Drug Development & Delivery

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

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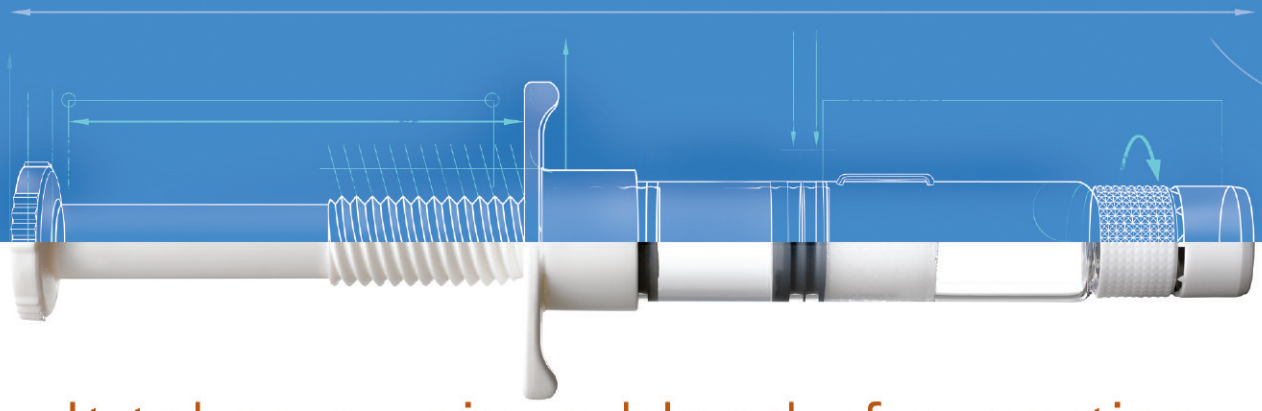
From clinical development to commercial production



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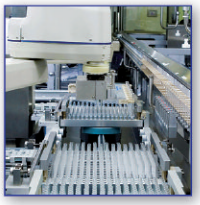

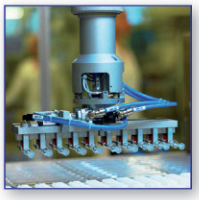

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Container Closure System

"Considering the complexity of modern biopharmaceutics, there is no 'one-size-fits-all' solution for all protein formulations. The container closure system has become a decisive factor for sustained market success, with autoinjectors and injection pumps as growing areas of interest."

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Complex Drugs Require High-Quality Prefillable Solutions

NovaPure® Components

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Injectable Nanomedicines

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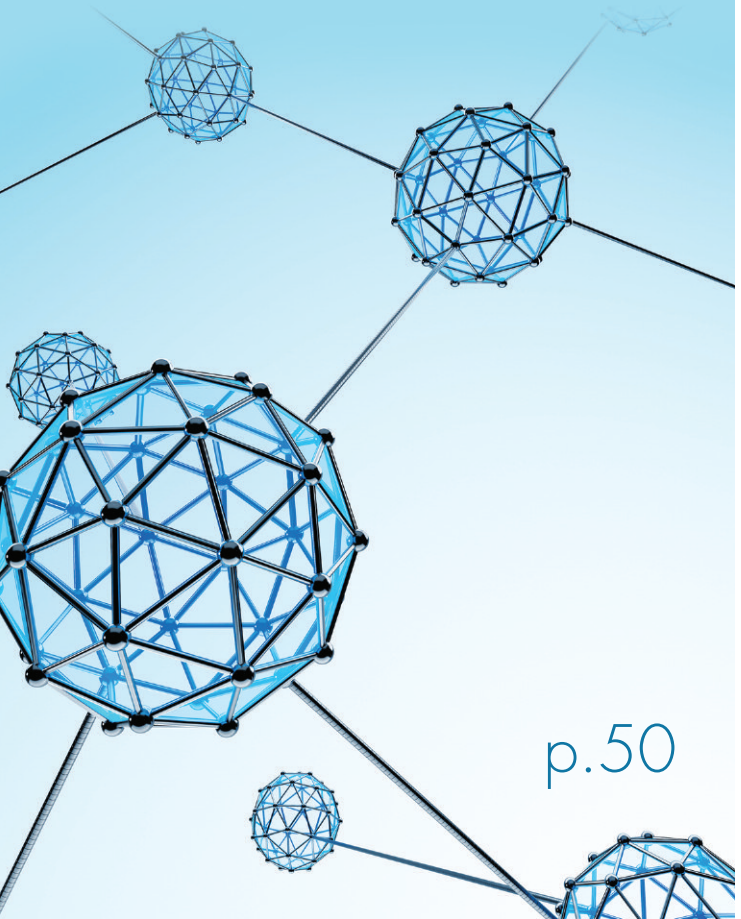

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Aptar Pharma
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Isn't our industry all about taking on challenges and pushing boundaries? Imagine just how dull life would be if we never tried to be better? Settling for the perceived standard is essentially settling for second best, and no-one can afford to do that.

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Amerigen & Dipharma Announce Approval of First Generic of Miglustat

Amerigen Pharmaceuticals Limited and Dipharma S.A. recently announced that Amerigen's Abbreviated New Drug Application (ANDA) for Miglustat 100 mg capsules has received final approval from the US Food and Drug Administration.

This is the first ANDA to be approved as a generic equivalent to Actelion Pharmaceuticals' Zavesca. The ANDA filing was the result of an exclusive collaboration between Amerigen and Dipharma in developing and commercializing Miglustat 100-mg capsules worldwide. Miglustat active ingredient is supplied to Amerigen by Dipharma who holds two granted US patents, US9079856B2 and US8802155B1, one pertaining to a method of synthesis of miglustat and the other to a crystalline form of the same. Amerigen has the right to enforce these patents in the US whilst Amerigen's affiliates will manufacture the finished product and commercialize it in the US, where it has already been launched.

Miglustat is a glucosylceramide synthase inhibitor indicated as monotherapy for the treatment of adult patients with mild-to-moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option.

John Lowry, Amerigen's President and CEO, commented "We are delighted to launch this product following a fruitful collaboration with Dipharma. This is Amerigen's fifth US product launch and the third time we have brought a first generic to market, with important savings for the American healthcare system."

"This marks the first approval of a series of products our group has been developing in collaboration with Amerigen for various markets," added Marc-Olivier Geinoz, Chief Executive Officer of Dipharma. "Thanks to this approval, chronically ill US patients and payers will have available a high quality, more affordable alternative to current treatment. For our young company it is a great achievement and it marks a significant milestone in our growth strategy."

Amerigen Pharmaceuticals is a group of companies engaged in all phases of the generic pharmaceutical business, with operations in the US and China. Amerigen's focus is orally delivered products that are challenging to develop, require specialized technologies or high containment to manufacture, and present complex regulatory and intellectual property obstacles to bring to market. All Amerigen's products are developed and manufactured by the company or its partners around the world to meet the highest quality standards, including the US FDA.

Dipharma S.A. is a Swiss specialty pharmaceutical company, developing high quality, improved, medicines for rare diseases. Dipharma S.A. is part of a third generation group of family-owned companies that have grown to a global presence. With a portfolio of generic orphan products for the treatment of Phenylketonuria, Gaucher Disease, Hereditary Tyrosinemia Type 1, Urea Cycle Disorders and others, Dipharma S.A. works every day to provide improved solutions for people affected by inborn metabolic diseases at an affordable cost and with a global reach.

Bormioli Pharma Addresses Drug Stability & Value-Added Medicines With Packaging Innovation

Bormioli Pharma, one of the world's leading glass and plastic packaging manufacturers for the pharmaceutical sector, offers its innovative dual-chamber AccuRec system as a solution for unstable drug formulations and to deliver value-added medicines.

AccuRec is a revolutionary dual-chamber packaging system that lets patients reconstitute, in a few easy steps, an impressive range of oral drug products right in the packaging container. Predosed solvent and drug powder are stored in separate chambers in a tamper-evident and child-proof package; a simple twist releases the powder into the solvent at time of dosing.

The AccuRec system, and the precise, effective reconstitution it allows, maximizes drug stability in reconstituted oral medicines by eliminating the need to include excipients with the active ingredient. Excipients are traditionally used in pharmaceuticals to make drugs more stable, but this can contribute to additional adverse side effects from drug toxicity, allergy, or intolerance. AccuRec circumvents the need for excipients because the chambers prevent active ingredients from contacting and interacting with the solvent until the moment of administration.

Until now, reconstitution at the time of dosing has been complex and challenging for patients. The easy-to-use AccuRec system helps eliminate the chance for human error by providing guided self-administration and effective mixing of pre-dosed solvent and drug powder.

AccuRec's design makes it attractive for value-added medicines, which are medicines based on known molecules that address healthcare needs and deliver relevant improvements for patients, healthcare professionals, and/or payers. The value of existing medicine can be enhanced through a broad range of processes, including reformulation/repackaging.

Among the drivers for value-added medicines, patient non-adherence is the top-most compliance concern, according to IQVIA Institute. Of the estimated avoidable costs, non-adherence (57%) far outpaced delayed evidence-based treatment practice (13%), antibiotic misuse (11%), and medication errors (9%) among total avoidable costs. Value-added medicines are meant to deliver such benefits as greater convenience, improved compliance, a better patient experience, safety, better outcomes, or a more effective drug.

AccuRec is designed to improve the patient experience with easier, simplified drug reconstitution. Turning a complex procedure like reconstitution into an easy one can lead to better patient compliance and offer pharmaceutical companies new ways to solve dosing and compliance problems.

"We are very excited by the potential AccuRec offers to stakeholders across healthcare, from payers to patients," says Anna Malori, Business Development Manager at Bormioli Pharma. "Its simplicity, accuracy, and design make it a suitable solution for drug stability issues and an attractive option for value-added medicines."

Bormioli Pharma exclusively serves the pharmaceutical and biopharmaceutical market with integrated glass and plastic containers, closures, and accessories for packaging, using state-of-the-art materials and technologies. This includes transparent and amber bottles in Type I, II, and III glass for a range of dosage forms, as well as child-proof and tamper-evident closures.

Q Therapeutics Announces Joint Venture With REPROCELL

Q Therapeutics, Inc., a developer of clinical-stage cell therapies for central nervous system (CNS) diseases, and REPROCELL Inc., Japan's first induced pluripotent stem cell (iPSC) company, recently announced the formation of MAGiQ Therapeutics, Inc., a Japanese joint venture company. MAGiQ will develop iPSC-derived, glial-restricted progenitor cells (GRPs), in collaboration with Q Therapeutics and REPROCELL, to treat demyelinating and degenerative diseases of the CNS.

"MAGiQ Therapeutics aims to bring this promising cell therapy product to market first in a favorable regulatory environment and to begin treating patients as soon as possible," said Koji Kuchiishi, MAGiQ's founding CEO and a board member of REPROCELL.

Under the leadership of Kuchiishi and Chief Scientific Officer Mahendra Rao, MD, PhD, MAGiQ, will first target the demyelinating disease transverse myelitis and the degenerative disease amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease). The iPSC-derived GRP cell (iGRP) product will be tested in proof-of-concept human trials, sponsored by REPROCELL, under the accelerated approval pathway permitted by Japan's PMDA. This unique regulatory process, designed to move cell and gene therapies to human use more rapidly than in most countries, will enable clinical data and conditional product approval for application to regulatory filings worldwide.

MAGiQ is a 50:50 joint venture, in which Q Therapeutics will contribute its patented technology to derive and manufacture glial-restricted progenitor (GRP) cells from any tissue source, including iPSC. REPROCELL will support manufacturing process development of iGRPs through to completion of proof-of-concept clinical trials in addition to providing integration-free, virus-free, and clinically relevant human iPSC lines using proprietary RNA reprogramming technology. The clinical data will equip both MAGiQ and Q Therapeutics to bring the iGRP product to other indications and markets.

"I am pleased to advance Q's relationship with REPROCELL. Our joint venture will extend the product pipeline, build on our foundational experience in developing glial cell therapies, and demonstrate the clinical benefits of glial cell technology in multiple clinical trials," said Steven Borst, CEO of Q Therapeutics. "I look forward to serving on the MAGiQ Therapeutics Board of Directors, along with Dr. Chikafumi Yokoyama, CEO of REPROCELL."

"REPROCELL is committed to expanding its business from tools and services to cell-based therapies. Our joint venture with Q Therapeutics is a next step in our business development strategy and builds on our previous collaborations in the cell therapy arena. Our regulatory expertise will allow MAGiQ to move this clinical effort quickly toward conditional approval in Japan," said Dr. Yokoyama, "The PMDA and the Japanese government have provided a clear path to accelerate development of regenerative medicine therapies."

Q Therapeutics is a clinical-stage company developing adult stem cell therapies to treat debilitating CNS disease and injury. The company has patented processes to derive and manufacture glial-restricted progenitor (GRP) cells from any tissue source, including iPSC.

Porton Pharma Solutions & Codexis Launch Global Partnership

Codexis, Inc and Porton Pharma Solutions, Ltd. recently announced a strategic collaboration to deploy Codexis' world-leading biocatalyst technology within Porton's global custom intermediate and active pharmaceutical ingredients (API) development and manufacturing business. The partnership will accelerate the creation and commercialization of new, low-cost, sustainable manufacturing processes, exploiting the benefits of biocatalysts to a growing number of the world's small molecule pharmaceuticals.

Codexis will license core elements of its biocatalyst technologies to Porton, including its proprietary biocatalyst libraries, high-throughput screening, and enzyme manufacturing know-how. Codexis will also provide preferential access to its CodeEvolver protein engineering platform technology for the creation of new biocatalytic process solutions. Porton will install new operations to drive adoption and optimal application of these biocatalyst technologies into its custom contract development and manufacturing (CDMO) offerings to global pharmaceutical customers. Additionally, Porton pledges financial commitments to utilize Codexis' CodeEvolver protein engineering platform technology.

The partnership reinforces the benefits of reduced costs, enhanced sustainability, and improved product quality that biocatalysts can deliver to the manufacturing of the world's small molecule pharmaceuticals. These benefits are already impacting a growing set of the world's drug manufacturing processes and have earned Codexis three US EPA Presidential Green Chemistry Challenge awards for its biocatalysts' contributions in these commercial-scale drug manufacturing innovations.

"Technological leadership is central to our strategy to grow and deliver value to our pharmaceutical clients around the globe," said Oliver Ju, Chairman and CEO at Porton Pharma Solutions. "We believe that biocatalysis is the most impactful technology to improve the future of pharmaceutical manufacturing, and there is not a more capable player to partner with than Codexis."

"We are delighted to establish this unique partnership with Porton," said John Nicols, President and CEO of Codexis. "Given Porton's significant and fast-growing presence as a leading global CDMO, we will now be able to reach a greater share of the world's pharmaceutical manufacturing market."

Codexis is a leading protein engineering company that applies its proprietary CodeEvolver technology to develop proteins for a variety of applications, including as biocatalysts for the commercial manufacture of pharmaceuticals, fine chemicals and industrial enzymes, and enzymes as biotherapeutics and for use in molecular diagnostics. Codexis' proven technology enables improvements in protein performance, meeting customer needs for rapid, cost-effective, and sustainable manufacturing in multiple commercial-scale implementations of biocatalytic processes.

Porton Pharma Solutions is an industry-leading partner and provider of custom API development and manufacturing services to the global drug industry. Backed by more than 1,700 customer-centric employees, cutting-edge Process R&D Centers, USFDA and PMDA-inspected cGMP production sites and marketing offices located across Asia, North America, and Europe, Porton helps its customers more efficiently deliver improved health outcomes to their patients through chemical process innovation, rapid scale-up and high-quality, cost-effective manufacture of APIs and/or drug intermediates.

Synteract Repositions Itself With Centers of Therapeutic Development & Unveils Updated Brand Platform

Synteract recently announced the creation of therapeutic centers of development that include some of the most progressive in the biopharma industry: oncology, especially leading-edge immunotherapy studies, neuro-degenerative disorders, pediatrics, and rare and orphan disease. In addition, Synteract revealed its new market positioning with an updated logo, tagline, and website to reinforce its core capabilities.

Synteract's leadership has been proven in these core development areas, over its nearly 30-year history, through its contributions to more than 240 product approvals. Formal establishment of its new centers of development bring more visibility to Synteract's long-standing, specialized expertise in these complex areas of clinical research.

"By aligning operational excellence, therapeutic expertise, and supportive technology in our focused centers of development, Synteract is perfectly positioned to help clients advance the innovative therapies that patients need," said Synteract CEO Steve Powell. "We wanted to realign our brand to the next step in our development and more clearly communicate our strategy and the value this brings to our customers and the market."

"For nearly 3 decades, we have been guiding virtual, emerging, and mid-sized biopharma companies across the continuum of Phase I-IV clinical studies with services that address their specific needs. By more clearly delineating our attention on these growing development areas, we have a real opportunity to expand our presence in the mid-market space and drive Synteract's commercial success," added Chief Commercial Officer Jack Shannon.

"We have aligned our new position after listening to and collaborating with our customers and our amazing team at Synteract," said Trisha Vonder Reith, Executive Director for Marketing Communications. "Synteract employs caring, highly skilled clinical research professionals who are passionate about the work we do for our clients every day, because everything we do is intended to develop better therapies and treatments. After all, patients are waiting."

With 800 staff members across 21 countries, Synteract is an innovative, full-service contract research organization supporting biopharmaceutical companies in all phases of clinical development to help bring new medicines to market. Synteract has conducted nearly 4,000 studies on six continents and in more than 60 countries, working with more than 26,000 investigative sites and nearly 750,000 patients. The CRO offers a notable depth of expertise in oncology and neuro-degenerative indications, as well as rare and orphan, pediatric, and immunotherapy studies. Its new tagline of "Bringing Clinical Trials to Life" seeks to elevate Synteract's commitment to a better future for patients and the promise of better therapies for challenging diseases. More on the company's story and its centers of development can be found at www.synteract.com or on LinkedIn and Twitter.

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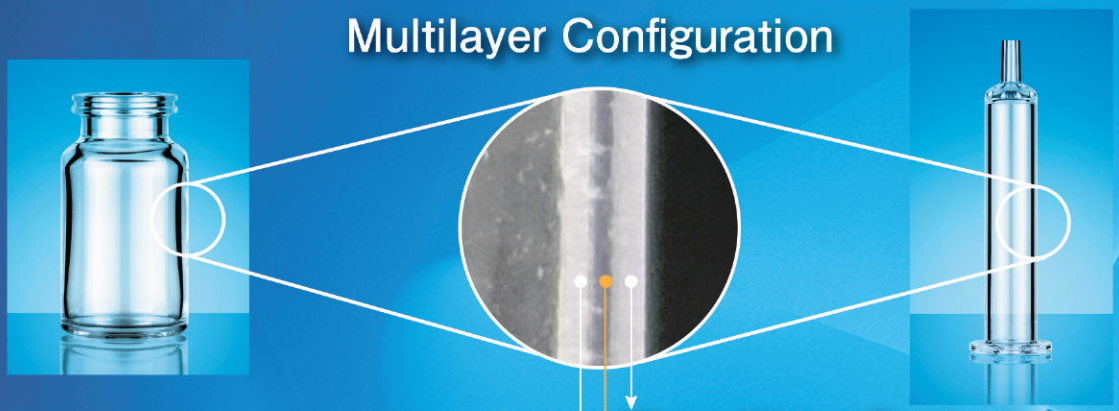

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Foamix Announces $16-Million Investment by OrbiMed

Foamix Pharmaceuticals Ltd. recently announced it has raised aggregate gross proceeds of approximately $16 million through a direct registered offering of its ordinary shares to OrbiMed.

On April 13, 2018, Foamix entered into a Securities Purchase Agreement (the Purchase Agreement) with OrbiMed pursuant to which the company agreed to issue and sell, in a registered offering by the company, an aggregate of 2,940,000 shares of the company's ordinary shares, par value New Israeli Shekels (NIS) 0.16 per share (the Shares) at a purchase price equivalent to $5.50 per share, representing a premium to the company's last closing share price, for aggregate gross proceeds of approximately $16 million, before deducting offering expenses. The issuance and sale of the shares is expected to close on April 16, 2018, subject to certain closing conditions.

Under the terms of the Purchase Agreement, the shares were offered pursuant to a registration statement on Form S-3 (File No. 333-224084), which was filed with the Securities and Exchange Commission on April 2, 2018, and was declared effective on April 12, 2018.

OrbiMed agreed to a lock-up period for 60 days from the date of the Purchase Agreement, during which time OrbiMed agreed not to sell the shares, enter into any derivative transactions with respect to the shares or publicly disclose the intention to do any of the foregoing, in each case without the company's prior written consent.

OrbiMed is a leading investment firm dedicated exclusively to the healthcare sector, with over $14 billion in assets under management. OrbiMed invests globally across the spectrum of healthcare companies, from venture capital start-ups to large multinational companies utilizing a range of private equity funds, public equity funds, royalty/debt funds and other investment vehicles. OrbiMed maintains its headquarters in New York City, with additional offices in San Francisco, Shanghai, Mumbai and Herzliya. OrbiMed seeks to be a capital provider of choice, with the flexibility to provide equity and debt capital solutions that are tailored to the unique needs of our portfolio companies. The firm's global team of over 80 professionals brings the resources and experience required to be an exceptional long-term partner in building world-class healthcare companies. For more information, visit www.OrbiMed.com.

Foamix is a specialty pharmaceutical company focused on the development and commercialization of proprietary, innovative and differentiated topical drugs for dermatological therapy. Our leading clinical stage product candidates are FMX101, our novel minocycline foam for the treatment of moderate-to-severe acne and FMX103, our novel minocycline foam for the treatment of rosacea. We continue to pursue research & development of our proprietary, innovative foam technologies for the treatment of various skin conditions. We currently have development and license agreements relating to our technology with various pharmaceutical companies including Bayer HealthCare and others.

Organovo Achieves Key Development Milestones

Organovo Holdings, Inc. recently announced that along with its collaborators, it has achieved several breakthrough capabilities for its 3D bioprinted tissues. At the International Liver Congress, two posters were presented illustrating the Company's ability to create functional human liver tissue, produce a spectrum of NASH disease conditions, and then treat that disease successfully with a client's development stage non-alcoholic steatohepatitis (NASH) drug. These posters highlighted the performance of Organovo's human liver model in the generation of a robust non-alcoholic fatty liver disease (NAFLD) and NASH phenotype, including the presence of "gold standard" histopathologic features.

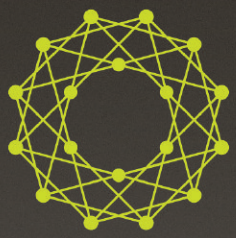
"No other in vitro modeling system allows drug researchers to explore the evolution of NASH and related treatment strategies using histology, the only accepted measurement for efficacy, based on visual confirmation of the cellular disease process under a microscope," said Taylor J. Crouch, CEO, Organovo. "Industry leaders at the International Liver Congress spotlighted the need for measurable ways to explore the efficacy of the approximately 250 NASH drug programs in relevant, translatable human systems. Organovo's ExVive tissue modeling capabilities represent a major advancement for drug development. We are particularly excited that we can work with clients to explore their clinical stage drug candidates, allowing them to address the patient specific needs of their drugs."

Organovo continues to map out a range of relevant conditions for creating NASH, including all components of the disease (fat accumulation, inflammation, and fibrosis). In addition to assessing donor-specific susceptibility to NAFLD/NASH conditions, the company is also systematically testing major reference classes of compounds targeting NASH to inform treatment strategies. Ultimately, Organovo's "patient-on-a-plate" platform allows researchers to conduct a broad range of high-value profiling studies in a more relevant, rapid, and cost-effective manner than traditional cell culture and animal models before committing significant resources to human clinical trials.

Organovo and Merck & Co. (Merck) also jointly published a peer-reviewed study describing the company's bioprinted human intestinal model, which exhibits compelling architecture, barrier and metabolic functions, while also being able to model key aspects of toxicity and inflammation.

"The gut model is an exciting addition to our portfolio of high-value drug modeling platforms," said Dr. Sharon Presnell, Chief Scientific Officer, Organovo. "Its performance and features outshine current in vitro systems, and also has the potential to facilitate systems biology approaches for the study of diseases, such as NAFLD and NASH, where disease initiation and progression involve significant interplay between the intestine and liver."

Organovo is developing and commercializing a platform technology to produce and study living tissues that emulate key aspects of human biology and disease for use in drug discovery, clinical development, and therapeutic applications. The company develops tissue systems through internal research programs and in collaboration with pharmaceutical, academic, and other partners.



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New Preclinical Studies Reinforce the Potential for Heightened Anti-Cancer Activity of Combination Therapies Based on Immunovaccine's Proprietary Delivery Platform

Immunovaccine Inc. recently announced that it presented new research on its T-cell activating platform at the American Association for Cancer Research (AACR) Annual Meeting 2018.

In collaboration with Incyte Corporation, researchers presented a poster supporting the enhanced anti-cancer immune responses from the combination of Immunovaccine's proprietary T cell activating technology and Incyte's IDO1 inhibitor program. A second poster analyzed the novel capability, as compared to other formulation technologies, of Immunovaccine's delivery technology to combine a large range of anti-cancer peptides into a single formulation.

"This is important data for our company as it further indicates the potential of our collaborative work, including our ongoing program with Incyte, to provide heightened T cell infiltration and overall anti-cancer immune responses," said Frederic Ors, Chief Executive Officer, Immunovaccine. "Our data at AACR continues to demonstrate that our novel mechanism of action may hold the key to bridging the gap between in vivo therapies that can elicit T cell activation, and immune responses that can trigger disease regression. We look forward to continued work on these important programs."

In the poster, Combination of a T cell activating immunotherapy with immune modulators alters the tumour microenvironment and promotes more effective tumour control in preclinical models, researchers presented new preclinical analysis on the combination of Immunovaccine's DPX-based therapies, Incyte's epacadostat, and low-dose cyclophosphamide in tumor models. As part of the analysis, researchers also examined the potential for heightened tumor response from T cell infiltration in the tumor microenvironment. The study indicated that the triple combination immunotherapy demonstrated a significant delay in tumor progression. Analysis of the T cells suggested that other immune modulating therapies, such as checkpoint inhibitors, could further enhance tumor control.

Related to Immunovaccine's neoepitope program, researchers presented the poster, A novel delivery platform containing up to 25 neoantigens can induce robust immune responses in a single formulation. This study investigated the effects on immune response when formulating a broad range of peptides across multiple delivery technologies, including the company's proprietary formulation.

The study indicated that Immunovaccine's novel technology could incorporate at least 25 neo-antigens into a single formulation, which generated strong CD8+ T cell responses, in excess of those induced by other formulations.

Immunovaccine Inc. is a clinical stage biopharmaceutical company dedicated to making immunotherapy more effective, more broadly applicable, and more widely available to people facing cancer and other serious diseases. Immunovaccine develops T cell-activating cancer immunotherapies based on the company's proprietary drug delivery platform. This patented technology provides controlled and prolonged exposure to a broad range of immunogenic stimuli.

Immunovaccine has advanced two T cell-activating therapies for cancer through Phase 1 human clinical trials and is currently conducting a Phase 1b study with Incyte Corporation assessing its lead cancer therapy, DPX-Survivac, as a combination therapy in ovarian cancer.

BriaCell Presents Encouraging Clinical Data

BriaCell Therapeutics Corp., an immuno-oncology-focused biotechnology company with a proprietary targeted immunotherapy technology, recently announced it presented a late-breaking poster presentation at the Annual Meeting of the American Association for Cancer Research (AACR) held April 14-18, 2018, at McCormick Place North/South, Chicago, IL. The poster highlighted the preliminary safety and efficacy of its lead product candidate, Bria-IMT. Dr. William Williams, BriaCell's President and CEO, discussed the latest update on the company's clinical trial of Bria-IMT in patients with advanced breast cancer. BriaCell is currently enrolling patients in a Phase IIa trial (NCT03066947) with Bria-IMT and a rollover trial (NCT03328026) with Bria-IMT alone or in combination with other immunotherapies.

The poster described preliminary findings on safety and efficacy of Bria-IMT in patients enrolled in the ongoing study WRIGEV-007, A Phase I/IIa Study of SV-BR-1-GM in Metastatic or Locally Recurrent Breast Cancer Patients, listed in ClinicalTrials.gov as NCT03066947, and evaluated the hypothesis that patients who match Bria-IMT for HLA type may have enhanced tumor response to the Bria-IMT regimen.

"The results presented add to the growing body of evidence for the clinical utility of Bria-IMT," said Dr. Bill Williams. "We are very pleased with the results we have seen to date and looked forward to presenting them to the scientific community at AACR. We believe our data supports the use of HLA typing in advanced breast cancer patients to select those most likely to respond to Bria-IMT, and bolsters our decision to develop Bria-OTS, the first off-the-shelf personalized immunotherapy for breast cancer, along with, BriaDX, its companion diagnostic test, to bring hope to advanced breast cancer patients with far too few effective treatment options."

BriaCell is an immuno-oncology-focused biotechnology company developing a targeted and safe approach to the management of cancer. Immunotherapy has come to the forefront in the fight against cancer, harnessing the body's own immune system in recognizing and selectively destroying cancer cells while sparing normal ones. Immunotherapy, in addition to generally being more targeted and less toxic than commonly used types of chemotherapy, is also thought to be a potent approach with the potential to prevent cancer recurrence.

Bria-IMT (SV-BR-1-GM), the company's lead product candidate, is derived from a specific breast cancer cell line. It is genetically engineered to release granulocyte-macrophage colony-stimulating factor (GM-CSF), a substance that activates the immune system. We believe that Bria-IMT helps the body to recognize and kill tumor cells by activating T cells that attack the tumor and B cells that produce anti-tumor antibodies.

The results of two previous proof-of-concept clinical trials (one with the precursor cell line not genetically engineered to produce GM-CSF and one with Bria-IMT) produced encouraging results in patients with advanced breast cancer.

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CONTAINER CLOSURE SYSTEM

Recent Prefillable Syringe Developments Mirroring Increasing Biotech Drug Product Demands

By: Stefan Verheyden

INTRODUCTION

The global biopharmaceuticals market accounted for $160 billion in 2014, and is expected to grow with a CAGR of 9.6% during 2015-2020, outpacing the global pharma market growth. Many biotech-derived drugs have to be administered by injection using vials, cartridges, or prefillable syringes as primary packaging containers. The specific needs of protein-based drug product formulations pose new challenges to the already existing primary packaging solutions. Some of the trends that can be generally observed in the pharma injectable market are:

- A shift to self-medication to increase patient convenience and safety costs, which is linked to an increasing demand of easy-to-use delivery devices like autoinjectors, and pump systems
- Increased regulatory scrutiny and quality requirements for patient safety
- Increased focus on understanding and anticipating user needs (continuous exploration of the patient experience, patient adherence/compliance)

In addition to this, some of the ongoing biopharmaceutical manufacturing trends ask for increased flexibility on the supplier side. For example, they want more and more biological product applications, but often for small indications, which results in smaller batch sizes with high and specific quality demands. This is supported by the growing market for biosimilars/biogenerics. As a result, more automation, monitoring, and process control during production requires higher quality packaging materials.

For syringes, all these trends are grouped in four different areas, demanding different innovative primary packaging solutions as well as continuous production process improvements (Figure 1).

Regarding biocompatibility of the prefillable syringe system, three main topics kept the industry busy in the recent years - glue residuals, tungsten residuals/oxides, and silicone oil particles.

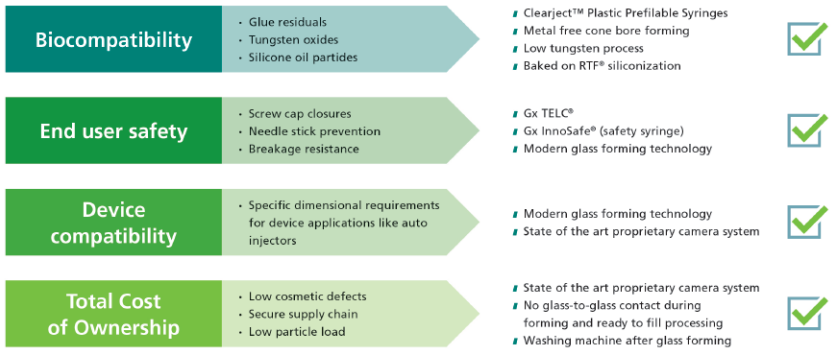
GLUE RESIDUALS

To fix the metal cannula inside the syringe bore, an organic UV-activated methacrylate-based glue is the industry standard. Glue residuals may leach into the drug product solution and interact with the protein.[1] The level of glue residuals can be controlled by optimized curing process conditions after implementation of product specifications with methacrylate in the picogram range per syringe have been realized.

TUNGSTEN

Tungsten pins are used to form the bore in the syringe luer cone. Tungsten is the pin material of choice, as it offers a range of advantages. It is a heavy metal that melts at 3,422°C with the highest tensile strength at ≥ 1,650°C, and the thermal expansion is very similar to borosilicate glass. These features make tungsten a preferred contact material for the forming of glass syringes. The

FIGURE 1



Global Pharma Injectable Packaging Market Trends

glass-forming temperature of borosilicate glass is around 1,200°C. The down side is that tungsten pins always leave tungsten residuals inside the syringe cone. This can be either tungsten oxides caused by the high temperatures used for glass-forming or abrasive particles. For many proteins, this does not pose a problem, but there have been several reported incidences when tungsten residuals did interact with proteins causing protein aggregation.[2]

Regulatory bodies like the FDA did react on this, asking pharma companies to define tungsten limits for their drug products. In the FDA Guidance for Industry – Immunogenicity Assessment for Therapeutic Protein Products, it is recommended to perform a dedicated leachables and extractables laboratory assessment for packaging components. With regard to tungsten, spiking studies are suggested to assess the risk of tungsten-induced protein agglomeration. Also, the PDA TR No. 73, Prefilled Syringe User Requirements for Biotechnology Applications, recommends to perform spiking studies to determine the effect of tungsten. As the sensivity of different proteins to tungsten residues does vary a lot, there is no fixed tungsten limit defined.

On the syringe manufacturing side, there are several possibilities to encounter this problem.

- All syringe suppliers offer so called "low tungsten" syringes. This can be achieved by improving the glass-forming conditions and/or adding an additional washing step after glass-forming, lowering the tungsten load
- Substituting tungsten pins by other metal pin materials
- Metal-free glass syringe cone bore-forming using ceramic pins instead of tungsten pins
- Injection-molded plastic polymer syringes made from cyclic olefins

As already written, there does not exist a defined tungsten limit, and the achievable low tungsten specifications for luer cone and staked-in needle syringes vary significantly due to the size of the pin used to form the bore.

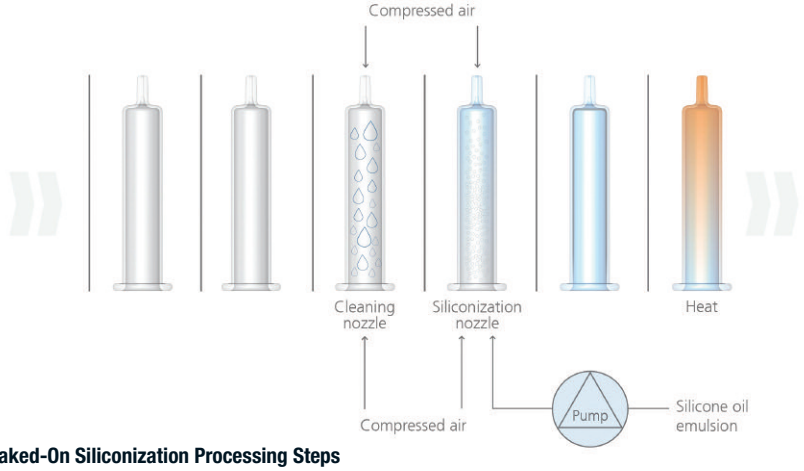
Metal-Free Glass Syringe Cone Bore-Forming

The best way to avoid any problems with tungsten residues is to replace the tungsten pin with a non-metal one. This can be achieved using ceramic materials, which require some adjustments in the glass-forming process. We did identify a ceramic material with optimal properties. The ceramic shows nearly no abrasion and does not leave any new residues behind. This allows us to offer a tungsten-free (below the detection limit) RTF syringes. In the first step, this process was qualified for luer cone syringes and can be combined with other specialties like baked-on siliconization.

SILICONE OIL

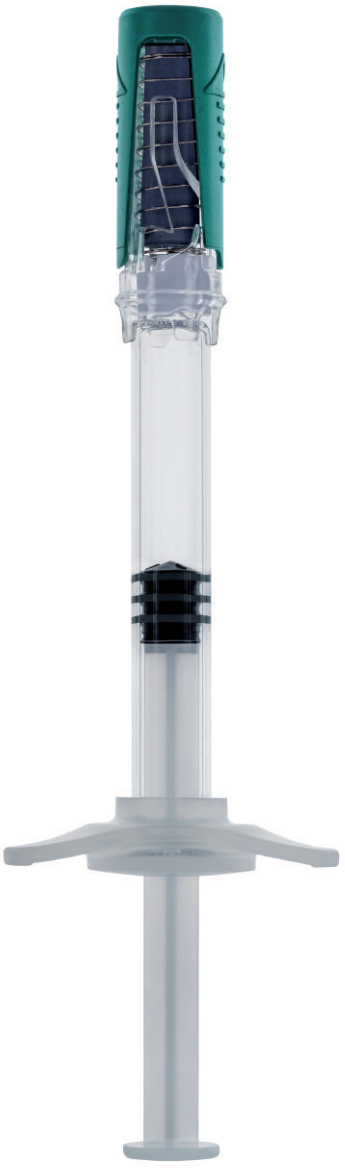
Silicone oil as a lubricant is required to enable the plunger stopper to glide inside the syringe barrel, but silicone oil par-

FIGURE 2



Baked-On Siliconization Processing Steps

FIGURE 3



Gx InnoSafe Syringe With Integrated & Passive Safety System for Needlestick Prevention

ticles especially in the subvisible range are also known to be able to induce protein aggregation.[3] In addition, silicone particles increase the overall particle load inside a syringe and are difficult to differentiate from protein particles. The overall particle load is of specific importance in the field of ophthalmic applications with the most stringent particle requirements for parenterals defined by USP 789 Particulate Matter in Ophthalmic Solutions, and especially with regard to protein formulations, subvisible particulates in the 2- to 10-µm range should also be characterized and quantified.

BAKED-ON SILICONISATION

Using the so-called baked-on process (Figure 2) enables syringe suppliers to significantly lower the amount of free silicone oil particles by fixating a certain amount of the silicone oil emulsion on the inner walls while maintain functionality. Particle measurements derived from a recent study compared oily (0, 5, and 8 mg/syringe) and baked on siliconized syringes. WFI and a Tween 80 0.03% solution were chosen as model liquids. The samples were stoppered (fluoropolymer coated plunger stoppers), and the number of silicone oil particles was determined according to EP 2.9.19 after 1 day of storage, 3 months, and after 3 months under stress conditions simulating a transport situation.

It is obvious that baked-on siliconized syringes (BoS) syringes show much lower particle loads compared to oily siliconized syringes in both cases for all particle classes examined. For RTF syringes, baked-on siliconization is an offline process using a specific oven. The amount of free silicone oil inside a 1-ml long baked-on siliconized syringe is not higher than 1 mg. Also in this case, fixed and diving nozzles are used for siliconization to ensure an even silicone oil distribution also in larger syringes and enables Gerresheimer to specify USP 789 compliance if necessary.

Selecting the appropriate syringe, it has to be also taken under consideration that plunger stopper siliconization contributes heavily to the overall silicone oil particle load. It is therefore recommended to choose silicone oil-free or cross-linked siliconized fluoropolymer-coated plunger stoppers offered by several suppliers.

GX RTF BAKED-ON NEEDLE SYRINGE

Baked-on siliconization so far was only applicable to luer cone syringes as the high temperatures during the baking process negatively impact the organic glue used for the fixation of the cannulas inside the syringe cone. Using an additional process step that involves atmospheric plasma to remove potential silicone oil residuals from the inside of the syringe bore provides a defined surface for the subsequent cannula gluing process. Using low-temperature plasma flame at atmospheric pressure inside the syringe bore converts residual silicone oil-in-glass to nearly carbon-less layers. This conversion is accompanied by a 50% layer thickness reduction and requires no aggressive or contaminant primers. The already siliconized inside barrel of the syringe is shielded to avoid any impact of the plasma on the surface.

Baked-on siliconized staked-in-needle syringes are the optimum choice for sensitive protein therapeutics.

END USER SAFETY - GX INNOSAFE

In addition to biocompatibility, end-user safety is a major trend. The use of staked-in-needle syringes is very convenient/user friendly but always bears the risk that healthcare workers may stick themselves after injection and thereby infect themselves. To avoid this, since 2000,

FIGURE 4

Gx InnoSafe Syringes in RTF Packaging

there is in the United States a needlestick safety and prevention act in place followed by similar regulations in Europe that became effective in 2013. Since 2000, all staked-in-needle syringes sold in the United States have to be equipped with a needlestick prevention feature. To date, most of these safety devices have to be assembled on the filled syringe during secondary packaging operations. Recently, the Gx InnoSafe (Figure 3) was launched as a so-called safety syringe.

In this second-generation safety syringe, the safety feature is an integral part of the ready-to-fill syringe looking somehow like a rigid needle shield. Syringes are supplied sterile using standard ready-to-fill packaging (nest and tubs). The safety system is very intuitive and fully passive, meaning it does not require any activation step by the end user. For the pharma company, it has the advantage that no additional assembly step after filling is required. The slim design also allows the use of small blisters, and therefore more cost-efficient secondary packaging and storage (Figure 4).

PLASTIC PREFILLABLE SYRINGES

Glass as a primary packaging material has many advantages, such as gas tightness, transparency, and high chemical inertness. For the production of glass prefillable syringes, only borosilicate glass Type I is used (51 or 33 extension). Nevertheless, there are also some drawbacks, especially with regard to breakage. Sensitive areas for breakage are the finger flange and cone area. Plastic prefillable needle syringes made from cyclic olefins have been available for a few years. They are break resistant, show the same transparency like glass, and allow a much higher grade of customization. In addition, no glue is used to fix the cannula inside the syringe bore, and no tungsten pin is required for forming that cause tungsten residuals. ClearJect with needle syringes are siliconized using high-viscous DC MD 12500 silicone oil to reduce specifically the amount of subvisible particles compared to conventional oily siliconization. The syringes are supplied with standard rigid needle shields, plunger stoppers, back stops, and plunger rods. Also in this case, the appropriate plunger stopper selection is important regarding the final total silicone particle load.

Especially for particles below 10 µm, a significant reduction compared to glass syringes can be observed, which is another reason to recommend the use of these syringes for silicone oil particle sensitive protein therapeutics.

SUMMARY

Considering the complexity of modern biopharmaceutics, there is no "one-size-fits-all" solution for all protein formulations. The container closure system has become a decisive factor for sustained market success, with autoinjectors and injection pumps as growing areas of interest. This demands an even earlier involvement of packaging specialists in the drug product development process to avoid development risks (shift from Phase 2/3 to Phase me). It is recommended to consult early on in the development process the packaging supplier to determine what is feasible. The future may see further developments for alternative syringe coatings or silicone oil-free syringe solutions, and modern syringe production technologies provide continuously higher qualities with regard to cosmetic defects. ◆

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BIOGRAPHY

Stefan Verheyden is Global Vice President Gx Solutions & Syringes at Gerresheimer. In this role, he leads the new Gx Solutions unit, dedicated to the development of innovative packaging solutions that meet specific and continuously evolving market requirements. Prior to joining Gerresheimer, he was active as Senior Vice President, Sales PharmaPackaging International, at Nipro. Before then, he was Director of Sales EMEA - Global Pharmaceutical Solutions/Drugs & Devices within the Terumo Corporation.

2017

Global Drug Delivery & Formulation REPORT

Notable Transactions and Technologies of 2017

Part 3 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

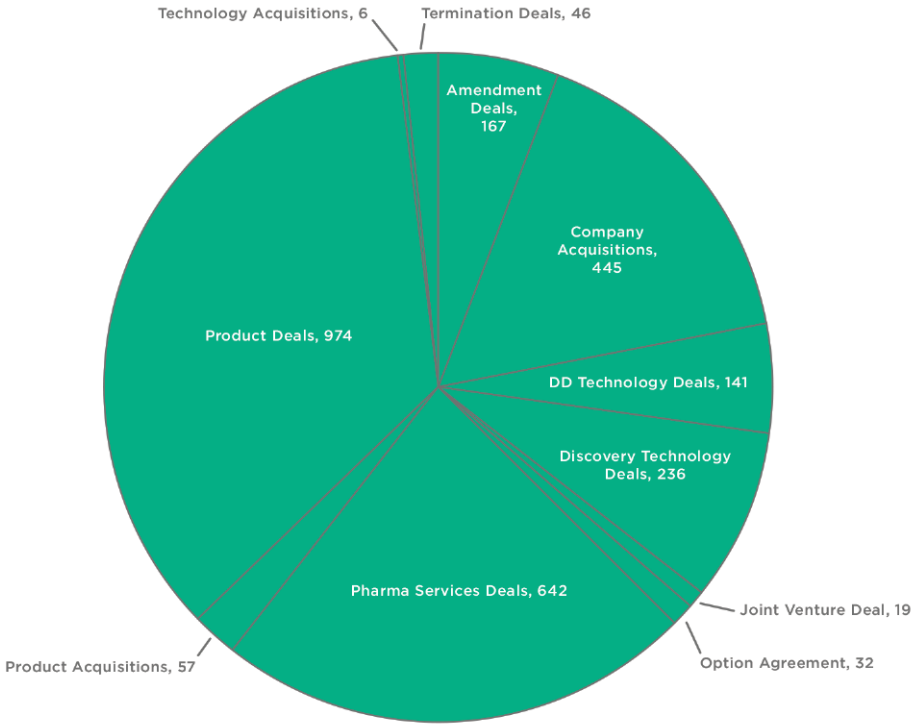
By: Kurt Sedo, VP of Operations, and Tugrul Kararli, PhD, President & Founder, PharmaCircle

Introduction

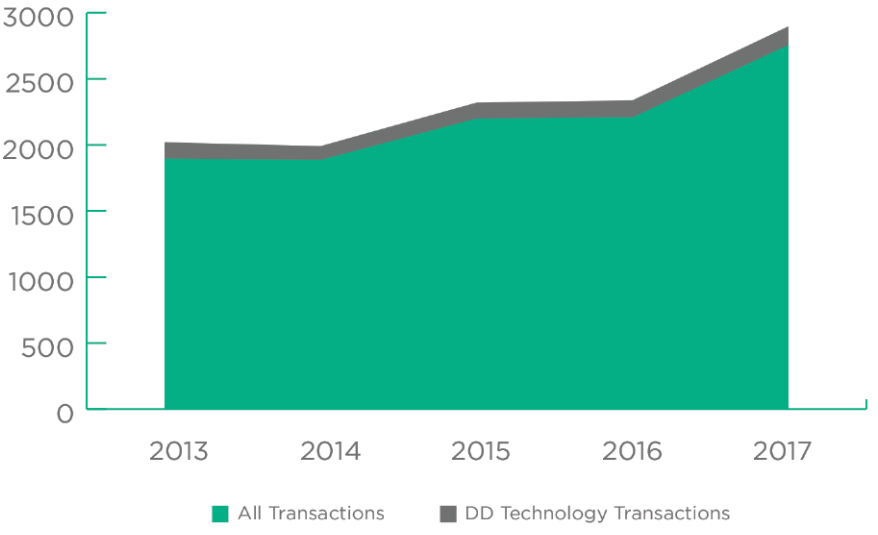
The pharmaceutical sector, once considered the domain of prescription pharmaceuticals, has evolved to encompass therapeutic products ranging from potent over-the-counter products to relatively unregulated products such as medical marijuana and botanicals. This review focuses on pharmaceuticals in the traditional sense with a brief look at sectors that have developed at the edges. While studying product approvals can tell us about the past and the present, it is transactions and technologies that that provide greater insight into what we can expect in terms of product development and approvals over the next decade.

Deals and Transactions 2017

What stands out when looking at 2017 transactions is the industry's preference for sooner rather than later and reduced risk. This explains the relatively large number of Product Deals and Company Acquisitions, even as they become increasingly expensive. Product Deals led all 2017 transactions with a 35% share, followed by Pharma Service Deals (23%) and Company Acquisitions (16%). Drug Delivery Technology deals, transactions largely catering to "do it yourself" companies, followed with 141 recorded transactions and a 5% share.



This 5% share for Drug Delivery Technology transactions in 2017 is consistent with the figures for the past five years although it has dropped somewhat from 6% five years ago.



Transactions - Bigger Trends

Beyond the more obvious attention-grabbing acquisitions of product rich emerging biopharma companies, J&J/Actelion ($30 billion) and Gilead/Kite ($12 billion), there has been a roll up of companies in the diversified pharmaceutical and pharma service sectors. 2017 saw Abbott acquire St. Jude ($25 billion), Becton Dickenson acquire C.R. Bard ($24 billion), Thermo Fisher acquire Patheon ($7.2 billion) and Lonza acquire Capsugel ($5.5 billion). This is consistent with a decade long series of acquisitions in the Pharmaceutical Services sector where companies have invested in establishing leadership positions and critical mass.

One interesting trend in 2017 was the announcement of a half dozen drug delivery and formulation agreements involving cannabis. Cure Pharmaceutical announced a pair of deals with CannaKids and the Technion-Israel Institute of Technology that involved cannabis formulations and the investigation of cannabis related products and formulations for the treatment of cancer. Delivra, Dosecann and ARA-Avanti Analytics announced a collaboration to develop a range of novel formulations for the medical cannabis market. Revive Therapeutics announced a pair of academic partnerships for cannabis related products as well as positive preclinical results using tannin-chitosan hydrogel formulations of cannabidiols applicable to topical gels, creams and ointments as well as transdermal patches. Additional cannabis related deals announced in 2017 included Pivot Pharma's acquisition of Solmic's Solubilisation Technology for application to cannabinoid containing extracts, and quite tellingly GW Pharmaceuticals reacquisition of Sativex commercialization rights in the USA.

The progressive legalization of cannabis related products presents a significant challenge and possibly an opportunity for the pharmaceutical industry. Despite the approval of medical and recreational cannabis in several U.S. states and its impending full legalization in Canada, the U.S. Drug Enforcement Agency still has marijuana and cannabis listed as Schedule I products. This creates the perverse situation where cannabis related prescription products, despite being tested for efficacy and safety, will be subject to much more restrictive use than any number of medical marijuana formulations. The low cost and low risk development of non-prescription cannabis-based products, may help explain Otsuka's decision to return U.S. rights for Sativex to GW Pharmaceuticals. Is the expense of development and regulatory filing recoverable when a product will be competing against non-prescription cannabis formulations that may offer more choice in terms of formulations and delivery routes?

Beyond the cannabis segment the only other notable drug delivery and formulation technology area seeing strong transaction activity in 2017 was the cell and gene therapy sector. Whether this can be considered a drug delivery or formulation play is questionable, at least at this stage. Most notable was Gilead Science's acquisition of Kite Pharma for almost $12 billion. There were also a number of transactions in 2017 where Big Pharma companies secured access to viral vector systems. Cell and gene therapy is an area where things are starting to heat up in terms of technologies and transactions with the prospect that once proof of concept is firmly established there will be considerable opportunity for more capable and refined technologies capable of providing competitive advantage and strong intellectual property positions.

The only significant traditional type of drug delivery and formulation transaction was announced late in the year with Alexion's licensing of Halozyme's Enhanze technology for application to a total of four targets. The terms were a usual multimillion dollar upfront ($40 million) with additional payments of up to $160 million per product and a mid-single digit royalty.

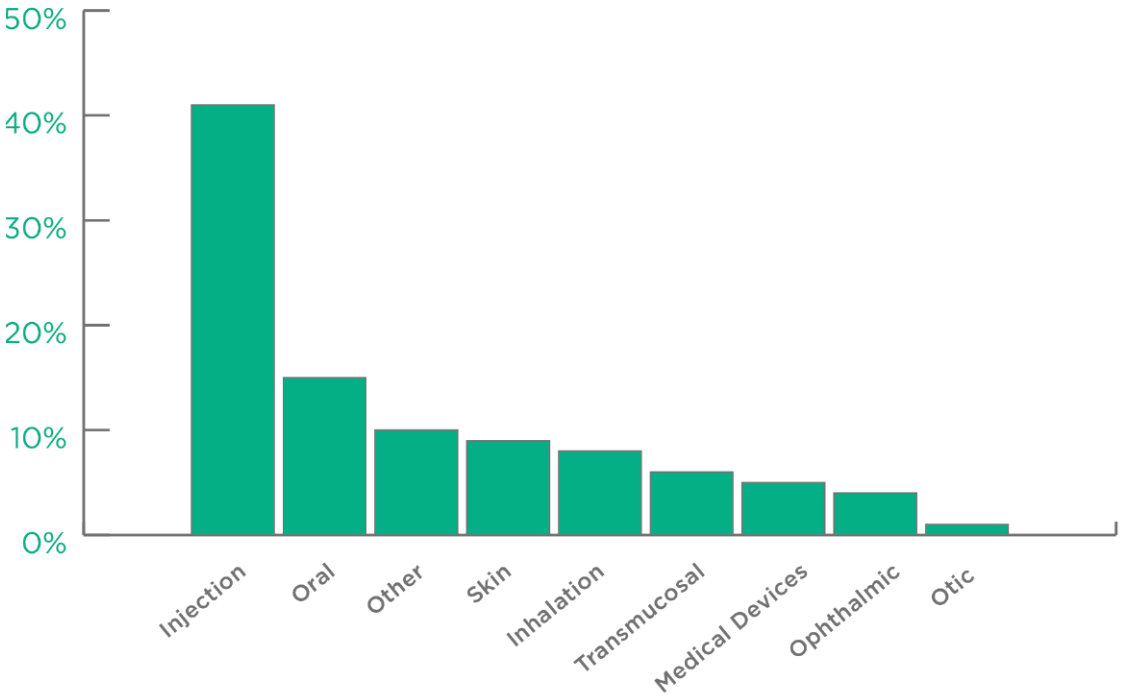
The past year reinforced the argument that pursuing drug delivery and formulation technology out licensing deals is not a first choice corporate development strategy. Any significant success achieved by companies with substantial drug delivery and formulation technology assets has come from developing their own pipeline of products for commercialization or out licensing to hungry Big Pharma and Specialty Pharma companies.

Drug Delivery and Formulation Technologies - 2017

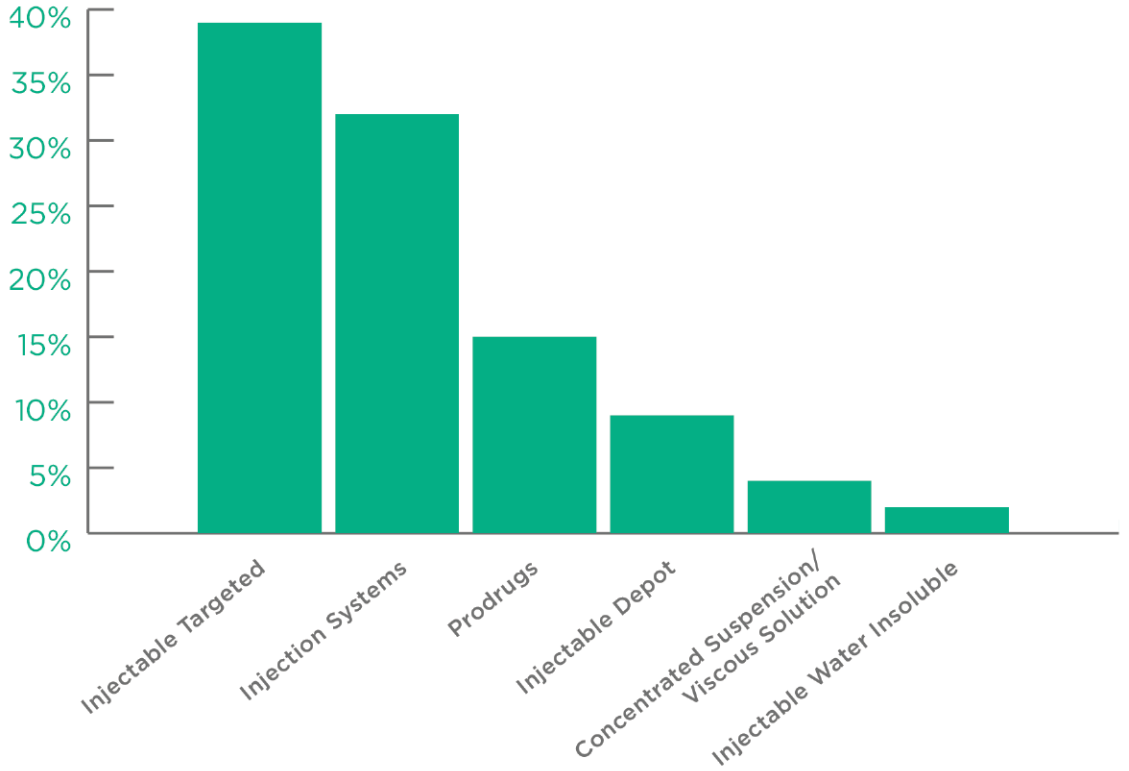
As of March 2017, PharmaCircle had identified a total of more than 6,400 different drug delivery and formulation technologies intended for application to prescription and over-the-counter medications, of which some 4,800 were active.

Of the 4,800 active technologies only 2,819 are associated with one or more identified products. The remainder, about 2,010 technologies, largely disclosed in patents, publications, posters and press releases are yet to take the next big step into the development process. The balance of this article relates to the 4,800 Active Technologies irrespective of whether they are or aren't yet associated with a product.

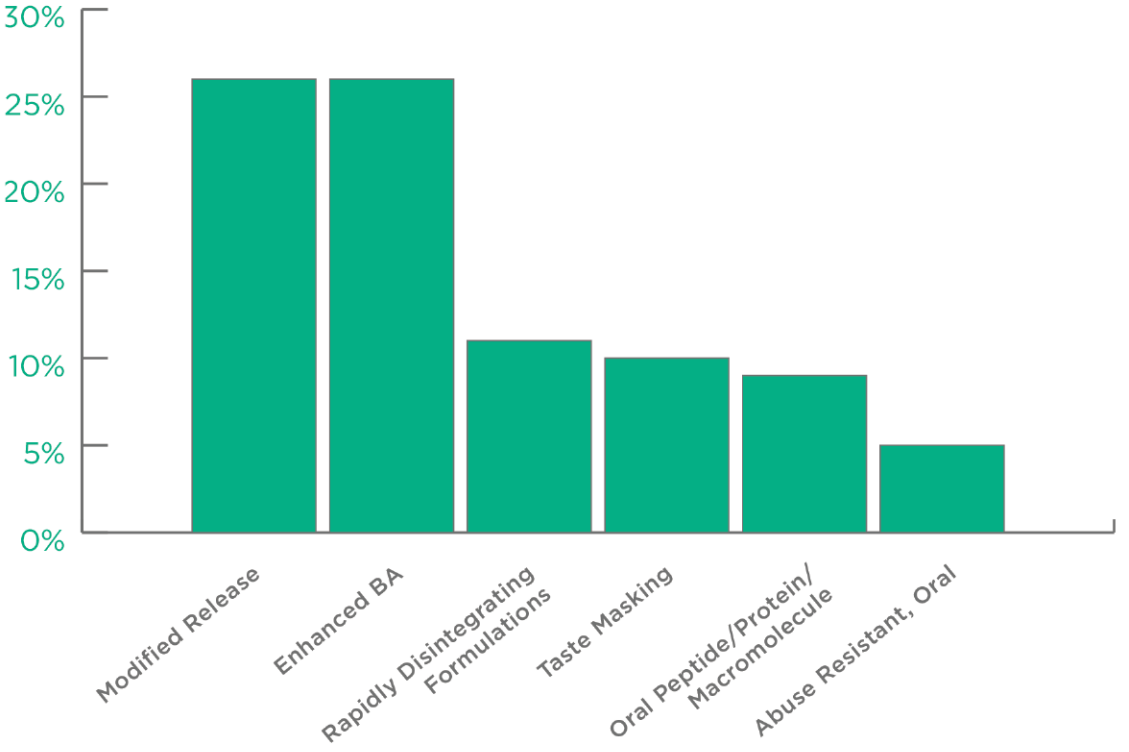
In terms of Drug Delivery Categories, Injection (41%) and Oral (16%) represent the two largest groups of applications for Active Technologies.



The leading active Injection Technologies were Injectable Targeted and Injection Systems, which together accounted for more than 70% of all technology applications. Injection Systems refers to a wide range of injection options including autoinjectors, prefilled syringes, infusion pumps and needle free injectors.



Among Oral Technologies the leading applications were Oral Modified Release followed by Oral Enhanced Bioavailability. Abuse Resistant, Oral technologies came in at a perhaps surprising 5% of the total. The remaining technologies, including effervescent, lozenge and chewable, accounted for 13% of the total.



In the expanding sector of gene and cell therapy, PharmaCircle has identified a total of 233 active drug delivery and formulation related technologies, including viral vector and non-viral nanoparticle systems. The rapidly expanding gene and cell therapy sector suggests we will be seeing a whole new set of technologies that meld traditional pharmaceutical sciences with molecular biology.

More difficult to understand is the number of technologies applicable to the burgeoning pipeline of cannabis related products. These products straddle the areas of prescription and a less restrictive over-the-counter type status, making it hard to properly identify actual technologies and products. Companies developing nonprescription cannabis-based products may prefer to seek trade secret protection rather than the disclosure required for patent filings. In the end it is most likely that cannabis will largely make use of the substantial knowledge base and technologies applicable to similar small molecule actives.

One hopeful sign is the early Phase 3 results with Novo Nordisk's NN9924 Oral Tablets, an oral formulation of their injectable GLP-1 analog, semaglutide, a peptide weighing in at 4.1 kD using Emisphere's Eligen technology. Dosing requirements for type 2 diabetes mellitus are much higher with the oral formulation, about 10mg per day versus 1mg per week for injectable semaglutide (Ozempic). Nonetheless, if shown to be safe and effective Novo Nordisk's NN9924 promises to shake up the GLP-1 injectable market and deliver Emisphere major validation after some 25 years of technology development.

Drug Delivery and Formulation Technologies and Transactions – Final Thoughts

Reviewing 2017 drug delivery and formulation transactions and technology developments provides little evidence that the immediate future holds anything more than incremental advances down already well traveled paths. The pharmaceutical industry is still in need of technologies that make possible the oral administration of macromolecules like insulin, cytokines and antibodies, and more selective tissue targeting. Without a significant breakthrough the industry will be limited to marginal improvements in delivery systems and devices offering patients enhanced convenience, if not objectively improved product performance. Perhaps the new generation of immune-oncology products will demand a new generation of drug delivery and formulation technologies. Delivering on that will take an investment of time and resources.

INTEGRATED DELIVERY SYSTEMS

The Value of an Integrated System for Combination Products

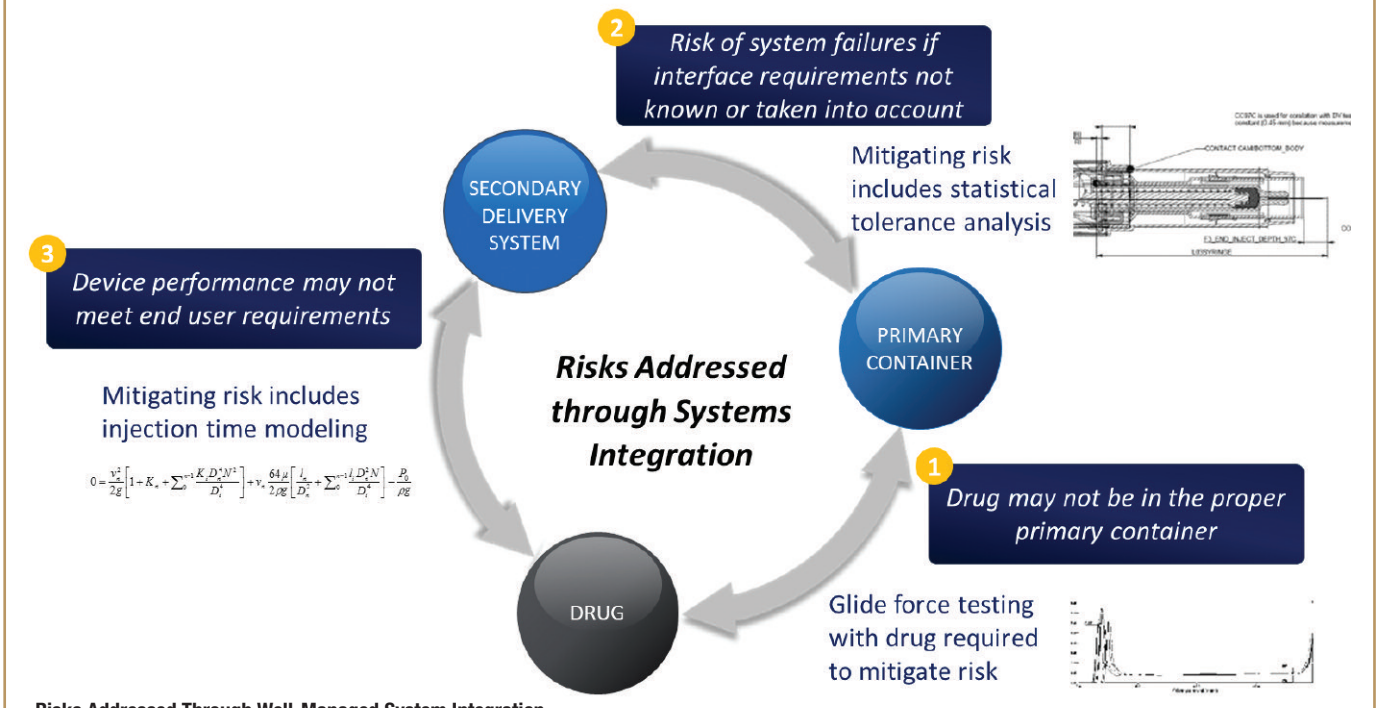
By: Theresa Bankston, PhD

INTRODUCTION

The number of biological therapies in development to treat chronic diseases has risen steadily throughout the years. The fact that many of these therapies are designed for home delivery by patients or caregivers via subcutaneous injection, combined with increasing complexity of longer-acting formulations, larger injection volumes, and longer injection durations, has raised the bar for seamless injection delivery technology. Patients today receive these drugs prefilled inside injection devices, together called combination products. These combination products include autoinjectors, wearable injectors, and prefilled syringes.

To bring a drug-device combination product to market, pharmaceutical companies must select and assemble multiple components that optimally work together to safely and effectively deliver the drug formulation. These components include, but are not limited to, a primary container consisting of a syringe barrel, stopper, plunger rod, and backstop; a secondary delivery system, such as an autoinjector; and potentially an add-on needlestick safety guard.

FIGURE 1



Risks Addressed Through Well-Managed System Integration

"For combination products to perform most effectively, special attention must be paid to component interfaces throughout product development, from the early design phases to manufacturing strategy and execution. BD is a leading provider of primary containers globally and offers secondary delivery systems including needlestick safety systems and autoinjectors for a complete combination product solution."

Drug makers and their contract manufacturing partners have the option of sourcing these components from a variety of suppliers. However, pharmaceutical companies that purchase components separately take on additional risks that can be significantly reduced by selecting an integrated system instead.

Broadly, risks of system integration include the delivery system not functioning as intended, such as primary container breakage, inconsistent system performance, and incompatibility with key container components (Figure 1). When realized, these risks bring an increase in project management complexity and time, a potential delay to launch, and unforeseen issues post-launch, among others. Moreover, problems may not be revealed until late in development or possibly after commercialization, when the combination product has already been manufactured in large quantities and reached the hands of patients. Consequences can range from high scrap rates and waste during the filling or assembly process to loss of costly drug and delay of therapy in the care setting.

These risks and the costs associated with them, while real, may not be immediately obvious to the pharmaceutical company.

SYSTEM INTEGRATION PROVIDES SOLUTIONS

Assurance Through Expertise

For combination products to perform most effectively, special attention must be paid to component interfaces throughout product development, from the early design phases to manufacturing strategy and execution. BD is a leading provider of primary containers globally and offers secondary delivery systems including needlestick safety systems and autoinjectors for a complete combination product solution.

Due to its legacy of developing and providing billions of prefillable syringes and components to the pharmaceutical industry every year, BD has the experience, analytical tools, and lab test capabilities to optimize the components of combination products to operate cohesively. As a result, pharmaceutical companies can benefit from delivery system interfaces that have been properly managed well in advance of product assembly and launch.

BD designs their secondary delivery systems to integrate with the well-established primary containers most pharmaceutical manufacturers are already accustomed to using in their autoinjectors, wearable injectors, and safety systems. This not only provides convenience, but also enables more flexibility in device selection before manufacturers make downstream decisions about device features and functionality. For example, BD integrates their best-in-class BD Hypak™, BD Neopak™, and cannula technology into its self-injection systems, providing multi-platform flexibility across a range of dose volumes. BD's wearable injector, the BD Libertas™, is the leading model of BD systems integration, designed from the bottom up with an array of proven BD components, including BD Neopak™ technology and cannula.

BD also offers a leading brand of passive needle guards through its BD UltraSafe Passive™ and BD Plus™ Needle Guards. Unlike most add-on safety devices, BD UltraSafe Passive™ and BD Plus™ Passive Needle Guards are designed to work with BD prefillable syringes. "Because BD develops both components, we can test compatibility, long before a pharmaceutical customer has the opportunity to test the components together with a specific drug," says Sarah Baer, Global Strategic Marketing Leader.

"It's widely known that BD offers world-class primary containers for combination product development. Our customers are also increasingly coming to understand our investment and full capabilities in delivering exceptional secondary delivery systems. They understand the benefits of working with BD to manage the increasingly complex combination product world," adds Bernard Egoyan, Vice Presi-

dent BD Medical – Pharmaceutical Systems.

Solutions at Each Interface

BD's integrated systems offer solutions to the complexities of combination products at every interface between the drug, primary container, and secondary delivery systems. Consider a few examples of this. At the interface between the drug and primary container, BD leverages expertise and capabilities in glide force testing to ensure the drug is in the appropriate primary container to meet the manufacturer's needs. Between the primary container and the device, BD provides statistical tolerance analysis to specify interface requirements that minimize risk of system failures. Finally, between the drug and secondary delivery device, BD employs injection time modeling to improve overall device performance.

THE VALUE OF INTEGRATION

Risk Mitigation

System integration provides value to pharma and patients at several levels. A well-integrated system anticipates and mitigates system performance risks early in development. BD performs system validation and design verification testing on established reference systems, challenging system performance at the limits of process capability. The outputs of this process are provided to pharma in summary report documentation.

BD can also anticipate where problems can arise throughout the development process and how to troubleshoot them effectively. Because BD produces both primary and secondary systems, they have a unique appreciation of nuances that can support customers in meeting ISO standards.

Visibility across secondary system platforms results in product designs that reflect detailed component specifications to ensure system integration between BD prefillable syringes and BD secondary systems, both during development and after manufacturing scale-up through commercialization. Internal experts share learnings from implementation experience across project teams. Moreover, quality commitment is maintained at the component and system (including primary container) level, which forces tighter specifications and reduced variability in system performance. This drives a high degree of accountability for BD, as the pharmaceutical sponsor can hold a single party accountable for performance of the total delivery system.

"BD creates and manufactures to specifications that are so tight, pharma can accurately predict performance and put components together successfully with less waste," says Janice Adkins, Associate Director, Marketing.

Finally, BD conducts human factors engineering testing on our most advanced products across a range of users to confirm that the integrated devices are safe and usable as a system. While pharmaceutical companies will conduct their own testing with the actual formulation, this early testing of the system increases confidence in the usability of the components together and reduces risks of unforeseen issues.

Time & Cost Savings

BD's system integration has been designed to facilitate significant time and cost savings. On a case-by-case basis, BD provides data at the system level incorporating the primary container, which creates a more readily usable format for the critical step of combination product registration filing. And as BD continuously improves its manufacturing processes and product designs, the "fit" between primary and secondary containers is proactively verified and tracked, and potential problems are resolved to avoid performance issues that may ensue.

BD's leading primary container designed for biotech drugs, BD Neopak™, ensures fit with many secondary systems, including BD handheld autoinjectors, wearable injectors, and passive safety devices. This enhanced fit supports greater choice and flexibility for pharma to serve diverse patient groups, therapeutic areas, and markets with the appropriate delivery format. Furthermore, a single prefillable syringe technology that integrates with a broad range of secondary delivery systems can minimize the costs associated with managing multiple component interfaces and suppliers.

The most significant time and cost savings come from potentially avoiding delayed launch timelines. BD's integrated approach is focused on ensuring that every component, including the barrel, stopper, needle, needle shield, primary container, and secondary delivery system, functions cohesively. This approach is intended to develop a seamless delivery system that performs as designed and meets the rigorous regulatory requirements for safety, effectiveness, functionality, and usability.

"BD ensures that our components will work together. There are no surprises that the primary container selected doesn't work or fit perfectly with the device," says Justyna Dudaronek, Manager of Technical Services.

FIGURE 2

End-to-End Services Add Value

Based on BD's experience in designing and integrating components into systems and extensive collaboration with drug developers, BD has developed a range of end-to-end services offered to customers. These services are designed to help pharmaceutical partners choose the correct components and system for their application, to assess and offer solutions to any potential challenges or sensitivities, and to help produce the necessary data packages needed to demonstrate the safety and performance of the integrated combination product. These include the following:

- Analytical and bioanalytical chemistry capabilities
- Formulation services
- Functional and performance testing
- Clinical/human factors consultancy
- Combination product documentation support and testing
- Process consultancy
- Regulatory customized support

For example, testing for performance feasibility may include in vivo testing, demonstrating that a range of injection volumes or flow rates are feasible. Combination product support occurs throughout the development process, from matching the right set of components with the formulation in Phases I and II, to validation testing of the system in Phases II and III.

Only BD offers this breadth of capabilities in combination with the entire system of components to enable customers to anticipate and resolve challenges before they become issues from a system interference perspective.

BD'S FULLY INTEGRATED DEVICES

Autoinjectors

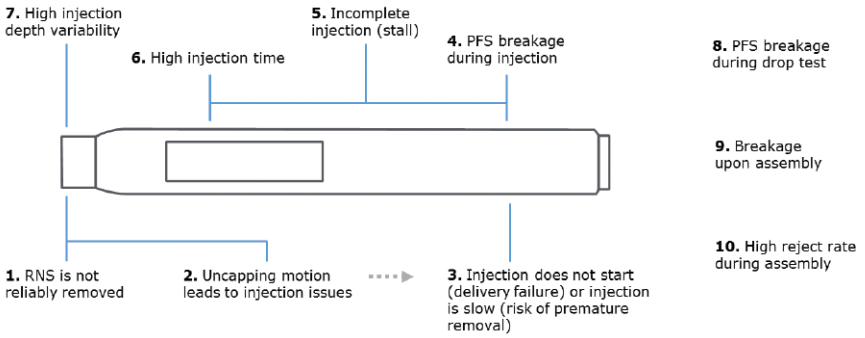
BD Physioject™ - a disposable autoinjector that fully integrates with the BD Neopak™ 1-mL glass prefillable syringe or the BD Hypak™ for biotech 1-mL glass prefillable syringe.

BD Intevia™ - an autoinjector platform technology specifically designed for high-viscosity drug delivery. BD Intevia™ supports the evolving biologics/biotech need for high dosages, while offering integration with BD Neopak™, offering manufacturers the flexibility to accommodate formulation changes.

Wearable Injector

BD Libertas™ - a pre-assembled, fully integrated, mechanical wearable injector designed to deliver 2-10-mL doses of high-viscosity biologics. It was purposefully designed to work as an integrated system with BD Neopak™ and fits within current manufacturing assembly technology, providing high performance while enabling prefilled convenience for patients.

FIGURE 3



Most Common Challenges Encountered With Non-Integrated Components From Different Suppliers for Autoinjectors

Safety Systems

BD UltraSafe Passive™ & BD Plus™ Needle Guards - This family of products are add-on passive needle guards for prefillable glass syringes, offering versions for both cut flanges and small round flanges. BD UltraSafe Passive™ and BD Plus™ Needle Guards are market-leading safety solutions for prefillable glass syringes. BD conducts a multi-phase set of compatibility tests to ensure primary container integration.

EXAMPLES OF CHALLENGES ADDRESSED WITH INTEGRATED SYSTEMS

Drawn from years of experience with customers, the following are examples of real-world challenges faced with non-integrated components from different suppliers, and the corresponding solutions offered by integrated systems.

Cap Removal Malfunction & Wasting Drug Limitation of a Non-Integrated System - When patients remove the cap from an autoinjector, the rigid needle shield (RNS) may not always be pulled from the needle. The result could be an uncapping motion that damages the needle and the drug delivery device. In this case, the device becomes unusable, and the patient may fail to receive his/her important and expensive medication. For the pharma company, this issue may produce complaints, drug waste, and negative quality perception. Although some companies may recognize this issue during development and may resolve it by switching to a different autoinjector, others may not observe it until after scale–up and launch.

Integrated System Solution - With BD's integrated autoinjectors, the caps are designed to integrate with and reliably remove the RNS so that the needle is not damaged. Knowing that even minor changes, such as replacing mold tools, can affect RNS dimensions, design and manufacturing updates are routinely and proactively assessed by BD for their impact to cap/RNS integration. BD designs for system performance to help manufacturers avoid project delays and post–launch issues.

Needle Extension Variability

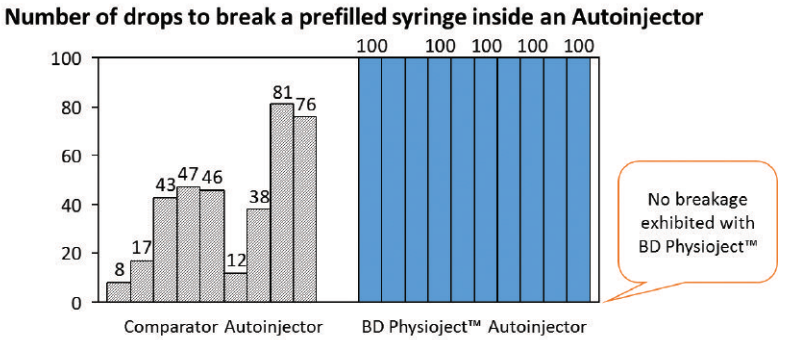
Limitation of Non-Integrated System - Needle extension (depth) is not always well-controlled or understood when the autoinjectors and prefillable syringes are combined. The range of specifications for each component can result in an unexpectedly wide variation when the tolerances are stacked. As a result, unexpected clinical outcomes may occur when bridging from syringe injection to autoinjection. The implications of this issue are that pharma may have to repeat clinical studies, or re–design the autoinjector or prefillable syringe. Either case could result in product launch delays.

Integrated System Solution - Injection depth was thoroughly characterized and controlled during the development of BD Physioject™ and BD Intevia™, through close work with the prefillable syringe team to evaluate needle length variability and methods of controlling this dimension. With the BD Physioject™ system, BD has addressed needle depth variability and conducted clinical studies to show how injection with BD Physioject™ compares to injection with a syringe alone. These studies provide evidence of more predictable clinical outcomes with BD's integrated system. According to Fabien Dubuc, Platform Leader for Autoinjectors, with BD Intevia™, the team went a step further to optimize the system. They set a goal to eliminate the variability of requiring a skin pinch upon injection, simplifying the process for the patient. BD's ability to tightly control variability of components enables consistent targeting of the subcutaneous space. Preclinical studies demonstrated that, without the use of a skin pinch, BD could reliably control injection depth, greatly improving the injection experience.

Primary Container Defects

Limitation of Non-Integrated System - Like needle extension, component dimensional variability (eg, prefillable syringe variability) is not always well accounted for in the design of the autoinjector assembly process. Higher reject rates and possible

FIGURE 4



Comparison of autoinjectors with 1.0-mL prefilled syringes, filled with water. The same type of syringe was used inside all autoinjectors tested. Each bar represents one autoinjector. Autoinjectors were dropped a maximum of 100 times, or until prefilled syringe exhibited breakage. All BD Physioject™ samples confirmed intact by X-ray analysis. BD internal study.

primary container breakage during assembly may occur as a result.

Integrated System Solution - With BD's visibility to detailed, proprietary prefillable syringe component specifications, critical dimensions to assembly which incorporate both BD Physioject™ and prefillable syringes are accounted for within the assembly process design. As shown in Figure 4, in an ISO 11608 drop test (1 meter drop) study comparing BD Physioject™ with one of the most commonly marketed disposable autoinjectors, BD Physioject™ outperformed the comparator autoinjector in terms of prefilled syringe breakages and successful complete injections. BD provides guidance for system assembly, ensuring that the process works smoothly with both the secondary delivery system and primary container, reducing the need for troubleshooting or other workarounds.

BD Libertas™ Example – Another example of where a systems integration approach adds value is the tolerance stack up analysis conducted to design the BD Libertas™ wearable injector for high-scale production. For example, to establish the axial clearance between the primary container and device flow path, an analysis of design parameters and geometric tolerances on nine dimensions is performed to ensure resulting device functional performance. This development approach enables identification of critical inputs from a systems performance perspective, and yields a database of system specifications. This database houses hundreds of geometric tolerance stack-up chains that comprise system specifications and enables a comprehensive understanding of how the device components, as a well-integrated system, result in a high-performing combination product, the BD Libertas™ wearable injector.

SUMMARY

With a long history and expertise in combination products, BD is applying its learnings to the current needs in product development. The growing complexity and regulatory rigor of combination products has called for increasingly innovative delivery devices. BD's integrated systems offer a means to incorporate already-existing, world-class technologies with novel secondary delivery systems to provide complete solutions that meet the evolving needs of pharmaceutical manufacturers. Combined with BD's continuous process and service improvements, BD integrated solutions are designed to mitigate system performance risks, facilitate cost savings, and prevent launch timeline delays to help pharmaceutical companies succeed in bringing their drug-device combination products to market and achieve commercial success.

BD Intevia™ and BD Libertas™ are products in development; some statements made are subject to a variety of risks and uncertainties. The combination products and the claims are subject to regulatory approval.

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

BIOGRAPHY

Dr. Theresa Bankston is Director, WW Technical Services for BD Medical – Pharmaceutical Systems, where she leads the group that is responsible for providing technical support, solutions, and services around delivery systems for injectable drug therapies. She has more than 15 years of combined experience in the pharmaceutical and medical device industries. Her areas of expertise include process chemistry and engineering development, analytical method development, and drug-container integration science. She earned her BS in Biochemistry from Florida State University and her PhD in Chemical Engineering from the University of Virginia.

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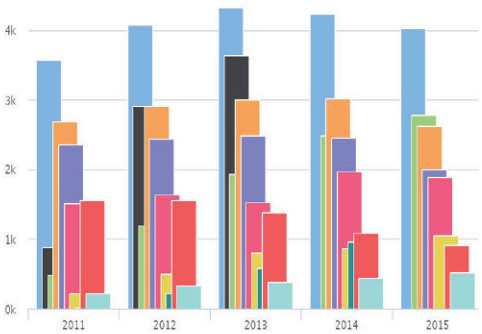
Elite equips you with the layered analytics and actionable insights needed to make strategic business decisions.

BUSINESS APPLICATIONS

- Research new therapeutic areas, and identify market gaps
- Uncover emerging science and evaluate new and promising technologies
- Target potential partners in a specific country or region, and screen potential licensing and investment opportunities
- 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



Dynamic, customizable data display

Easy to Use Apps

Prospector
Search on industry sector, indication, route, most advanced phase and molecule/API type. Find companies within the search criteria in any region of the world by drawing a circle around the location of interest. Click for detailed information on companies within the selected search parameters and geographic area.

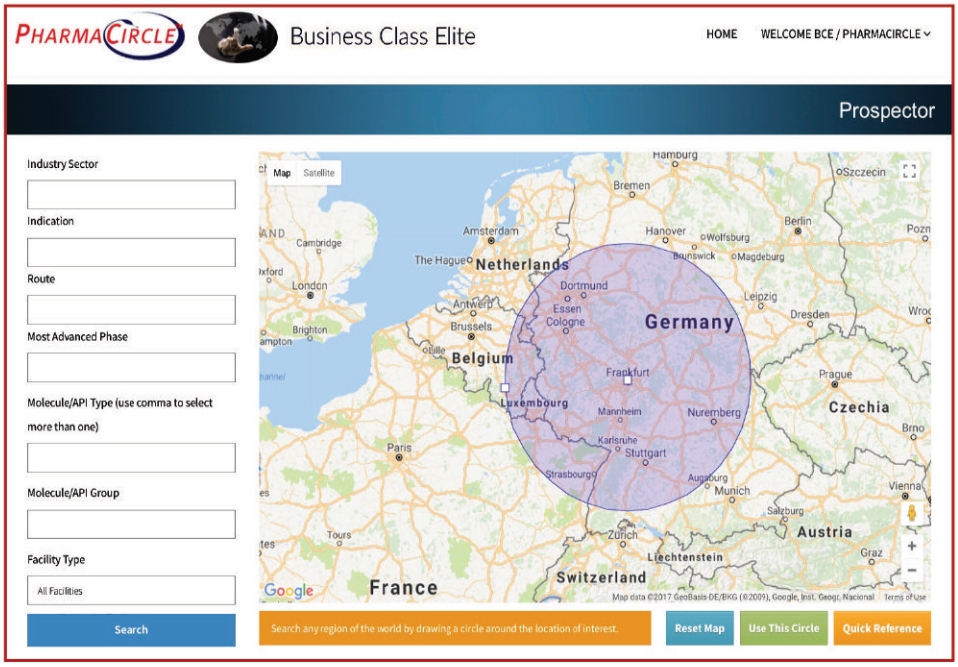
Spyglass
Create your personal watch list and track up to 30 indications, companies and products. Receive latest industry news with daily updates on your selections.

Timescape
View development timeline. Chart phase dates by region/country. Export chart as an image file and underlying data to an Excel spreadsheet.

Label Comparison
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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Key Product Sales & Forecasts	✓	✓
Strategic Deals Analyzer	✓	✓
Venture Capital Investment Tracker	✓	✓
News & Insights	✓	✓
Prospector - Business Prospecting Application	✓	✓
Spyglass - Watch List Application	✓	✓
Drug Delivery Technology Analyzer		✓
Patent Exclusivity Trackers		✓
Paragraph IV Filings & Case Tracker		✓
API & Finished Dosage Form Manufacturer Finder		✓
Drug Label Comparison Tools		✓
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SOLID FORM SCREENING

Phase Appropriate Strategies for Solid Form Discovery & Development

By: Pingyun Chen, PhD

INTRODUCTION

Solid form screening and selection is an integral part of drug development. Traditionally, it has focused on the search for a crystalline form, such as salts and polymorphs.[1-5] In recent years, it has been expanded to include co-crystals and amorphous solid dispersion (ASD) screens for poorly soluble compounds. Solid forms with different properties can be used to overcome various development challenges, such as solubility, stability, or manufacturability. However, in the early phases of drug development, medicinal chemists and formulators must work together to balance cost, timelines, and quality. The pressure to keep costs down in the early phases, combined with the need to quickly progress development and the high attrition rate of candidates, has led to an increased interest in a phase-appropriate strategy for solid form screening for small molecule candidates.

A phase-appropriate approach is an iterative process, with screening activities becoming more comprehensive as resources become available and technical requirements change. During early development, limited screens are focused on finding a suitable solid form to enable a rapid progression to the next milestone. While later in development, after the clinical proof-of-concept, more material and resources become available, and comprehensive screens may be performed to find all solid forms for intellectual property protection, and identification of the optimal solid form for commercialization.

Poor solubility is a growing issue in drug development, which often leads to unoptimized drugs or increased development timelines.[6,7] Utilizing solid form screening to identify a more soluble form, eg, salt or ASD, is a key step for improving the bioavailability and the molecule's chance of success.[1-3,8] For certain molecules, a more soluble solid form can enable preclinical and clinical studies without the use of more advanced enabling formulation technologies.

Throughout the past decade, screening technologies with automated sample preparation and integrated analyses have been developed to support the discovery and evaluation of different solid forms.[9,10] These technologies require smaller amounts of material, take less time, and enable the solid form studies to be applied at earlier stages, eg, when comparing pharmacokinetics (PK) of multiple compounds during lead optimization.[2] The followoing describes a rational, fit-for-purpose strategy for solid form screening and selection to ensure a successful yet cost-effective progression of drug candidates from discovery, clinical trials, and commercialization. It also discusses key considerations and highlights how solid form selection can impact cost, timelines, and product quality.

PHYSICOCHEMICAL & BIOPHARMACEUTICAL CONSIDERATIONS

Solid forms can have a significant influence on many physical properties, including melting point, solubility, stability, hygroscopicity, and bulk density. In fact, most screening and selection processes focus on improving physical properties to enhance the

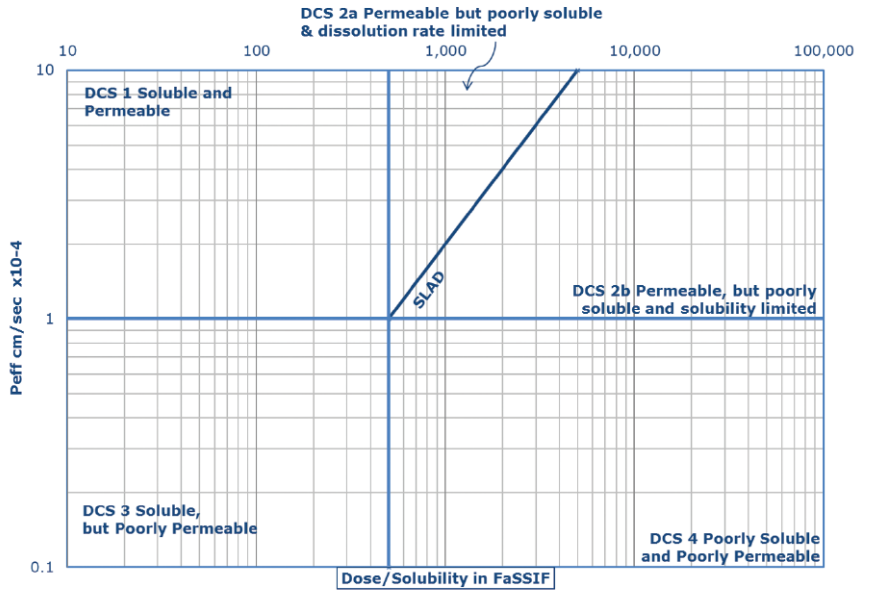
drug-handling characteristics, absorption, and delivery options.[11]

Key preformulation activities include physical properties characterization of drug substances undertaken by medicinal chemists, and measurement of solubility at different pH values and in biorelevant media. These data, along with predicted permeability and projected doses for preclinical and clinical studies, are used to:

- Calculate the acid-base dissociation constant (pKa) value(s) and determine the feasibility of salt formation
- Assess if drug absorption will be limited by solubility and dissolution rate using the Developability Classification System (DCS)
- Identify chemical stability that may be improved via solid form selection and formulation development
- Develop solid form screening and formulation strategies[12]

More than 90% of small molecule drug candidates are poorly soluble and belong to DCS 2 (2a and 2b) or 4 (Figure 1). Challenges with poorly soluble compounds include non-linear dose proportionality, variable pharmacokinetic profiles (inter-species and inter-subject), and limited toxicological coverage. All of these may compromise human dosing prediction and studies. For these molecules, solid-form screening and bioavailability-enhancing formulations are required to achieve the desired toxicological coverage, and uniform exposure in different animal species and humans.

FIGURE 1



Source: Butler, J. *The optimal use of biorelevant media & simple modeling for the prediction of in-vivo oral behaviour* (http://www.apsgb.co.uk/Events/PastEvents/20110609/James%20Butler.pdf)

DCS Classification Chart

SOLID FORM SCREENING & SELECTION

Crystallization Screening

Crystallization is the most widely used technique to isolate and purify the API at a large scale. This is especially critical for high volume and low margin products for which the API is a major contributor to the overall cost of goods. It is therefore essential to identify a suitable crystalline form of an API to ensure it can be manufactured on a large commercial scale even if a crystalline form is not required for formulation.

During candidate selection, identification of a developable crystalline form can facilitate isolation and purification of the drug substance, ensure the supply of drug substance with consistent and desired physical properties, and simplify development of formulations that support preclinical and clinical studies.

Crystallization screening can be conducted using small amounts of materials (~100 mg), and should explore a variety of solvents (polarity, H-bonding donor and acceptor) and crystallization conditions, such as temperature and cooling rate. If the molecule has an ionizable group for salt formation, the crystallization of the free form can be done as part of a salt screening.

Salt Screening

Salt formation is arguably the most effective means to modify solubility of a molecule with ionizable groups. More than half of all small molecule drugs on the market are developed as salt forms to improve solubility and other physical properties, stability, and manufacturability.[13]

For example, Eli Lilly's Zyprexa® (olanzapine), indicated for schizophrenia, was developed with several delivery methods using the free as well as different salt forms in order to achieve the necessary pharmacokinetic profiles. The drug maker developed an orally disintegrating tablet version using Catalent's Zydis® fast-dissolve technology platform that can be taken without water; a combination product using the hydrochloric salt; and an extended-release injectable suspension using the poorly

soluble pamoate salt, which allows the molecule to dissolve slowly over several weeks.

If salt formation is feasible for a poorly soluble compound, a salt screening should be conducted. A salt with adequate solubility and stability will help reduce PK variations (dose-to-dose, inter-subject, and inter-species), increase exposure and toxicological coverage, and enable simple formulations, such as powder in bottle (PiB), powder in capsule (PiC), and suspensions to be used in preclinical and clinical studies. Salt screening for poorly soluble compounds may be focused on the discovery of more soluble salts with small, hydrophilic counter-ions, such as acetate, methanesulfonate, and citrate. It is important to recognize that salt solubility alone may not be a reliable surrogate for bioavailability. Dissolution and precipitation kinetics and PK studies may be required to select the best salt (vide infra).

Cocrystal Screening

A co-crystal is a multi-component crystal containing an API and one or more neutral molecules, such as excipient, commonly referred to as a co-former. For a given API, a co-crystal can be formed between the free form and a co-former, or a salt and a co-former. Co-crystallization offers an effective crystal engineering approach for modifying the crystal structure (binary, tertiary, etc) and properties of drugs.[14] The number of examples of solving drug formulation and manufacturing problems by co-crystallization is rapidly growing.[15] An interesting example is Novartis' Entresto® (sacubitril/valsartan), which is a co-crystal of two APIs and is more efficacious than a combination drug product.[16]

Co-crystal screening is similar to salt screening in many aspects. However, co-crystal formation depends primarily on the H-bonding and other molecular interactions between the API and co-former, which are weaker than the ionic interactions for salts. An effective co-crystal screening relies on both in-depth understanding of structure-property relationship, solubility of both API and co-former, and specialized screening methods, such as solvent-drop grinding (SDG) and thermal methods. However, the lack of knowledge and effective screening technologies limit its use, especially for early stage development.

It is important to recognize that some co-crystals are relatively easy to discover, to produce on a large scale, and to formulate into drug products similar to salts. Most co-crystals, however, will require significant development of a co-crystallization process for large-scale manufacturing, stability assessment, and evaluation of biopharmaceutical characteristics in formulated products. As shown by Entresto and other approved co-crystal drugs, this can be rewarding for otherwise difficult or intractable compounds. As understanding and screening technologies become more efficient, co-crystals will undoubtedly become a more important tool for drug development.

Polymorph Screening

Polymorphs are crystals that have different arrangements and/or confirmations of the molecules in the crystal lattice. As such, they have different physico-chemical properties, such as solubility, stability, and bulk density and flow properties. It is important to conduct polymorph screening to identify different polymorphs, hydrates, and solvates, and to determine their thermodynamic relationship. And most importantly, one must determine the most suitable, and typically most stable, polymorph near ambient temperature for development.

Polymorph screening is generally required based on the International Conference on Harmonisation (ICH) guidelines and for the chemistry, manufacturing, and controls (CMC) section of a regulatory filing. Polymorph screening ensures that the API and drug product manufacturing processes are robust and that the drug product is stable, efficacious, and safe for patients.

It is critical to conduct a polymorph screening of the selected free form or salt to identify the various polymorphs that may be encountered during API isolation and formulation so the optimal polymorph is selected, made, and formulated to support preclinical and clinical studies. Otherwise, switching to a different polymorphic form at a later stage will likely require additional process development, reformulation, and possibly bridging toxicology and PK studies, which can result in significant delays and increased costs.

An effective polymorph screening technique should explore a variety of parameters that may influence nucleation and growth kinetics of different crystalline forms. These include a diverse set of solvents and mixtures, aqueous mixtures of different water activities, and different crystallization modes, such as slurry ripening, rapid and slow cooling and evaporative crystallization, solvent and anti-solvent additions, and temperature. It is also important to include experiments to assess the process-induced polymorph transformation, such as API micronization, wet granulation, tableting, and formation of new solvate with excipients.[17] For comprehensive screening during the later stage, one

should also use the final route material and different forms, including amorphous material for screening studies.

Amorphous Solid Dispersion (ASD) Screening

High–risk compounds will require special formulations that may include amorphous solid dispersions for poorly soluble compounds. An amorphous dispersion screen is performed to find a suitable amorphous dispersion that exhibits acceptable properties, typically higher solubility to improve the exposure. The solubility enhancement of an amorphous solid compared to crystalline form typically varies from approximately 2 to 1,000 folds, depending on the lattice energy of the crystalline form and H-bonding donors and acceptors of the molecule.[18] Further enhancement can be achieved for ASD with polymers and surfactants, which may also inhibit precipitation and re-crystallization of a supersaturated solutions.

ASD can be prepared using different techniques, such as fast evaporation, freeze-drying (FD) or spray drying (SD) of solutions, or hot melt extrusion (HME). Some of these can be conducted with small amounts of material in the laboratory. SD and HME can be scaled up to large scale for commercialization.

The screening performed in early development may focus on parameters such as API solubility screening in organic solvents suitable for SD, API miscibility screening with polymers and surfactants to determine the drug loading, followed by preparation of ASD. ASD should be characterized by polarized light microscopy, X-ray powder diffraction, differential scanning calorimetry, thermogravimetric analysis, dissolution profiles, and accelerated stability assessment. The promising ones should be tested in animal PK studies.

TABLE 1

Stage	Key Development Objective	Solid Form Studies
Discovery (lead to candidate selection)	A crystalline form to enable API isolation & purification (anhydrates, hydrates, solvates)	-Crystallization, salt if feasible based on pK_a, cocrystal screening for intractable compounds
Early Development (PK, GLP tox, Ph I & IIa)	-Assess polymorphism and select the most stable form of the selected free-form or salt for development -ASD to enhance the exposure for poorly soluble compounds	-Polymorph screening and selection -Revisit salt screening and selection as needed -ASD screen
Late Development (Ph IIb & III, Launch)	-The optimal form to support the pivotal study through product launch -Finalize API crystallization process & formulation	-Comprehensive polymorph screening -Process risk assessment and mitigation (solvents, temp, handling attributes)
Life-Cycle Management (New indications & formulations)	-Comprehensive solid form knowledge -Optimal form for new API manufacturing, new indications and formulations	-Comprehensive salt and cocrystal screening

Typical Solid Form Studies at Different Development Stages

FORMULATION STRATEGY & DRUG DELIVERY

Solid form selection should also take into consideration the route of administration, dose, dosage form, and release profile that are required to support preclinical and clinical studies and the target commercial formulation. For example, a soluble salt is typically preferred for oral delivery of a poorly soluble drug, while its uncharged parent may be required for topical applications for which transdermal permeability is more critical than solubility.

Different dosage forms may require different physico-chemical properties and, frequently, different solid forms. For oral solid dosage forms, key considerations include solid-state stability, sufficient solubility and dissolution rate, compatibility with excipients, bulk density, and compressibility. However, it is important to recognize that higher aqueous solubility of a salt does not necessarily mean higher bioavailability because of the precipitation events that can occur in vivo. In these cases, excipients and surfactants that inhibit the nucleation and crystallization should be included in formulation.

For inhaled formulations, chemical and physical compatibility with excipients and device components, hygroscopicity, and milling are particularly important. Solution formulations are commonly used to support toxicological studies, parental formulation, intranasal, and pulmonary delivery. In these cases, solubility and chemical stability in the formulation vehicle will be the most critical factor in solid-form selection. Natural pH of the salt solution should also be considered carefully as it may be outside the acceptable pH range. Solution formulations also require knowledge of form space to ensure the drug concentration is below the equilibrium solubility of the most stable form in the formulation vehicle.[8]

SOLID FORM SCREENING & SELECTION STRATEGIES

Every drug candidate is unique, and solid-form strategies and requirements vary over the course of drug development. Table 1 outlines how solid form studies are typically aligned to achieve specific development objectives at different stages of development. During the early stages, the focus is identifying a suitable crystalline form to support isolation and purification of an API and to provide drug substance

with adequate solubility and stability for preclinical and clinical studies. As development progresses, additional studies are conducted in later stages to assess and discharge the solid form risks during the API and drug product manufacturing processes, to increase the understanding of the solid form, as well as maximize opportunities via the selection of the optimal solid form for new indications and formulations.

BRIDGING MOLECULE & FORMULATION DEVELOPMENT

Typically, in product development, there is a separation between drug discovery (medicinal chemistry) and drug development (formulation), and the transition between them is not as smooth and efficient as it could be. During lead optimization, medicinal chemists are charged with producing a molecule with best selectivity and in vitro potency. They are not typically thinking about how the drug will be dosed to animals and patients, and whether their choices are in alignment with the formulation and dosage form technologies that may be needed. This focus on in vitro potency can lead to selection of candidate molecules with poor physico-chemical and biopharmaceutical properties.

To avoid such issues, it is important to bring in preformulation and formulation scientists during lead optimization. Exactly when a company engages formulation scientists during discovery varies between companies. This is frequently too late, especially when salt form and polymorphic form have been decided. This is where the disconnect can be seen in the approach that most small companies follow in trying to resolve the solubility issues - addressing one function after the other, rather than together, at the same time. A 2007 study that reviewed the state of the art found that early in the development process, salts are selected based on ease of synthesis and crystallization, cost of raw material, etc. Unfortunately, focus on downstream processes (physical and chemical stability, processability into dosage forms, solubility, and dissolution rate at different pH conditions) is often absent. In later stages of development, it is difficult to change the salt form without significantly increasing timelines and costs. With a change in the salt form, the developer is required to repeat biological, toxicological, formulation, and stability tests significantly extending timelines and costs.[13]

CONCLUSION

The solid form of an API can have a profound impact on physical properties and nearly all drug development activities. The process outlined in this discussion takes into consideration the fundamental physico-chemical properties of a molecule, the impact of different solid forms on API purification, physical properties, and formulation strategies. It can be used to develop an appropriate selection strategy to ensure a rapid and successful progression of small molecule drug candidates.

Finally, it is important to recognize that finding a soluble solid form or formulation to improve the solubility and dissolution of a candidate is only half of the solution. The other half is to determine doses and dosing strategies in order to avoid precipitation before drug absorption occurs, a subject which is beyond the scope of this article.◆

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BIOGRAPHY

Dr. Pingyun (P.Y.) Chen is Director of Early Development at Catalent Pharma Solutions. He began his career in pharmaceuticals in 1999 as a research investigator in pharmaceutical development at GlaxoWellcome. After spending 1 year as a principal research scientist at Eli Lilly in 2004, he returned to GlaxoSmithKline to co-lead the solid-form sciences team to provide global salt and polymorph screening and selection support for drug candidates from discovery through commercialization. He joined Catalent Pharma Solutions as Manager of OptiForm® technologies in 2010. Dr. Chen has delivered multiple presentations as an invited speaker in scientific conferences and co-authored more than 40 publications and book chapters. He is named as a co-inventor on multiple patents.

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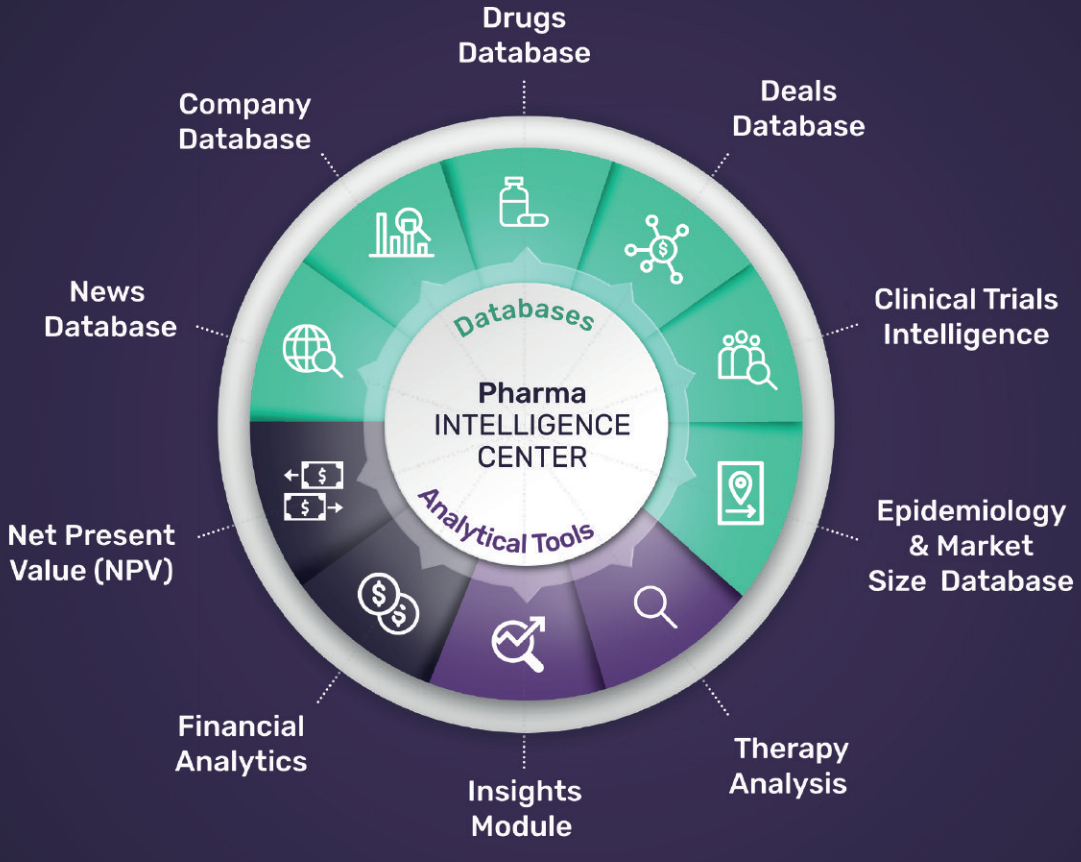

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THROAT SPRAY SYSTEMS

Key Considerations When Developing a Throat Spray Solution

By: Degenhard Marx, PhD, and Günter Nadler

INTRODUCTION

Adults on average suffer from a common cold at least four times every year. Symptoms include headaches, a blocked or runny nose, and often a sore throat. As it's a viral infection, there is no real cure to the common cold; however, symptom relief is a well-established market that commands a great deal of consumer attention, demand, and spending.

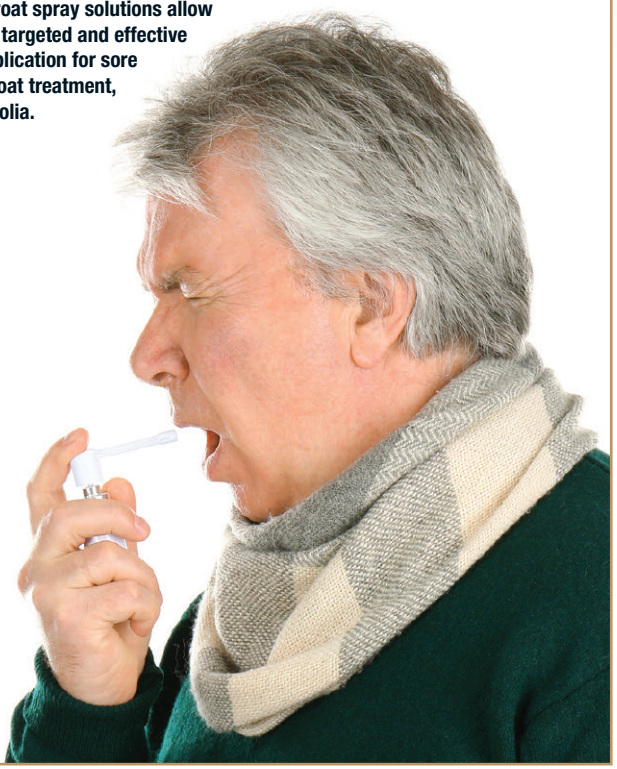
In 2017, more than $8.6 billion was spent over the counter (OTC) for upper respiratory remedies in the US alone, with a further $1.5 billion spent on throat sprays and mouth washes.[1] Although these figures are not for cough and cold treatments alone, as they include remedies for other upper respiratory tract ailments too, they do indicate the scale of the market opportunity. This is further reinforced by data collected in Germany, where in 2017, $1.81 billion was spent on OTC cough and cold medications.[2]

One such opportunity is in throat spray systems. This article will focus on the treatment of sore throats via a pump spray and explore the considerations to be made when developing a reliable spray product.

REMEDIES RANGE FROM SWEETS TO SPRAYS

The root cause of a sore throat is irritation or inflammation of the throat mucosa. This causes the pain and discomfort, which is worsened by swallowing. The reasons for the irritation or inflammation are varied – they may be viral or bacterial infections, allergic responses, or even snoring. The level of pain, difficulty in swallowing, and the duration of symptoms can be equally varied.

FIGURE 1



Throat spray solutions allow for targeted and effective application for sore throat treatment, Fotolia.

Just as diverse are the suggested remedies – everything from cold drinks, herbal infusions, and gargling with saline, to lozenges with numbing ingredients.

For relieving mild sore throat symptoms, herbal infusions, cold drinks, or lozenges and candies containing herbal extracts with soothing or numbing ingredients are often the first choice of treatment. However, ingredients in lozenges and candies are released quite slowly and are not always targeted within the oral cavity.

Gargling with saline water, herbal infusions, or other gargling solutions is another often-used therapy to treat sore throat symptoms. Even though gargling is quite effective, it requires a sink and a correct technique for consumers to avoid swallowing part of the gargling solution. Therefore, it is not convenient for on-the-go treatments.

One preferable and convenient, while highly targeted, remedy for a sore throat is the use of a throat spray. With the right actuator, the soft mist dispersed from the throat spray will easily reach the inflamed tissue in the back of the throat to provide fast relief.

A range of different throat sprays are available. Formulations may contain a local anesthetic (eg, lidocaine, benzocaine), an antiseptic (eg, chlorhexidine, cetylpyridinium chloride), herbal extracts, or a combination thereof. Whatever the formulation, it should not contain too much sugar or ethanol, which further irritates the mucosa. And finally, the user should not experience any unpleasant aftertaste.

THROAT SPRAY TECHNOLOGIES RANGE FROM THE VERY SIMPLE TO THE VERY SOPHISTICATED

The standard for throat sprays is currently a metering pump attached to a bottle containing between 10 to 30 ml of a liquid formulation. The formulation is filled into a glass or plastic bottle with the pump fixed by a screw closure, crimped on or simply snapped onto the bottle neck. Irrespective of the fixing option selected, the system should be tight, with no leakage observed during carrying or handling by the user.

Typically, a throat spray pump will deliver a dose in the range of 50 to 200 µl per actuation. For a targeted administration, the pump will be equipped with an actuator with a prolonged nozzle. The nozzle length may range from 30 to 70 mm. It is easier to target the affected area with such a long-fixed nozzle, but this can be too bulky for users to carry, which is why actuators with foldable or swivel-mounted nozzles were developed.

Less common are devices utilizing continuous valves. A continuous valve delivers a targeted treatment but not precise dosing, as the formulation will be aerosolized while the actuator is pressed down. One technical solution is a tin or aluminum can with pressurized head space. When actuating the valve, the elevated internal pressure will force the formulation out of the can - as long as the valve stem is pressed down. This approach does, however, have some disadvantages, namely that the can does not provide the user with a view of the remaining liquid available for further dosing.

A related but more sophisticated system is the bag-on-valve (BOV) system. In this case, the product is placed inside a bag while a propellant (in most cases just compressed air) is filled in the space between the bag and the outer can. The product is squeezed out of the bag by the compressed air when the continuous valve is actuated. A BOV system will work with any 360 degree orientation. However, the device will not give you an idea of the remaining product.

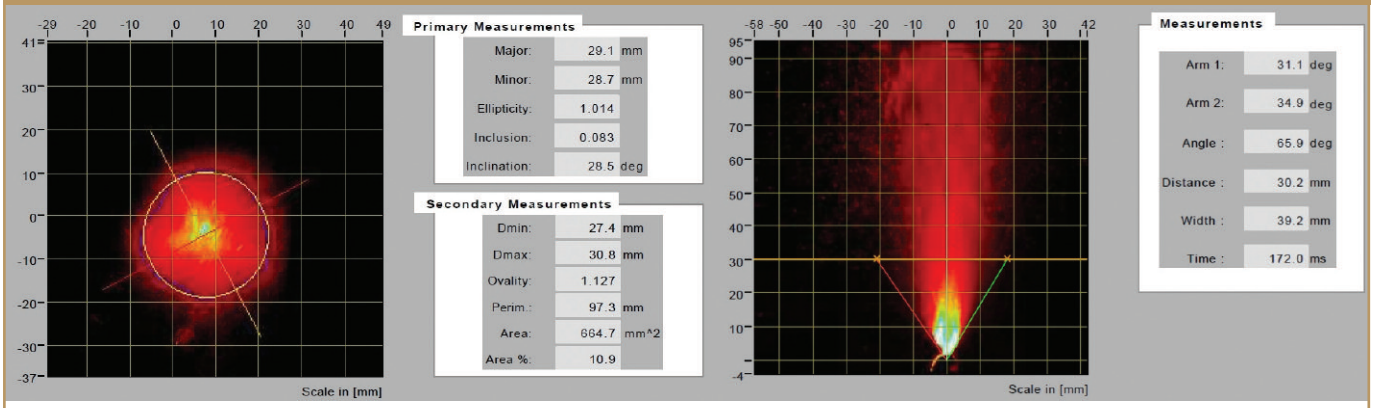
FIGURE 2

Components of a throat spray system.

FIGURE 3

Actuators with fixed or swiveling nozzles are available.

FIGURE 4



Spray performance tests ensure the formulation's spray pattern and plume geometry is appropriate for the intended use.

HOW TO DEVELOP AN APPROPRIATE SORE THROAT REMEDY BASED ON A PUMP SPRAY SYSTEM

Container Selection is Paramount

Bottles or containers are an integral part of throat spray systems and significantly influence the performance and appearance of the final product. Usually made from glass or plastic, each have their own characteristics, advantages, and disadvantages. Glass has the most obvious disadvantages – it weighs more than plastic and is susceptible to breaking. Critically, the bottle and pump interface must be effectively tested to negate filling line problems and leakages in the final product. Gaskets are often used to ensure perfect tightness between the pump housing and the container. Experienced and expert pump suppliers will be able to recommend a range of fit-for-purpose, reliable quality bottles, whether you are considering a standard or bespoke solution.

Ensuring the Compatibility of the Delivery System

To ensure the compatibility of the selected system, pump, or valve components and the drug formulation, it is necessary to conduct some basic compatibility testing.

The pump and valve manufacturer will make recommendations based on the necessary mechanical function and to mitigate against the risk of chemical interactions. In practice, potential interactions between the formulation and functional parts due to sorption or swelling cannot be entirely excluded and should therefore be evaluated in an early development stage.

Throat spray formulations may contain ingredients that are very aggressive and can lower the surface tension. This in turn could damage the metal parts and impair the functionality of the pump. Typical tests to mitigate against this include immersion of the functional parts of the pump or valve in the formulation to detect swelling or discoloration. Initial tests with assembled systems from this immersion test will provide insight into the potential effects on mechanical function, such as higher friction, incomplete metering, leakage etc.

A simple test for spray performance will ensure the formulation can be aerosolized by the system and that the delivered spray pattern and particle size is appropriate for the intended use. It is recommended to perform such preliminary compatibility tests with a range of different pumps to establish which can provide the best performance with the given formulation.

Assessing Performance Characteristics

Spray pattern and droplet size distribution are the most important parameters for the targeted treatment of a sore throat. Spray pattern is a term used to describe the spray angle and the shape of the plume for a fully developed spray. The droplet size is characterized once the spray is fully developed using a laser diffraction method. Fine particles (droplets with less than 10 µm mean dynamic diameter) should be as low as possible to avoid droplet deposition in the lower airways. Regulatory authorities often require characterization of this parameter using a cascade impactor. However, this is an unusual assessment, as the parameter can be easily assessed using a laser diffraction method.

As previously discussed, testing for potential leakage should be done in the early development stage. This ensures that the product integrity is maintained throughout its proposed shelf-life and during use. Exposing the pumps to pressure tests can replicate user behavior and will help prevent complaints from users at a later date. It should be recognized that the manufac-

"Choosing an effective and convenient drug delivery system is key in order to develop brand loyalty for this growing market. The most challenging part of the development process is selecting the correct pump or continuous valve system that will generate a well-defined spray plume with negligible fine particle fraction for the provided formulation."

turers of such pump systems will test the pumps together with some standard bottles using standard media, such as physiological saline. However, it is important to repeat such tests using the actual formulation.

PREVENTION IS BETTER THAN CURE

People often fear the symptoms and impact of a common cold or upper respiratory infections on daily life, and there are plenty of tips around on how to protect yourself. For example, a Canadian review from 2011 concluded that vitamin C can be recommended to patients for prevention of the common cold (which is not undisputed) and that there is moderate evidence supporting the use of Echinacea purpurea and zinc lozenges for treatment to shorten the duration of the cold.[3]

Another cold prevention solution that often comes in a spray system is zinc, an essential mineral. There have been several studies conducted on zinc as a cold remedy, both in the form of zinc nasal sprays and zinc lozenges, to establish preventive or therapeutic effects. These studies were not able to demonstrate a clear beneficial effect, as the best-run studies found mixed results, but such sprays are still widely used.[3] In June 2009, the US Food and Drug Administration issued a warning statement about intranasal zinc products, available over the counter under the brand name Zicam. The authority stated that zinc nasal gel sprays and other zinc nasal products like swabs may cause permanent or long-lasting damage to the sense of smell. The manufacturer of Zicam products, Matrixx Initiatives, voluntarily withdrew its gel spray and swabs from the market, but later released a reformulated version.

Recently, some carragelose-based nose and throat sprays emerged, claiming protection to virus born upper respiratory infections. For example, the Austrian company Marinomed developed Mavirex, a technology platform based on polymers derived from red seaweed. The first polymer of this platform is Carragelose®, a broadly active anti-viral compound for treating respiratory diseases. The compound prevents the binding of viruses on the mucosal cells, in addition to its moistening effect. There are several nasal, as well as mouth and throat sprays, available and marketed as medical devices with a CE mark in Europe. Yet, these sprays have to be used on a regular basis during the cough and cold season and frequently during the day to have any effect, as the mucociliar clearance will clear the upper airways from the carragelose film. To maintain the optimum protection, the nasal and throat sprays have to be used simultaneously.

There is also evidence that maintaining the mucociliar clearance in the upper airways during the cough and cold season is beneficial, which can be easily done simply by wetting with saline solutions. Consequently, a lot of nasal saline products on the market today are successful. However, for now, there is no device available that has the ability to deliver a reasonable amount of liquid into the nasal cavity and the throat at the same time. This would provide a more effective protection.

Perhaps a type of portable nebulizer with a higher output rate than the conventional ones, and a tuned droplet size for deposition in the upper airways, could be a perfect solution for this task. Breathing through a face mask could then deposit droplets on the mucosa of the whole upper airways. To meet these needs, new technologies would be beneficial as the standard nebulizers are neither portable nor deliver a sufficient output rate for people needing convenience. New technologies could benefit the market, and we look forward to seeing new advances.

SUMMARY

The potential throat spray market is of considerable size, with peak sales during the cough and cold season. The formulation may contain ingredients that prevent the attraction of a viral infection or to relieve symptoms. The barriers to the development of a throat spray are not particularly high, making throat sprays an attractive delivery method for OTC products, such as sore throat remedies.

Choosing an effective and convenient drug delivery system is key in order to develop brand loyalty for this growing market. The most challenging part of the development process is selecting the correct pump or continuous valve system which will generate a well-defined spray plume with negligible fine particle fraction for the provided formulation.

As throat sprays are most likely used as a quick remedy for symptoms, a foldable nozzle should be considered. Reliable and smooth actuations are mandatory, and any evidence of leakage out of the finished product will represent a significant fail.

To ensure an accelerated and successful product transition from bench to market, it is recommended to establish a development partnership with an experienced pump supplier early on in the process. ◆

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BIOGRAPHIES

Dr. Degenhard Marx, following the study of veterinary medicine and the successful completion of his thesis at the University of Leipzig, joined the Arzneimittelwerke Dresden/Asta Medica co-operate research in 1992. In 2001, he took over a senior research position at Altana Pharma/Nycomed in Constance, Germany. During this time in the pharmaceutical industry, he collected ample experiences in the drug development of anti-inflammatory and cardio-vascular drugs. In 2008, he became Business Development Manager at Ing. E. Pfeiffer, Pharma Division, which became Aptar Pharma in 2010. He is now Director Scientific Affairs within the Aptar Pharma Consumer Health Care Division.

Günter Nadler is Director Business Development in Aptar Pharma's Consumer Health Care Division. He studied Business Administration and Mechanical Engineering, and started his career at Aptar Pharma 17 years ago in R&D. Before joining the Business Development Team in 2010, he worked in different technical and commercial positions at Aptar Pharma and gained an extensive knowledge of the pharmaceutical drug delivery industry.

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INJECTABLE NANOMEDICINES

New Developments in Long-Acting Injectable Nanoformulations

By: Dongwei Guo, PhD, and Jingjun Huang, PhD

ABSTRACT

Nanotechnology has been extensively investigated in the application of different drug delivery systems for various routes of administration. Novel nanoparticles have been developed and utilized for the treatment of many diseases. Due to the advantages of their targeted drug delivery, reduced toxicity, long circulation, and enhanced half-life, nanoparticles are particularly useful for use in long-acting formulations. In this paper, we focus on the overview of nanoproducts in the market and the technologies to make long-acting injectable nanoformulations. Different types of injectable nanomedicines have been introduced to markets, including liposomes, polymeric nanoparticles, nanocrystals, and relatively new antibody drug conjugates. Their properties are illustrated and their applications, as well as commercial available products, are summarized.

INTRODUCTION

Nanomedicine is an emerging field that combines nanotechnology with pharmaceutical and biomedical sciences, with the goal of developing drugs and imaging agents with higher efficacy and improved safety and toxicological profiles. According to BCC Research (www.bccresearch.com), the global nanotechnology market should reach $90.5 billion by 2021, from $39.2 billion in 2016 at a compound annual growth rate (CAGR) of 18.2%. The nanomaterials market (which includes nanomedicines) should reach $77.3 billion by 2021 from $32.5 billion in 2016 at a CAGR of 18.9% (Figure 1).

Nanomedicines include several distinct application areas, including drug delivery, drugs and therapies, in vivo imaging, in vitro diagnostics, biomaterials, and active implants. In these fields, nanomedicine has seen increased research activity throughout the past decade. Currently, nanomedicine accounts for about 5% of nanotechnology research publications worldwide. In this review, we focused on the progress of long-acting injectable nanoformulations.

EVALUATION & APPLICATION OF DIFFERENT NANOMEDICINES

Nanomedicine products began appearing on the market more than a decade ago, and some have become best-sellers in their therapeutic categories. The principal areas in which nanomedical products have made an impact are cancer, CNS disease, cardiovascular disease, and infection control. Figure 2 presents the trends in the development of nanomedicines in terms of drug products approved by FDA or currently under clinical investigation. Different types of long-acting injectable nanoparticles are included, although liposomal and polymeric nanoparticles are the most commonly used.

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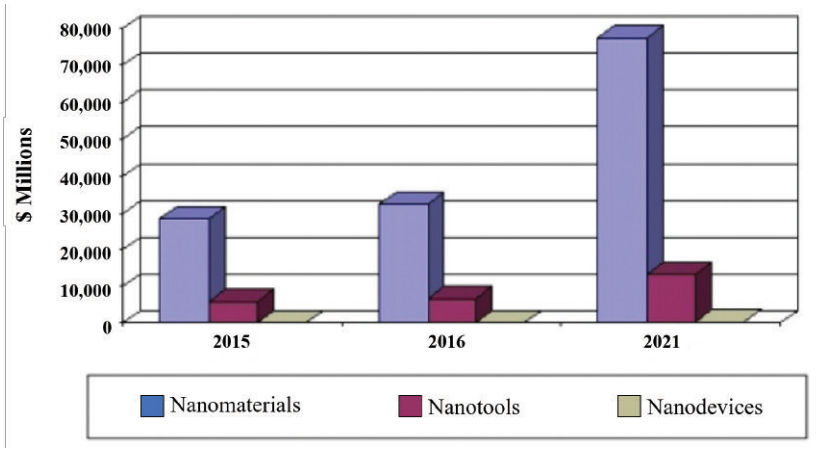
LIPOSOMES

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

The concept of a liposomal drug delivery system has had a revolutionary effect on the pharmaceutical field. Since Alec Bangham first described liposomes in 1961, a massive amount of research has been carried out, and their applications are now well-established in various areas, such as drugs, biomolecules, and gene delivery. Due to extensive developments in liposome technology, a number of long-acting liposome-based drug formulations are available for human use, and many products are under clinical trials. Most commercial available liposomal drug formulations are listed in Table 1.[1,2]

FIGURE 1



Summary of Global Nanotechnology Market (2015-2021)

Liposome Technologies for Long-Acting Drug Delivery

Several widely used liposome technologies include Stealth Liposome Technology (SLT), Non-PEGylated Technology (NPL), DepoFoam™ Technology, and Lysolipid Thermally Sensitive Technology (LTST).[3]

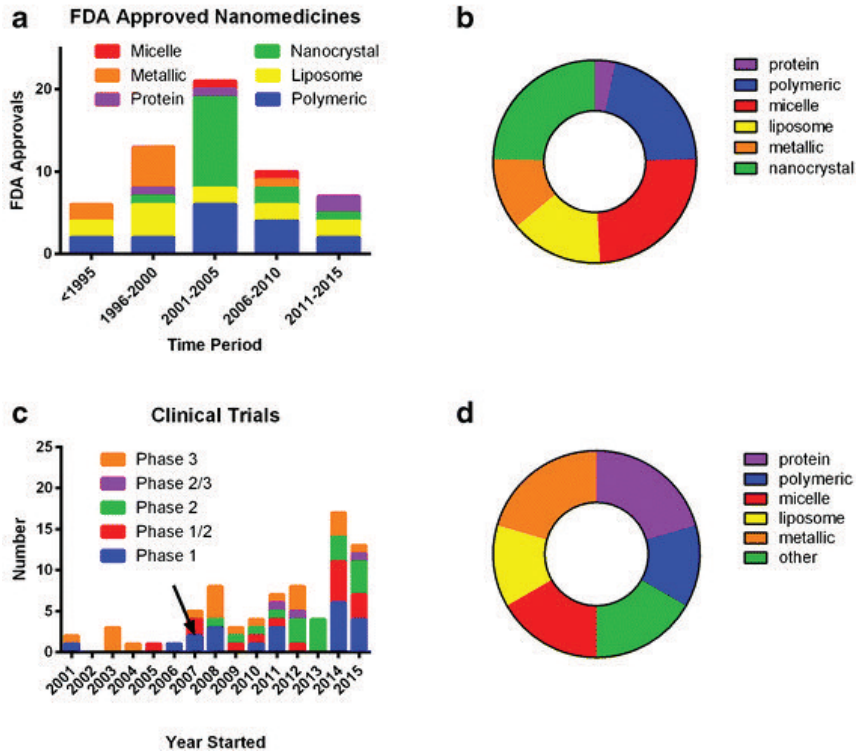
In SLT, strands of the polymer(s) are attached to drug molecules, or to a system that can improve the safety and efficacy of the therapeutic agents. In general, PEGylation is attained by the incubation of a reactive derivative of PEG with the target moiety. Covalent linkage of the liposome to a PEG protects the active moiety from the recipient's immune system, which results in reduced immunogenicity and antigenicity.[2] It also produces alterations in the physiochemical properties of the active moiety, including changes in the hydrodynamic size, which further reduce its renal clearance and thereby prolongs its circulatory time. Also, it provides hydrophilicity to hydrophobic drugs and reduces dosage frequency.

NPL is a unique drug delivery system that came as a breakthrough in cancer therapy by offering the benefits of a PEGylated-liposome while eliminating the side effects associated with PEG, such as hand-foot syndrome.[3] NPL Doxorubicin (NPLD) injection provides a better safety profile over conventional DOX and Doxil®. NPLD not only reduces the cardiac toxicity associated with DOX, but also the dose-limiting toxicity linked with the use of Doxil.

DepoFoam technology encapsulates drugs in its multivesicular liposomal platform without modification of their molecular structure. The multivesicular liposomes release drug(s) over a required period of time ranging from 1 to 30 days. Upon administration, DepoFoam particles release the drug over a period of hours to weeks following erosion and/or reorganization of the lipid membranes.[3] DepoFoam technology improved the properties of both small and large molecules. This technology considerably improved patient care by providing a remarkable solution for medications that require frequent multiple injections and have a short period of action or side effects.

Thermosensitive liposomes have been studied for drug release at sites of elevated temperature. These novel liposomes are being developed to exhibit temperature-dependent release of encapsulated drug(s). Local tissue temperature is generally ele-

FIGURE 2



Trends in the Development of Nanomedicines
(a) FDA-approved nanomedicines stratified by category; (b) FDA-approved nanomedicines stratified by category overall; (c) clinical trials identified in clinicaltrials.gov from 2001 to 2015 with arrow indicating approximate start date of US law (FDAAA 801) requiring reporting to FDA database; (d) nanomedicines under clinical trial investigation stratified by category overall.[5]

vated to 42°C by radiofrequency ablation, a technique based on the application of radiofrequency.[3] Lipid components present in the liposome undergo a gel to liquid transition at elevated temperatures, making it more permeable, and thus releasing the drug.

POLYMERIC NANOPARTICLES

Polymeric nanoparticles possess the advantage of stability - both in storage and in vivo application. For polymeric particles, the drug is entrapped within the polymer matrix, usually a biodegradable polymeric matrix. Polymer nanomedines typically fall into one of two categories: (1) polymer-drug conjugates for increased drug half-life and bioavailability, and (2) degradable polymer architectures for controlled-release applications.[4] However, it should be noted that aspects of polymer chemistry are emerging in nearly all of the categories because many of the components required (eg, amphiphilic block copolymers) can be designed and controlled through organic synthesis methods.

Polymeric nanoparticles are recognized as foreign bodies and can be removed from the blood circulation by the phagocyte cells of the RES. A majority of the nanoparticles can be phagocytosed by the macrophages of the liver and spleen shortly following intravenous (iv) injection. The nanoparticle clearance is mediated by adsorption of blood components to the surface of the particles, namely opsonization. The polymers themselves include those that are synthetic, pseudo-synthetic, or those that arise from natural sources. Their application has spanned the full nanomaterial size-scale from single polymer chains up to large aggregates, depending on the required therapeutic outcome. To realize long-acting attributes, the polymeric nanoparticles can protect the drug from degradation, thus achieving prolonged drug delivery (and a long shelf-life). For therapeutic purposes, the most commonly used polymers include polyethylene glycol (PEG), poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), alginate, chitosan, and gelatin base. Polymeric nanoparticles comprise a very heterogeneous group of nanosized therapeutics (Table 2).[1,5]

The most basic class of polymeric nanomedicines utilizes single polymer chains, either directly as the therapeutic itself, or as a modifying agent for a drug or diagnostic agent. More frequently in terms of polymeric nanomedicines, drugs are attached to a hydrophilic polymer to increase circulation or to improve biocompatibility/solubility. The most well-established polymer is poly (ethylene glycol) (PEG), and PEGylation results in a significant increase in biological half-life in plasma. In addition to PEGylation, other hydrophiles can be utilized to increase circulation half-life. A polymer-drug conjugate of paclitaxel and polyglutamic acide (poliglumex/PPX) has entered Phase 3 trials and is showing significantly improved standard of living for patients who undergo paclitaxel therapy for non-small cell lung cancer.

Beyond just extending the circulation time of established drugs, polymeric nanoparticles can be developed based on hydrophobic materials that facilitate controlled release of the therapeutic. This is achieved by using slowly degradable func-

tionality that subsequently leads to kinetically driven release of the drug. A long-established polymer nanoparticle that has had significant success is based upon incorporation of leuprolide (a testosterone-inhibiting drug) into a polylactide-co-glycolic acid (PLGA) nanoparticle.

NANOCRYSTALS

Nanocrystals are composed of mainly hydrophobic drug with a small amount of excipient or surfactant, and different kinds

TABLE 1

Name	Description	Mechanism	Approval/Indication
Abelcet®	Amphotericin B complex 1:1 with DMPC and DMPG (7:3), ~250 nm, ribbon like structures of a bilayered membrane	Mononuclear phagocyte system (MPS) targeting: Selective transfer of drug from lipid complex to fungal cell with minimal uptake into human cells has been postulated.	FDA 1995 and 1996 Marketed outside US as Amphocil® Systemic fungal infections (IV)
AmBisome®	Amphotericin B encapsulated in liposomes (60-70 nm) composed of hydrogenated soy phosphatidylcholine, cholesterol, and distearoyl phosphatidylglycerol (2/0.8/1 molar)	MPS targeting: Liposomes preferentially accumulate in organs of the MPS. Negative charge contributes to MPS targeting. Selective transfer of the drug from lipid complex to target fungal cell with minimal uptake into human cells has been postulated.	FDA 1997 Systemic fungal infections (IV)
DaunoXome®	Daunorubicin citrate encapsulated in liposomes (45 nm) composed of distearoyl phosphatidylcholine and cholesterol (2/1 molar)	Passive targeting via EPR effect: Concentration of available liposomal drug in tumors exceeds that of free drug. Liposomal daunorubicin persists at high levels for several days.	FDA 1996 HIV-related KS (IV)
DepoCyt®	Cytarabine encapsulated in multivesicular liposomes (20 □m; classified as nanopharmaceutical based on its individual drug containing "chambers") made from dioleoyl lecithin, dipalmitoyl phosphatidylglycerol, cholesterol, and triolein	Sustained release: This formulation of cytarabine maintains cytotoxic concentrations of the drug in the cerebrospinal fluid for more than 14 days after a single 50-mg injection.	FDA 1999/2007 Lymphomatous malignant meningitis (IV)
DepoDur®	Morphine sulfate encapsulated in multivesicular liposomes (17-23 □m; per se not a nanopharmaceutical - classified as such based only on its individual drug containing "nano-sized chambers") made from dioleoyl lecithin cholesterol, dipalmitoyl phosphatidylglycerol, tricaprylin, and triolein	Sustained release: After the administration into the epidural space, morphine sulfate is released from the multivesicular liposomes over an extended period of time.	FDA 2004 For treatment of chronic pain in patients requiring a long-term daily around-the-clock opioid analgesic (administered into the epidural space)
Doxil®	Doxorubicin hydrochloride encapsulated in Stealth® liposomes (100 nm) composed of N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero3- phosphoethanolamine sodium, fully hydrogenated soy phosphatidylcholine, and cholesterol	Passive targeting via EPR effect: Extravasation of liposomes by passage of the vesicles through endothelial cell gaps present in solid tumors. Enhanced accumulation of doxorubicin in lesions of AIDS-associated KS after administration of PEG-liposomal doxorubicin.	FDA 1995 AIDS-related KS, multiple myeloma, ovarian cancer (IV)
Inflexal® V	Influenza virus antigens (hemagglutinin, neuraminidase) on surface of 150-nm liposomes	Mimicking native antigen presentation: Liposomes mimic the native virus structure, thus allowing for cellular entry and membrane fusion. Retention of the natural presentation of antigens on liposomal surface provides for high immunogenicity.	Switzerland 1997 Influenza vaccine
Marqibo®	Vincristine sulfate encapsulated in sphingomyelin/cholesterol (60/40, molar) 100-nm liposomes	Passive targeting via EPR effect: Extravasation of liposomes through fenestra in bone marrow endothelium.	FDA 2012 Acute lymphoid leukemia, Philadelphia chromosome-negative, relapsed or progressed (IV)
Mepact™	Mifamurtide (synthetic muramyl tripeptide-phosphatidylethanolamine) incorporated into large multilamellar liposomes composed of 1-palmitoyl-2-oleoyl-sn-glycerol-3-phosphocholine and 1,2-dioleoyl-sn-glycero-3-phospho-L-serine	MPS targeting: The drug, an immune stimulant, is anchored in negatively charged liposomal bilayer membrane.	Europe 2009 Non-metastasizing resectable osteosarcoma (IV)
Myocet®	Doxorubicin encapsulated in 180-nm oligolamellar liposomes composed of egg phosphatidylcholine/cholesterol (1/1, molar)	MPS targeting: Forms "MPS depot," slow release into blood circulation resembles prolonged infusion.	Europe 2000 Metastatic breast cancer (IV)
Onivyde™	Irinotecan encapsulated in to DSPC:MPEG-2000:DSPE (3:2:0.015 molar ratio)	The drug contains SN-38, an active metabolite of irinotecan that binds reversibly to the topoisomerase 1-DNA complex and prevents re-ligation of the single strand breaks.	FDA 2015 Combination therapy with fluorouracil and leucovorin in metastatic adenocarcinoma of the pancreas
Visudyne®	Verteporfin in liposomes made of dimyristoyl-phosphatidylcholine and egg phosphatidylglycerol (negatively charged); lyophilized cake for reconstitution	Drug solubilization: Rendering drug biocompatible and enhancing ease of IV administration. No other apparent function of liposomes. Liposomal formulation instable in the presence of serum. Fast transfer of verteporfin from Visudyne® to lipoproteins	FDA 2000 Photodynamic therapy of wet age-related macular degeneration, pathological myopia, ocular histoplasmosis syndrome (IV)

Double emulsions made using Dolomite products; a range of highly consistent double emulsions can be produced using commercially available systems.

"The revolutionary development of nanoscience and nanotechnology in pharmaceutical research and development opens new horizons for the creation of novel drug products, which will utilize the unique characteristics of nanosized long-acting injectable formulations. The application of engineered nanomaterials to medicine will produce nanomedicines with unprecedented benefits for the clinical outcome in many therapeutic indications."

of hydrophobic drugs can be nanoformulated into nanocrystals with high-loading and encapsulation efficacy. Micronization is widely used as a common formulation method for sparingly soluble compounds. The saturation solubility of the nanocrystals is highly related to the particle size, and solubility increases with particle size decrease due to the increased surface area, especially when the nanocrystals are below 300 nm. Consequently, the concentration gradient between gut lumen and blood is increased, which usually results in improved absorption by passive diffusion. In these suspension formulations, the rate-limiting step for drug absorption is the speed for drug particle dissolution in the formulation or in the in vivo fluid surrounding the drug formulation. In many formulations, a fatty acid ester of a drug is used to prepare an oil-based parenteral solution, and the drug-release rate from the solution is determined by the drug partitioning between the oil vehicle and the tissue fluid; it can also be influenced by the drug bioconversion rate from the prodrugs to the parent drugs.

To increase the circulation half-life, it is a widely accepted way in long-acting formulations for the parent drug to be synthesized into a prodrug through use of long-chain fatty acids (esterification). Due to their extremely low water solubility, the fatty acid ester of a drug dissolves slowly at the injection site after intramuscular (IM) injection. With the help of in vivo hydrolase, the prodrug is hydrolyzed into the parent drug and becomes available in the systemic circulation. Several other factors such as injection site, injection volume, the extent of spreading of the drug depot at the injection site, and the absorption and distribution of the oil vehicle can also affect the overall pharmacokinetic profile of the drug.

Most of the nanocrystals approved by the FDA are used as oral formulations, and there are also some approved as a bone substitute. For long-acting injectables, the FDA has approved Invega® Sustenna® for schizophrenia and schizoaffective disorder treatment in 2009, and Ryanodex® for malignant hypothermia treatment in 2014. Invega Sustenna is a good example of long-acting injectable prodrug formulation (paliperidone palmitate is the prodrug of paliperidone palmitoyl ester). This long-acting injectable formulation is indicated as a once-every-28-days injection after an initial titration period.

The production of nanocrystals has been applied to both organic drugs as well as inorganic materials. Synthesis methods include either "top-down" diminution approaches that are often employed for the organic compounds, and "bottom-up" precipitation methods that are more commonly applied to inorganic materials. Wet milling and high pressure homogenization technologies are widely used for nanocrystal preparation.

Wet Milling Technology

Wet milling (a top-down process) is a relatively effective milling technique for nanocrystal preparation. The process is done in media milling, and it treats a dispersion of concentrated drug in an aqueous or non-aqueous liquid medium with milling balls. Wet milling has several advantages in its economic value and ease of scaling up. With the right media milling equipment, manufacturers can cost-effectively create uniformly fine particles with limited or no contamination. However, due to the intensive mixing forces in the vessel, erosion of the milling balls is a common occurrence, and must be monitored appropriately.

High Pressure Homogenization Technology

High pressure homogenization (also a top-down process) can also achieve suspensions with narrow particle size distribution. It is a purely mechanical process, which is evoked by forcing a fluidic product through a narrow gap (the homogenizing nozzle) at high pressure (150-200 MPa, or 350-400 MPa for ultra-high pressure homogenization, UHPH).[6] The liquid product is subjected to very high shear stress causing the formation of very fine particles. High pressure homogenization can effectively process large volumes of liquid suspension sample thoroughly and reproducibly. Because it doesn't use milling balls, contamination of the final product is much less; however, the high pressures applied cause a temperature increase (due to the heat of compression), and this needs to be controlled, especially for a thermally labile drug substance. Alternatively, a combination of bottom-up and top-down processes can be employed, eg, solvent dissolution of API, crystallization via a non-solvent, and then homogenization of freshly formed particles.

ANTIBODY-DRUG CONJUGATES

Antibody-drug conjugates (ADCs), a form of immuno-conjugate or bio-conjugate, are an emerging class of medicines designed for high-specificity targeting and destruction of cancer cells. The mechanism of action is targeted delivery of a cytotoxic agent to the cancer cell via monoclonal antibody targeting of a specific cell surface marker. Upon binding, a biochemical reaction activates internalization of the ADC into the cell cytoplasm, where the drug becomes active, killing the cancer cell.[7] The ultimate advance with ADC therapeutics is

TABLE 2

Name	Description	Mechanism	Approval/Indication
Adagen®	PEGylated adenosine deaminase, one enzyme molecule is modified with up to 17 strands of PEG, MW5,000, 114 oxymethylene groups per strand	Increased circulation time and reduced immunogenicity.	FDA 1990 Adenosine deaminase deficiency - severe combined immunodeficiency disease)
Cimzia®	PEGylated antibody (Fab' fragment of a humanized anti-TNF-alpha antibody)	PEGylation generally increases hydrodynamic radius, prolongs circulation and retention time, decreases proteolysis, decreases renal excretion, and shields antigenic determinants from immune detection without obstructing the substrate-interaction site.	FDA 2008 Crohn's disease, rheumatoid arthritis
Copaxone®	Polypeptide (average MW 6.4 kDa) composed of four amino acids (glatiramer)	No mechanism attributable to nanosize. Based on its resemblance to myelin basic protein, glatiramer is thought to divert as a "decoy" an autoimmune response against myelin.	FDA 1996/2014 Multiple sclerosis (SC)
Eligard®	Leuprolide acetate (synthetic GnRH or LH-RH analog) incorporated in nanoparticles composed of PLGH copolymer (DL-lactide/glycolide; 1/1, molar)	Sustained release	FDA 2002 Advanced prostate cancer (SC)
Genexol®	Paclitaxel in 20-50-nm micelles composed of block copolymer poly(ethylene glycol)-poly(D,L-lactide)	Passive targeting via EPR effect	South Korea 2001 Metastatic breast cancer, pancreatic cancer (IV)
Opaxio®	Paclitaxel covalently linked to solid nanoparticles composed of polyglutamate	Passive targeting via EPR effect: Drug release inside solid tumor via enzymatic hydrolysis of polyglutamate	FDA 2012 Glioblastoma
Zinostatin stimalamer®	Conjugate protein or copolymer of styrene-maleic acid and an antitumor protein NCS. Synthesized by conjugation of one molecule of NCS and two molecules of poly(styrene-co-maleic acid)	Passive targeting via EPR effect	Japan 1994 Primary unresectable hepatocellular carcinoma

Commercially available injectable polymeric nanoparticle drug formulations

that targeting and release of the drug specifically within the cancer cell means that healthy cells are not adversely affected, and cancer cells can be more effectively destroyed. Success in ADC therapeutics stems from a deep understanding around each of the trilogy "Antibody-Linker-Payload (drug)" technologies, with having a complementary optimization of all three to generate an effective and potent ADC. With non-cleavable ADCs, the linker unit remains attached to the drug, which mitigates externalization and the resulting side effect of the drug entering healthy neighboring cells.[8] With cleavable ADCs, the drug is completely cleaved from the linker unit upon internalization, the antibody is degraded to its amino acid form, and the entire complex becomes active drug. Innovation in linking technology aspires to improve the coupling of payloads as well as to improve cleavage reactions, allowing improvements in payload delivery. The majority of ADC payloads are small molecules, which act via disruption of microtubules or inducing DNA damage.

To date, there are only four ADCs that have received market approval. However, after a request from the US Food and Drug Administration (FDA), Pfizer/Wyeth, the developer and marketer of the first ADC to receive marketing approval - in 2001 for the treatment of patients with acute myelogenous leukemia (Gemtuzumab ozogamicin, trade name: Mylotarg®), withdrew the drug from the market in June 2010 (although it is still marketed in Japan). It was re-introduced into the US market in 2017. The second and third marketed ADCs are Brentuximab vedotin (trade name: Adcetris®, marketed by Seattle Genetics and Millennium/Takeda) and Trastuzumab emtansine (trade name: Kadcyla®, marketed by Genentech and Roche). They were approved by the FDA in 2011 and 2013, respectively. The newest ADC, Inotuzumab ozogamicin, was approved by the European Commission as monotherapy for the treatment of adults with relapsed or refractory CD22-positive-B-cell precursor acute lymphoblastic leukemia on June 30, 2017 under the trade name Besponse® (Pfize/Wyeth) and approved for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia by the FDA on August 17, 2017.

Technical & Manufacturing Challenges

The biggest technical challenge associated with any drug manufacturing process is to provide consistently efficacious drug product, which is of the required purity and is safe from environmental and process-related contamination. This challenge must be accomplished in a manner that protects employees, operators, and the general environment from the harmful substances inherent in the process, and at a cost that makes the final drug marketable. The starting point for ADC manufacturing is the parent monoclonal antibody (mAb). Often, the supply of mAbs of suitable quality for therapeutic purposes is taken for granted due to the successful developments in purification templates and platform processes in previous years.

SUMMARY

The revolutionary development of nanoscience and nanotechnology in pharmaceutical research and development opens new horizons for the creation of novel drug products, which will utilize the unique characteristics of nanosized long-acting injectable formulations. The application of engineered nanomaterials to medicine will produce nanomedicines with unprecedented benefits for the clinical outcome in many therapeutic indications.◆

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BIOGRAPHY

Dr. Dongwei Guo earned her PhD in Pharmaceutical Sciences from the University of Nebraska Medical Center, and joined Ascendia Pharmaceuticals in 2016 following graduation as a Senior Formulation Scientist. Dr. Guo has expertise in long-acting drug delivery systems, and she has extensive experience on different types of formulations, including micelles, liposomes, dendrimers, polymeric nanoparticles, nano- and micro-suspensions, and emulsions. She has also been a reviewer for the Journal of Pharmaceutical Sciences, Journal of Pharmacy and Pharmaceutical Sciences, Journal of Chinese Pharmaceutical Sciences, International Journal of Pharmaceutical Sciences and Drug Research, and International Journal of Pharmaceutical Compounding.

Drug Development
EXECUTIVE

Brent Lieffers
Senior Director, Operations
Singota Solutions

Singota Solutions: Keeping Up With Trends & Technology as a CDMO

Each day at Singota Solutions, their team of experts focuses on getting products to patients faster by being an agile, accountable, and transparent CDMO. So, what sets Singota apart? Responsiveness and dedication to getting things done quickly are what they say their clients value. Singota collaborates closely with their clients, customizing services to support products moving through the development process. It is not always easy being a smaller CDMO, but clients that fit into their niche end up staying. Drug Development & Delivery recently interviewed Brent Lieffers, Senior Director of Operations, to discuss the need for keeping up with trends and technology as a CDMO.

Q: What does the typical Singota client look like?

A: Our clients range from small virtual firms with no internal testing or manufacturing capabilities whatsoever to some of the largest pharma companies in the world. Obviously, the needs across the spectrum of our clients are wide-ranging, which is fine, because we take an individual approach to each client we serve. We try to keep in mind that each of our clients, while unique, are all working toward an important goal – helping patients. And without exception, they want their project done on time, so we must be smart and judicious with our time to meet their needs.

"Our Singota Solutions tagline is Focused on Faster. We see it every day on our website and documents we use as a constant reminder. We strive to serve our clients, and ultimately their patients, faster. We fully understand that time is money in the drug development world, and our goal is to shorten the amount of time between milestones for our clients wherever possible. Being a flexible and agile CDMO is important; however, expertly providing those services faster than other CDMOs is what makes Singota different."

Q: As a CDMO, you do not have any of your own products. Do you find it difficult to connect the dots from your service to the end users – patients?

A: Our company was founded with the goal of getting needed therapies to patients faster. We take that goal seriously, and actively foster a patient-centric culture. For example, we recently screened a movie for all our employees over a couple of lunch hours. The film was written and produced by a patient suffering from a disease for which one of our clients is pursuing a new and better treatment. We also seek out opportunities to meet patients who have directly benefited from work we have done for our clients. Those types of interactions keep our passion for helping patients alive and strong.

Q: Technology is advancing quickly in your industry. For instance, I noticed Singota is using a gloveless, robotic isolator workcell for aseptic filling. What prompted Singota to select this technology?

A: The innovative technology that allowed Singota to recently add aseptic filling to our CDMO capabilities was not even available just a few years ago. The speed with which technology advances continues to amaze me. However, it's no secret that our industry has been slower than other sectors in adopting and embracing some of the newer technologies. Thankfully, I believe we are seeing more progress now, and I'm very encouraged with the support we have seen from the regulatory agencies and especially some of their focus groups, such as the Emerging Technology Team at FDA.

We decided to add the aseptic filling workcell to expand our services and offer a technology to our clients that would be flexible for different component types and help accelerate production times while providing the product quality they expect – if not better. The increase in availability of Ready to Use (RTU) containers, closures, components, and consumables was integral to our design and planning and allowed us to go from idea to User Requirements Specification (URS) to build/install to validation with very short and aggressive timing. And that again fits the company philosophy, to help our clients shorten their timelines and get products to patients in the clinic faster.

Q: Is it difficult to maintain and meet quality standards when trying to move quickly? How does a CDMO achieve that?

A: Quality always comes first. It might sound a bit cliché, but ensuring quality is everyone's job, and at Singota, it's our culture. There are some things that take time and can't be avoided - equipment qualifications, personnel training, writing and reviewing copious amounts of documentation, etc. We work hard to do things right the first time, and in the long run, that saves time. We also work within our capabilities, being careful to not over promise…making sure we can do what is needed. We can control our internal processes and also seek out suppliers who hold the same values for quality.

We greatly value the work our key suppliers do for us.

Singota utilizes a Vanrx SA25 Aseptic Filling Workcell

When we enter into a relationship with a supplier, we look at it as a collaborative partnership versus a traditional vendor/buyer association. We have developed some wonderful supplier relationships that allow us to work together closely to find the best ways to meet our clients' unique needs while never compromising our quality standards.

Q: What are some industry trends you are seeing?

A: The trend toward smaller is well underway. The promise of personalized medicine has been around for a long time, but it is more than just a promise today. I believe the era of blockbuster drugs and massive manufacturing operations to generate millions of doses is transitioning to one of smaller patient populations and, by necessity, smaller and more flexible manufacturing processes. There will still be a need for some of those high-volume drugs, but that is not where Singota is looking to make a difference. Rather, we focus on high-value drug products that serve smaller patient populations and fit into our smaller manufacturing model.

Another industry trend we've noticed is the acceptance of robotics in pharmaceutical manufacturing. Automation and robotics are firmly established in most manufacturing sectors. And look at how far along autonomous vehicles have come in the past year or so. We can finally see this technology having an effect on our industry. Isolator technology has allowed us to remove the impact of operators from the initial aseptic environment, and robotics are now allowing us to remove operator variability from the process as well.

Q: Because flexibility is essential for smaller operations, how does Singota intend to address scale-up issues?

A: I recently heard the term "scale-out" used, as opposed to "scale-up," and that is exactly how we are approaching our parenteral manufacturing. By adopting a platform approach, we can add capacity by directly duplicating current unit operations, not starting over creating larger versions of our processes. This allows a more seamless capacity expansion and avoids unnecessary downtime during the transition. Singota is a single-site company, but you can easily see how this philosophy is very attractive for multi-site manufacturers as well. ◆

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FROST & SULLIVAN

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

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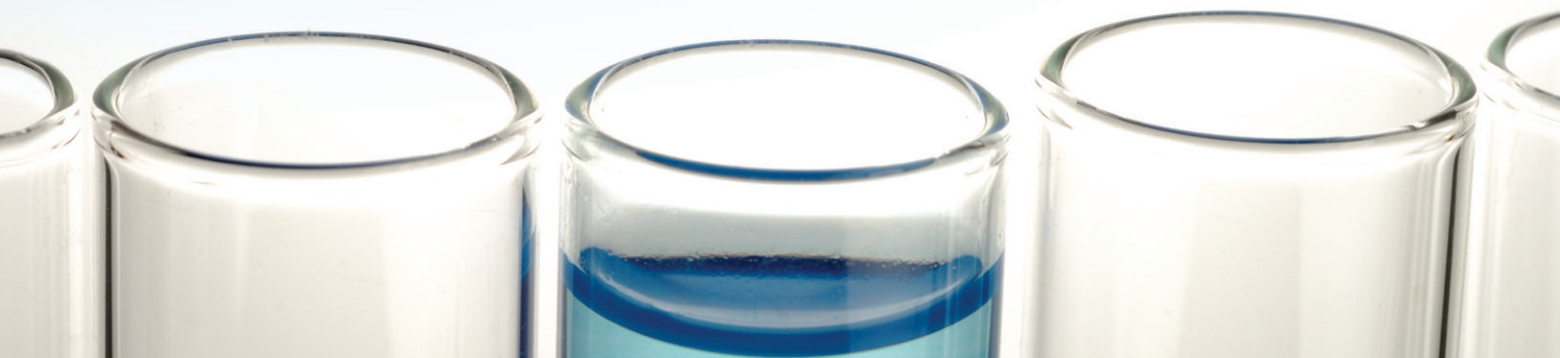

Technology & Services Showcase

Protect Your Brand™

Protect Your Brand™ is a unique offering designed to support pharma-biotech companies pursuing a dual sourcing strategy. Under this program, Alcami will support tech transfer and validation of products in advance of potential manufacturing needs without any long-term commitment or minimum annual volume. It's that simple. Protect Your Brand offers three distinct dual supply solutions to prevent disruptions from occurring at the earliest during clinical supply through to post-approval commercial production. This service can be used for drug substance, drug product, and for clinical supplies, launch quantities, and commercial supply. Protect Your Brand allows you to determine the ideal State of Alcami Readiness™ needed for your product. Responding quickly allows Alcami to minimize the effects of a supply disruption, helping prevent shortages and delays. Alcami can be ready quickly to bridge unexpected gaps in your critical supply needs. For more information, visit Alcami at **www.alcaminow.com.**

Ensuring Quality Commitment

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Technology & Services Showcase

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Liposomal & PEGylated Formulations

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Complex Drug Product Formulations

Exelead is a CDMO dedicated to the development and commercialization of therapeutics to treat life-threatening diseases. Exelead's core technologies focus on the manufacture of sterile drug products specializing in liposomal and PEGylation formulation technologies. Exelead has development capabilities that can be utilized to improve drug delivery and drug product characterization. The Indianapolis, Indiana manufacturing facility produces proprietary parenteral pharmaceuticals for oncology and enzyme replacement treatment, as well as for the treatment of numerous infectious diseases. Exelead manufactures drug products that are distributed globally and offers solutions at every phase of the drug development process (Pre-Clinical, Phase I/II/III, and Commercial). For more information, visit Exelead at **www.ExeleadBioPharma.com.**

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Noble works with drug delivery device manufacturers and biopharmaceutical companies to develop self-injection training devices, including autoinjectors, prefilled standard and safety syringes, wearables, and respiratory platforms to provide biopharmaceutical companies improvements in launch strategies and patient adherence. Noble's training and onboarding platforms are built true to form and function to device specifications and are available as off-the-shelf and customized solutions, with the optional inclusion of proprietary technologies for products ranging from mechanical training devices to smart error-correcting training platforms. These devices are designed to emulate a device's form factor and functionality, including tactile feedback, operational forces, and administration steps to provide patients with accurate simulation of actual delivery devices while being a low-cost reusable solution to safely and effectively onboard users. Companies providing reusable, device-comparable training products will be well positioned for competitive differentiation through improved patient satisfaction, adherence, and outcomes. For more information, contact Noble at (888) 933-5646 or visit **www.gonoble.com.**

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Vetter is a leading contract development and manufacturing organization (CDMO) that specializes in the aseptic filling and packaging of syringes, cartridges, and vials. The company has extensive experience with biologics and other complex compounds, including monoclonal antibodies, peptides, interferons, and vaccines. Collaborating with pharma/biotech clients worldwide, Vetter supports products from preclinical development through global market supply. Through its US and European facilities, Vetter Development Service provides state-of-the-art support for early stage products, with seamless transfer at Phase III to Vetter Commercial Manufacturing for large-scale production. The company offers state-of-the-art technology and innovative processes to promote product quality and maximize API yield. For US inquiries, please contact (847) 581-6888 or infoUS@vetter-pharma.com. For Japan inquiries, please contact +81-3-6717-2740 or infoAsiaPacific@vetter-pharma.com. For Asia Pacific inquiries, please contact +65-6808-7766 or infoAsiaPacific@vetter-pharma.com. For EU and other international inquiries, please contact +49-751-3700-0 or info@vetter-pharma.com. For more information, visit **www.vetter-pharma.com.**

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West is a leader in developing and manufacturing pharmaceutical delivery systems. The company has unique technologies in self-injection systems, including the SmartDose® drug delivery platform and the award-winning SelfDose® patient-controlled injector, that enable patients to self-administer injectable medicines at home. West is also collaborating with HealthPrize Technologies on a connected health offering that is designed to improve and reward medication adherence with unique technologies. The offering integrates HealthPrize's Software-as-a-Service medication adherence and patient engagement platform into injectable drug delivery systems, providing biopharmaceutical companies and their patients with an end-to-end connected health solution. For more information, contact West at (800) 345-9800 or visit **www.westpharma.com.**

Special Feature

Prefilled Syringes and Parenteral Manufacturing: Drug and Packaging Ensure Safety, Compatibility, and Stability

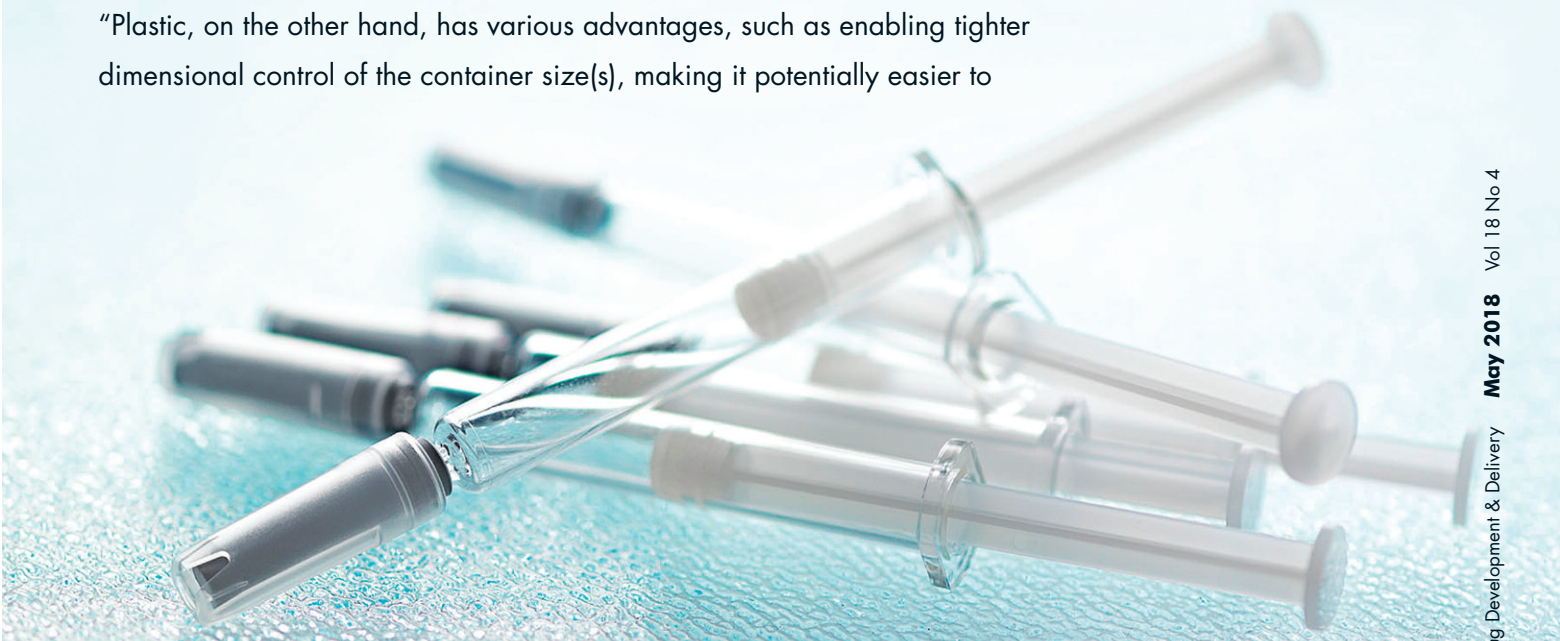
By: Cindy H. Dubin, Contributor

The global prefilled syringe market is expected to reach $6.36 Billion by 2021, up from $3.93 Billion in 2016.[1] Growth drivers in the market are an increasing prevalence of chronic diseases, escalating adoption of self-injection devices, technological advancements in the drug delivery platforms, and effectiveness of the prefilled syringes.

Also gaining momentum in the market is a shift in parenteral packaging from glass to plastic prefilled syringes because of advanced polymer materials such as polypropylene and crystal-clear polymer, which are biocompatible with the other components of the syringe.

"Glass has long been the preferred choice, and developments in glass have lowered chances of breakage, which reduces the need for material changes of the primary package," says Adam Shain, Director, Global Business Development – Injectables, Aptar Pharma. "Plastic has made advances, but the jury is still out on whether glass or plastic is the material of choice in terms of construction and compatibility."

"With glass, there have been reports and incidents of issues arising as a result of process, formulation and container interaction, such as glass delamination, particles by glass leachables, and formulation components," says Prof. Dr. Hanns-Christian Mahler, Head, Drug Product Services, Lonza Pharma & Biotech. "Plastic, on the other hand, has various advantages, such as enabling tighter dimensional control of the container size(s), making it potentially easier to



The Daikyo Crystal Zenith® Insert Needle syringe system minimizes issues of potential contamination associated with glass, and may help to reduce the risk of interactions between the drug product and its packaging (West Pharmaceutical Services, Inc.).

integrate with plastic device components of autoinjectors and pens. However, plastic also has many, not fully researched and understood liabilities, especially when developing biologic drug products, including extractables and leachables, oxygen and water permeability, and process residuals. All in all, glass containers would be currently considered still most suitable for biologic drug products in general, with plastics being appropriate for some certain, specific circumstances."

This annual *Drug Development & Delivery* report highlights some of the key players in the market and where they are focusing their efforts to ensure products are of the highest quality, safe, and easy to use.

Aptar Pharma's proprietary elastomeric formulations for prefilled syringes are designed and manufactured to provide a high level of quality, safety, and patient comfort.

Aptar Pharma: Focused on Reducing Particulate Levels

Pharmaceutical companies are increasingly looking for ways to eliminate the risks associated with contamination. Specifically, the focus has been around reducing the level of particulates found in drug product. This focus on particulates is raising the bar for all players associated with the development and manufacturing of injectable products, with attention targeted towards a zero-defect achievement. Aptar Pharma has addressed this trend with the development of its Premium portfolio of injectable components: PremiumFill®, PremiumCoat™, and PremiumVision™.

"PremiumFill is a guaranteed specification to Aptar Pharma's high quality of production, resulting in lower embedded particles, improved particulate cleanliness, and an overall reduction in defects," says Adam Shain, Director, Global Business Development – Injectables, Aptar Pharma.

Also produced with the PremiumFill guarantee is PremiumCoat, the new standard for film-coated stoppers. And, PremiumVision uses an in-line automated vision inspection system designed to further validate against critical defects and offers the ability to customize and further reduce the particulate level guarantee for PremiumFill.

"Aptar Pharma has always developed and manufactured pure elastomeric formulations," explains Mr. Shain. "Using the fewest materials possible, we create ultra-clean formulations offering the lowest levels of extractables and leachables, which has contributed to the above advances."

Aptar Pharma's services and development capabilities have proven successful for Next Breath, a full-service cGMP analytical service company. Recently, Next Breath expanded its development services to injectable delivery systems with a core focus on extractables and leachables. Next Breath works with customers to define the characteristics of elastomeric components that are best suited for their drug product, assess functionality for the intended use, examine extractables and leachables, and determine physical and chemical compatibility. "This systematic approach makes Next Breath services ideal for any company looking to accelerate their development timelines for regulatory filing," says Mr. Shain.

Catalent: Using Next-Generation Technology for More Flexible Filling

There is a shift in the industry to extend the ready-to-use platform and capabilities for filling flexibility. Catalent has combined the activities of what would tra-

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Catalent produces around 300 million prefilled syringes annually at its Brussels, Belgium and Bloomington, Indiana facilities.

ditionally be three lines into one single line under barrier isolation located in one filling suite. The project was part of a complex manufacturing upgrade, within an existing operation, to complement its existing syringe and vial lines with first-of-its-kind flexible filling technology, explains Brian Galliher, Senior Process Engineer, Catalent Biologics. "The project is an exceptional example of Catalent helping to lead industry in the adoption of ready-to-use vials (and cartridges) and applying next-generation robotics technology uniquely to create unparalleled flexibility," he says. "Catalent's version of flexible filling not only adds capacity, but also enables better service to its customers through that flexibility to benefit patients."

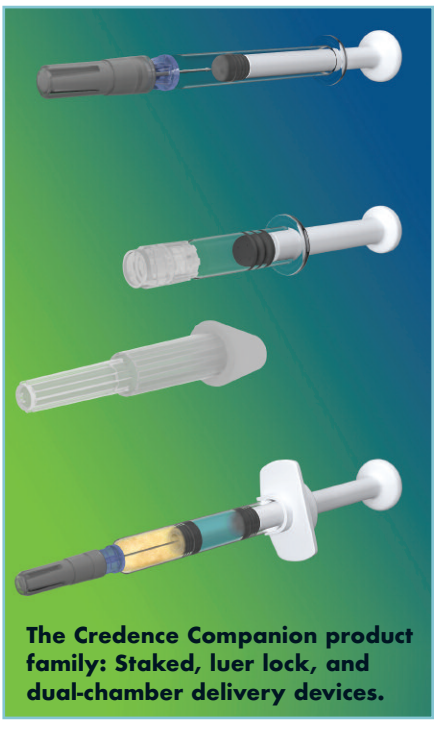
On the device side, Mr. Galliher sees an increase in the number of off-the-shelf offerings for autoinjectors. "In the past, 1mL-long presentations were predominantly the only offerings for off-the-shelf autoinjector presentations. Today, there are 2.25mL presentations also available in an off-the shelf format. Catalent has the capability of processing both 1mL and 2.25mL configurations."

In the area of autoinjectors, Catalent supports combination device assembly. This begins with early clinical device assembly and progresses through builds needed to support human factors assessments and design verification all the way through qualification and commercial launch/production, says Mr. Galliher.

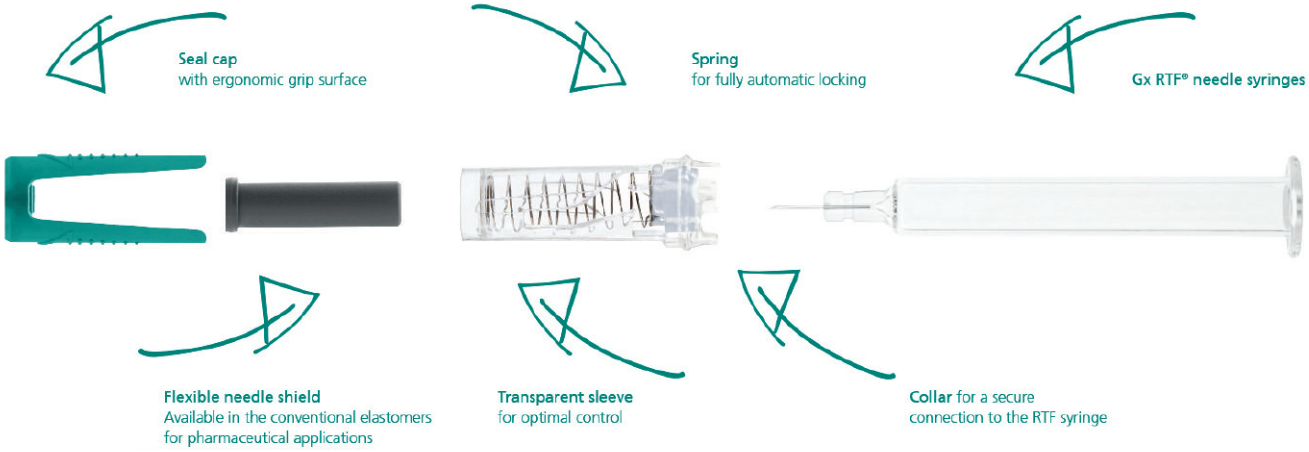
Credence MedSystems: Platform for a Range of Applications

There is the continued drive from pharma customers to differentiate their drug-device combination products in a crowded and competitive market place. Credence MedSystems is helping its customers differentiate their drug products through innovative delivery systems while preserving their trusted processes, thereby making differentiation through drug delivery safer, more achievable, and less disruptive, explains John Merhige, Chief Commercial Officer, Credence MedSystems.

"That marketable differentiation comes from the end-user experience when administering our customers' medications with Credence devices," he says. "Credence's innovative technology provides an enhanced, safer, and more intuitive experience for users across the platform of injection and reconstitution products. Whether it is the Companion staked syringe, luer syringe, or dual-chamber reconstitution device, safety activation clicks, end-of-dose feedback cues, and automatic



The Credence Companion product family: Staked, luer lock, and dual-chamber delivery devices.



With the Gx® InnoSafe®, Gerresheimer is now offering a syringe with an integrated passive safety system that avoids inadvertent needlestick injuries, prevents repeated use, and is designed with pharmaceutical companies' production processes in mind.

needle retraction create a better, safer experience for patients and healthcare professionals."

Simple, safe, and intuitive usability throughout the product lineup provides users a familiar and identifiable experience regardless of the drug product or route of administration. This makes Credence technology applicable to a range of applications, whether they include a drug that requires subcutaneous delivery in a staked syringe, the flexibility to change needles on a luer lock syringe for intramuscular delivery, or the need for point-of-care mixing, says Mr. Merhige. "The technological innovation with applicability across a wide breath of requirements has driven pharma customers to evaluate and value the Companion technology as a platform for applications ranging from vaccines to biologics."

Just as the Companion's features can improve the user experience and safety of drug administration, additional important benefits can come from eliminating risky materials and maintaining trusted and validated processes. Credence provides the user the convenience and safety of a preattached needle, but eliminates glue from the needle-attachment mechanism. "Removing glue from the fluid path protects the integrity of the drug by eliminating the risk of any unwanted interaction between glue and drug product, and allows silicone-controlling techniques that were previously incompatible with staked syringes," says Mr. Merhige. "This positions the Companion system as an enabling technology for sensitive biologic drugs."

Further, the Companion technology is compatible with existing prefilled syringes and primary package components, allowing pharma the freedom to choose its preferred sources for these components. "This approach empowers pharma with the ability to maintain its preferred sourcing strategy and manufacturing processes and avoids disruption to filling lines and simplifies secondary packaging operations," says Mr. Merhige. "As a continuation of this design strategy, not only is Credence open to glass barrels from any supplier, but the technology also allows the use of both glass and plastic polymer prefilled syringes, allowing the pharma customer to determine the best container for the application."

Gerresheimer: Packaging & Safety Remain the Focus

Primary packaging components are critical for pharma customers, and Gerresheimer believes that glass will prevail in the market, as pharma understands the benefits and drawbacks of glass syringes. "They understand the risks, and are aware of improvement in glass with regard to composition and the processing," says Bernd Zeiss, Manager Technical Support Medical Systems at Gerresheimer Bünde.

Aside from glass syringes, Gerresheimer offers the Gx® RTF Clearject® syringe, a high-end syringe made from break-resistant COP with advantages over glass, such as high tolerance and glue-free needle mounting. Polymers like COP have found their specific fields of applications in biotech and aesthetics.

In addition to packaging material, syringe safety and needlestick prevention continue to be critical areas of concern for pharma. To address that concern, Gerresheimer will soon offer the Innosafe® safety syringe, a fully passive, integrated prefillable safety syringe. "This lean system does not require assembly at the pharma

company after filling as the safety needle is previously mounted at Gerresheimer in the ready-to-fill process," says Mr. Zeiss. "The system is not only convenient and safe for healthcare workers, but also easy to handle at the filling site with less process steps."

Gerresheimer is continuously upgrading its process capabilities with next-generation technologies like the Gx 3G camera system for reliable detection of dimensional and cosmetic defects. New features are a highly accurate dose marking for very small injection volumes and the use of a ceramic pin in metal-free cone forming to avoid tungsten. "We also put effort into reducing free silicone oil with improved baked-on siliconization processes," says Mr. Zeiss.

Lonza's Drug Product Services team provides a holistic approach to drug product development that anticipates and prevents problems early and helps ensure the product is optimally designed for manufacture, supply chain, and patient use.

Lonza: Supporting Solutions for High-Concentration Products

Lonza Pharma & Biotech's Drug Product Services (DPS) organization helps to develop products and drug/device combination products for parenteral administration. In addition, they can specifically address issues related to formulation, excipients, active ingredient, process, container closure, and device interaction as they relate to product stability. Issues related to container and device can include delamination, fogging, injection force variability, particle assessment, surfactant-mediated, and comparability exercises.

Many biologic drugs, such as monoclonal antibodies or antibody fragments, require a sufficiently large dose when administered subcunatenously (s.c.) or intravireally (i.v.t.) (intraocularly). Products for i.v.t. administration have specific requirements, both considering maximum injection volume and usable needle sizes and configurations. This leads to high concentration formulations that have specific challenges in product design and manufacture, including increased aggregation and particle formation, and significant increase in viscosity, which can impact the ability of manufacture and administer. "We have supported various customers for the development of high-concentration products for s.c. and i.v.t. administration, overcoming these challenges and enabling them to enter clinical development quickly with the ability to manufacture and administer, and making these products also commercially viable," says Prof. Dr. Hanns-Christian Mahler, Head, Drug Product Services, Lonza Pharma & Biotech.

The DPS team provides a holistic approach to drug product development that anticipates and prevents problems early and helps ensure the product is optimally designed for manufacture, supply chain, and patient use in full compliance with global regulatory requirements and expectations. The DPS team provides a complete portfolio of services for parenteral dosage forms, including products for injection and infusion for intravenous, subcutaneous, intraocular, and other routes of parenteral administration. These offerings also include specialized services, such as: particulate identification; characterization and quantification; excipient and surfactant characterization; extractables and leachables assessment; and container closure integrity testing.

"Lonza enables its customers to commercialize their products by also supporting them in the choice, development, manufacture, and analysis of devices," says Dr. Mahler. "We are also advancing and improving test equipment related to the development of these systems."

SCHOTT: Keeping Drugs Stable During Shelf Life

The shift from large blockbuster drugs to more targeted treatments, including biologics, has elicited two consequences for pharma manufacturers. First, they must make their filling process more flexible to meet the growing market demands. Second, the biologics are highly sensitive and require special packaging to ensure drug stability, says Dr. Nicolas Eon, Global

Product Manager, SCHOTT Pharmaceutical Systems.

SCHOTT has addressed this trend by introducing the iQ™ platform, which standardizes the tub format of syringes, vials, and cartridges to run on one filling line with reduced changeover times. The newest member of the iQ family is syriQ BioPure®, a prefillable glass syringe designed to keep highly sensitive and complex drugs stable during shelf life and ease administration. SCHOTT offers more than 48 pre-validated configurations with elastomer components for the new syriQ BioPure syringes. Moreover, accurate dimensions of the syringes allow for optimal device compatibility, which enable home treatments.

Choosing the right material for parenteral containers can be difficult. SCHOTT helps its customers take a holistic approach for each use case, which focuses on the product, patient, and process, Dr. Eon says. "The primary packaging materials can interact with its contents over time. The goal is to minimize this because, in the worst-case scenario, this interaction can impact the effectiveness of the medication or even lead to side effects. Newer biotech products are especially susceptible to this interaction due to their complex molecular structures, and require special packaging. In order to ensure that patients are well protected from potential problems with these products, pharmaceutical companies and their suppliers must change the nature of their cooperation and focus on innovative solutions right from the beginning."

SCHOTT has experience with many active ingredients and buffer systems, and, says Dr. Eon, SCHOTT knows which packaging will probably be a good choice for the client. "If you can limit the options and minimize stability risks, this can save time and resources. An efficient collaboration between both parties allows medications to be brought to market in a quicker and safer manner."

SCHOTT's syriQ BioPure® is a prefillable glass syringe designed to keep highly sensitive and complex drugs stable during shelf life and ease administration.

Vetter: A Strategic Partner in Determining All Facets of PFS Use

CDMOs today need to advance their aseptic processes and technologies to meet the competing demands for the highest levels of quality and flexibility. One means of accomplishing this goal is to combine the advantages of the two commonly used techniques for aseptic manufacturing within the industry today – isolators and restricted access barrier systems (RABS). Combined, they help in an enhanced way to improve quality, safety, and flexibility in the aseptic filling process while making processes more efficient at the same time.

Vetter has devised such a solution called Vetter CleanRoom Technology V-CRT®, incorporating a number of innovations that result in improved operation in aseptic manufacturing, explains Bernd Stauss, Senior Vice President Pharmaceutical Production/Engineering, Vetter Pharma-Fertigung GmbH & Co. KG. "The system includes a fully automated H_2O_2 decontamination process of the entire cleanroom within a uniquely fast – approximately less than 3-hour cycle – to avoid microbial contamination and to achieve the highest safety level possible," he says. "Continuous online monitoring of several variables helps ensure the effectiveness of the decontamination process. The overall equipment effectiveness of RABS, combined with the sterility assurance level (SAL) of an isolator, achieves high operational efficiency." Vetter will implement this decontamination concept in all of its cleanrooms within the next few years.

When it comes to the manufacturing of injectable drugs, a high level of expertise is required. "Quite often, smaller pharma and biotech companies lack some in-house knowledge necessary to

Running a fully automated decontamination process (Vetter Pharma International GmbH).

cover all the processes independently prior to completion of the entire final product," says Mr. Stauss. "That is where Vetter, as an experienced CDMO, can bring them significant added-value with our end-to-end solution portfolio because we act as both a consulting and processing partner in our relevant fields."

To illustrate, consider the issue of dosing. Prior to the decision to use a prefilled syringe, a pharma or biotech company must consider the different drug concentration presentations it wants to bring to market. The answer to that question will result in different subsequent actions. Additional critical issues that must also be taken into consideration include silicon oil reactivity, the use of non-fluro tech or flurotech stoppers, glide and release forces, and the length of time that the drug will be held in storage. Also, matters such as plunger rod and finger flange design, secondary packaging issues such as blistering, and other manufacturing issues must be carefully verified, discussed, and decided upon prior to making the final decision to use prefilled syringes. "As a strategic partner, we have the opportunity to be involved with a variety of customers and their individual production and marketing strategies."

West Pharmaceutical Services, Inc.: Improving Self-Administration of Biologics

There is growing interest in the use of polymer syringes for ocular injections, such as those used to treat wet age-related macular degeneration (AMD). Along with its partner, Daikyo Seiko, West has been developing and supplying Daikyo Crystal Zenith® systems for use with many marketed drugs. The Crystal Zenith syringe offers advantages for ocular injections, including the absence of silicone oil, high cleanliness, and the use of a fluropolymer-filmed plunger that reduces drug interaction. "The precision of the system may help to improve break-loose and gliding forces, and provide increased control and comfort to the clinician while injecting into the eye," says Graham Reynolds, Vice President and General Manager, Global Biologics, West Pharmaceutical Services, Inc.

At the heart of the system is a Daikyo Crystal Zenith container, combined with Flurotec® closures to enhance the security of the drug product and optimize performance. This is important, says Mr. Reynolds, as self-injection of biologic drugs can be challenging, especially as molecules become more complex, dose volumes increase, and dosing frequency is reduced to improve patient convenience. Taking an integrated approach to the development of drug delivery systems, West has developed systems such as the SmartDose® drug delivery platform, which offers fully integrated containment and delivery systems for the self-administration of biologic drugs.

SmartDose allows patients to self-administer medication in accordance with their prescribed treatment. "West developed the SmartDose drug delivery platform with extensive human factors testing and analysis to understand the interaction between the patient and the delivery system," says Mr. Reynolds. The SmartDose drug delivery platform adheres to the patient's body, usually on the abdomen, so patients can be hands-free during administration.

"The market demand for biologics, coupled with the growth of self-administration, required the drug delivery sector to develop new innovations to administer these therapies, such as the West SmartDose technology platform," says Mr. Reynolds.

In 2016, Amgen announced that it had selected the SmartDose technology platform for a single, monthly 420mg dose delivery option for Repatha® (evolocumab). "The combination of Amgen's treatment with West's patient-focused technology platform is an example of how West closely collaborates with its pharmaceutical and biotechnology partners to deliver advanced, integrated solutions for drug delivery and containment."

ZebraSci: Gain an Edge in Lifecycle Management With Characterization

ZebraSci is noticing increasing interest in adding Container Closure Integrity Testing to its primary container characterization programs. "In addition to assessing the variability in critical geometries for container components, such as syringe barrels and pistons, adding a sensitive leak testing method like helium leak detection upfront in the development phase allows you to gage the inherent integrity of the packaging system," says Eric Creveling, Director, Laboratory Services, ZebraSci.

He adds that helium leak detection can help determine the relationship between a specific syringe barrel/piston combination, as well as how silicone/lubrication levels impact seal quality. Variations in silicone quantity and distribution lot-to-lot can not only affect the amount of particles and protein aggregation in solution, but play a critical role in the injection performance when the PFS is intended for use in an autoinjector system. A thorough Design Verification Testing program is critical to demonstrate that the device doesn't introduce a safety issue or compromise the performance/delivery of the drug.

"By fully characterizing prefilled syringe performance characteristics upfront, our pharma clients gain an edge when it comes to device selection and lifecycle management," says Mr. Creveling. "A robust program that looks at the variability in critical geometries, lubrication, and injection forces, across multiple lots of syringes helps them assess how a container will interact and perform with a given device. Later in the life cycle, if a device injection failure or stall leads to a failure investigation, the baseline data captured in the characterization program can help steer the investigation to the suspected failure mode more quickly, saving time when a response to the agency is required." ◆

Reference

1. Prefilled Syringes Market worth 6.36 Billion USD by 2021, MarketsandMarkets, https://www.marketsandmarkets.com/PressReleases/prefilled-syringes.asp.

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