown in Figure 1, for example, is designed to maintain the tension on the surface of the skin on an area such as the face to allow the microneedles to penetrate the surface into the dermis more effectively. Due to the microneedles' design, injections such as vaccines can be administered in lower doses because the target layer of skin contains more immune cells than subcutaneous tissue.

As importantly, Microdermics utilizes a mold for microneedle fabrication on metallic sheets from which customizable arrays may be cut before integration into a device. These micromolds are also reusable, speeding up production time along with transferability and scalability. This means that mass production and commercialization of microneedles is now a possibility.

MICRODERMICS & VETTER PHARMA

Microdermics microneedles will allow pharma companies to unlock the potential of the skin for their current and planned drug products. These microneedles could provide lifecycle extensions of existing drugs, innovative applications that are only possible with access to delivery through the skin, or the accommodation of specific patient needs.

Unlike other technologies in this field such as jet injectors, transdermal patches, or other hollow microneedles, the Microdermics platform can adapt quickly and provide a solution that meets both the technical and economic needs of their pharma partners.

In 2017, Vetter Pharma, a leader and innovative provider of aseptic prefilled drug delivery systems announced a strategic cooperation agreement with Microdermics. The companies have entered this agreement to overcome the roadblocks to commercialization, particularly in scalable aseptic manufacturing at the later phases of development. Vetter is one of the leading contract development and manufacturing organizations, providing a combination of device development and associated drug product manufacturing

and packaging services to pharmaceutical companies. Together, Microdermics and Vetter can provide intradermal solutions that are more commercially viable than other, similar technologies such as other hollow microneedles, jet injectors, or transdermal patches.

Dr. Claus Feussner, Vetter's Senior Vice President Development Service stated at the time of the agreement that Vetter was "very happy to enter into this agreement with Microdermics, and we are excited by the initial experience of cooperation and entrepreneurial spirit we have established with key individuals at this company. We believe that microneedles are a particularly innovative technology and may prove to be a promising future alternative for selected areas of drug delivery."

Microdermics' hollow metallic microneedles can be adapted to deliver any number of specialized and expensive biologics and other drugs, particularly those with uncommon viscosities and doses. Microneedle devices can be manufactured to the specifications and requirements for high-cost biologics.

MICRODERMICS MOVING FORWARD

Microdermics devices have been and continue to be used for the intradermal delivery of small molecules as well as peptides and proteins of differing sizes. To date, the data collected supports the development of the Microdermics microneedle device, showing improved pharmacokinetic profiles to conventional injection methods. Microdermics has planned additional research programs focusing on the potential use of the device to deliver vaccines. These studies will investigate the use of microneedles in vaccines already approved for intradermal delivery as well as comparisons between intradermal delivery and other routes of administration. It has long been known that intradermal delivery offers advantages over other routes of administration, but the development has been largely hindered by the difficulties associated with these injections. Hopefully, the simple and scalable Microdermics microneedle system will allow for the widespread use and adoption of intradermal delivery. ◆

REFERENCES

1. Van Damme P, Oosterhuis-Kafeja F, Van der Wielen M, Almagor Y, Sharon O, Levin Y. Vaccine, 2009;27:454-459.
2. Singh R, Singh S, Lillard JW, Jr. J Pharmaceut Sci. 2008;97:2497-2523.
3. Weniger B, Papania M, eds. In: Vaccines 5th edition, Elsevier, Philadelphia, PA. 2008, chapter, 61:1357-1392.
4. Hickling JK, Jones KR, Friede M, Zehrung D, Chen D, Kristensen D. Bulletin of the World Health Organization, 2011;89:221-226.

BIOGRAPHIES

Dr. Boris Stoeber is a Co-founder and Chief Technology Officer for Microdermics. He has been researching microelectromechanical systems (MEMS) and microfluids for 20 years. He earned degrees in general, electrical, and mechanical engineering and was a Post-Doctoral Fellow of chemical engineering with the University of California. He is currently a professor at the University of British Columbia (UBC) in the departments of Mechanical Engineering and Electrical and Computer Engineering. He holds the Canada Research Chair for Microfluidics and Sensing Technology and holds three US patents with six international patents pending for MEMS and measurement technology.

Dr. Sahan Ranamukha is a Co-founder and Vice President of Research and Development for Microdermics. He has been involved in development and testing microneedle-based drug delivery technologies for more than 5 years. He earned his PhD in Biomedical Engineering at UBC under Dr. Stoeber, and was a recipient of the Vanier Canada Graduate Scholarship. His research interests are in drug delivery, medical device development, and therapeutic drug monitoring.

Rory St. Clair is the Director of Technical Operations and oversees Microdermics' daily operations. He brings skills in project management, cross-functional collaboration, financial planning, and operations management. Previously, he has worked with various start-up companies – life sciences and otherwise – to build consensus, manage growth, improve accountability, and drive efficiency. He has a bachelor's in economics and biology, with a minor in mathematics.

SCALE-UP & MANUFACTURING

Smart Formulation, Processing & Engineering Solutions to Solve Drug Product Scale-Up & Manufacturing Challenges With Minimum to No Regulatory Impact

By: Anil Kane, PhD, MBA

INTRODUCTION

Given the increasing pressure to speed up drug development and make the process more cost-effective, pharmaceutical companies want to ensure that their most promising drug candidates hit the market. However, while speed to the clinic – and then to market – is often thought to be key to success, it is equally important that formulation, process development, scalability, and stability challenges are addressed by systematic, smart scientific solutions to de-risk the drug development process so that costly late-stage failures can be avoided.

As drug products move from preclinical through Phase IV development stages, clinical material demand grows tremendously. Production scale-up is rarely straightforward, with time-consuming, expensive, and unexpected challenges often entering the picture. In early stages of drug development, the drug substance (DS) is developed using a certain synthetic route and may not be a final process. The physicochemical properties of the DS may change with improved synthetic routs or a better crystallization process, resulting in an improved impurity profile. However, this may drastically change the physicochemical properties and the behavior of the active pharmaceutical ingredient (API). The challenge is greater with products with a higher dose and higher drug loading in formulations.

Formulation and processing scientists face many scalability and processing challenges. It is important to address these challenges with smart solutions with minimal or no impact to in vitro release profiles, in vivo performance, as well the efficacy of the drug. Any major change to drug product formulation or process may require rework – repeat bio or clinical study and data generation to support the robustness of the process and stability in the filings/submissions.

CHALLENGES & POTENTIAL SOLUTIONS EXPERIENCED ON SCALE-UP

Early clinical-stage capsules or tablets are developed on a small scale sufficient for a proof-of-concept and for a small clinical study. Often due to the small batch size requirement, the drug products are manufactured on manual, semi-automated equipment. Alternatively, they are manufactured on slow-speed equipment to conserve the material and to have better control over the critical process parameters. Upon successful Phase I clinical read out, the drug products need to be scaled up or reformulated into a scalable dosage form. Often, capsules made using a simple blend formulation need to be modified, and scalability is a critical consideration. The challenges experienced and smart solutions to overcome them are described further.

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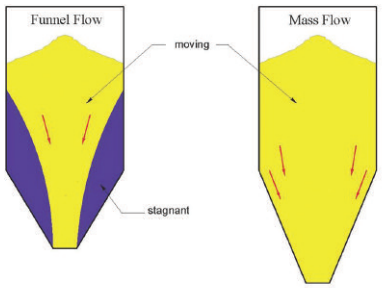
FIGURE 1



Flowability

To improve the flow-ability of powders and formulating a scalable tablet or capsule, many techniques can be used. The most commonly used solution is to formulate the API into granulations using the appropriate granulation technique – dry granulation, high shear wet granulation, or fluid bed granulation, based on the stability of the API and its forced degradation profile. Additionally, suitable binders will help in creating a flowable granule structure with improved flow properties. Commonly used binders are cellulosic derivatives (HPC, HPMC, PVP, Pregel Starch, etc). The optimal granule properties can be obtained by choosing the right viscosity of the binders. With high drug loading and poor flow characteristics of the API, the flow of the blends can be improved using a different grade of fillers such as microcrystalline cellulose (eg, Avicel PH 102, 302, 200 etc) or varying lactose grades or mannitol grades to a varying particle size that can improve flow properties. A formulator can also use co-processed excipients such as microcrystalline cellulose with silicon dioxide (eg, various grades of Prosolve, etc).

Drug substances that have a tendency to pick up moisture can impact the granule flow properties. Small amounts of adsorbents, such as colloidal silicon dioxide or other silicates, can help in adsorbing the excess moisture and also act as lubricant, thereby improving the flow of granules. Use of lubricants and glidants, such as magnesium, calcium stearate, or sodium stearyl fumarate of different particle size and surface area, can help improve flowability of granulation.

As mentioned, modifying the process from a direct blend to granulation by one of the aforementioned techniques can transform the poorly flowing blend into a flowable material. Based on the type of binder used and the type of granulation method used, one can obtain either a dense or a light granulation. Typically a high shear granulation and dry granulation (or roller compaction) results in a dense granulation, whereas a fluid bed granulation results in a less dense granulation. The flow properties by any of these granulations will certainly be better than pure API or its blends.

The ideal flow of materials in pharmaceutical processing is a mass flow that results in a uniform flow through a hopper into blending, encapsulation, or tableting. A mass flow ensures content uniformity of the API and the functional excipients in the blend irrespective of the drug loading in the granulation. Figure 1 depicts the types of flow through the hopper.

Funnel flow is a non-uniform flow and is often referred to as a phenomenon called "rat holing," whereby material adheres to the walls of the hopper, resulting in challenges in content uniformity of the API in the blend due to erratic and inconsistent flow pattern.

Various engineering solutions have been adopted in the industry to overcome the challenges of flowability of granulations. Examples include changing the geometry of mixers, blenders, and hoppers. One such example is shown in Figure 2.

FIGURE 2

A double transition hopper design was adopted to improve the flow properties of the granulation. This design provided flow along the walls (mass flow) based on wall friction results and minimizing arching potential, based on cohesive strength results. This hopper design was "more robust," with respect to providing mass flow, than a simple conical hopper.

Other examples of improving flow of materials through the hopper are using vibratory mechanisms to ensure a mass flow or having a paddle stirrer in the hopper to avoid the "bridging" and adherence of the granulations to the side of the walls.

The uniform flow of granulation on the turret of the tablet press and a uniform feeding of the granulation into the die cavities can be accomplished by forced feeders. The type of paddles and its design will impact the flow of granules in the die cavities of a rotary press. It is more critical in case of high-speed tableting, where the rate of feeding without the potential of segregation is important for uniform tablet weight. The right geometry of the forced feeders on the tablet press has shown to impact the feeding as well. In one of the case studies during tableting of a bilayer tablet on a Korsch XM12, the feeding of

FIGURE 3

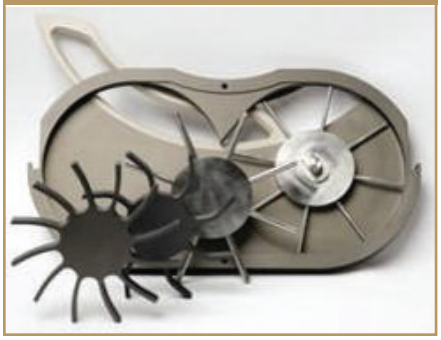
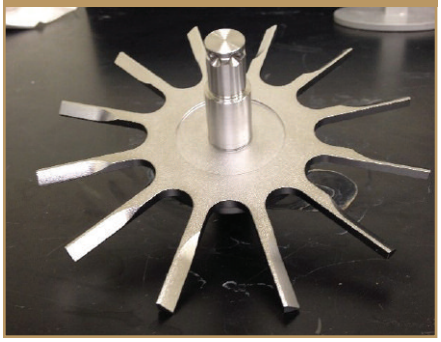


FIGURE 4



the granulation into the die cavity for the first layer was satisfactory, but the granulation feeding for the second layer was not satisfactory, resulting in an underweight and inconsistent layer 2 of the bilayer tablet. This was observed on a scale-up study using a larger batch size at a pilot scale during Phase IIb/Phase III, hence changes in the formulation composition or major process change to densify granulation was not an option. Trials were conducted through switching the granulations for the layer 1 and layer 2, but the results were still not satisfactory for layer 2, as the feeding continued to be inconsistent. Changing the geometry and angle of the impellers of the forced feeders finally resulted in a consistent and uniform granulation feeding into the die cavities for both layers and the bilayer tablet could be compressed at a high speed. Figure 3 shows the initial impeller, and Figure 4 shows the changed impeller.

Cohesivity & Static Charges

A large number of new small molecular entities exhibit high hydrophobicity and cohesivity, or sticking tendency, to the contact surfaces of the processing equipment such as blenders, granulators, and tablet presses. Active substances are often micronized to increase the surface area of the drug substance with an aim to improve the solubilization rate and extent. A micronized API often exhibits static charges and adheres to the walls of the containers, plastic bags used to transfer, as well as processing equipment. Cohesion or adhesion to surface parts can result in inconsistent funnel flow, rat holing, and content uniformity issues.

In addition to flow aids such as stearates, colloidal silicon dioxides and other lubricants help to reduce the static charge issue, sticking/adherence of materials need further investigation to adopt appropriate solutions. Sticking tendency or adhesion of powder blends or granulation can be a result of high residual moisture content in powder blends/granules or a low melting point of one or more ingredients in the formula. Low melting point APIs, waxes used in controlled release matrices or permeability enhancers such as Gelucires (Gelucire 44/14, 48/16 or 50/13) exhibit softening tendency in pharmaceutical processes where shear or friction is involved. Typically, the adherence of materials is observed during milling (adherence to the screen), tablet compression (sticking to the die walls, in the die cavity, to the turret table or to the tooling) or encapsulation (sticking to the tamping pins). Using different grades of stearates or silicon dioxide with different surface areas can have a remarkable influence in lubrication and reducing the problem of sticking.

Tableting processes that are susceptible to film formation and sticking are problematic, inefficient, and not cost-effective. In many cases, the compression process must be terminated early or processing times increased (due to the requirement of frequent cleaning and reinstalling to restart the compression process). This may lead to physical properties of the tablet, such as tablet thickness and embossing quality, being compromised. Lower tablet yields and long equipment downtimes can substantially increase manufacturing costs and reduce product profit margins.

Modification of a tableting process can sometimes reduce or eliminate film formation or sticking during compression without making any drug formulation changes. Modifications include changes to pre-compression force, compression force and tableting turret dwell time/speed. These modifications may be helpful in delaying the sticking behavior. Use of antistatic mats or grounding of equipment have shown to reduce the challenges of static charges.

An alternative solution could include using coatings on the tablet tooling or tamping pins of an encapsulator. The commonly used surface materials used in coating are described further.

Coated tooling have been commonly used to avoid sticking and also prolong the life of the tooling. Another potential solution that can be attempted is the use of a different grade of steel for manufacturing the tablet tooling.

In one case study, during compression of a granulated blend on a high-speed tablet press, we observed adherence of the material to the tooling as well as damage to the tooling after inspection. The tooling showed scratches as shown in Figure 5. Varying pre-compression, main compression forces, turret dwell time and press

speed failed to eliminate or reduce film formation, sticking, and damage to the tooling tip. Press turret, fill cams, guiding cams, lower and upper punch bore were re-inspected for any mis-alignment or traction damage.

Coatings on Tablet Tooling

Galvanic Chrome Coating - most popular way of surface protection that has been proven in many standard applications

PVD Coating - better stability, contour prevention, and wear protection

CrN (Chromium Nitride) Coating - Surface properties are much better than galvanic chrome plating, surface hardness is 3 to 4 times higher, low sticking susceptibility comparable with galvanic coating, and higher wear protection, higher quality/price ratio

TiN (Titanum Nitride) or TiAIN (Aluminum – Titanium Nitride) Coating - surface hardness is as much as four times higher than galvanic coating, higher wear protection than CrN coating, and very smooth layer with low roughness

TABLE 1

Type	Grade	Description	Application
Standard	S1, S5, S7	manganese, silicon, chromium, tungsten, and molybdenum in various combinations	General-purpose shock steels
Standard	408		Preferred general-purpose steel Improved flexibility and more elasticity than "S" grade.
Standard	A2, D3, A1	high-carbon, high-chrome grades of steel	General-purpose, wear resistant steels
Premium	A2, D2	punches	High-carbon, high chrome steels Great wear resistance with common granulations.
Stainless Steel	440C	This grade has a low toughness rating and the wear resistance falls between the S and D series of steels	Corrosion resistant. Great for product release

DLC (Diamond Like Carbon) Coating - DLC provides some of the properties of diamonds to metal surfaces

After evaluating all variables, new tooling was designed with die hardness higher than the upper and lower punch. Increases in the die hardness also increased the tensile strength of die material and improved the compression process without interruption. Tooling made with S7 grade of steel finally solved the problem.

Various engineering solutions have been adopted to overcome pharmaceutical manufacturing challenges in blending, high shear wet granulation, roller compaction, compression, coating, encapsulation, extrusion spheronization, and many other unit processes. These engineering solutions include the following:

Blending
- Geometry of blenders
- Intensifier bars
- Angle of baffles

High Shear Granulation
- Position of blades
- Angles of blades
- Roller Compaction
- Types of Knurling on rollers

Fluid Bed Driers
- Shape of bowl
- Angle of bowl
- Air flow pattern
- Screen design

Encapsulators
- Coated tamping pins
- Coater
- Baffle angles, etc.

CONCLUSIONS

Often a formulator, process scientist, or engineer faces scale-up, manufacturing, and process challenges due to the nature of API, its formulation, or selected process. In early phases of development, there are options to modify the qualitative formulation to overcome the challenges of flowability, cohesion, and others by adding newer functional excipients. Beyond a certain critical stage of development and clinical trials, it is often impossible to make major changes in formulation or process, as these changes may warrant repeating clinical studies, stability studies, and the need to justify the impact of these changes to the quality and safety of the drug product to the regulators. Many smart formulation process or engineering solutions can

FIGURE 5

be applied to overcome challenges of the material properties to successfully manufacture quality products at the development and commercial scale with minimum to no clinical or regulatory impact. ◆

To view this issue and all backissues online, please visit www.drug-dev.com.

BIOGRAPHY

Dr. Anil Kane is the Executive Director, Global Head of Technical & Scientific Affairs, Pharma Services, Patheon, part of Thermo Fisher Scientific. He has more than 25 years of experience in the science and business of taking molecules through the entire drug development process. His extensive knowledge spans early stage development to scale-up and commercial manufacturing, and includes technical transfers between global sites and drug life cycle management. Dr. Kane earned his Bachelors, Masters, and PhD from the University of Bombay, India, and served as a post-doctoral fellow at the School of Pharmacy, University of Cincinnati, OH. He has also earned an executive MBA from Richard Ivey School of Business, University of Western Ontario, Canada. He is a member of various international pharmaceutical professional organizations, and is often asked to speak about scientific topics on formulation, technology, other technical aspects, QbD, etc at major industry events. He has also published many articles in International journals and delivered many talks at meetings and conferences cross the globe.

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Elite equips you with the layered analytics and actionable insights needed to make strategic business decisions.

BUSINESS APPLICATIONS

- Research new therapeutic areas, and identify market gaps
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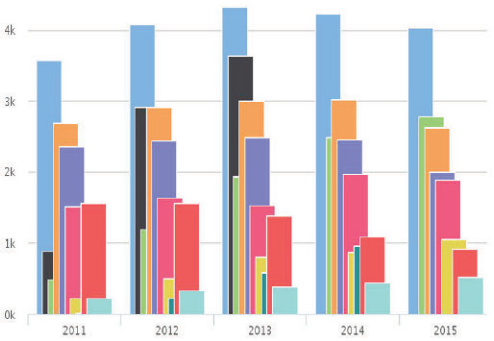
- Review comparable deals, acquisitions and financings
- Find and compare contract manufacturers and other outsourced services
- Assess competitive landscapes around an indication and research competitor pipelines
- Track generics and biosimilars, and identify Rx to OTC switch opportunities



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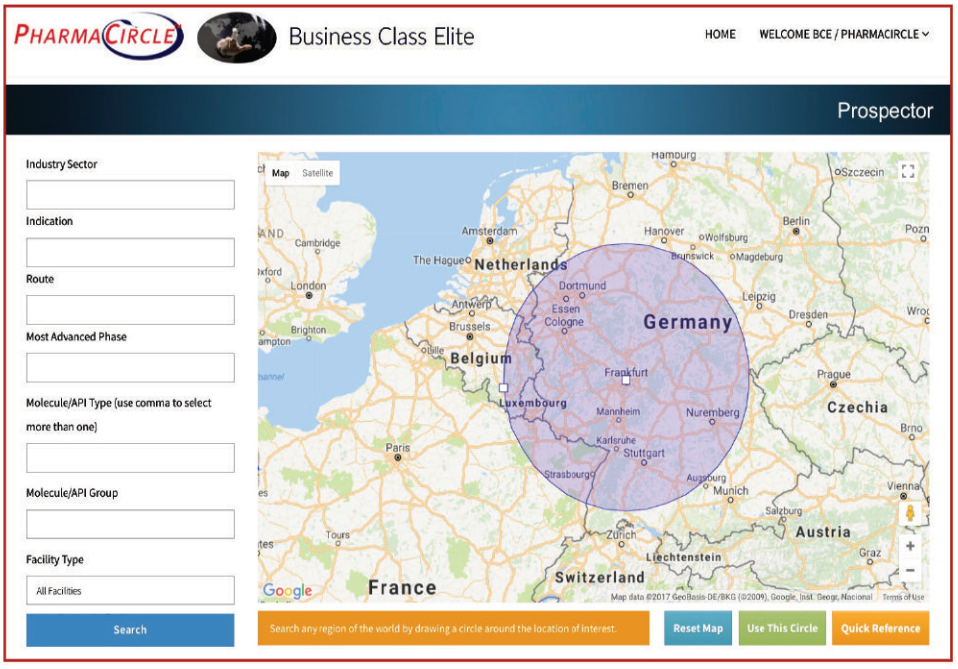
Compare current and previous versions of the label for the same product with changes highlighted, and view labels for different products side-by-side. Export comparisons to Excel and PDF.

Reconnaissance
Quick view and instant analytics on the competitive landscape around an indication, competitive intensity within an indication, and competitor pipelines across indications. Chart drugs and biologics by owner companies, highest development status within the indication, mechanism type, NME/ Generic/OTC, route, and dosage form. Programs/products are linked to development summaries.

Merge Simulator
Create a virtual company incorporating global assets of two business entities. Overlay and analyze pipeline/product, technology, operations, and financial details to assist with initial due diligence on prospective acquisitions and mergers.



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NANOMEDICINES

V-Smart® Nanomedicines: Non-Invasive Targeted Brain Therapeutics for CNS Diseases

By: Susan Rosenbaum, JD, and Irwin Hollander, PhD

INTRODUCTION

Most brain diseases, especially neuro-degenerative brain diseases, such as Alzheimer's disease, Parkinson's disease, and ALS (Lou Gehrig's disease), have no treatments or, at best, treatment options that are palliative, ie, they control symptoms for a limited time, but do not affect the underlying disease. Research in the past decade or two has brought far more understanding of the causes or driving forces behind these diseases. As a result, many new therapeutics have been proposed that have great promise in affecting actual disease processes with the possibility of stopping, or even reversing, the diseases themselves. However, most of these therapeutics cannot even be tested safely in humans because they cannot pass through the blood-brain barrier (BBB) and reach the areas of the brain that require the treatment.

What is the BBB? The blood vessels in the brain act differently than those in other parts of the body to protect the brain from substances that happen to be in the blood. The endothelial cells that line the walls of the brain blood vessels (which cells are essentially the walls of the blood vessels) form tight junctions with each other and prevent the uncontrolled transport of water-soluble molecules between the vasculature (capillaries, arteries in the brain) and the brain parenchyma.[1,2] Thus, nothing passes from the blood in-between those cells and into the brain; anything that can go into the brain, has to go through those cells. In the rest of the body, most "delivery" from blood to tissue is through the loose junctions between the endothelial cells of the blood vessel walls.

Due to the aforementioned nature of the BBB, most potential therapeutics for brain diseases cannot cross the BBB and enter the brain or central nervous system (CNS). Moreover, many potential therapeutics (eg, neurotrophic factors), even if injected directly into the brain (thus, bypassing the BBB), bind to the extracellular matrix in the brain, and cannot spread to all brain areas that require treatment. Even small molecules (eg, those designed to inhibit a critical brain enzyme to treat a brain disease), cannot cross the BBB, unless they have certain chemical properties. In general, small molecules need to at least have a certain amount of lipophilicity (ie, not be very water soluble), although they might have other limitations that restrict them from crossing the BBB.

Other small molecules, as well as proteins and peptides, cannot cross the BBB without there being an inherent receptor-carrier for the respective molecule in the endothelial cells of the BBB. In such a way, the molecule (eg, protein) binds to its receptor-carrier which, then, carries it through the endothelial cells. An example is the transferrin carrier that "ferries" transferrin into the brain from the blood and, thus, supplies the brain with needed iron.[3]

Potential therapeutics for brain diseases not only have to survive the bloodstream, cross the BBB, and reach all areas of the brain or CNS, they, frequently, also need to target the specific disease sites, neurons, or brain cells in the brain and, thus, reduce possible adverse effects in other areas of the brain. Lauren Sciences LLC has the unique and novel solution to this greatest challenge in medicine for brain disease treatment, considered the "Holy Grail of Neuroscience," with its breakthrough innovation - V-Smart® Nanomedicines: Non-Invasive Targeted Brain Therapeutics.

V-SMART PLATFORM NANOTECHNOLOGY

Lauren Sciences' V-Smart platform uniquely solves this greatest challenge in medicine for treatment of brain diseases - that most therapeutic agents, including biologicals, with potential to treat or cure brain diseases, do not cross the BBB - with its breakthrough innovation - V-Smart Nanomedicines: Non-Invasive Tar-

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geted Brain Therapeutics. The New York biotechnology company, with its labs in Israel, licensed the groundbreaking V-Smart platform nanotechnology from Ben-Gurion University, Israel, where it was invented by Professors Sarina Grinberg, Charles Linder, and Eliahu Heldman, then launched development of the innovative V-Smart targeted drug delivery platform and, now, has in development a pipeline of transformative V-Smart targeted therapeutics - V-Smart Nanomedicines.

Lauren Sciences LLC is the revolutionary neuro biotech that has 10 foundation grant awards, a pipeline of 6 products, 18 published peer-reviewed papers,[4,5] 23 conference presentations, 6 presented posters, and 10 patent families on V-Smart technology. V-Smart Nanomedicines are game changers that are designed, engineered, and customized to deliver non-brain penetrant therapeutic agents across the BBB, target and selectively release at specific brain sites or cells and be administered systemically. Lauren Sciences' innovative pipeline of transformative drugs in successful development for CNS are designed to treat neurodegenerative brain diseases, including rare/orphan indications, such as Parkinson's disease, ALS (Lou Gehrig's disease), Alzheimer's disease, Neuro-HIV, and Glioblastoma Multiforme (GBM).

V-Smart Nanomedicines have been proven to encapsulate therapeutic agents (especially, hydrophilic agents that do not cross the BBB on their own), cross the BBB into the brain ("macro" target), target and deliver to specific brain sites ("micro" target), selectively release its therapeutic agent at target sites, be administered systemically, as well as be safe and effective (in animal model). They solve the problem that most therapeutic agents, including biologicals, with potential to treat or cure brain diseases, do not cross the BBB, and offer unique and total BBB competitive advantages over other brain delivery technologies.

V-SMART DRUG DELIVERY PLATFORM

The innovative V-Smart targeted drug delivery platform is universal, versatile, flexible, and has none of the difficulties or limitations associated with other brain drug delivery systems (DDSs). V-Smart is the only drug delivery platform that has all of the following competitive advantages:

High Encapsulation Capacity

V-Smart can encapsulate a wide variety of therapeutic substances (eg, small molecules, biologics: peptides, proteins [neurotrophic factors, enzymes, antibodies, etc], nucleic acids [siRNA, plasmids, etc]; these types of substances are generally non-brain-penetrant). Other DDSs encapsulate only lipophilic molecules, or only tiny amounts of hydrophilic molecules, and cannot encapsulate large proteins with maintenance of activity.

Requires No Modification of Therapeutic Agent

Many other DDSs require that the therapeutic be modified (eg, attached to some other molecule such as a carrier or stabilizer), which may cause the therapeutic to lose activity and/or become immunogenic. V-Smart can encapsulate therapeutics under a variety of conditions, and is able to maintain activity and stability of therapeutic without modification of the therapeutic. The therapeutic, thus, does not become immunogenic, and V-Smart itself is not immunogenic.

Stable in Storage & Blood Circulation

V-Smart does not leak contents, is stable in storage (days or months) and has a half-life in circulation much longer than the time needed to reach the brain. Because the therapeutic is encapsulated within the V-Smart, the therapeutic is protected from degradation (eg, by proteases in the blood), or interaction with non-target tissues (thus, reducing toxicity) in the circulation and non-target organs.

Efficient Controlled Release Mechanism

V-Smart can be engineered to release the therapeutic rapidly, or more slowly, at target sites. Quick release may be preferred to produce high concentration of the therapeutic at the target site. Slower release may be preferred to produce longer therapeutic effects (ie, extended release can produce delayed action).

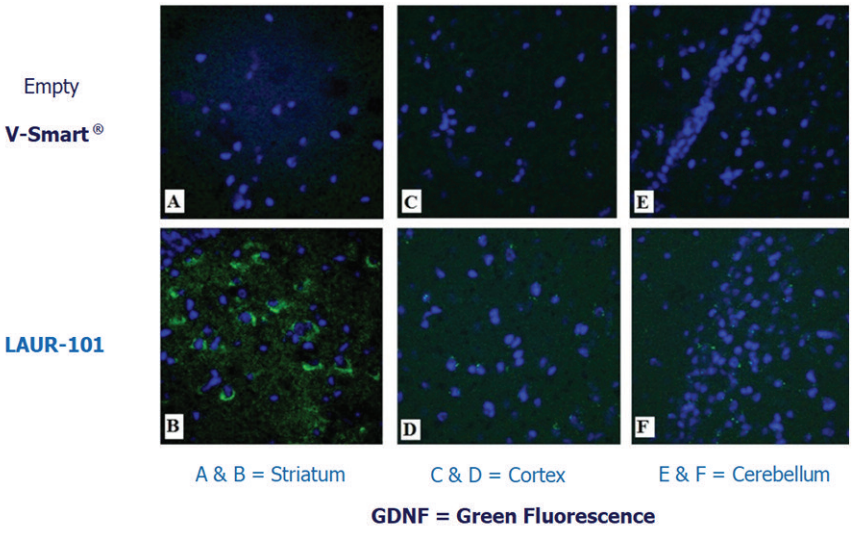
Can Be Designed for Selective Release

V-Smart can be engineered to release its encapsulated therapeutic only at target sites. For example, when the V-Smart is designed to be subject to hydrolysis by a specific enzyme at the target site, then, only when at the target site, will the V-Smart be hydrolyzed and release the encapsulated therapeutic agent.

Penetrates Intact Through Biological Barriers

V-Smart penetrates intact through biological barriers (eg, cell membranes, BBB, GI) without barrier disruption. Thus, V-Smart has been called, "a disruptive technology that does not disrupt the BBB." V-Smart passes through the BBB, and through cell membranes, without disruption of V-Smart, and without disruption of the BBB or cell membrane, followed by release of the therapeutic there.

FIGURE 1



After IV administration of LAUR-101 (V-Smart-GDNF for Parkinson's disease, targeted to dopaminergic neurons), GDNF accumulates preferentially in striatum (B), where there are high levels of dopaminergic neurons. (Supported with grants awarded by The Michael J. Fox Foundation for Parkinson's Research)

Can Be Designed for Specific Targeting Within the Brain and/or Elsewhere

V-Smart can be designed to target specific sites/cells within the brain ("micro" targeting), independent of its ability to cross the BBB ("macro" targeting).

Administration Options Are Both Oral & Parenteral

V-Smart has demonstrated successful encapsulation, delivery, and brain targeting, with model compounds and therapeutic agents, after both intravenous and oral administration.

Has Wide Therapeutic Window Potential

V-Smart itself is non-toxic at doses to be used for delivery of therapeutics. This advantage, combined with the V-Smart high-encapsulation capacity for therapeutics, selective release of the therapeutic in the brain (or other target site) and "micro" targeting ability, will limit concentration of the therapeutic at non-target sites, thus, limiting off-target toxicity.

V-SMART COMPARED TO OTHER BRAIN DRUG DELIVERY SYSTEMS

There are other drug delivery systems (DDSs), other than V-Smart, that contend to deliver non-brain penetrant therapeutic agents into the brain. Examples of these other DDSs are: carrier-conjugated-to-drug technologies, intracranial (IC) pumps/convection enhanced delivery (CED), intrathecal (IT) pumps, viral gene delivery, nasal inhalation, and others. Some of these have met with some modicum of success, in limited cases, but all suffer from a few or many difficulties/limitations (none of which V-Smart has), such as: (1) highly invasive, require brain surgery to place catheter in brain, (2) therapeutic will not diffuse throughout the brain, nor reach all areas that require treatment, (3) no selective release at target cells, (4) no potential for oral administration, or even intravenous administration, (5) cannot deliver/encapsulate large hydrophilic molecules, such as proteins or, possibly, even small hydrophilic molecules, in doses needed, (6) cannot protect therapeutic in the blood stream (circulation) from degradation, or from causing toxicity in other organs, (7) require modification of the therapeutic, thus, possibly, affecting activity and/or immunogenicity of the therapeutic, (8) no micro-targeting within the brain to areas or cells that require treatment, (9) high amounts of therapeutic need to be administered, with potential toxicity, in order to attain therapeutic amounts at target sites, (10) inability to control amount of therapeutic in the brain, (11) inconsistent dose delivery due to overwhelming of receptor systems or to changes to barrier, (12) intracellular delivery, if needed, may not be possible, (13) inflammation or other reactions, at site of repeated administration.

V-SMART NON-INVASIVE TARGETED NANOMEDICINES

V-Smart Nanomedicines consist of novel, unique, V-Smart nanovesicles. The V-Smart nanovesicle has high encapsulation capacity for hydrophilic agents (the V-Smart nanovesicle has a hydrophilic core that is large), high stability and ability for controlled release of the therapeutic agents (by utilizing V-Smart building blocks engineered to be hydrolyzed at the target site). V-Smart Nanomedicines are independently designed for a distinct medical indication, engineered for delivery to the brain, or other target site, specific targeting within the brain and selective release, customized for encapsulation of a chosen therapeutic agent and optimized for mode of systemic administration and other respective variables.

THE V-SMART NANOMEDICINES PIPELINE

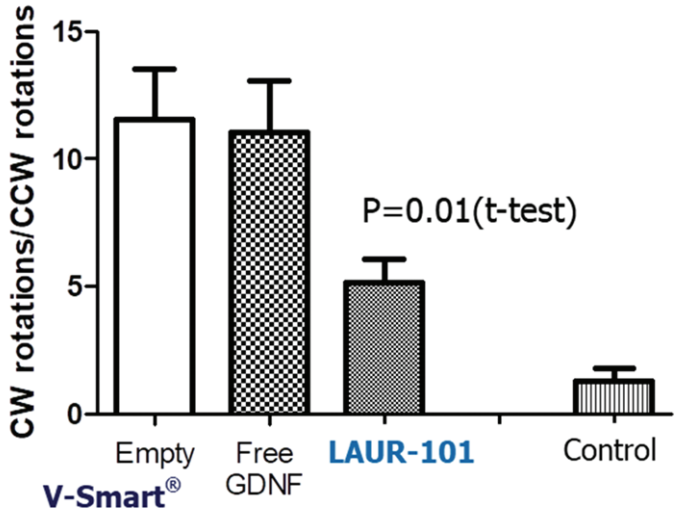
The V-Smart Nanomedicine pipeline is extensive and demonstrates the versatility of the V-Smart technology. The pipeline includes both micro-targeted V-Smart Nanomedicines (eg, LAUR-101 targeted to dopaminergic neurons) and macro-targeted V-Smart Nanomedicines (eg, LAUR-201 targeted to the entire brain). The active therapeutic agents (APIs) in V-Smart Nanomedicines include both small molecules and large proteins, all of which are non-brain penetrant.

LAUR-101: V-Smart-GDNF for Parkinson's Disease

Glial cell-derived growth factor (GDNF) has shown potential efficacy as a therapeutic treatment for Parkinson's disease, based on numerous animal and clinical studies. GDNF protects degenerating dopaminergic neurons (brain cells affected in Parkinson's disease) and induces regeneration of new neurons, in preclinical Parkinson's disease animal models. V-Smart solves the problem that GDNF is non-brain penetrant and, even after direct brain injection, has limited diffusion such that it cannot reach all the dopaminergic neurons to obtain therapeutic effect.

Lauren Sciences designed LAUR-101 for Parkinson's disease, engineered it to target, and selectively release at, dopamin ergic neurons (the brain cells affected in Parkinson's disease) in the striatum and substantia nigra (those parts of the brain rich in dopaminergic neurons), which was demonstrated *in vitro*. Lauren Sciences, then, customized LAUR-101 to encapsulate active GDNF at high efficiency, demonstrated its retention of GDNF activity and successful delivery of its GDNF to the targeted brain regions *in vivo* (mice), without toxicity, following intravenous administration (Figure 1).

FIGURE 2



After IV Administration of LAUR-101 (V-Smart-GDNF for Parkinson's disease, targeted to dopaminergic neurons), rotation behavior of mice (caused by unilateral striatal administration of 6-OHDA) improved significantly. (Supported with grants awarded by The Michael J. Fox Foundation for Parkinson's Research)

LAUR-101 demonstrated efficacy in a Parkinson's disease mouse model (6-OHDA/Hemi-Parkinsonian). LAUR-101 treatment (dosed every other day) reduced rotation behavior (Figure 2), protected TH positive cells and decreased reduction in dopamine levels. LAUR-101 is to be tested in a second mouse model of Parkinson's disease, to determine minimal effective dosage and safety, to be followed by preclinical IND enabling studies and, then, clinical trials in patients.

LAUR-301: V-Smart-GDNF for ALS

GDNF has also shown potential efficacy to treat ALS. GDNF has been shown to protect degenerating motoneurons (those brain and CNS cells affected in ALS), and induce regeneration of new neurons, in ALS animal studies and in patient clinical studies.

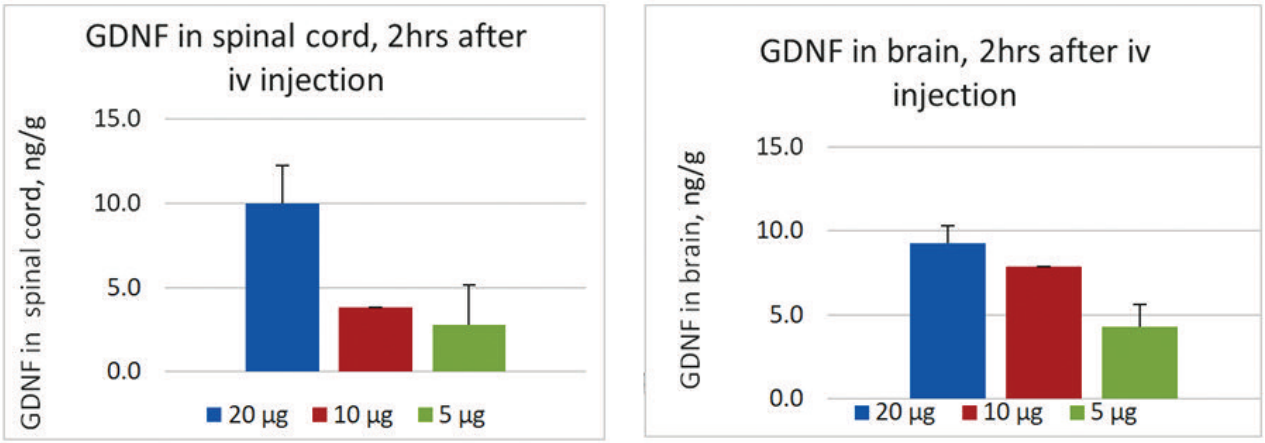
Lauren Sciences designed a V-Smart Nanomedicine for ALS: LAUR-301 (V-Smart-GDNF for ALS), engineered it to target ALS deteriorating CNS motor neurons, customized it to encapsulate active GDNF at high efficiency and selective release of GDNF in these CNS regions. Lauren Sciences has proven LAUR-301 encapsulation of GDNF, maintenance of GDNF activity, cell targeting and dose-dependent delivery and selective release in CNS (both brain and spinal cord) of normal mice,without toxicity, after intravenous administration (Figure 3).

LAUR-301 is to be tested for targeted delivery *in vivo* to ALS deteriorating motor neurons in brain and spinal cord of ALS (SOD) mice, following intravenous admin istration, and for therapeutic efficacy in an ALS mouse model (SOD) for: improvement in motor behavior, protection against motor neuron degeneration and increased lifespan, followed by pre-clinical IND enabling studies and clinical trials.

LAUR-201: V-Smart-Tenofovir for Neuro-HIV

Tenofovir, a hydrophilic small mole-

FIGURE 3



LAUR-301 (V-Smart-GDNF for ALS disease, targeted to deteriorating motor neurons) shows dose dependent GDNF concentrations in spinal cord (left) and in brain (right) after IV administration of 3 different doses of LAUR-301. Each bar represents mean ± STD of 3 wild-type mice. (Supported with grants awarded by The ALS Association)

cule, is one of the leading anti-retroviral drugs for AIDS; however, it does not cross the BBB. Failure to eradicate HIV effectively in the brain is thought to be responsible for development of neurological symptoms in AIDS patients (Neuro-HIV).

Lauren Sciences designed LAUR-201 for Neuro-HIV, engineered it for delivery to, and selective release in, the brain, and customized it for tenofovir encapsulation. Lauren Sciences maximized tenofovir encapsulated in LAUR-201 and demonstrated successful delivery of therapeutic concentrations of tenofovir into the brain *in vivo* (mice), after a single intravenous administration, without toxicity (Figure 4). LAUR-201 efficacy studies will be conducted in a Neuro-HIV mouse model for: viral growth inhibition, and alleviation of cognitive deterioration, in brain. These will be followed by IND enabling studies and clinical studies.

LAUR-401: V-Smart-Irinotecan for GBM

Irinotecan (CPT-11) is a small molecule that does not cross the BBB, but has shown potential as a therapeutic for Glioblastoma Multiforme (GBM). Studies have shown that CPT-11 is the most effective chemotherapeutic as a single agent on patient-derived GBM tumors grown in mice.[6] There is also evidence that it will synergize with temozolomide (TMZ), the standard of care (SOC) chemotherapeutic in GBM treatment.[7,8]

Lauren Sciences designed LAUR-401 for GBM, engineered it to target to, and to selectively release at, GBM brain tumor cells. Lauren Sciences customized LAUR-401 for encapsulation of CPT-11 and demonstrated its targeting to GBM cells and selective release, *in vitro*. This work has been supported by Voices Against Brain Cancer.

LAUR-401 has multiple types of selectivity for GBM tumors, resulting in high potency and low toxicity. The active metabolite of CPT-11 (SN-38) is only generated in the liver and in tumor cells. Because LAUR-401 does not release its payload (the CPT-11) in the liver, but primarily in the brain, little systemic toxicity is expected. Because LAUR-401 is targeted to GBM cells, there will be accumulation at GBM cells, in comparison to other areas of the brain or outside the brain (similarly to how LAUR-101 demonstrates accumulation at dopaminergic neurons). At these sites, LAUR-401 is designed to release the CPT-11 rapidly (compared to other areas of the brain), where the GBM cells can absorb the drug and then metabolize (thus, activating) it into SN-38. Because normal neurons cannot metabolize the CPT-11, there will be little SN-38 in other areas of the brain. In addition, LAUR-401 has potential synergy with TMZ, which may allow for an even lower dosage of CPT-11 to be effective.

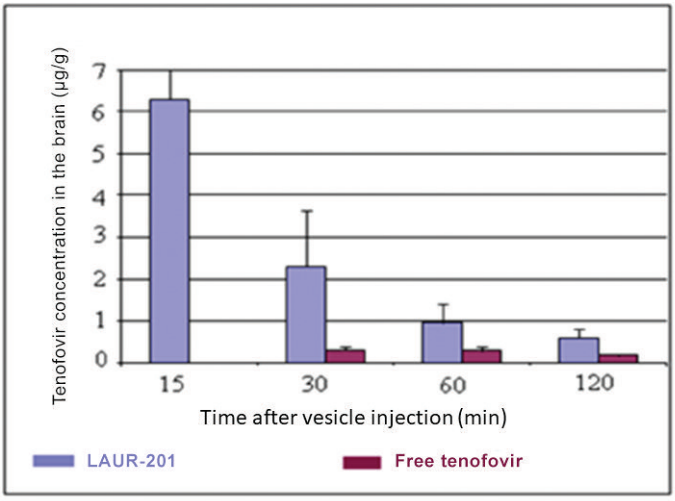
LAUR-401 is to be studied *in vivo* (mice), to determine that, following intravenous administration, therapeutic concentrations of CPT-11 are attained in the brain. LAUR-401 efficacy will be studied in these mice for: reduction of tumor burden (in patient-derived tumor xenografts (PTX) in subcutaneous and orthotopic models), increased survival as single agent and in combination with SOC. These studies will be followed with preclinical IND enabling studies and clinical trials.

LAUR-601: V-Smart-BDNF for Alzheimer's Disease

BDNF, a protein that does not penetrate the BBB, has shown efficacy for the treatment of Alzheimer's disease in Alzheimer's disease animal models and in clinic. Lauren Sciences designed LAUR-601 for Alzheimer's disease, engineered it to target to, and selectively release at, Alzheimer's disease deteriorating brain neurons, and demonstrated targeting and selective release, *in vitro*.

LAUR-601 is be customized to encapsulate and deliver this neurotrophin to brain regions affected in an Alzheimer's disease mouse model (*in vivo*), following intravenous administration. LAUR-601 efficacy is to be studied in an Alzheimer's disease mouse model for: improvement in cognitive function/behavior, neuroprotection, and neurogenesis.

FIGURE 4



LAUR-201 (V-Smart-Tenofovir for Neuro-HIV) penetrates brain and delivers therapeutic concentrations of tenofovir into brain: attains at 15 mins, 6 ug/gm (>20 uM) tenofovir levels in brain, >10X therapeutic level, and ~25% of blood concentration - active metabolites not measured. (Supported with grants awarded by The Campbell Foundation)

PARTNERSHIP OPPORTUNITIES

Lauren Sciences created its novel V-Smart platform nanotechnology, from which it designed its innovative V-Smart drug delivery platform, which it has validated by, and used in development of, its transformative V-Smart Nanomedicines pipeline. V-Smart Nanomedicines have been shown to encapsulate therapeutic agents (a variety of small molecules, peptides, and proteins), deliver them and other agents across the BBB safely with targeting within the brain and with therapeutic efficacy in animals.

Pharmaceutical companies continuously develop new drugs to address brain diseases that cannot reach the brain safely and can benefit from V-Smart, which can enable their therapeutics by development of a V-Smart Nanomedicine that can deliver the therapeutic into the brain safely and even target selective brain areas.

Lauren Sciences welcomes the opportunity to discuss partnership development of: (1) V-Smart Nanomedicines in its pipeline, (2) V-Smart Nanomedicines in its pipeline for use as a sub-platform for proprietary therapeutics to the same target (eg, LAUR-101 has been used as a sub-platform to develop LAUR-102 to deliver other therapeutic agents for Parkinson's disease to the dopaminergic neurons in the substantia nigra and striatum), and (3) new V-Smart Nanomedicines to be designed for additional indications, engineered to target other sites, with proprietary therapeutic agents, all as a means for therapeutics to reach their targets safely and effectively.

Additionally, V-Smart can extend exclusivity of proprietary products, particularly in connection with drugs that are approaching patent expiration. The V-Smart technology has extensive intellectual property coverage.

Lauren Sciences is a dynamic and sustainable drug development company with a differentiated and versatile superior platform technology, V-Smart. Lauren Sciences is poised for continued success with the valuable potential, and vast opportunities, it offers with V-Smart.

SUMMARY

Lauren Sciences' V-Smart technology is the breakthrough innovation that solves the greatest challenge in medicine for the treatment of brain diseases. Lauren Sciences unique and novel V-Smart Nanomedicines have been proven to encapsulate therapeutic agents, cross the BBB ("macro" target the brain), target and deliver to specific sites in the brain ("micro" target brain sites/neurons/cells), selectively release at target sites, be administered systemically, as well as be safe and effective (in animal model). V-Smart Nanomedicines, thus, solve the challenge that most therapeutic agents, including biologics, with potential to treat or cure brain diseases, do not cross the BBB.

V-Smart Nanomedicines, developed with the universal, versatile, flexible V-Smart enabling technology, are independently designed for a distinct medical indication, engineered for specific targeting and selective release, customized for a chosen therapeutic agent, optimized for mode of systemic administration (intravenous or oral) and other respective variables.

V-Smart Nanomedicines will significantly improve the lives of patients who will benefit from therapeutic agents whose use is currently unavailable due to inability to cross the BBB, poor pharmacokinetics (PK), bioavailability or toxicity issues, required long-term and non-invasive treatment, or even where oral administration is preferable.◆

REFERENCES

1. Fenstermacher JD, Rappoport SI. (1984). The blood-brain barrier. In Handbook of Physiology: The Microcirculation (ed by E.M. Renkin and C.C. Michel.), pp. 969-1000. Washington D.C., American Physiological Society.
2. Risau W, Engelhardt B, Wekerle H. Immune function of the blood-brain barrier: incomplete presentation of protein (auto-)antigens by rat brain microvascular endothelium in vitro. J Cell Biol. 1990;110,1757-1766.
3. Roberts RL, Fine RE, Sandra A. Receptor-mediated endocytosis of transferrin at the blood-brain barrier. J Cell Sci. 1993;104, 521-532.
4. Dakwar G, Abu Hammad I, Popov M, Linder C, Grinberg S, Heldman E, Stepensky D. Delivery of proteins to the brain by bolaamphiphilic nano-sized vesicles. J. Controlled Release. 2012;10;160(2):315-321.
5. Popov M, Abu Hammad I, Bachar T, Grinberg S, Linder C, Stepensky D, Heldman E. Delivery of analgesic peptides to the brain by nano-sized bolaamphiphilic vesicles made of monolayer membranes. Eur J Pharm Biopharm. 2013;85(3 Pt A):381-389.
6. Hare CB, Elion GB, Colvin OM, Ali-Osman F, Griffith OW, Petros WP, et al. Characterization of the mechanisms of busulfan resistance in a human glioblastoma multiforme xenograft. Cancer Chemother Pharmacol. 1997;40(5):409-414.
7. Reardon DA, Friedman HS, Powell JB Jr, Gilbert M, Yung WK. (2003) Irinotecan: promising activity in the treatment of malignant glioma. Oncology (Williston Park). 2003;17(5 Suppl 5):9-14.
8. Patel VJ, Elion GB, Houghton PJ, Keir S, Pegg AE, Johnson SP, Dolan ME, Bigner DD, Friedman HS. Schedule-dependent activity of temozolomide plus CPT-11 against a human central nervous system tumor-derived xenograft. Clin Cancer Res. 2000;6(10):4154-4157.2014;5(21):10650-10664.

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BIOGRAPHIES

Susan Rosenbaum, JD, is a successful visionary entrepreneur and strategic executive for the past 10 years in the field of biotechnology. She is Founder, Chairman, and CEO of Lauren Sciences LLC, a New York biotechnology company committed to development of its novel V-Smart® platform to create a robust pipeline of transformative V-Smart Nanomedicines, consisting of central nervous system-active drugs that normally do not cross the blood brain barrier. Ms. Rosenbaum also is Founder, Chairman, and CEO of Maya Sciences LLC, a New York biotechnology company that developed the novel pan-Akt inhibitor, MY-101, which is now ready for clinical trials in cancer. She has 20 years of prior experience in corporate finance, law, development & management; was founder of (past): an investment banking firm (Rosenbaum & Co.), and law firm (Rosenbaum, P.C.); has served on private and public company boards of directors; and is a national/international author and speaker. Ms. Rosenbaum can be reached at info@laurensciences.com.

Dr. Irwin Hollander is Vice President of Research and Development of Lauren Sciences LLC. He earned his PhD in Biological Sciences at MIT, Cambridge, MA. He completed his post-doctoral work at Boston Univ. Medical School in atherosclerosis, plasminogen activator research at St. Elizabeth Hospital Boston, MA, and antibiotic research at MIT, where he was the first to purify penicillin cyclase. After research as a Research Biochemist at Monsanto/Searle in St. Louis, MO, in immunology and allergy, he was a Principal Research Scientist at Lederle/Wyeth/Pfizer in Pearl River, NY. While there, he helped develop Mylotarg, the first antibody-drug conjugate (ADC) approved by the FDA, in addition to irreversible kinase inhibitors and a PI3K inhibitor, PKI-587, now in clinical trials. Dr. Hollander is an author on 8 patents, and over 30 publications. He is also the Vice President of Research and Development of Maya Sciences LLC. He can be reached at info@laurensciences.com.

GAS-POWERED DELIVERY

Innovating Injectable Devices to Deliver Today's Pharmaceuticals

By: Steven Kaufman

THE RISE OF BIOLOGICS

The way medications are reaching patients is changing. The advent of biotherapeutics has been driven by their ability to address targets intractable to small molecules, inherently higher target specificity, reduced risk for off-target toxicity, and safety issues. In fact, biologics can be applicable in multiple therapeutic areas and address a variety of targets. With improvements in biomanufacturing processes making biologics more available as well as more cost effective and an increase in approvals, the industry is seeing a corresponding increase in their use for chronic conditions.

To reduce the burden on health services and patients, many medications for long-term illnesses are now administered by the patients themselves at home. The new generation of drug delivery devices designed for biologics therefore have to be easy to use, intuitive, and tailored to the needs of different patient groups.

Self-injection and autoinjection devices, including wearable systems, are an increasingly common way to deliver biologics, and this trend is expected to continue. Valued at $1.7 billion in 2016, the global market for autoinjectors is anticipated to grow at an average rate of 15.1% throughout the next decade, projected to be nearly $7 billion by the end of 2026.[1] The increase in chronic diseases and the use of biologics has also been cited as a factor in the increasing value of the global injectable drug delivery market as a whole, which is projected to reach $624.50 billion by 2021 from $362.38 billion in 2016.[2]

Manufacturers are now making it a priority to fully understand the real-world challenges of patients living with these complex chronic health conditions. In the past decade, autoinjectors have been of increasing interest to biopharma companies developing biologics. Initially used as a device for patients with severe allergies to self-administer epinephrine in emergencies and for military applications, the use of autoinjectors has now broadened into indications such as arthritis and asthma. As new therapeutic areas emerge that lend themselves to self-administration, there are an increasing number of new patient populations in need of autoinjectors.

To address this, pharmaceutical companies and device companies need to work together to develop devices that are adaptable to different patient groups. For example, some patients may not use a device every week, which may lead to challenges around the patient not remembering how to use the device. Autoinjector devices must therefore be intuitive to use and designed with the patient in mind.

WHY IS DELIVERY A CHALLENGE?

Although favored for their efficacy and selectivity, biologic formulations can be challenging to deliver.[3] Inhalation, intranasal, and transdermal routes have seen little success, and when taken orally, are inefficient at passing the GI tract.[4] Injection is therefore predominantly used as a delivery route; however, the properties of a biologic can cause difficulties for a standard delivery device.

Patient compliance for injectables is often poor, and this is exacerbated by high regularity of dosing. In an effort to improve compliance, the industry is attempting to reduce the frequency of administrations needed. These efforts include the production of more concentrated formulations, and the identification of more potent APIs, both of which enable more drug to be delivered in

the same volume.[3] With increased concentration comes an increase in viscosity, which creates a number of challenges in delivery via an autoinjector.

The stability of biotherapeutics often means that a comprehensive supply cold-chain is required to ensure that the dose maintains its efficacy. With self-administration, the maintenance of the cold-chain can be variable and potentially lead to reduced efficacy. Therefore, there is a desire to improve the stability of the active ingredient through the use of novel formulation techniques. This can encompass partial structural modification of the biotherapeutic or the use of a more complex formulation. Such attempts to enhance stability can lead to further increases in the viscosity of the resulting formulation. In fact, it is difficult to evaluate true viscosity as temperature is such a key factor.

Traditional spring–based technologies for autoinjectors have offered a good solution to a certain point; however, viscosities over 10 to 20 centipoise (cP) a challenge for most standard spring-based autoinjectors systems, and can cause serious issues with completeness of injections. Whilst many companies are looking at adapting spring-based delivery systems for higher viscosities, there are some drawbacks to this mechanism. The kickback produced when the injection discharges can be uncomfortable, even frightening to patients in some instances. This could potentially deter the patient from using the device as often as is required; discomfort can have a negative impact on compliance.

The high impact of spring-based delivery can also lead to breakage of the primary drug container in certain situations. Most prefilled syringes were never designed to be used with autoinjectors, and as such, industry has seen issues with breakage prior to injection and during injection. Other issues include poor siliconization leading to stalling or incomplete injections, flange strength is often insufficient, and the rigid needle shield can prove incompatible with the grabber/removers of some devices.

FIGURE 1

Bespak is innovating the delivery of difficult to administer formulations, such as biologics, with its VapourSoft® compact energy source.

Another challenge is the volume of a dose. The volumes used in autoinjectors routinely fall between 0.2 to 1.2 ml. However, to address many of the aforementioned viscosity issues, and to facilitate larger volume injections, the volumes now required are moving well beyond this level. To this end, 2.25-ml autoinjectors are now entering the market. As volumes increase well beyond 0.2 to 1.2 ml, the time required to administer also increases. For 1-ml injections, a target time of less than 10 seconds is considered the norm for autoinjectors. This threshold exists because patients have difficulty holding a device against their skin for longer than 10 seconds. There is no standard threshold for volumes of 2 ml at this time; however, it still stands that beyond 10 seconds patient compliance is potentially affected.

When designing autoinjectors, device companies must also take into account that patients are expected to use autoinjectors by themselves at home, with no supervision from medical professionals. This has a potential impact on both patient safety and compliancy, as one bad experience with a device or medication in general can be a barrier to future use. As a result, autoinjectors are given to patients as part of a package of tools that train patients in their use or support patients in training themselves. This will often include a teaching session with a nurse or practitioner, image-based protocols, as well as video tutorials. Trainer devices that allow the patient to practice the action of injection without the presence of a needle are also available. Additional training is sometimes provided through home visits by nurses hired by the pharmaceutical company. This has worked particularly well in the area of multiple sclerosis.

LATEST INNOVATIONS

Clearly new mechanisms are needed to improve the experience for patients and contribute to enhanced compliance and

FIGURE 2

Bespak's Syrina® range of assisted syringes and autoinjectors, utilising its proven VapourSoft® power source.

adherence. Several companies are looking at new and disruptive technologies to find a solution, such as unique spring configurations or electromechanical processes. With autoinjectors in high demand by the biopharma industry, gas-powered delivery systems may have the solution to many of the difficulties the industry is facing.

To meet the demands for suitable autoinjectors, Bespak has developed a novel container of liquefied gas that provides sufficient energy, as pressurized vapor, to power delivery of the drug. The container is essentially a miniaturized form of the gas canisters used in inhaler devices, which the company has been producing for more than 50 years. The adaptation, known as VapourSoft®, provides a smooth, dampened delivery action that reduces injection impact seen with current spring-based mechanisms.

BENEFITS OF GAS-POWERED DELIVERY

Gas-powered delivery has the advantage of being incredibly flexible. Due to the variety of liquefied gases available, it's possible to provide the complete spectrum of pressure ranges within a single container format. This allows a single device system to manage a variety of delivery options, including different viscosities (up to 300 cP and much higher with a new variation on the technology), injection volumes, and primary containers. Its size means that it can also be readily incorporated into different types of delivery systems, such as autoinjectors, wearables, and bolus systems.

A smooth delivery profile also makes gas-powered delivery suitable for glass primary containers, for which breakage has historically been a serious issue, resulting in a number of recalls.[5] Issues with breakage and incomplete delivery are exacerbated when using viscous solutions as more force is required to power delivery. Because gas-powered delivery has a soft start and low actuation force, this technology has no impact on the glass syringe and thus can be used in combination safely even with high-viscosity solutions, without fear for contamination or loss of part of the dose.

Being able to provide a constant delivery profile in all situations is vital. Such a delivery system is able to deliver a smooth, consistent delivery profile, vital for patient comfort, completely avoiding any recoil, often seen in spring-based systems. Consequently, this smooth delivery profile also ensures that the full contents of the syringe are dispensed regardless of initial fill level.

BEYOND THE DELIVERY PROFILE

Patient compliance is known to be influenced by the size and shape of the delivery device. A compact and versatile format allows gas-powered delivery technology to be used in unique, non-linear form factors, enabling ergonomic designs and making it an ideal choice for devices that need to be highly customized for specific patient groups.

For patient groups required to carry a device on their person, the size of the device can influence compliance. A compact device will more readily fit into a pocket, and so becomes more convenient to carry.

Ease-of-use has become a much bigger consideration with the rise of self-administration. In indications such as arthritis in which movement can be difficult or painful, ease-of-use becomes even more important, and flexibility of device design becomes key. Device manufacturers work with human factors experts to find out what type, shape, or form of device is preferred by patients.

The space required in a device for a gas-powered delivery system is significantly reduced compared to other options. The compact nature of the technology and additional space afforded by the removal of a plunger rod allows for very unique configurations of the device. These are driven by the drug and the target patient

group and the preference of the pharma company. Although some companies do choose to go with standard device designs, many prefer to have a unique shell for the device, allowing for features that improve grip dexterity and other aids to use, in addition to providing brand differentiation.

One trend we continue to see is the use of the two-step autoinjector, which is placed uncapped against the injection site, and triggered by a simple push-on-skin action. In addition to providing greater flexibility with regard to the size and shape of the final device, a compact delivery mechanism also allows the inclusion of additional features to further enhance compliance, such as connectivity.

WHAT'S NEXT FOR SELF-ADMINISTERED DEVICES?

The ability to include additional features, such as connectivity capabilities into patient-acceptable devices is already in demand. An increased emphasis on smart devices is also predicted, with data used to improve adherence by increasing transparency between the doctor and patient and making complying with the correct dosing regimen easier for the patient. In general, "Smart Health" has become a hot topic in the industry, and is set to revolutionize patient-care. Used in conjunction with autoinjectors, such technology will enable healthcare professionals to track where, when, and how medication is used by each patient. This will provide invaluable insight into an individual's usage history, including dose regime compliance. For allergy sufferers, such data could help identify potential triggers, whilst for those with a chronic condition this information could inform personalized dose regime modifications.

Throughout the next several years, injectable devices will have to continually evolve to keep pace with developments in biologics. Dosing is likely to become less frequent still, and this will likely have an impact on the volumes needing to be administered. Upward of 2 ml, wearable delivery devices will likely provide the solution. Wearables are able to offer more flexibility around volumes and timing of delivery, enabling low-dose, long-term injection – delivering the drug slowly over a long period of time, or even delivering the drug 24 hours after fitting the device for convenience.

A compact gas-powered delivery approach, based on proven long-established technologies, is ideal for delivering the challenging biotherapeutic formulations in the most demanding situations. As new injection mechanisms emerge, their success will depend on a balance of factors; size of the technology and therefore real-estate required in the device, smoothness of delivery profile, as well as cost. Importantly, to supply the breadth of different devices needed by today's industry, device companies need to be able to provide a choice of delivery mechanisms to customers. ◆

REFERENCES

1. Autoinjectors Market: Rising Incidence of Anaphylaxis Attack Among the Adult Population Expected to Elevate the Demand for Autoinjectors: Global Industry Analysis and Opportunity Assessment 2016-2026 - http://www.futuremarketinsights.com/reports/auto-injectors-market.
2. Injectable Drug Delivery Market worth 624.50 Billion USD by 2021 - http://www.marketsandmarkets.com/PressReleases/injectable-drug-delivery.asp.
3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3964020/.
4. http://www.pmlive.com/pharma_intelligence/oral_biologics_delivery_still_elusive_908436.
5. http://www.contractpharma.com/issues/2012-01/view_features/the-glass-quandary

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BIOGRAPHY

Steven R. Kaufman is Global Business Development Lead, Bespak Europe Ltd, where he is responsible for the global business development of injectable devices, such as auto-injectors and wearable injection systems. He has more than 13 years of experience in bringing drug delivery devices to market and forming strategic alliances with related suppliers and consultants. He works actively with the Bespak Innovation team, which designs and develops advanced drug delivery devices, and is part of the Senior Leadership Team. He earned his IMBA in Marketing and International Business from the National Chengchi University.

Special Feature

Improving Bioavailability & Solubility: A Top-Down vs. Bottom-Up Approach

By: Cindy H. Dubin, Contributor

Nanocrystals will account for 60% of a $136 billion nanotechnology-enabled drug delivery market by 2021. Nanocrystals are ground in special mills producing nano-sized drugs, which are applicable intravenously as nanosuspensions. This procedure enhances the surface-to-volume ratio and thus the solubility and bioavailability of most insoluble pharmaceuticals.[1]

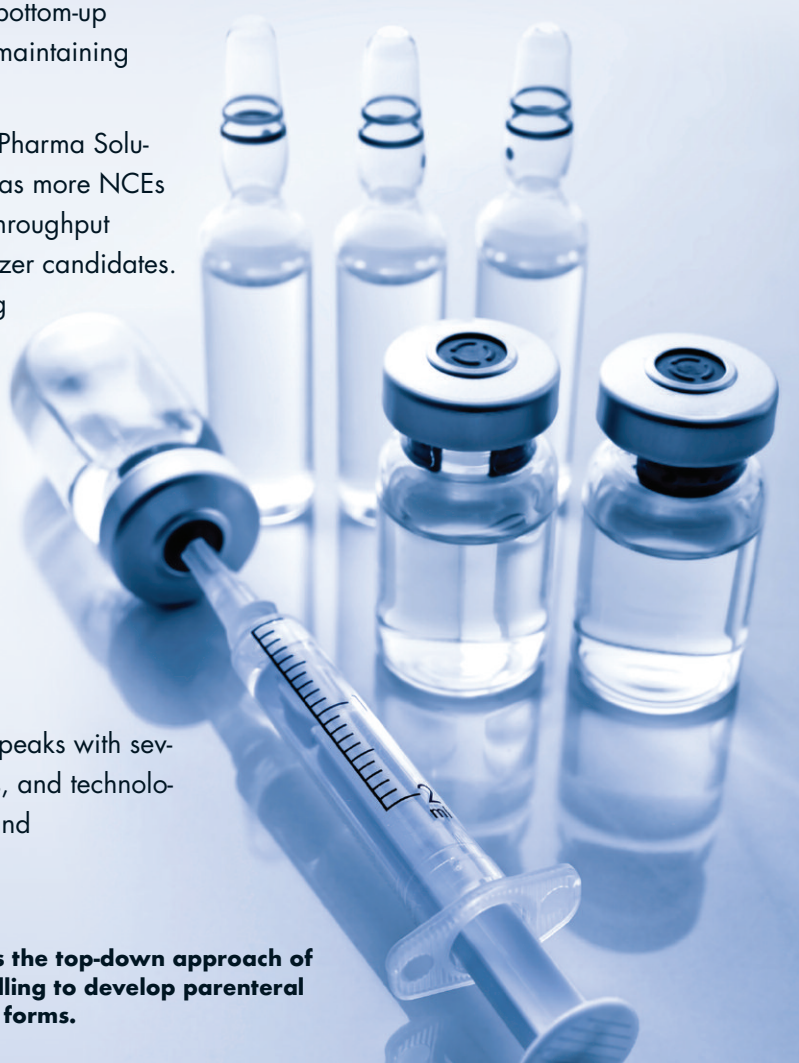
According to Smruti Chaudhari, PhD, Development Scientist I, Metrics Contract Services, two principles can be used to produce nanoparticles: Top-down approaches like milling or ultra-homogenization, and bottom-up approaches such as precipitation. Metrics uses the top-down approach of micronization to reduce an API's particle size to enhance solubility.

Also using a top-down scalable approach of nanomilling is Particle Sciences, Inc., as it carries minimal regulatory risks. Inayet Ellis, PhD, Scientific Affairs Manager, Gattefossé USA, says that a bottom-up approach to particle modification may be worth exploring if the solubility of an API is limited in lipids. "It depends on the API and process capabilities. A top-down approach, by which larger particles are made into finer ones, can have limitations during the process as the finer particles tend to agglomerate. A bottom-up approach may require careful selection of a solvent and maintaining at the saturated level."

Shaukat Ali, PhD, Technical Support Manager, BASF Pharma Solutions, agrees that a bottom-up approach is more relevant as more NCEs turn out to be poorly soluble. The first step requires high throughput screening of APIs to identify appropriate polymer/solubilizer candidates. Screening studies are critical to provide the understanding of structure-function relationship, and whether this information can be applied to identify the appropriate technology and/or excipients for development.

"The top-down approach is widely used in the industry based on its proven benefits in manufacturing scale," summarizes Dr. Jessica Mueller-Albers, Evonik Health Care Scientific Communications. "However, we see a value in further developing bottom-up technologies in order to stay as flexible as possible to select the right technology meeting the requirements of the drug."

In this annual feature, *Drug Development & Delivery* speaks with several innovative companies about their science, techniques, and technologies aimed at addressing the current challenges, issues, and opportunities in bioavailability and solubility.



PSI uses the top-down approach of nanomilling to develop parenteral dosage forms.

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Ascendia Pharmaceuticals: Achieving Significant Results in Nanoemulsion Solubility

Ascendia Pharmaceuticals is a specialty CDMO that creates formulation solutions for poorly water-soluble molecules. Some of the newer approaches Ascendia offers include nanoemulsions and solid-lipid nanoparticles. The goal with nanoemulsions is to dissolve and stabilize the drug in a suitable oil vehicle, and then produce oil-in-water nanoemulsions using either a high-shear homogenization or a micro-fluidization process. Minimizing the amount of co-surfactants and co-solvents required for long-term physical stability is a key strategy. With solid-lipid nanoparticles, the surface area advantage that nanoparticles have in improving drug dissolution is extended by having the drug homogeneously dispersed in a lipid carrier prior to nanonization, explains Jingjun "Jim" Huang, PhD, CEO of Ascendia. Solid-lipid nanoparticles are especially useful for long-acting injectable formulations of poorly soluble drugs.

An alternative is to coat a drug nanocrystal with a lipidic material prior to final dosage form preparation. Both nanoemulsions and nanoparticles can be administered orally or via injection.

"There continues to be a demand for innovative technologies to address poor drug solubility as many emerging pharmaceutical companies have promising compounds that require novel delivery science to achieve their bioavailability targets," says Dr. Huang. Ascendia helps clients quickly determine the best formulation approach by investigating multiple options in parallel. Capabilities include spray-drying, hot-melt extrusion, ball-milling, micro-fluidics, and homogenization. Ascendia also has the capability to transition an optimized formulation into cGMP manufacture of clinical materials for animal PK, toxicology, or first-in-man studies.

Ascendia's EmulSol nanoemulsion.

For example, for one client, Ascendia developed a nanoemulsion formulation of a drug that has only 3ng/ml water solubility. Dr. Huang explains that the drug exhibited significant dose proportionality and food-effect issues. Ascendia experimented with a matrix of oils and surfactants to develop several prototype formulations. "In the oil phase of the nanoemulsion, we achieved drug solubility in the 30-100 mg/ml range – a 1,000,000-fold improvement."

Multiple formulations achieved good chemical stability, physical stability, and water dispersibility. All of the formulations produced nanoemulsions with droplets sizes less than 1µm, and ranged from as small as 20nm to ~ 700nm. This feasibility study yielded a viable oral formulation for the client that is now being tested clinically to determine the improvement in dosing kinetics and the elimination of the food-effect.

BASF: Innovative Polymers Tackle Modern Formulation Challenges

With the recent surge in poorly soluble APIs, BASF continues to introduce unique polymers, such as one derived from vinylpyrrolidone and acrylic acid monomers, for insoluble molecules. With its greater solubility at low and high pH, it significantly increases the solubility and bioavailability of weakly alkaline drugs, says Shaukat Ali, PhD, Technical Support Manager, BASF Pharma Solutions, BASF Corp. "Polymers like this create potential for the next generation of NCEs and as they continue to be characterized as brick dust or insoluble with high melting points, the industry is taking a more pragmatic approach to adapt non-conventional technologies in drug development. This requires the use of new polymers, excipients or solubilizers that have never been used before due to regulatory challenges."

Additionally, formulation technologies such as solid amorphous dispersions offer opportunities for highly crystalline APIs to increase solubility and enhance bioavailability, especially those requiring medium/high doses. Spray drying and hot-melt extrusion technologies amongst

others have also been widely used for improving bioavailability. That said, these technologies are highly dependent on the functionalities of polymers and solubilizers in oral dosage forms, says Dr. Ali.

He also points out that nanocrystal and nanotechnologies have been used as alternative approaches to solid dispersions for improving solubility and bioavailability, but do bring some challenges of their own. In some cases, precipitation of drugs in liquid suspension/solutions occur due to its inability to maintain supersaturation, causing lower bioavailability.

With the availability of excipients and polymers with greater solubilization capabilities, the solubility of APIs can be improved exponentially and supersaturation can be maintained over longer periods. As a result, the industry is looking to select high functionality excipient/polymers. "The pharma industry's interest in new excipients has fueled the development of novel polymers and solubilizers to tackle unmet formulation needs," says Dr. Ali.

Soluplus®, a polymer designed for hot-melt extrusion technology is an example. Molecules with a higher melting temperature and difficult to formulate have been used with Soluplus in amorphous solid dispersions for improving solubility and bioavailability. "With its unique characteristics of higher lipophilicity and crystalline inhibitory properties, Soluplus has been used both in conventional and non-conventional formulations for improving solubility, loading, and stability by maintaining APIs in supersaturation over an extended period," he says.

Copovidone and cellulosic excipients have been used in solid dispersions technologies, including spray drying, hot-melt extrusion and electro spinning/spraying. "As the interest in continuous manufacturing continues to grow, the twin screw extruder (TSE) will likely occupy more space in conventional granulation technology to offer an added benefit for many of the poorly soluble drugs requiring low to medium doses, and alleviate the stability challenges with amorphous solid dispersions."

Evonik's EUDRAGIT® functional polymers and EUDRATEC® drug delivery technologies have been developed to optimize the bioavailability of many classes of APIs.

Evonik: Functional Polymers & Formulation Technology Enhance Bioavailability

From a technical standpoint, the solubility and permeability of many new chemical entities are key issues for the development of new drug formulations. As a result, the industry is in urgent need of new approaches to drug development and specifically to tailored drug delivery.

"In oral drug delivery, we see an increasing interest in excipients and new formulation techniques to enhance drug solubility and bioavailability," says Dr. Jessica Mueller-Albers, Evonik Health Care Scientific Communications. "The industry is adopting more innovative formulation technologies, which appropriately target the improvement of the transcellular and paracellular uptake of both small molecules and biologics. This often requires the use of new types of excipients, like permeation enhancers, enzyme inhibitors, and polymers with advanced functionalities. An example is Evonik's proprietary drug delivery technology EUDRATEC® PEP, which enables the peroral administration of peptide drugs." EUDRATEC PEP technology is a versatile formulation toolbox where challenging actives (peptides, proteins, BCS II, III and IV compounds) and functional ingredients are combined in a modular way to enhance bioavailability.

For solubility enhancement, solid dispersions are still one of the most important technologies used today and will continue to play a significant role in the future. "If you have a BCS class IV API with poor solubility and poor permeation, increasing the solubility alone may not solve all your problems, but delivering the now soluble drug to the right area of the GI tract may be able to boost bioavailability," says Dr. Mueller-Albers. "Many scientific research groups are working on the development of new excipients that inhibit enzymatic degradation or improve permeation of biological barriers. However, dissemination of these new entities is often limited by

"In the case of a bottom-up process, one is always presented at the end of the nanoparticle formation with organic solvent in the mixture. This may require downstream processing to remove the organic co-solvent."— Mark Mitchnick, MD, CEO, Particle Sciences, Inc., and Chief Medical Officer, Lubrizol LifeSciences

undiscovered toxicology and cost-extensive scalability."

Functional excipients like Evonik's EUDRAGIT® polymers can help with significant increase in bioavailability by delivering the active to the appropriate area of the GI tract where absorption is the highest. Dr. Mueller-Albers says that with the increasing development activities of nanoparticles for oral drug delivery, there is a strong need for carrier formulations that enable the preparation of solid dosage forms and protect the nanoparticles from early degradation or drug leaching in the GIT. By co-spray drying EUDRAGIT polymers together with the nanoparticles, they can be embedded in a polymer that fulfills these requirements.

For example, the recently launched EUDRAGIT FS 100 polymer was specifically designed to enhance drug solubility at the same time as targeting the colon to treat localized diseases, such as colon cancer and irritable bowel syndrome with delivery site-specific APIs. The polymer is suitable for processing via melt extrusion and spray drying.

Gattefossé USA: Lipid-Based Formulations Prove Versatile

While there are multiple existing and emerging strategies to enhance the solubility and bioavailability of poorly soluble drugs, there is also a general lack of clarity on the benefits of these technologies for one or another category of molecules. No single technology can be a solution to all challenges, and in reality, the drug development scientist may resort to two or more approaches to optimize solubility and oral bioavailability based on the API characteristics, process limitations/manufacturability, and safety of the components needed for developing the intended dose. Among the technology choices, lipid-based drug delivery systems (oily solutions, SEDDS, SMEDDS) have emerged as versatile and efficient in enhancing the solubility and bioavailability of BCS II molecules, and more recently, in the optimization of oral bioavailability for various peptides.

"In the realm of lipid-based formulations, the preferred approach is to design formulations capable of forming micro/nanoemulsions *in vivo*," says Inayet Ellis, PhD, Scientific Affairs Manager, Gattefossé USA, Paramus, NJ. "Commonly referred to as SEDDS or SMEDDS, these are anhydrous systems of glycerides and nonionic medium-to-high HLB lipid excipients, and they demonstrate great dilution capacity upon mixing with gastric fluids, reducing the risk of API precipitation in the GI tract."

As a pioneer of lipid excipients, Gattefossé aims to improve solubility and bioavailability simultaneously. With most drug actives, solubility enhancement is a start but doesn't always translate into improved exposure *in vivo*. "The Gattefossé Technical Center of Excellence assists clients with excipient selection and formulation development that will improve solubility and create a stable and consistent dose with potentially good bioavailability," says Dr. Ellis. "Scientists provide support in solubility screening, *in vitro* lipolysis testing to predict *in vivo* performance, animal dosing, and formulation development."

Metrics Contract Services: Micronization & Amorphous Solid Dispersion Approaches to Formulation

Recent advances in combinatorial chemistry have led to the discovery of many new drugs. These drugs have either low solubility or low bioavailability or both, and they present special challenges to formulators. There are two ways to increase solubility: Chemical modification or formulation approaches. Chemical modifications include taking a pro-drug approach or using the salt form of the drug.

"There is a certain level of complexity involved in using a salt form to increase solubility due to the need to develop salt-form synthesis and purification methods," says Smruti Chaudhari, PhD, Development Scientist I, Metrics Contract Services. "For-

mulation methods such as micronization, amorphous solid dispersion, nanocrystals, and nanoparticle are more popular in the field of solubility enhancement."

Metrics Contract Services offers formulation approaches like micronization and amorphous solid dispersion. Micronization is a simple top-down approach, in which the particle size of the API is reduced, which leads to an increased surface area and eventually solubility enhancement. Although these concepts have shown positive results for many drugs, there are some APIs that need further formulation to increase solubility, says Dr. Chaudhari.

Most of the APIs available in the market are crystalline in nature, which have poor solubility. Such crystalline APIs can be converted into an amorphous form, which has higher solubility through the formation of amorphous solid dispersions using spray-drying technology.

Nanocrystal is an up-and-coming technology that offers advantages in improving solubility and bioavailability of poorly soluble APIs. Nanocrystals are basically crystalline particles in the size range of 2nm to 1,000nm.

"Due to crystalline characteristics, they offer better stability as compared to their amorphous counterparts," says Dr. Chaudhari. They can be administered as a dispersion in the liquid medium or in the solid state. Nanocrystals can be prepared by bead milling, high-pressure homogenization, and precipitation. One of the main advantages of this technology is that it allows formulating tablets or capsules with a high drug load. This technology uses surfactants as stabilizers, which may result in enhanced side effects or adverse effects.

Apart from these methods, target-specific and site-specific drug delivery is gaining momentum where the drug can be released in an area of optimal absorption. Dr. Chaudhari says: "Metrics has experience in optimizing drug delivery to the small intestine using enteric-coated multiparticulate systems, or tablets and capsules. This technology is beneficial, particularly for acid-sensitive drugs."

Another characteristic of nanocrystals is that they are 100 percent drug with no carrier. Nanocrystals work to improve solubility through the increase of surface area beyond that provided by just micronization. "This is especially helpful in improving solubility of drugs for which solubility is limited by dissolution rate," says Dr. Chaudhari. "Amorphous nanoparticles are even more advantageous in improving solubility but they come with the challenge of requiring stability to prevent conversion to the crystalline forms."

Particle Sciences, Inc.: Nanomilling Is Reliable, Scalable, & Well-Suited for Sterile Products

Particle Sciences (PSI) routinely uses a variety of nanotechnology-based drug delivery technologies, including polymeric nanoparticles, solid-lipid nanoparticles, nanoemulsions, and nanoparticulate suspensions (i.e., nanocrystals).

"We frequently evaluate nanocrystals produced using a high energy media milling process (i.e., nanomilling) for water-insoluble APIs," says Robert W. Lee, Executive Vice President, Pharmaceutical Development Services, PSI. "Nanomilling has been used in marketed products and there continues to be a lot of interest in nanocrystals. Most of our programs are intended for parenteral administration and we consider this to be a go-to technology for sterile products."

When it comes to sterile products, most of the nanocrystal formulations are not amenable to terminal sterilization so PSI offers aseptic nanomilling using a proprietary high-energy milling system that was designed specifically to better accommodate aseptic processing. Dr. Lee says: "There are several technologies for formulating BCS II APIs for oral administration, but we feel the true value of nanomilling is for the development of parenteral dosage forms. The capability of providing aseptic nanomilling may allow our clients to offer better products to their patients."

PSI uses the top-down approach of nanomilling because it's proven scalable and the regulatory risks are minimal as the technology has been used in several marketed products, says Dr. Lee.

Aside from these considerations, nanomilling is typically done in an aqueous vehicle. This contrasts with a bottom-up approach, such as controlled precipitation, in which the API is solubilized in a water-miscible organic solvent then mixed with water as the antisolvent. "In the case of a bottom-up process, one is always presented at the end of the nanoparticle formation with organic solvent in the mixture," says Mark Mitchnick, MD, CEO, Particle Sciences, Inc. and Chief Medical Officer, Lubrizol Life-Sciences. "This may require downstream processing to remove the organic co-solvent."

Another consideration is that the concentration of the API in controlled precipitation may be very low – on the order of single-digit percentages in most cases. "In contrast, with nanomilling we can achieve concentrations up to 50% API. Nanomilling leads to a more efficient process requiring fewer unit operations to produce the final drug product. It facilitates

Figure shows (left-right): a) Quadrant 2® model of a poorly soluble drug in a solid dispersion; b) Pilot scale spray dryer and analytical laboratory at Thermo Fisher's site in Bend, OR; and c) Commercial spray drying facility in Florence, SC.

scale-up and eventual commercialization."

For most drug delivery systems, excipients play a facilitating role. To increase the range of materials at its disposal, PSI maintains strategic relationships with a variety of excipient suppliers, such as with PLGA for use in polymeric nano- and micro-particulate formulations. Additionally, as part of Lubrizol LifeSciences, PSI can access a variety of polymers that can be matched with the solubility of APIs such as thermoplastic polyurethane-based technologies. "These relationships help speed our clients' development programs," says Joey Glassco, Global Market Manager, Drug Eluting Devices & Pharmaceutical Services, PSI. PSI is also seeing more clients interested in functional excipients, such as some that serve as permeation enhancers for mucosal delivery.

Quotient Sciences: Using the Human System to Understand & Resolve Bioavailability

Sub-optimal bioavailability isn't always a function of poor solubility. Broader corrective drug delivery strategies may be required to achieve desired pharmacokinetic (PK) profiles. As demonstrated through the Biopharmaceutics Classification System (BCS), permeability of the molecule may also be a barrier to achieving the desired systemic exposure, requiring strategies to increase absorption and/or inhibit efflux membrane transporters. Additional strategies would also be required if rate-limiting factors such as gut-wall metabolism or molecule lability in the gastrointestinal lumen were observed. Thus, it is imperative that the fundamental factors causing poor or variable bioavailability are fully understood or strongly hypothesized before formulation strategies are defined, advises Peter Scholes, Chief Scientific Officer, Quotient Sciences.

"Poor solubility is arguably the area that has the greatest potential for success for formulation scientists, given continued research to identify technologies to improve oral bioavailability and realize the therapeutic potential of new drugs (or improve the posology of old ones)," he says. "New drug delivery technology companies continue to emerge, focusing on novel ways to address either kinetic or thermodynamic limitations inherent in drug substance properties. Promising preclinical and clinical data attributed to some of these innovations are now coming into the public domain."

Even with these additional tools, key challenges for the formulation scientist are technology selection, achieving the target product profile, and optimizing the system to meet the unique *in vivo* delivery needs of each molecule in humans. "Surrogate tools remain sub-optimal in predicting clinical performance of enabled formulation systems," says Dr. Scholes. "Nonclinical PK data is widely acknowledged and reported as having poor correlation with corresponding human bioavailability, even to the point of questioning the ethics of continuing to use this practice to assess candidate formulation systems to take into human screening."

There have been significant advances, however, in the use of *in vitro* and *in silico* methods as characterization and predictive tools to aid technology selection. As an example, physiologically based pharmacokinetic (PBPK) modelling is widely used to explore the potential for

formulation factors to influence oral bioavailability by developing models with existing datasets and then running PK simulations based on formulation variables such as drug particle size, he explains.

Quotient Sciences advocates the use of the "human system" to understand and resolve bioavailability risks and challenges. The integration of real-time adaptive GMP manufacturing and clinical testing is the established principle behind the science of Translational Pharmaceutics®, which enables both the manufacture of drug products within a week of dosing and the ability to modify compositions in response to emerging clinical data. This adaptive platform consequently reduces the timeframe and cost barriers to evaluating multiple formulation technologies in the clinical setting to provide definitive data on technology selection.

"This is highly advantageous when addressing solubility issues," says Dr. Scholes. "For example, arising PK data have recently been used to screen different spray dried polymer dispersions, identify optimum drug:excipient ratios and compare different solubilization technologies head-to-head (e.g. particle size reduction, lipidic and amorphous systems) in the strive to overcome sub-optimal bioavailability."

Thermo Fisher Scientific: Predictive Platform Provides Formulation & Product Development Pathway

Patheon, a part of Thermo Fisher Scientific, uses a differentiated approach to solubility enhancement called Quadrant 2®. This is a predictive *in silico* platform that provides a strategic pathway through the formulation development landscape, explains Sanjay Konagurthu, PhD, Sr. Director, Global Science and Technologies, Pharma Services, Patheon, part of Thermo Fisher Scientific. "The landscape consists of several solubility enhancement technologies plus additional components related to the materials and processes needed for an individual technology. The Quadrant 2 strategy is an agnostic approach towards achieving the molecule's target product profile and improved bioavailability. It is specifically designed to reduce the amount of experimental work typically performed in preformulation and early clinical development projects and laying a robust pathway to commercialization," he says.

Quadrant 2 analyzes the molecular structure and physicochemical characteristics of a compound to provide input for the *in silico* platform that selects the most promising solubility enhancement technologies, such as size reduction (micronization and nanomilling), amorphous solid dispersions (spray drying, hot-melt extrusion and coated multiparticulates), lipid-based approaches, complexes, etc. "This approach contrasts sharply with empirical trial-and-error methods," says Dr. Konagurthu. "Our algorithms have been developed based on Thermo Fisher Scientific's comprehensive understanding of multiple proven solubility enhancement technologies, materials science, and molecular modeling. Using this toolbox, timelines can be shortened, and compounds advanced to the clinic using a solubility enhancement technology suitable for clinical trials and commercialization."

Selection of the proper excipients early in a development program is critical to successfully formulating and manufacturing a drug product. Quadrant 2 includes excipient selection algorithms that provide a scientific basis for formulation design. *In silico* predictions involving quantum mechanical and molecular dynamics modeling, combined with statistical analysis, are used to select appropriate excipients.

Thermo Fisher Scientific supports developing and commercializing these technologies through a network of worldwide manufacturing sites. Comprehensive services provide solutions at every stage, including API manufacturing, drug product for clinical trials, and commercial manufacturing, including packaging, labeling, and distribution). ◆

Reference

1. Kwaśniewski, Michał, Nanotechnology for Drug Delivery: Global Market for Nanocrystals, Pharmaceutical Research Reports, https://pharmaceuticals.report/?pharma_reports=nanotechnology-for-drug-delivery-global-market-for-nanocrystals, Posted on January 9, 2018.

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BIOGRAPHY

Cindy H. Dubin is an award-winning journalist who has been reporting on the pharmaceutical industry for more than 17 years about a variety of topics, including formulation development, drug delivery, and drug quality.

3D PRINTING

3D Printed Drugs Hold Great Potential for Personalized Medicine

By: Cindy H. Dubin, Contributor

INTRODUCTION

This past year marked a milestone in the pharma industry when Aprecia Pharmaceuticals' Spritam® (levetiracetam) tablets became the first FDA-approved prescription drug product manufactured using 3D printing technology.

"As we explored potential applications for our 3D printing technology in prescription drug products, it was important that we identified disease areas with a real need for patient-friendly forms of medication," said Don Wetherhold, CEO of Aprecia, in a printed statement.

Spritam is formulated with Aprecia's proprietary ZipDose® Technology, which combines the precision of 3D printing and formulation science to produce rapidly disintegrating formulations of medications. An inkjet printing process produces the porous water-soluble drug layer by layer by printing aqueous fluid onto layers of powdered medication, without compression or traditional molding techniques, explains Sonia Mannan, Commissioning Editor, *Journal of 3D Printing in Medicine*. She says researchers from University College London's School of Pharmacy are using hot-melt extrusion to 3D print different shaped drugs to explore the connection between drug geometry and drug release.

"It's exciting to see the ways 3D printing is being used in the medical environment," says Laura Dormer, Editorial Director for Future Medicine, publishers of *Journal of 3D Printing in Medicine*. "To date, this has predominantly involved printing of plastics and metals, such as surgical planning, prosthetics, or reconstructive surgery. Surgeons are now able to 3D print accurate models of their patients' organs, allowing them to plan complex procedures with a higher degree of confidence than with imaging alone. 3D printing has also been used to create tailored bone inserts for use in complex facial reconstructive surgery. 3D printing of pharmaceuticals is less advanced, but offers an exciting opportunity for the future, as does the possibility of printing with organic materials (bioprinting) for use in regenerative medicine."

PERSONALIZED MEDICINE THROUGH 3D PRINTING

One area of 3D printing that also holds exciting promise is in personalized medicine. As new drugs are developed that have increasing potency and differential effects within populations, there is a need to consider new manufacturing methods and novel supply chains to realize the paradigm of personalised medicines. 3D printing offers the possibility of creating a personalized medicine system through automated control over drug dose and is suitable for both low and high drug concentrations.

FabRx is a research-driven specialist biotech company, focused on developing 3D printing technology for fabricating pharmaceutical dosage forms and medical devices. FabRx was founded in 2014 as a spin-out from University College London (UCL) and operates from the UCL School of Pharmacy, giving the company access to the latest equipment in 3D printing and analytical technology. The company also develops formulations and printing technologies for third-party organizations.

"Our team has a wealth of experience in all aspects of oral drug formulation and knowledge of the challenges of bringing new medicines through the (often complex) regulatory processes of the pharma sector," says Prof. Simon Gaisford, Printing Technology Director at FabRx. "We are developing printable formulations for personalized drug delivery, and as part of this we are adapting printing technology."

FabRx has specialist experience in using all the 3D printing technologies that can be used in pharmaceutics, but focuses par-

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9:45am – 10:00am	Exhibit Hall Grand Opening & Exhibitor Awards								
10:00am – 5:00pm	Show Floor Open & IPX/BPI Poster Hall								
10:30am – 11:15am	**Pharmaceutical Technology Keynote Series** ***Oral Solid Dosage Manufacturing*** **10:30am - 10:55am** Employing the Internet of Things and PAT for Solid Dosage Forms Manufacturing **11:00am-11:25am** PCMM (Portable, Continuous, Miniature and Modular) OSD Manufacturing Facility Platform **11:30am - 12:30pm** Continuous Manufacturing Roundtable: Best Practices for Implementation	Integrating a Programmable Robotic Bioreactor System with a Biochemical Analyzer for Real-time Analysis	**10:30am - 11:30am PDA Roundtable** State of the Industry Practices for Pre-Use Post-Sterilization Integrity Testing	Accelerating Freeze-Drying: From Model to Production of a Semi-Continuous Aseptic Spray Freeze-Dryer	Bioprocess Simulations the Means to Decision Making From Feasibility Through Detailed Design	MasterControl Inc.	**ELSEVIER:** Driving Digital Transformation in Chemistry & Advanced Materials Industry through Decision Support Information Solutions	A Molecules Journey is Breaking Down Roadblocks to Commercial Success - Navigating Through the Important Considerations Necessary to Successfully Bring a Biologic Molecule to Market	**10:15am - 11:00am** Formulation and Delivery of Biologics and Complex Small Molecule Compounds
11:30am – 12:15pm		Data Integrity and Management in the Pharmaceutical Industry. Understanding and Complying with GMP & FDA Requirements	Building the Foundation for Continued Process Verification with Industry 4.0 Manufacturing Analytics	Impact of Tank Cone Bottom Interior Angle on Agitator Design, Lowest Mixable Volume, and Process Results	Cleaning Validation Different Approaches to Limit Setting for Detergents	MilliporeSigma	Coming Soon	Coming Soon	**11:15am - 12:00pm** Advantages of Continuous Manufacturing for Solid Dosage
1:30pm – 2:15pm	**Pharmaceutical Technology Keynote Series** ***Aseptic, Sterile, and Biologics Drug Manufacturing*** **1:30pm - 2:10pm** Analytics and Instrumentation: Best Practices for Lyophilization **2:15pm - 3:00pm** Continuous Manufacturing for Biopharm, Visions of an End-to-End Approach	Start-ups: Moving out of the Incubator Into a New Pilot/Manufacturing Facility	**CRB TECH TANK** Flexible Manufacturing - Adapt or Die!	Tablet Press and Encapsulating Machine Transactions	Remediation Challenges of Aging Facilities	**1:00pm** Rockwell Automation	Coming Soon	Coming Soon	**1:30pm – 2:15pm** Pharma Intelligence: 2018 Industry Outlook
2:30pm – 3:15pm		Optimized Manufacturing of mAb-based Products: Flexibility, Speed, and Efficiency can Co-exist	**CRB TECH TANK** Keep'em separated! Integrating segregation for gene vector production	Single Use Viable Air Monitoring in Critical Environments of a Specialty Multi-Purpose Contract Manufacturing Organization	On-dose Identification for Tablets and Capsules Dosage Design and Equipment Innovation to Mitigate Risks in Patient Safety and Brand Protection	**2:00pm** LB Bohle LLC	Coming Soon	Coming Soon	**2:15pm – 3:00pm** Biosimilars 4.0
3:30pm – 4:15pm	Case Studies: Steam Sterilization Regulatory Requirements and End User Impact Analysis and Common Mistakes	**Case Study: Capacity** Expansion and Conversion to Single-Use BioProcessing at an Existing cGMP CDMO Facility	**CRB TECH TANK** Solving the riddle of flexible facilities - biotech & fill/finish	A Case Study for an Improved Approach to Cleanroom Disinfection, Minimizing the Impact and Reducing Downtime	Risk Analysis: Present State and Industry's Demand	**3:00pm** Sika Corp.	Coming Soon	Coming Soon	**3:00pm – 3:45pm** Automated Visual Particle Inspection for Hard to Inspect Containers
4:15pm – 5:00pm	Coming Soon	Process Economics: The Driving Force Behind the Criteria for Cell Therapies Facility Design	Continuous OSD: Designing a Controls Model *(Continuous Manufacturing track)*	A Novel, Real Time Adaptive Process Control System for Optimizing Feeding in Bioreactors	Settling the Frontier of Fill-Finish Operations - High Tech Filling in a Proper Abode *(Optimizing Facilities track)*	**4:00pm** SP Scientific/PennTech	Coming Soon	Coming Soon	**3:45pm – 4:30pm** The Impact of Critical Utilities **4:30pm – 4:45pm** Show Wrap Up Day 1

WEDNESDAY, APRIL 18, 2018

	INTERPHEX INNOVATION STAGE	MEETING ROOM 1 Optimizing Facilities through Innovation and Technology	MEETING ROOM 2 PDA, CRB Tech Tank and Continuous Manufacturing	MEETING ROOM 3 Manufacturing Efficiencies and Improvements	MEETING ROOM 4 Quality Metrics and Systems/Risk Management	MEETING ROOM 5 (Vendor Presentations)	FORMULATIONX	CMO/CDMO	INTERPHEX LIVE Crystal Palace
10:00am - 12:00pm	IPS TECHNOLOGY TOUR *(Tour Registration Required)*								
10:00am – 11:00am	**10:00am - 11:00am FDA Presentation with PDA:** The Future of Pharmaceutical Quality and the Path to Get There		**10:30am – 11:00am** Ensuring Reliable, Consistent Production in Pharmaceutical Water Systems		**10:30am – 11:00am** Cleaning Agent Screening: Key Aspects in Selecting a Suitable Cleaning agent for a GMP Cleaning Procedure	**10:30am – 11:00am** Rockwell Automation	**ELSEVIER:** Linking Data to Boost Discovery and Manufacturing Productivity	Coming Soon	**10:15am - 11:00am** New Regulations, Real Case Studies: ASME BPE Cabinet Washer Standards (SD-5.3.1)
11:00am – 12:15pm	**Pharmaceutical Technology Keynote Series** ***information Technology Trends and Best Practices*** **11:00am - 11:30am** Regulatory Requirements for Data Integrity, Applying ALCOA+ **11:30am - 12:30pm** Best Practices in Data Integrity and Process Security with Automated Systems	**10:30am – 11:30am FACILITY FOCUS 1:** Flexibility by Design: GMP Manufacturing for the Diverse Product Portfolio	Integrating IoT into your Life Sciences Packaging and Supply Chain Strategy - Best Practices to Take this Valuable Leap	The use of Extractables Data from Single Use Components for Risk Assessment	Verifiable Containment Performance of Isolator Technologies	ADENTS	Coming Soon	Coming Soon	**11:15am - 12:00pm** Automation Trends Facing the Industry
1:00pm - 3:00pm	IPS TECHNOLOGY TOUR *(Tour Registration Required)*								
1:15pm – 2:00pm	**Pharmaceutical Technology Keynote Series** **1:30pm - 2:10pm** The Industrial Internet of Things, Blockchain, and Smart Contracts **2:15pm - 3:00pm** Serialization: Moving Beyond Compliance to Value	**1:00pm - 2:00pm FACILITY FOCUS 2:** Restrictive Access Barriers: Best Industry Practices for Retrofitting a Legacy Filling Lines with a RABS Barrier	Global Pharmaceutical Packaging Trends, Beyond Serialization *(Optimizing Facilities track)*	Mass Spectrometry in Freeze Drying, Over 25 Years Since the First Installation: How Far have we Come?	Harmonized Method for Cleanroom Hard Surface Disinfectant Efficacy Evaluations	**1:00pm** Eschbach GmbH	Coming Soon	Coming Soon	**1:30pm – 2:15pm** Utilizing AR/VR in Pharma Development and Manufacturing
2:15pm – 3:00pm		**2:15pm - 3:15pm FACILITY FOCUS 3:** Central Utilities for GMP Manufacturing: A Practical Dialog on Cost and Reliability	**2:00pm - 3:00pm PDA Roundtable** Technology and Process for Cell and Gene Therapy Manufacturing	Making 'Spray and Pray' Obsolete with New Technologies	Data Driven Control Strategy for Critical Drug Container Closure Systems (CCS) Performance at Digital Age	**2:00pm** Bimba Manufacturing Company	Coming Soon	Coming Soon	**2:15pm – 3:00pm** Emerging and Transformational Technologies in Personalized Medicine – A Paradigm Shift
3:15pm – 4:00pm	Coming Soon	Current Trends & Considerations for Drug Delivery Device Assembly of Self-Administered Products	Single Use Applications in Continuous Biopharmaceutical Processing	Total Organic Carbon for Enhanced Verification of Bioprocess System Cleaning CQ	A Comprehensive Approach to Cleanroom Certification for Reduced Risk of Environmental Contamination and Improved Regulatory Compliance	**3:00pm** MilliporeSigma	Coming Soon	Coming Soon	**3:00pm – 3:45pm** Data Security/Data Lockdown
4:15pm – 5:00pm		Lessons Learned from Microbial Contamination in Pharmaceutical Manufacturing; Benefit of End User and Supplier Collaboration	Facility Prefabrication - Coupling Flexibility, Mobility and Rapid Deployment into Turnkey Solutions *(Optimizing Facilities track)*	Real-Time Analytics with Timeline View for Improved Analytics	Bridging the Gap Between Rinse Water Analysis and Surface Cleanliness	Vendor Presentation	Coming Soon	Coming Soon	**3:45pm - 4:30pm** FDA Inspection Preparations: What's New, What's Different **4:45pm - 5:00pm** Show Wrap Up Day 2

THURSDAY, APRIL 19, 2018

	INTERPHEX INNOVATION STAGE	MEETING ROOM 1 Optimizing Facilities through Innovation and Technology	MEETING ROOM 2 PDA, CRB Tech Tank and Continuous Manufacturing	MEETING ROOM 3 Manufacturing Efficiencies and Improvements	MEETING ROOM 4 Quality Metrics and Systems/Risk Management	MEETING ROOM 5 (Vendor Presentations)	FORMULATIONX	CMO/CDMO	INTERPHEX LIVE Crystal Palace
10:00am – 3:00pm	Show Floor Open & IPX/BPI Poster Hall								
10:30am – 11:15am	Life Cycle Cost for Multiple-Effect Water Stills	The Theory Behind Automatic Inspection Technologies for Subvisible-to-Visible Particle Detection and Container Closure Integrity	**10:30am - 11:30am PDA Roundtable** Use of Big Data for Predictive Process Control	Work Smart: Risk based Approach for Cleaning Validation	Endotoxin Remediation Strategies	**10:30am** Rockwell Automation	Coming Soon	Coming Soon	**10:15am – 11:00am** Regulatory Requirements Relating to Water
11:30am – 12:15pm		Prescriptive Maintenance Leveraging IIoT Technology Can Become Your Competitive Advantage	How Understanding Loss in Weight Feeder Principles and Optimization of Feeder Refill and Overall Design can actually improve the Continuous Pharmaceutical Process	Achieving Manufacturing Efficiencies with Advanced Batch Management Technology		Vendor Presentation	Coming Soon	Coming Soon	**11:15am - 12:00pm** Process Control Interpretation within a Manufacturing Line **12:15pm - 12:30pm** Show Wrap-In Day 3

*As of February 15, 2018. Schedule subject to change.

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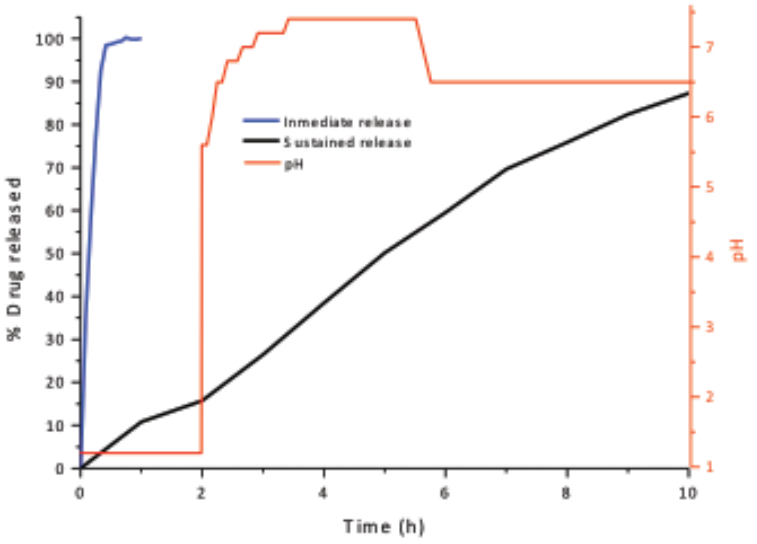
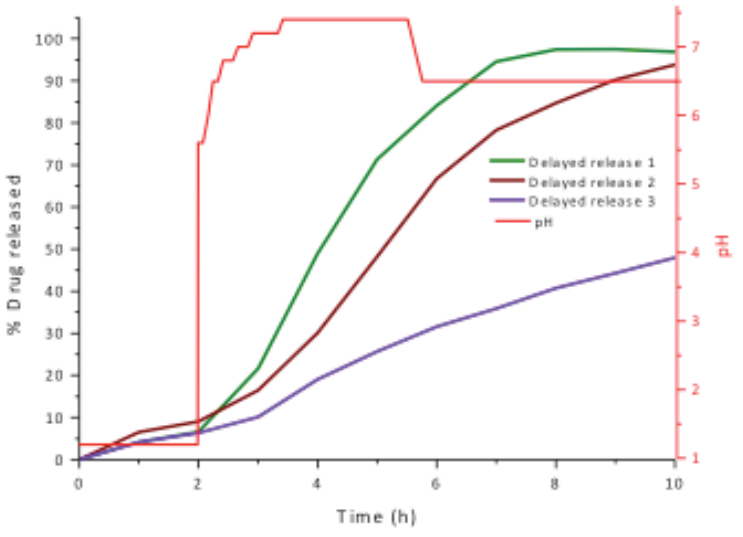
FIGURES 1A&B





Drug release tests were performed in a Dynamic Dissolution Model that modulates pH over time, precisely mimicking gastro intestinal conditions during transit.

ticularly on fused deposition modelling (FDM), powder bed printing, and stereolithography (SLA) to formulate 3D printed medicines. Its proprietary 3D printed medicines are called Printlets™.

"These are novel drug formulations that achieve personalized dose and controlled drug release profiles that can be tailored to the individual needs of each drug and that cannot readily be prepared by other manufacturing methods," says Dr. Alvaro Goyanes, Director of Development at FabRx. "Printlets technology offers a proprietary platform technology to formulate and manufacture 3D printed medicines with nearly any drug compound with a high control of the dose strength (the main requirement for personalization). FabRx technology allows manufacturing of Printlets with a diverse range of shapes, sizes, colors, textures, and flavors to make them more attractive to various patient groups, particularly the young or the elderly, facilitating compliance of the treatment." Additionally, he says it is possible to incorporate multiple drugs within one Printlet, to make fixed-dose combinations.

Selection of the excipients or the dosage form design means the time of release and/or the release kinetics of each active can be finely tuned. FabRx can fabricate Printlets with a range of GRAS pharmaceutical excipients. Proper selection of excipients allows FabRx to design Printlets possessing any desired drug release profile, ranging from immediate release to sustained and delayed release (including zero-order).

"3D printing could be used to customize specific drugs or drug cocktails based on an individual, but if you want to take it another step further, we could see a future where diagnostic and genomic sequencing technologies are interoperable with the 3D printer to automate calibration and production of the drug for a given individual," says Reenita Das, Transformational Health Partner and Senior Vice President, at Frost & Sullivan. "One-size-fits-all is not a model that is not ideal for healthcare where you have such a wide spectrum of individuals based on age, height, weight, gender, ethnicity, hereditary traits, co-morbidities, disabilities, etc. The core value driver of 3D printing is the ability to allow for mass customization at scale. 3D printed drugs offer the ability to individualize dosing, tailor drug release profiles, drug combinations, and optimize the supply chain for certain hard-to-get therapeutics."

"3D printing could give rise to personalized medicine where medication can be customized to an individual's needs to make it more effective and safer," says Ms. Mannan. "This means many aspects of the

FIGURE 2

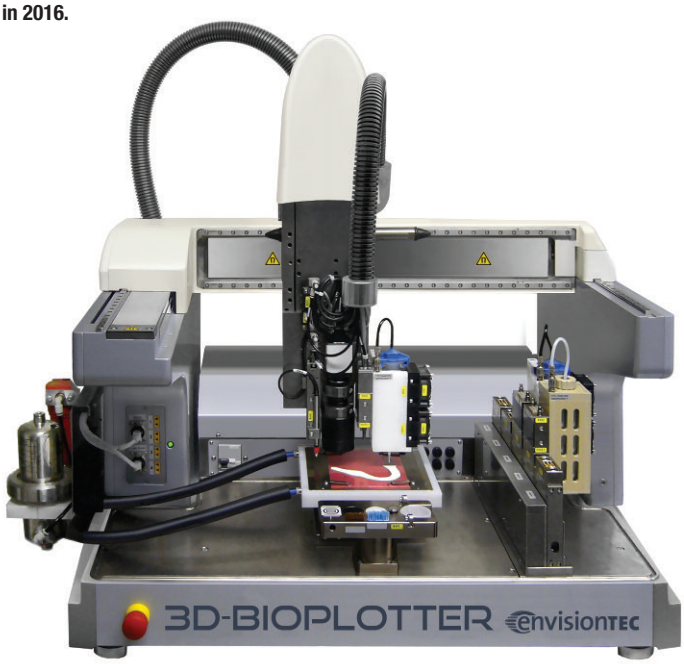
Printlets™ manufactured with pharmaceutical-grade excipients by FDM.

drug can be customized to better suit the individual, such as size and dosage. Drugs can also be designed to have a specific rate of delivery or be designed to be absorbed from the intestines or mouth rather than stomach."

Researchers believe in the future there could even be the possibility for community pharmacists to tailor and print out customized drugs, adds Ms. Mannan. However, while 3DP has the potential as a point-of-dispensing manufacturing technique, Dr. Goyanes says current technology cannot be used to manufacture medicines for human use. "Today, medicines are usually manufactured in large-scale processes, which limit the range of dose strengths available. "3DP technology will be rapidly developed, optimized, and adapted to pharmaceutical manufacture. The technology will allow fabrication of individual tablets to pharmaceutical quality standards and will enable the dose in each tablet to be verified with *in situ* analysis — the key legal requirement for a medicine to be dispensed."

FIGURE 3

3D printed hydrogel scaffold for organ regeneration created by the Shah Lab at Northwestern University in 2016.



During a TED talk, Prof. Lee Cronin, a chemist at the University of Glasgow, took the concept of individual manufacturing one step further, describing a prototype 3D printer capable of synthesis of chemical compounds. It would then be possible to take a digital blueprint and the materials needed, and then synthesize the drug on demand. In the future, Prof. Cronin suggests that some drugs could be instead made available as blueprints, with the materials effectively allowing drug apps to be used.[1]

MORE FDA APPROVALS REQUIRE AGENCY UNDERSTANDING

Like devices made using other manufacturing processes, devices made using 3D printing technology are subject to regulatory requirements. In 2016, the FDA issued draft guidance on the Technical Considerations for Additive Manufactured Devices to advise manufacturers who are producing devices through 3D printing techniques. The draft guidance provides manufacturers with recommendations for device design, manufacturing, and testing considerations when developing 3D printed devices.[2]

"The FDA is currently updating the regulations on medical products and is conducting research to advance regulatory science, as well as act as a resource to promote 3D printing and protect public health," says Freya Lesak, Editor and Community Manager, 3DMedNet, a network

that unites all members of the diverse community of 3D printing for medicine.

"However, further clarity is required on how the FDA and other regulatory agencies will regulate the production of 3D printed drugs (and medical devices)."

The FDA's Center for Drug Evaluation and Research established an Emerging Technology Team (ETT) to examine and advance applications for new technologies, including 3D printing. "What makes this approach novel is that this dialogue can occur during early technology development prior to the submission of a drug application to the FDA," says Jeremy Kahn, FDA Spokesperson. "Such early engagement enables the FDA to proactively identify and address potential roadblocks and helps eliminate potential delay in the adoption of promising new technologies."

The FDA issued a draft guidance in December 2015 entitled Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base that provides recommendations to pharmaceutical companies on effective ways to work with the ETT.

"The main issue with any chemical that is made is purity, ensuring that there are no byproducts," says Prof. Cronin. "The standards in big manufacturing facilities are very high — a key question is how this could translate to lots of smaller facilities."

The FDA is becoming increasingly knowledgeable about 3D printers, and there is interest in how 3D printing can change the way drugs are delivered through implants and other means, says Sarah A. Webster, Global Marketing Director, EnvisionTEC, Inc. EnvisionTEC offers 3D printers that use a variety of technologies to build objects from digital design files. In fact, the FDA is using the EnvisionTEC 3D-Bioplotter Manufacturer

SIDEBAR

VAPOR PRINTING COULD TRANSFORM DRUG DELIVERY

Researchers at the University of Michigan have invented a vapor printing technique they say can print precise doses of multiple drugs onto a variety of surfaces and could possibly revolutionize personalized medications and diagnostics.

Lead researcher Max Shtein, Professor of Materials Science and Engineering, explains the process of organic vapor jet printing (OVJP): It proceeds by thermally evaporating the substance (API) into a stream of inert carrier gas (eg, nitrogen), followed by jetting onto a substrate, where the API forms a film. The organic material is evaporated into a carrier gas; the mixture of evaporated material and carrier gas is jetted onto the cooled substrate, where the organic material condenses. The process is controlled via several parameters, which regulate the deposition rate, the deposit shape, as well as the resulting film morphology.

"There are a number of possible ways in which our technology could transform drug delivery," he says. "If a medicine is taken by mouth, it can be printed onto tablets, onto dissolvable film, or even directly into a liquid or gel capsule. His co-author Dr. Olga Shalev adds: "And for medicines administered primarily by injection, many of those exhibit poor bioavailability. Their active ingredient is often a small organic molecule, as in many cancer medications. We printed a variety of different medicines, including some cancer drugs and observed improved bioavailability of cancer drugs printed with vapor jet printing as compared to the conventional drug powder. This suggests there is indeed great potential to replace some of the injections with printed drug films."

Dr. Shtein points out that vapor printing can be easily adopted by pharmacies and hospitals with just a vapor jet printer, along with the ingredients pre-packaged in cartridges, not unlike a home or office printer. "Of course, this would have to be done in a tamper-proof and traceable way, and cost effectively to attain affordable, yet personalized medications," he says.

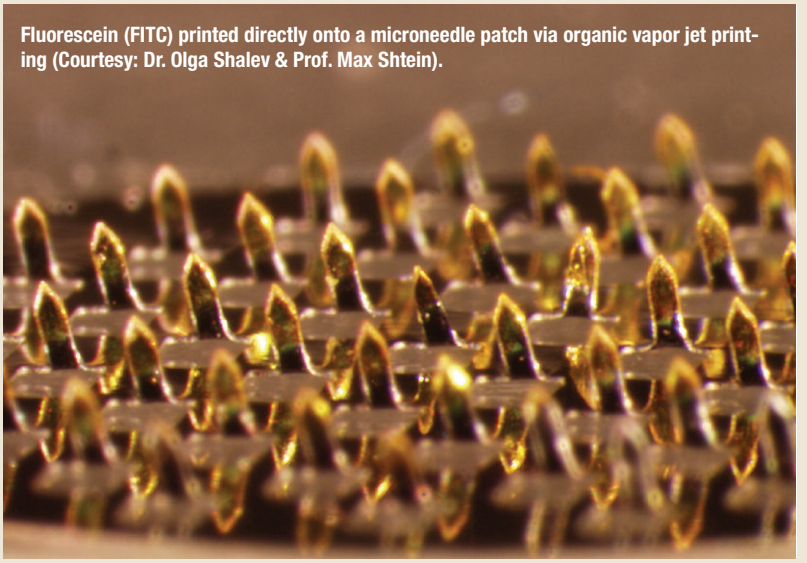
Vapor printing and 3D printing are both additive manufacturing techniques, but in the case of vapor printing, the researchers explain that the material goes down onto a surface from the bottom up, layer by layer. "In the case of 3D printing, there are usually additional substances (such as polymers and/or solvents) involved. With our method, we obtain a coating that contains pure medicines, and none of those unwanted additives. Some have used 3D printing to print actual pills, but in our case, the active ingredient can be coated onto almost any surface/object you need. For oral use, for instance, you can use a sugar strip; for transdermal use, you can coat it onto needle or patch, etc."

Interestingly, 3D and vapor printing techniques can be combined. As vapor printing enables printing on almost any surface, any small molecular medicine can be printed on a 3D printed object. As there are no pre- or post-processing steps needed, development time is shortened, he says.

"The medicines can be printed with very high, nanogram accuracy," adds Dr. Shalev. "This means that we can use the technique not only for therapeutics but also for certain kinds of diagnostics. This accuracy would be very difficult to achieve with 3D printing. We can combine different ingredients, and the system is highly controllable and can be very precisely calibrated to deliver the exact amount needed, very consistently."

REFERENCE

1. Shalev, Olga, et. al., Printing of small molecular medicines from the vapor phase, *Nature Communications*, http://www.readcube.com/articles/10.1038/s41467-017-00763-6.



Fluorescein (FITC) printed directly onto a microneedle patch via organic vapor jet printing (Courtesy: Dr. Olga Shalev & Prof. Max Shtein).

Series model to better understand the 3DP technology. The 3D-Bioplotter is an open source-materials 3D printer to ensure that the printers can build objects according to all customers' needs.

"Our 3D-Bioplotter is the most popular bioprinter in the world and is used by medical researchers to print biologic materials and do testing with drugs directly embedded in structures that sometimes involve living tissues," she says. "Combining drugs with implants and living tissue for release in the body is an area of increasing interest and has obvious potential therapeutic value in terms of improving outcomes with implants or organ donation."

Whether using 3DP to print individual drugs or drugs used with implants, industry insiders say the industry shouldn't get too far ahead of itself. "Regulators will need to adapt to and accept printing as a method of manufacture," says Dr. Goyanes. "The approval of Spritam has shown that this is possible, although the market is not yet at the point to accept individual manufacture of medicines at the point of dispensing. However, we believe we will be able to develop and commercialize printed tablets within the next 5 to10 years."

"I believe over the next 5 years we will continue to see a few select technologies with lower risk profiles achieve regulatory clearance, whereas some of the more advanced applications will move from proof-of-concept and academic research on a path toward commercialization," agrees Ms. Das. "The approval of Spritam was a significant first step that opens the way from which other, more complex concepts can build. Other developers can now move forward with greater confidence that there is a pathway for their concepts to achieve regulatory clearance. I believe we were amazed at the magnitude and pace at which 3D printing has been adopted and leveraged in other industries. In healthcare, we are just scratching the surface and expect that we will see a similar level of disruption over the next 5 to 10 years." ◆

REFERENCES

1. Can you 3D print drugs? By Chris Gayomali, The Week, June 26, 2013, http://theweek.com/articles/462825/3d-print-drugs.
2. FDA's Role in 3D Printing, https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/3DPrintingofMedicalDevices/ucm500548.htm.

Drug Development
EXECUTIVE

Marc Iacobucci
Managing Director
NanOlogy

NanOlogy

NanOlogy: Submicron Particle Platform Transforms Systemic Chemotherapy Into Local Delivery

Demand for new cancer drugs is enormous with public and private investment skyrocketing for the latest technologies. Immuno-oncology therapies have captured much of the attention, and much of the investment, in recent years. The first generation of these drugs has offered some breakthroughs but not a panacea; and development of more effective, safer, and cost-effective therapies is still years away. Moreover, in patients for which immuno-oncology agents are indicated, oncologists frequently combine their use with traditional chemotherapeutics. Such combination use has been found to be synergistic but also, unfortunately, additive in systemic side effects. In the near term, increasing the safety and effectiveness of proven chemotherapies, such as paclitaxel and docetaxel, have the potential to improve the outlook for cancer patients much more quickly and cost-effectively. NanOlogy, a clinical stage pharmaceutical development company, is attempting to do just that by utilizing a breakthrough technology for producing unique, patented, naked submicron particles of paclitaxel and docetaxel. NanoPac® (submicron particle paclitaxel) and NanoDoce® (submicron particle docetaxel) are the first investigational drugs based on this technology and are aimed at transforming the safety and efficacy of these proven therapeutic agents for multiple indications in cancer and other serious illnesses. *Drug Development & Delivery* recently interviewed Marc Iacobucci, Managing Director of NanOlogy, to discuss his company's technology, clinical program, and efforts to transform cancer therapy.

"NanoPac and NanoDoce are stable submicron particles of pure drug that are suspended – not dissolved – in simple vehicles like saline and delivered as particles in concentrated form directly to the site of disease via injection, instillation, inhalation, or topical application. When delivered, the particles release drug locally over several weeks with gradual clearance that does not appear to cause systemic side effects. The particles are so unique in terms of surface area, geometry, dissolution, and other aspects that we were recently granted a composition of matter patent on the particles (US Patent No. 9,814,685) that is valid until June 2036."

Q: How are NanoPac and NanoDoce different from paclitaxel and docetaxel?

A: NanoPac and NanoDoce are stable submicron particles of pure drug that are suspended – not dissolved – in simple vehicles like saline and delivered as particles in concentrated form directly to the site of disease via injection, instillation, inhalation, or topical application. When delivered, the particles release drug locally over several weeks with gradual clearance that does not appear to cause systemic side effects. The particles are so unique in terms of surface area, geometry, dissolution, and other aspects that we were recently granted a composition of matter patent on the particles (US Patent No. 9,814,685) that is valid until June 2036.

The patented production technology that forms these particles uses sonic energy and super critical carbon dioxide to reduce the size of unprocessed paclitaxel and docetaxel crystals by up to 400 times into submicron particles. These particles of pure drug remain stable and free-flowing in their naked form because no static energy is imparted to them. Conventional methods of making small particles like milling create static charge so coating agents or carriers are required to stabilize or solubilize the particles.

Q: What's the major significance of your submicron particle platform?

A: When paclitaxel was introduced in 1992, it was described by the National Cancer Institute as the most significant treatment of the decade, and since then, both paclitaxel and docetaxel have become among the world's most prescribed cancer chemotherapeutics. Despite their effectiveness, however, patients must also contend with debilitating side effects from systemic administration that are what immediately come to mind when one thinks of "chemo."

Physicians and scientists have known for years that paclitaxel and docetaxel are effective cancer-killing agents and have long searched for ways to retain high concentrations of drug at the disease site for a longer time. This is not possible with traditional chemotherapy due to the limitations of systemic delivery, associated side effects, and rapid clearance. NanoPac and NanoDoce are designed to solve this problem by delivering higher, sustained concentrations of drug delivered directly to the site of disease, and by eliminating the side effects caused by systemic administration.

In addition, there is growing evidence that paclitaxel or docetaxel used in combination with newer immune-oncology agents increase the effectiveness of these agents. The advantage of our products is that we may enhance this synergistic effect without adding to systemic side effects.

Q: What cancers are NanOlogy and Soria targeting?

A: We have an extensive clinical development program at NanOlogy for NanoPac sterile suspension with Phase 2 clinical trials launched in 2017 for ovarian cancer, which was granted orphan drug designation by FDA, prostate cancer, pancreatic cancer, and pancreatic mucinous cysts, which can progress to cancer if left untreated. We are very encouraged by early clinical results, which indicate disease regression without drug-related side effects. In mid-2018, we will also begin a clinical trial of NanoDoce sterile suspension for the treatment of bladder cancer.

In addition, NanOlogy affiliate, DFB Soria, has developed a topical product containing submicron particle paclitaxel suspended in an anhydrous base. Identified as SOR007, NanOlogy is conducting a Phase 1/2 clinical trial of SOR007 for treatment of cutaneous metastases and Soria is about to complete a Phase 2 trial for treatment of actinic keratosis (AK), a precancerous skin condition. Final results from the AK study are

expected in April, but preliminary blinded data are showing lesion reduction with no local irritation or systemic side effects. NanOlogy also is developing a form of NanoPac that is delivered via nebulized inhalation for treatment of lung cancer. Preclinical pharmacokinetic studies showed drug retained in lung tissue for greater than 14 days with no gross or histological abnormalities to lung tissue. A follow-on preclinical pharmacology study has just been completed that showed significant tumor regression without drug-related adverse events. We hope to present these exciting findings at a major medical conference later this year.

Q: Do you have any Phase 1 clinical results for NanoPac?

A: NanoPac was initially studied in a Phase 1 trial for treatment of peritoneal malignancies, such as ovarian cancer. NanoPac was delivered directly into the peritoneal cavity of seriously ill patients whose cancer had no other treatment options. Data showed that compared with intravenous administration of the paclitaxel, NanoPac remained entrapped in the peritoneum for weeks providing higher and prolonged levels of paclitaxel at the disease site with minimal systemic exposure and minimal drug-related side effects. Additionally, of the 21 very ill patients who received NanoPac in the Phase 1 trial, five survived at least 400 days, which was much longer than expected. The results from this trial helped us gain approval from the FDA for the Phase 2 trials we are conducting across multiple indications.

Q: How soon could NanoPac and NanoDoce reach patients?

A: Because systemically administered paclitaxel and docetaxel are already on the market and have a long history of use around the world, the regulatory pathway for our products falls under the FDA's streamlined 505(b)(2) regulatory pathway. This pathway is applied to new embodiments of approved drugs and is intended to reduce the overall time for advancing successful product candidates through the development process to regulatory approval. Depending on the success of our Phase 2 trials, we may also be eligible for Fast Track designation by the FDA for certain indications like pancreatic cancer.

Given the 505(b) 2 regulatory pathway and possibility of Fast Track designation, one or more of our products have the potential to reach patients in as few as 2 or 3 years, which is obviously much faster than the 10 to 15 years a new molecular entity (NME) can take.

Q: How were NanOlogy and Soria formed?

A: NanOlogy was formed in 2015 by DFB Pharmaceuticals, LLC of Ft. Worth, TX, in collaboration with CritiTech, Inc. of Lawrence, KS, and US Biotest, Inc. of San Luis Obispo, CA. DFB is a private investment and development group focused on new products and businesses in healthcare, and the company has realized more than $1.5 billion in value since its founding in 1990. CritiTech developed the production technology and plays a key role in product development. US Biotest brings their expertise in preclinical and clinical regulatory strategy and management to the company. DFB Soria is an affiliate of NanOlogy and wholly owned and operated by DFB. Soria licensed the CritiTech technology for dermatology and certain other fields outside of oncology and developed SOR007.

Q: What are your long-term plans for NanOlogy and Soria?

A: We believe we offer a strong value proposition that includes a therapeutic platform in clinical development targeted at disease indications totaling more than $13 billion in annual treatment cost in the US alone. Importantly, our platform has a streamlined path to regulatory submission coupled with an extensive IP portfolio, including a composition patent. This gives us NME-like advantages without the associated risk and time of NME development.

We are now generating exciting clinical data and will be exploring options over the next 12 months for further development. These options may include continuing to invest ourselves, which we have the wherewithal to do, or identifying a partner who sees the value in what we have created and wants to help us get our products to patients in need. ◆

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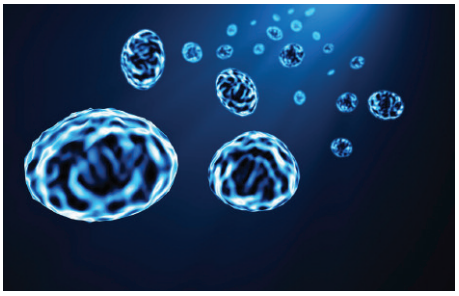

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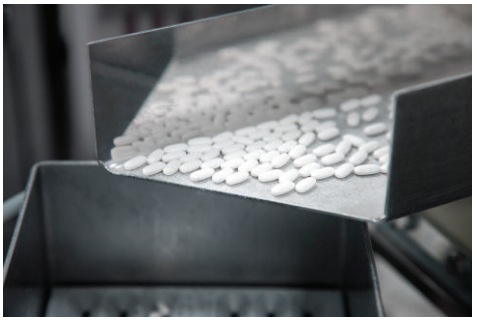

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NASAL DELIVERY

A Promising Route of Drug Delivery to the Brain: Scientific Considerations

By: Vinayak Pathak, MPharm, MBA

ABSTRACT

One of the factors that limit the ability of most of the drugs to treat Central Nervous System (CNS) disorders is related to the extent of drug that is able to cross the Blood Brain Barrier (BBB). The endothelial cells of the blood capillaries to the brain include tight junctions that act as a barrier to most drugs and inhibit the ability of drugs and solutes to cross this barrier. The BBB effectively restricts the transfer of hydrophilic compounds from the vascular compartment to the brain tissue. In contrast to the other tissues, no bulk flow occurs across the capillary walls due to tight junctions between the cells. Throughout the past few decades, there has been a number of innovative drug delivery approaches that may overcome the challenges associated with drugs to cross the BBB.

One such approach entails the delivery of drugs via the nasal route. There is growing scientific support that delivery of drugs via the nasal route may result in higher concentrations of drugs that can cross the BBB. However, this approach has significant limitations that require a careful consideration of the physico-chemical and pharmacological properties of the drug, it's potential CNS toxicity, as well as the dose and delivery vehicles that may be used. The final assessment after performing the review on this subject indicates there are significant differences in the nasal anatomy and physiology of different animal species and humans, which makes it very difficult to obtain a direct correlation between them. The published experimental data in scientific journals does support that different formulation approaches using mucoadhesive compounds, absorption enhancers, and specialized reagents can increase the efficiency of drug delivery to the brain via the nasal route. Further experiments are needed to establish a robust correlation between the properties of the compound being investigated, the physiology of the nasal cavity, and the impact of specialized drug delivery techniques that are known to influence drug delivery to the brain via the nasal route of administration.

INTRODUCTION & BACKGROUND

Drugs are delivered to the systemic circulation via several routes, such as oral, parenteral (intravenous, intramuscular), and in most cases, drugs administered via these routes encounter acidic or enzymatic degradation and may undergo excessive first-pass effect (hepatic metabolism) following administration. Due to these factors, effective doses of drugs sometimes may not reach the systemic circulation, resulting in ineffective treatment. It is therefore required to explore either alternate routes or specialized delivery technologies that can result in improved and effective drug delivery options. The nasal route of drug delivery is one such alternate route that provides access to highly vascularized mucosa, which can be exploited as an interesting site for local drug delivery, systemic drug delivery, and targeted drug delivery (CNS).

The anatomy and physiology of the olfactory region is such that it can provide a direct path to the CNS, resulting in higher concentration of drug in different regions of the brain. The additional benefit of this region is that it provides both intracellular and extracellular drug transport pathways to the CNS. In order

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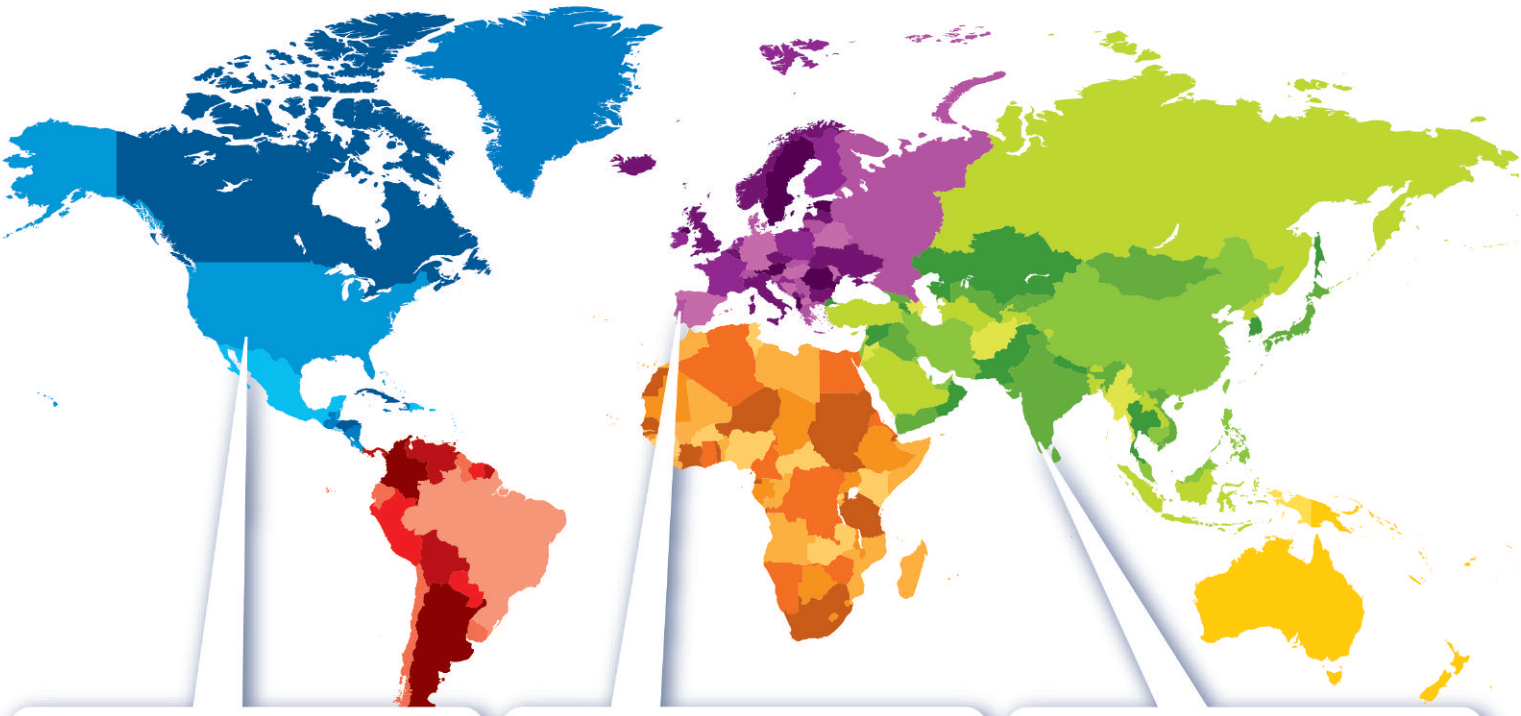

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TABLE 1

Species	Bodyweight (kg)	Nasal Cavity Volume (NCV) (cm^3)	Nasal Cavity Surface Area (NCSA) (cm^2)	Relative Surface Area (NCSA/NCV) (cm^{-1})	Olfactory Epithelium (% of NCSA)	Olfactory Epithelium (cm^3)
Mouse	0.03	0.03	25	96.3	47	1.37
Rat	0.25	0.26	13.4	51.5	50	6.75
Rabbit	3	6	61	10.2	10	6
Human	70	25	160	6.4	8	12.5

Nasal Cavity Differences Among Species

for a certain drug to get transported via one of these two pathways, it is also dependent on other factors that are related to the physico-chemical properties of the drug and specific receptors present on the olfactory neurons.

Nasal applications of topical decongestants or anti-inflammatory drugs are the most popular topical nasal drug deliveries. For some compounds, delivery of drugs via the nasal route provides direct access to systemic absorption. Absorption of drug via the nasal cavity can be described as diffusion of drug into system circulation via the nasal mucosa. Mucosal absorption via the nasal cavity usually follows: drug release, penetration (entry into a layer), permeation (transition of a layer), and absorption (uptake into the vascular system). Assuming the existence of an olfactory-pathway to the brain in humans, it remains an area to explore and understand as to what extent it contributes to central nervous availability of drugs administered via the nasal route.

THE NASAL ANATOMY

The nasal septum divides the human nose into two equal symmetrical halves. The posterior part of the nasal cavity is called the nasopharynx, and each symmetrical half opens to the environment. Both halves of the nasal cavity consist of the following four regions:[1,2]

Vestibule: is not very highly vascularized and permeability of the drugs via this region is very poor.

Atrium: vascularization in this part of the nasal cavity is low, which results in moderate permeability of drugs.

Respiratory Region: this part of the nasal cavity is highly vascularized and therefore the permeability of drugs from this region is good.

Olfactory Region: is highly vascularized, which results in high permeability of drug. This region is also reported as a potential site for nose-brain transport of drugs.

BARRIERS TO DRUG TRANSPORT FROM NOSE TO BRAIN

Physico-Chemical Properties of the Drug

Molecular weight, lipophilicity, and degree of dissociation are the primary properties of the drug that dictate to what rate and extent drugs will transport from the nasal mucosa to the brain.

Regarding relative molecular weight, there have been studies in which the effect of molecular weight was studied, and it was observed that as the molecular weight of drug administered via the nasal route increased, the concentration of drug in the brain decreased. Different molecular weight of fluorescent-labelled dextrans FD4 (4400 Da), FD20 (18900 Da), and FD40 (40500 Da) were administered via the nasal and intravenous routes.The concentration of drug in the cerebrospinal fluid (CF) were evaluated following iv administration, and it was found there were no fluorescent labelled dextrans detected in the CSF. Although FD4, FD20, and FD40 were detected in the CSF following nasal administration, the concentration decreased as the molecular weight of the dextrans increased. Most small molecular weight (< 400 Da) drug molecules get absorbed easily and are good candidates for transport to the brain via the nasal mucosa.[3] Molecular weights higher than 1000 Da show poor ability to get absorbed in to the brain via the nasal mucosa. Large molecules, such as peptides and proteins, have also been evaluated for their capability of getting absorbed via the nasal cavity.[3]

Regarding lipophilicity, lipophilic drugs are known to show high absorption via the nasal mucosa. This nasal epithelium is known to behave as a lipid sieve, which makes the lipophilic drugs penetrate the nasal mucosa. It is also observed that there exists a linear correlation between the drug's oil-water distribution coefficient and

its absorption rate constant.[4] Lipophilic drugs, such as sulfonamides, have been tested in animal models in which the drug concentration in the CSF increased as a result of direct nose-to-brain transport following nasal administration. Lipophilic drugs, such as alprenolol and propranolol, were well absorbed from the nasal mucosa when compared with the hydrophilic drug metoprolol.[5]

Regarding degree of dissociation, the drug concentration in the CF is inversely proportion to the degree of dissociation. It is therefore important to understand that the degree of ionization of a drug that is administered via the nasal route can affect the ability of drug to get absorbed in the nasal mucosa and its concentrations in the CSF. Diltiazem HCl and paracetamol have been used as model drugs to study the physio-chemical properties of the drug in relation with nasal absorption. The results of this study concluded that there exists a quantitative relationship between the partition coefficient and the nasal absorption constant.[4]

Drug Concentration, Dose & Volume of Administration

The concentration of drug, dose, and volume of dose administered are all important factors that can affect nasal drug delivery to the brain. Nasal drug absorption increases as the concentration of drug increases at the site of administration. This phenomenon is more prominent with drugs that are absorbed by passive diffusion as a primary mechanism of drug absorption. Higher concentrations of drug administered in high volume can negatively impact the absorption of the drug due to local adverse effects and in some cases, results in damaging the nasal mucosa. This is why it becomes important to realize that the nasal cavity has limited capacity and therefore the dosage for nasal administration must be relatively low (25 to 200 µl).[6]

Mucociliary Clearance

One of the important functions of the nasal cavity is the removal of dust, allergens, and bacteria as part of normal physiological function. For drugs to maintain the desired concentration and delivered volume following nasal administration so that the therapeutic dose can get absorbed, it is important the drugs display prolonged residence time within the nasal cavity. The deposition of drug in the nasal mucosa can be achieved by different formulation approaches and by maintaining the pH of the nasal formulation in the range of pH 4.5 to 6.5.[7] Different dosage forms have been used to increase the residence time in the nasal cavity. These include gelatin, emulsions, ointments, liposomes, microspheres, and nanoparticles prepared using ion exchange resin methods. Bioadhesive preparations, starch microspheres, and chitosan-based formulations have been extensively studied, which resulted in improved bioadhesive properties and increased residence time on the nasal epithelial surface.[8,9]

Presence of Enzymatic Activity

The presence of enzymes in the nasal cavity can form an enzyme barrier that is known to affect the stability of the drug in the nasal cavity. Proteins and peptides are prone to degradation by proteases and amino-peptidase within the nasal cavity. Although it is not exact as the first-pass effect that drugs undergo following oral administration, the enzymatic activity in the nasal cavity can result in decreased therapeutic effects. The presence of P450 enzymes are much higher in the nasal mucosa when compared to the respiratory mucosa.[10]

Difference in Animal Species

The nasal mucosa and its physiology is very different from one species to another. Surface area of the olfactory mucosa varies with different animals. Rats and mice have been widely used as experimental animals. The olfactory area in rats is more than 50% of the entire surface area of the nasal cavity as compared to humans in which the olfactory region is only 3% to 5% of the entire nasal cavity. It is therefore very important to take into account the anatomical and histological differences (Table 1) when extrapolating findings from animal experiments to humans.[11-13]

RECOMMENDATIONS TO OVERCOME BARRIERS TO DRUG TRANSPORT FROM NOSE TO BRAIN

There have been a number of novel approaches evaluated in animal models to overcome the barriers to nose-to-brain delivery of drugs via the nasal route. The efforts have been concentrated toward increasing the residence time in the nasal mucosa and modifying the physico-chemical properties of the drug using functional excipients and innovative drug delivery technologies. A few examples of these innovative technologies include a combination of mucoadhesive polymers, absorption enhancers, and drug delivery devices aimed for precise delivery of drug within the nasal cavity.

Prodrug Approach

As previously discussed, the physicochemical properties of drugs, such as the molecular weight and lipophilicity, are critical parameters that have the most influence on drug delivery to the brain via the

nasal epithelium. A prodrug strategy can help in modifying these properties in such a manner that the rate and extent of drug absorption increases in the nasal cavity. Experimental studies both in vivo and ex vivo have shown that rapid and complete absorption of drug can be attributed to the degree of lipophilicity and smaller molecular weight of the test compound. Several water-soluble alkyl ester prodrugs of L-dopa were administered to rats via the nasal route, and it was observed that the concentration of butyl ester prodrug of L-dopa was significantly higher in the CNS of rats as compared to parent drug.[14] While this approach has proven to work in many small molecules, this strategy presents some challenges for large molecules, such as proteins and other biologics. It has been difficult to increase the lipophilicity of proteins as there can be significant impact on the spatial structure of the protein, resulting in diminished biological activity.[14]

Innovative Formulation Approach

Maintaining high drug concentration for passive diffusion on the nasal epithelium is important, and in order to achieve this, precise drug deposition and extended residence time must be optimized. There are several nasal formulations and devices that are designed to overcome these challenges. Experimental design in which N-cyclopentyladenosine (CPA) was formulated with mannitol-lecithin and chitosan hydrochloride microparticles were administered to rats via nasal administration showed higher amount of CPA present in the CNS of rats compared to the free CPA. The chitosan hydrochloride formation resulted in a 10-fold higher amount of CPA in the CSF compared to the mannitol-lecithin microparticles formulation.[16]

TABLE 2

Company	Device Name
Optinose	Bi-Directional Technology™
Impel NeuroPharma	POD Device
Kurve Technology	ViaNase Technology/Controlled Particle Dispersion (CPD®) Technology Platform

Proprietary Nasal Drug Delivery Devices[22]

Absorption Enhancers & Enzyme Inhibitors

Drugs that are highly lipophilic in nature and also have a very low molecular weight might not need a specialized formulation approach, including use of absorption enhancers. Absorption enhancers can be used in cases where the drug exhibits poor membrane permeability, has large molecular size, and is susceptible to enzymatic degradation by aminopeptides.[17,19,20] Drugs that are formulated using absorption enhancers may impart the following properties that will result in increased drug bioavailability following nasal administration:

- Improve the solubility of the drug
- Reduce the surface tension of the mucus
- Decrease the enzyme activity which may keep the drug in its stable form

Nasal Drug Delivery Devices

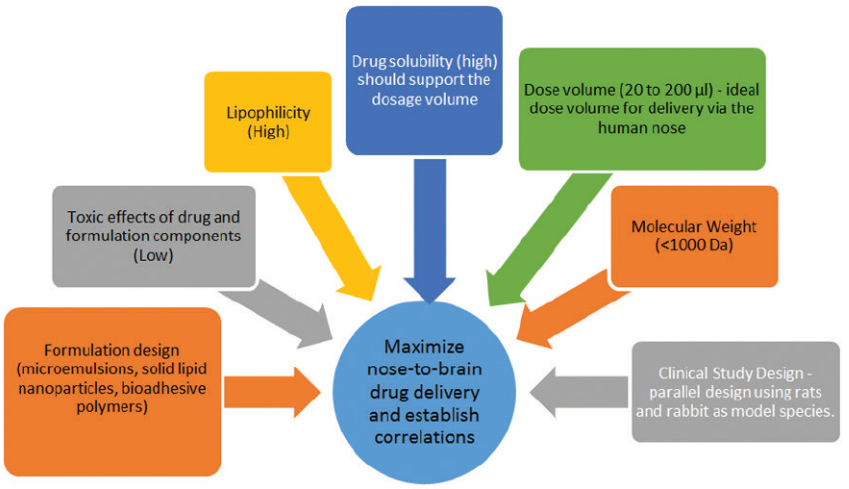
Drug delivery devices have been found to play an important role in ensuring that the entire drug is delivered to the target site in the nasal cavity. It is difficult to precisely deliver the drug to the olfactory region of the human nasal cavity as this region is found high up in the nasal cavity, above the superior conchae. This area is exposed to a very low volume of the air that penetrates the nasal cavity and can result in lower doses of the drug reaching the olfactory region. Some of the novel proprietary devices that have shown significant differences following administering the drug via the nasal route are shown in Table 2.[18-21]

Although the initial proof-of-concept studies using these novel nasal drug delivery devices does show promising results, they still need to be further tested using different types of molecules intended to be delivered to the CNS/brain via the nasal cavity/route of drug administration.

CONCLUSION

Administration of drugs via the nasal route is probably one of the most non-invasive methods of bypassing the BBB for delivering drugs targeted for CNS disorders. After reviewing the clinical experiments published in this area of drug delivery, it is evident that formulation design, altering the physico-chemical properties of the drug, addition of absorption enhancers and mucoadhesive polymers did result in higher bioavailability of drugs in animal models via the nasal route when compared

FIGURE 1



Combination of Ideal Parameters Resulting in Efficient Nose-to-Brain Drug Delivery

to parenteral administration of the same drug. Figure 1 shows a combination of ideal parameters that will maximize nose-to-brain drug delivery.

Because the ultimate goal of performing studies in animal models is to collect data and parameters that can be translated to human studies, there still exists a gap in establishing meaningful correlations. The differences in the anatomy and physiology of the animal nose and human nose are very significant and makes it difficult to correlate the outcome of the studies. In addition, the correlation between the amounts of dose delivered via the nasal route versus the amount of dose bioavailable in the CNS of animal species does not exist. This is due to the reason that high volumes of doses are used in the clinical studies using animal models, and these doses are practically not possible for human administration.

ACKNOWLEDGEMENTS

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REFERENCES

1. Temsamani J. Delivering drugs to the brain—beating the blood brain barrier. Eur Biopharm Rev Autumn. 2002:72-75.
2. Schwartz MW, Sipols A, Kahn SE, Lattemann DF, et al. Kinetics and specificity of insulin uptake from plasma intocerebrospinal fluid. Am J Physiol. 1990:259:E378–E383.
3. Djupesland PG, Skretting A. Nasal deposition and in man: comparison of a bidirectional powder device and a traditional liquid spray pump. J Aerosol Med Pulm Drug Del. 2009;25:280-289.
4. Sakane T, Akizuki M, Yamashita S, et al. The transport of a drug to the cerebrospinal fluid directly from the nasal cavity: the relation to the lipophilicity of the drug. Chem Pharm Bull. 1991;39:2456-2485.
5. Jiang XG, Lu X, Cui JB, et al. Studies on octanol-water partition coefficient and nasal drug absorption. Acta Pharm Sin. 1997;32:458-460.
6. Ross TM, Martinez PM, Renner JC, et al. Intranasal administration of interferon beta bypasses the blood brain barrier to target the central nervous system and cervical lymph nodes: a non-invasive treatment strategy for multiple sclerosis. J Neuroimmunol. 2004;151:66-77.
7. Arora P, Sharma S, Garg S. Permeability issues in nasal drug delivery. Drug Discov Today. 2002;7:967-975.
8. Illum L. Nasal drug delivery compositions containing nicotine. 1999;US5935604.
9. Pavis H, Wicock A, Edgecombe J, et al. Pilot study of nasal morphine-chitosan for the relief of breakthrough pain in patients with cancer. J Pain Symptom Manage. 2002;24:598-602.
10. Vyas TK, Shahiwala A, Marathe S, Misra A. Intranasal drug delivery for brain targeting. Curr Drug Deliv. 2005;2:165-175.
11. Mygind N, Dahl R. Anatomy, physiology and function of the nasal cavities in health and disease. Adv Drug Deliv Rev.1998;29(1):3-12.
12. Lochhead JJ, Thorne RG. Intranasal delivery of biologics to the central nervous system. Adv Drug Del Rev. 2012;64:614-628.
13. Gizurarson S. Anatomical and histological factors affecting intranasal drug and vaccine delivery. Curr Drug Deliv. 2012;9:566–582.
14. Dalpiaz A, et al. Brain uptake of a Zidovudine prodrug after nasal administration of solid lipid microparticles. Mol Pharm. 2014;11:1550-1561.
15. Zachary N, Warnken H, Smyth DC, et al. Formulation and device design to increase nose to brain drug delivery. J Drug Delivery Science & Tech. 2016;35:213-222.
16. Johnson NJ, Hanson LR, Frey WH II. Trigeminal pathways deliver a low molecular weight drug from the nose to the brain and orofacial structures. Mol. Pharm. 2010;7:884-893.
17. Wolf DA, et al. Lysosomal enzyme can bypass the blood-brain barrier and reach the CNS following intranasal administration. Mol Genet Metab. 2012;106:131-134.
18. Costantino HR, Illum L, Brandt G, Johnson P, et al. Intranasal delivery: physiochemical and therapeutic aspects. Int J Pharm. 2007;337:1-24.
19. Appu AP, Arun P, Krishnan JKS, et al. Rapid intranasal delivery of chloramphenicol acetyltransferase in the active form to different brain regions as a model for enzyme therapy in the CNS. J Neurosci Methods. 2016;259:129-134.
20. Karasulu E, Yavas A, et al. Permeation studies and histological examination of sheep nasal mucosa following administration of different nasal formulations with or without absorption enhancers. Drug Delivery Technology. 2008;15:219-225.
21. Djupesland PG. Nasal drug delivery devices: characteristics and performance in a clinical perspective - a review. Drug Deliv Transl Res. 2013;3:42–62.
22. Lisbeth I. Intranasal Delivery to the Central Nervous System: Book Chapter 25. (Blood–Brain Barrier in Drug Discovery: Optimizing Brain Exposure of CNS Drugs and Minimizing Brain Side Effects for Peripheral Drugs, First Edition. Edited by Li Di and Edward H. Kerns. © 2015 John Wiley & Sons, Inc. Published 2015 by John Wiley & Sons, Inc.)

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BIOGRAPHY

Vinayak Pathak currently serves as Associate Director, Product Development at West-Ward Pharmaceuticals, based in Columbus, OH. He earned his BS in Pharmaceutical Sciences from India and his Master's in Pharmaceutical Sciences from James L Winkle College of Pharmacy, University of Cincinnati. He also earned his MBA from Columbus State University, GA. He is leading a team of formulation scientists and involved in initial formulation development to pilot GMP mfg. and technology transfer. Previously, he served as Group Leader, Formulation Development at Accucaps Industries ltd, Canada, where he was responsible to lead a team and develop formulation and manufacturing process for soft gelatin capsules. He also worked at Pharmascience Inc, Montreal Canada, as Senior Scientist, Formulation Development, where he was responsible for formulation development and business support activities for various dosage forms involving solids, liquids, and suspensions. Mr. Pathak's research focus includes development of immediate-release, controlled-release systems, multiparticulate drug delivery systems, and nasal formulation development.

DNA THERAPEUTICS

DNAbilize-ING Antisense

By: Peter Nielsen, MBA

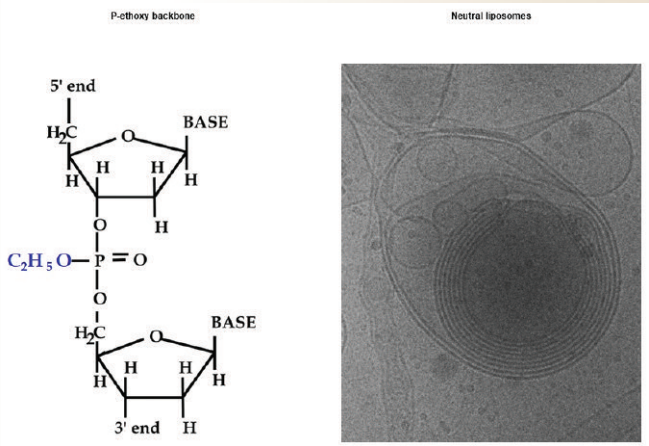
INTRODUCTION

Forty-five years ago, an article in the *Journal of Molecular Biology* detailed the strategy and technical knowhow involved in creating an antisense oligonucleotide for the first time. It took another 20 years of work until a company received clearance from the FDA to conduct the first clinical trial for an antisense product candidate. That company was ISIS Pharmaceuticals (now named Ionis Pharmaceuticals), and the product was ISIS-2105 (afovirsen).[1] Unfortunately, ISIS-2105 did not prove successful and the program was halted in Phase 2 due to a lack of efficacy. However, while this and other early efforts to develop antisense therapeutics failed, they demonstrated the potential of the technology and effectively launched the antisense revolution.

There are several types of antisense – short interfering RNA (siRNA), single-stranded DNA (ssDNA), and anti-microRNAs – each with unique attributes that lend themselves to specific applications. At Bio-Path Holdings, we fabricate our antisense oligonucleotides with single-stranded DNA using our platform technology, DNAbilize®.

As with any antisense approach, our goal is to target and shut down proteins that are over-expressed in diseases like cancer. Our candidates are differentiated from those in development at other companies by the type of modification to the antisense molecule and the method by which it is conveyed to its target cell.

FIGURE 1



Novel DNA modification and use of neutral liposomes allows for systemic distribution via IV infusion.

TECHNOLOGICAL CHALLENGES IN THE DELIVERY OF ANTISENSE

Technologies have evolved over several years that have vastly improved the stability of oligonucleotides, allowing them to escape degradation by DNA-cleaving enzymes during circulation.[2] Unfortunately, as often happens in the first efforts to develop novel technologies, serious limitations have been identified in these first- and second-generation technologies. Specifically, it has been shown that phosphorothioate oligonucleotides – a common first-generation modification in which an oxygen atom has been replaced with a sulfur atom – activate the complement system causing thrombocytopenia.[3]

The mechanism by which phosphorothioates induce this complement cascade has not been fully elucidated, but it is theorized that they bind to heparin-binding or similar proteins that interact with protective polyanions on cell surfaces.[4] By so activating this complement cascade, phosphorothioate oligonucleotides trigger an inflammatory reaction designed to trigger the clearance of foreign bodies.

Second-generation modifications that employ 2′-O-methyl (OMe) and 2′-O-methoxy-ethyl (OMOE) additions often cause hepatotoxicity due to their propensity to accumulate in the liver, as well as vascular inflammation and some instances of idiopathic thrombocytopenic purpura, a rare clotting disorder.[5]

NOVEL SOLUTION DISCOVERED

Bio-Path Holdings has sought to overcome these problems through a proprietary platform that offers a unique solution to both DNA stabilization and delivery into the cell. With a neutral charged (or uncharged) DNA backbone using ethoxy groups in place of simple standalone oxygen in the phosphate backbone, the oligonucleotide is protected from nucleases without creating unwanted serum-protein interactions. It is also slightly hydrophobic, allowing it to incorporate readily into the lipid bilayers of a neutral uncharged lipid nanoparticle, as seen in Figure 1. Incorporation into the lipid bilayers (as opposed to the hydrophilic core or the outer surface) allows for tight association and safe delivery through the body. The lack of surface charge on the lipid nanoparticle means that cell membrane perturbations and serum protein binding that would cause steric hindrance to uptake is avoided. The nanoparticles are endocytosed into cells where the oligonucleotide is released and has therapeutic effect.

Lipid nanoparticle encapsulation of oligonucleotides has been attempted before. Initially, research into this delivery concept focused on cationic lipids because they have an overall positive charge, which would be attracted to the negative charge of oligonucleotides and to the cell membrane, enhancing cellular uptake and delivery of DNA. The first generation of cationic lipids required conjugation to a "helper" lipid, dioleoyl phosphatidylethanolamine (DOPE), which destabilizes the endosome compartment so that the nanoparticle's nucleic acid cargo can be delivered into the target cell's cytoplasm. Unfortunately, these cationic lipid complexes were shown to have poor stability and to absorb serum proteins in circulation, which in turn diminished the efficiency with which DNA was transferred into cells. Non-specific toxicity to cell membranes was also increased in these cationic lipid complexes.[6]

To our knowledge, Bio-Path is the only company to have made significant improvements in both DNA stabilization and oligonucleotide delivery. In our preclinical and clinical trials to date, we have observed no dose-limiting toxicities either from the nanoparticles or the unique ethyl modifications we employ. The DNAbilize system therefore appears to be one of the most successful ssDNA oligonucleotide therapeutics in trials today for blood cancers.

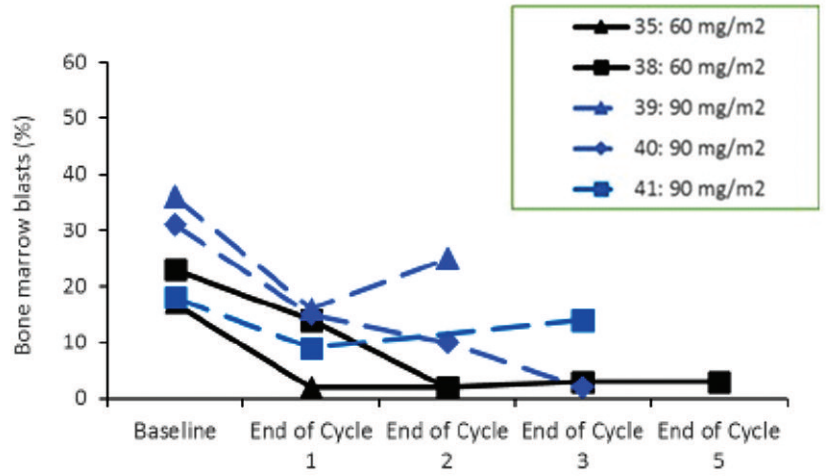
We have successfully employed this DNAbilize system in the development of prexigebersen (formerly BP1001), our lead candidate for the treatment of chronic myelogenous leukemia (CML) and acute myeloid leukemia (AML), as well as various solid tumors such as breast and ovarian cancers.

Prexigebersen is designed to inhibit GRB2, which is highly expressed in leukemic cells and cancers with activated tyrosine kinases (eg, EGFR, BCR-ABL, FLT3, KIT). It has been shown to act as a bridge between the activated kinase and the RAS/RAF/MEK/ERK and RAS/PI3K/AKT pathways, and is critical to the survival of many cancer cells. GRB2 is a protein that does not have enzymatic activity, putting it in a class of targets historically considered to be "un-druggable."

In preclinical *in vitro* studies, prexigebersen was effective in inhibiting the proliferation of BCR-ABL-positive leukemic cell lines as well as breast cancer cell lines that overexpress EGFR or ERBB2 leading to decreased ERK or AKT activation.[7] Prexigebersen was also effective in inhibiting FGF-induced motility of breast cancer cells.[6]

In vivo pharmacology studies showed that prexigebersen was widely distributed throughout the body with a tissue half-life of 2-to-3 days. Mice and rabbits tolerated intravenous injections of prexigebersen well, with no evidence of impaired renal or hepatic functions; and blood clotting time was normal, suggesting no activation of complement cascade. Importantly, in rodents, prexigebersen was shown to distrib-

FIGURE 2



prexigebersen + low-dose Ara-C suppressed bone marrow blasts in patients with refractory/ relapsed AML.

ute to many organs throughout the body, including liver, spleen, and bone marrow, where leukemia manifested; which provided us with confidence that prexigebersen would be effective in targeting this cancer.

In preclinical efficacy studies, mice with BCR-ABL-positive leukemia xenografts that were intravenously administered with prexigebersen twice a week showed a marked improvement in survival, with 80% of such mice surviving 32 to 44 days longer than control mice. Based on the positive safety and efficacy seen in preclinical models, the company entered human clinical studies.

CLINICAL EFFICACY & SAFETY DATA VALIDATES TECHNOLOGY

Prexigebersen completed a Phase 1 clinical trial as a monotherapy to treat patients with AML, CML, or myelodysplastic syndromes (MDS). The primary goal of this initial study was to assess the safety and maximum tolerated dose (MTD), as well as to further define prexigebersen's pharmacokinetics. One patient of 18 evaluable patients reported a treatment-related adverse event that was determined to be a result of treatment with a concomitant therapy. No other dose-limiting toxicities nor MTD was identified. Notably, nine of the 18 evaluable patients experienced at least a 50% reduction in peripheral or bone marrow blasts compared to baseline measures. Two patients with treatment-resistant CML had particularly impressive responses to treatment, experiencing a reduction in circulating blasts from 89% to 12% in one patient and from 24% to 7% in the other.[8]

A subsequent Phase 1b trial in six elderly refractory and relapsed leukemia patients was also conducted to assess the activity of prexigebersen in combination with low-dose Ara-C (LDAC). Five of the six patients enrolled experienced a clinical response, as seen in Figure 2, with complete responses (CR) observed in three patients and partial responses (PR) in two.[4] Again, no MTD was identified.

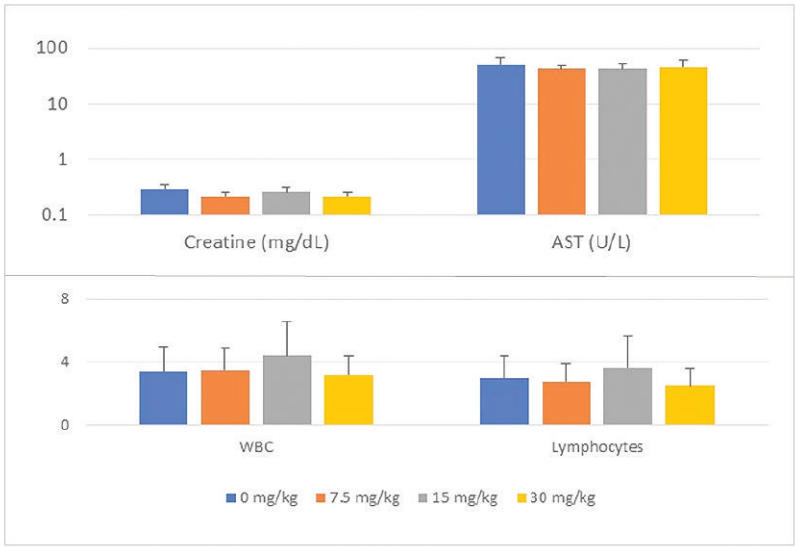
The evidence that prexigebersen has been well tolerated in these studies, and that no MTD has been reached to date, leads us to hypothesize that patients may be able to remain on prexigebersen treatment longer in combination with more aggressive anti-cancer drugs that are administered at low or moderate doses to avoid increasing toxicities.

Prexigebersen's success in targeting GRB2 stands in stark contrast to earlier industry efforts to target this gene. GRB2 is a highly sought molecular target, as it is implicated in cell cycle progression and angiogenesis, both of which are processes required for the spread of solid tumors and blood cancers. However, to date, we are not aware of any successful attempts to inhibit GRB2 either using antisense or small-molecules directed to the GRB2 protein.

We also employed DNAbilize to develop a second candidate, BP1002, which targets the BCL-2 gene, which codes for a family of proteins that promote cellular survival and inhibit apoptosis. BCL-2 is highly expressed in aggressive non Hodgkin's lymphoma (NHL) as well as other cancers. In *in vitro* studies, BP1002 induced greater than 50% inhibition in 11 of the 15 aggressive NHL cell lines, including diffuse large B-cell lymphoma, mantle cell lymphoma and Burkitt's lymphoma. In two *in vivo* studies, 87% of mice treated with BP1002 survived until the end of the study-period, compared to none of the control mice.[9]

BP1002 has been well tolerated in the animal studies we've conducted to date. Recently, for example, we completed a dose-ranging study that showed minimal impact of BP1002 on platelets, white blood cells, kidney function, or liver enzymes with any of the three doses we

FIGURE 3



BP1002 was well tolerated with minimal impact on platelets, white blood cells, kidney function, or liver enzymes.

tested. As you can see in the bar charts in Figure 3, side effects from BP1002 were similar to untreated control mice.

This was an important finding, as earlier industry efforts to target BCL-2 have been hampered by lack of efficacy or significant dose-limiting toxicities, such as thrombocytopenia.[10] Despite these setbacks, there remains great interest in the scientific community in targeting BCL-2, as it codes for a family of proteins that can promote cancer cell survival and generate resistance to chemotherapeutics.

If BP1002 succeeds in blocking the production of these proteins while maintaining a strong safety profile, it could be an important therapeutic option for oncologists. Not only might it have utility as a monotherapy, but the potential exists that it could restore sensitivity to cancers that had previously been resistant to treatment, opening up an array of treatment combinations. We are planning to initiate a Phase 1 trial to test BP1002 in patients with relapsed/refractory lymphoma.

DNABILIZING OTHER TARGETS

Beyond the treatment of cancer, we believe DNAbilize has the potential to generate antisense therapies against other non-enzyme targets currently considered to be un-druggable. We believe this to be a significant business development opportunity for Bio-Path and a significant R&D opportunity for the biotech industry, as non-enzymes make up a majority of the proteome. Such protein targets include those involved in structural integrity of cells, signaling pathways, subcellular transport, transcription, translation, and other critical functions. Indications associated with errant non-enzyme proteins include autoimmune and inflammatory disorders, such as inflammatory bowel disease, asthma, and atherosclerosis; neurological and developmental disorders, such as Coffin-Siris syndrome, focal segmental glomerulosclerosis (FSGS), Rett Syndrome, Cornelia de Lange Syndrome, and Roberts Syndrome; cardiovascular diseases, including arrhythmia, fibrosis, and hypertrophy.

As is the case with cancer patients, individuals with autoimmune, neurological, and cardiovascular diseases and conditions often have additional co-morbidities and are taking several medications to control symptoms. We believe that the low level of off-target toxicities seen with our two candidates to date suggest that DNAbilize products should not elicit any drug-drug interactions with patient's ongoing treatment regimens. Moreover, it should be able to be combined with broad spectrum pharmaceuticals to increase their therapeutic effect without increasing side effects.

We are engaged in discussions with corporate and academic research organizations for the out-license of rights to the many potential development opportunities in the DNAbilize platform in specific non-cancer indications, and will continue to explore these and other business development opportunities. Companies that are interested in exploring collaborations or licensing agreements for DNAbilize should contact our business development office at partnering@biopathholdings.com. ◆

REFERENCES

1. Cowsert LM, Fox MC, Zon G, Mirabelli CK. In vitro evaluation of phosphorothioate oligonucleotides targeted to the E2 mRNA of papillomavirus: potential treatment for genital warts. Antimicrob Agents Chemother. 1993;37(2):171-177.
2. Mansoor M, Melendez AJ. Advances in antisense oligonucleotide development for target identification, validation, and as novel therapeutics. Gene Regul Syst Bio. 2008;2:275-295.
3. Wang G. Deep dive on chemistry and safety profiles of therapeutic oligonucleotides.Jefferies Analyst Report. December 7, 2016.
4. Brown DA, et al. Effect of phosphorothioate modification of oligodeoxynucleotides on specific protein binding. J Biol Chem. 1994;28;269(43):26801-26805.
5. Frazier KS. Antisense oligonucleotide therapies: the promise and the challenges from a toxicologic pathologist's perspective. Toxicologic Pathology. 2015;43:78-89.
6. Ozpolat B, Sood AK, Lopez-Berestein G. Liposomal siRNA nanocarriers for cancer therapy. Adv Drug Deliv Rev. 2014;66:110-116.
7. Ashizawa AT, Cortes C. Liposomal delivery of nucleic acid-based anticancer therapeutics: BP-100-1.01. Expert Opin Drug Deliv. 2015;12(7):1107-1120.
8. Ohanian M, et al. Phase I study of BP1001 (Liposomal Grb2 Antisense) in patients with hematologic malignancies. Poster presented at 2016 ASCO.
9. Ashizawa A, et al. Activity of Bcl-2 antisense therapeutic in aggressive non-Hodgkin's lymphoma,. Poster presented at 2017 AACR.
10. Lindsey ML, et al. Killing two cells with one stone: pharmacologic BCL-2 family targeting for cancer cell death and immune modulation. Front Pediatr. 2016;4:135.

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BIOGRAPHY

Peter Nielsen co-founded Bio-Path Holdings, a public biotechnology company developing targeted oncology therapies, and currently serves as Bio-Path's President, Chief Executive Officer, Chief Financial Officer, and Chairman of the Board of Directors. At the time of Bio-Path's establishment in 2007, Mr. Nielsen licensed technology and targets from the University of Texas MD Anderson Cancer Center and coordinated preclinical development, optimization, and manufacturing of Bio-Path's lead product, prexigebersen. Over the next 10 years, Mr. Nielsen led the clinical advancement of prexigebersen into Phase 2 studies, the introduction of additional pipeline candidates, and the company's public market debut. Prior to co-founding Bio-Path, Mr. Nielsen has worked with several other companies, leading turnarounds and developing and executing on strategies for growth. He earned degrees in Engineering, Mathematics, and an MBA in Finance from the University of California at Berkeley.

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