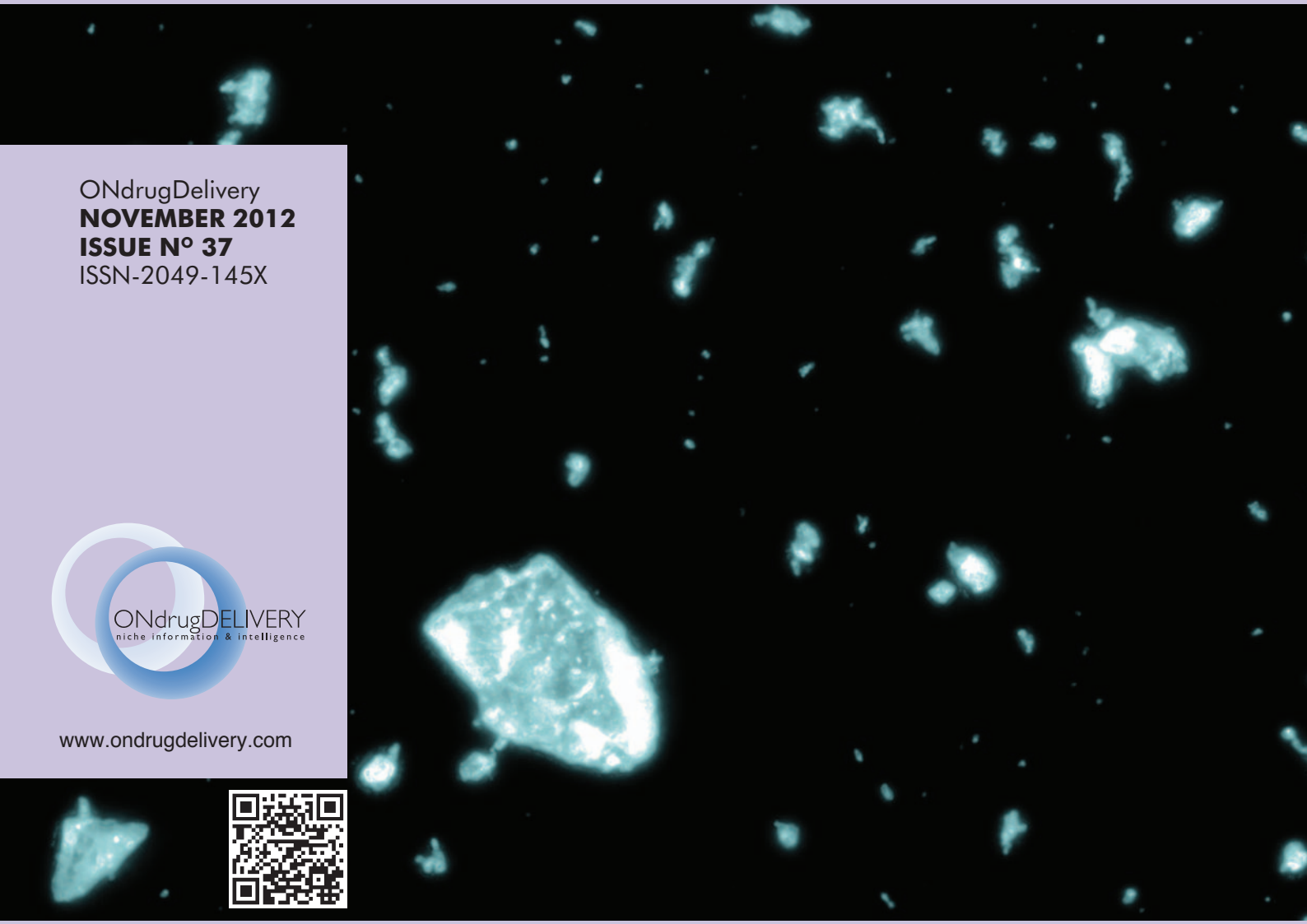
PULMONARY & NASAL DELIVERY:
POWDERS & LIQUIDS, FILLING & ANALYSIS



ONdrugDelivery
NOVEMBER 2012
ISSUE N° 37
ISSN-2049-145X

ONdrugDELIVERY
niche information & intelligence

www.ondrugdelivery.com

ONdrugDelivery Issue Nº 37, November 2012

"Pulmonary & Nasal Delivery: Powders & Liquids, Filling & Analysis"

This edition is one in the ONdrugDelivery series of publications from Frederick Furness Publishing. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

EDITORIAL CALENDAR 2013:

Jan	Oral Drug Delivery
Feb	Prefilled Syringes
Mar	Transdermal Delivery, Microneedles & Needle-Free Injection
Apr	Pulmonary & Nasal Drug Delivery
May	Injectable Drug Delivery: Formulations Focus
Jun	Injectable Drug Delivery: Devices Focus
Jul	Oral Drug Delivery
Sep	CROs & CMOs Offering Drug Delivery Solutions
Oct:	Prefilled Syringes
Nov:	Pulmonary & Nasal Drug Delivery
Dec:	Delivering Biotherapeutics

SUBSCRIPTIONS:
To arrange your **FREE** subscription (pdf or print) to ONdrugDelivery Magazine, visit: www.ondrugdelivery.com

SPONSORSHIP/ADVERTISING:
Contact: Guy Furness, Proprietor & Publisher
T: +44 (0) 1273 78 24 24
E: guy.furness@ondrugdelivery.com

MAILING ADDRESS:
Frederick Furness Publishing
48, Albany Villas, Hove, East Sussex, BN3 2RW
United Kingdom

PRODUCTION/DESIGN:
Mark Frost
www.frostmark.co.uk

ONdrugDelivery is published by Frederick Furness Publishing.
(ISSN 2049-145X print / ISSN 2049-1468 pdf)

Front cover image: "A dry-powder inhaler formulation which has been dispersed on a Morphologi G3 automated particle analyser, imaged using dark-field illumination", supplied by Malvern Instruments. Reproduced with kind permission.

CONTENTS

ONdrugDelivery EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
January 2013	Oral Drug Delivery	December 23rd
February 2013	Prefilled Syringes	January 14th
March 2013	Transdermal Delivery, Microneedles & Needle-Free Injection	February 4th
April 2013	Pulmonary & Nasal Drug Delivery	March 4th
May 2013	Injectable Drug Delivery 2013: Formulations Focus	April 2nd
June 2013	Injectable Drug Delivery 2013: Devices Focus	May 6th
July 2013	Oral Drug Delivery	June 3rd
September 2013	CROs & CMOs Offering Drug Delivery Solutions	August 5th
October 2013	Prefilled Syringes	September 2nd
November 2013	Pulmonary & Nasal Drug Delivery (OINDP)	October 7th
December 2013	Delivering Biotherapeutics	November 4th

HOW NASAL DELIVERY CAN MEET THE CHANGING NEEDS OF PATIENTS AND THE DRUG DEVELOPMENT INDUSTRY

In this article, Dr Shunji Haruta, Executive Officer, SNBL Ltd, General Manager, NDS Division, describes some of the challenges being faced by the pharmaceutical industry and how it is adapting to face them, and explains how the company's powder nasal delivery technology, Muco™ System fits well with the new environment.

The current dynamic environment of the healthcare and drug development industry is well known. One focal point of change is the rising cost of healthcare. This has proven a heavy burden to patients and finding ways to cushion these costs is increasingly important. Along with rising costs there is another focal point of change.

The patent cliff of 2012 and the coming years has caused companies to assess options for cost savings as blockbuster drugs will no longer hold the marketshare previously enjoyed; between 2012 and 2016, 38 major pharmaceuticals will fall off the patent cliff in the US alone. According to a recent analysis, $33 billion in lost sales is forecast for 2012 due to the largest patent cliff in pharmaceutical history; furthermore it is forecast that over $290 billion in sales is at risk between 2012 and 2018.[1] Blockbusters coming off patent will no longer be able to offer the financial security previously afforded, and companies are now reassessing business models.

Blockbusters during the early 2000s have dwindled significantly compared with the boom of the late 1980s and 1990s. In four of the last seven years, fewer than 30 new chemical entities per year were brought to market, illustrating clearly the dry pipelines now plaguing pharma.[2] In an effort to combat increasing development costs and billions lost in development to drugs that never make it to market, the industry has undertaken an immense shift in development. Budgets the size of those of the 80s and 90s are a thing of the past and the search for "the next blockbuster" is being replaced by an overhaul in development strategy.

"THERAPEUTIC EFFECT IS NOT ACHIEVED THROUGH A GOOD CARRIER FORMULATION ALONE, IT IS ALSO HIGHLY DEPENDENT ON THE FORMULATION BEING DELIVERED FULLY"

As such, the simultaneous changes in patient needs and drug development needs make this a unique time for those seeking to meet these needs. With this changing pharma landscape, there is a newly concentrated effort which leaves the blockbuster-drug paradigm on the back burner. In

Dr Shunji Haruta
Executive Officer, SNBL Ltd
General Manager, NDS Division

Contact:
Mic Iwashima
T: +81.80.4195.9383
E: iwashima-fumiyoshi@snbl.co.jp

SNBL Ltd.
NDS Division
2438 Miyanoura, Kagoshima
891-1394, Japan

www.snbl-nds.co.jp/en

order to combat these current hurdles, focus has shifted in four major ways: first, towards bringing drugs to market for smaller patient populations; second, developing drugs that are less costly to patients in an attempt to appeal to larger population segments; third, developing drugs designed for at-home care; and fourth, an increase in collaborative partnerships throughout development.

Now, non-traditional therapies such as orally inhaled and nasally delivered products are drawing much attention and exploration. Using such alternate routes of administration has the potential to address both the needs of patients and development. Coupled with service providers taking on greater roles as partners in development, "service provider" is increasingly being replaced with "solution provider". These solution providers offer much in the way of new OINDP technologies and are at the forefront of new drug development.

One company which offers this advantageous solution provider partnership is SNBL, Ltd. For more than a decade, SNBL has been ahead of the curve through the development of its nasal delivery technology, Muco™ System. Invented, designed and developed fully in-house, Muco™ System addresses a great number of needs for the systemic delivery of small molecules and peptides, while the experience of having developed this technology in-house has given SNBL unparalleled experience in nasal drug product development, from specialised delivery characterisation testing capabilities to a validated nasal administration PK model in NHPs.

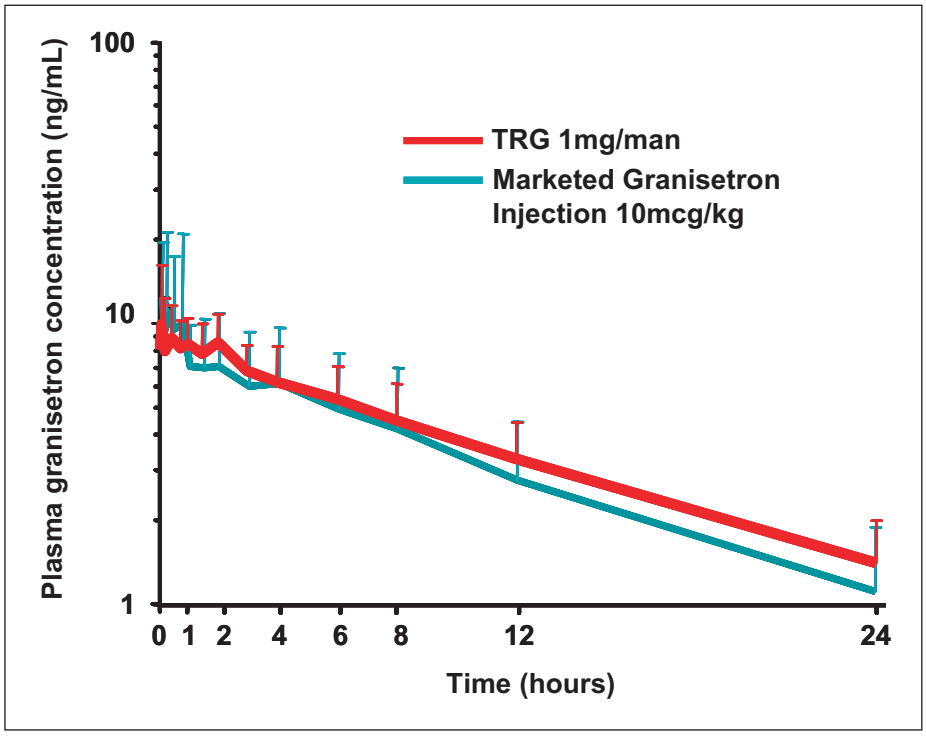


Figure 1: Absorption results in a Phase I clinical trial of nasal granisetron formulated and delivered using Muco™ System.

So how does Muco™ System fit in this new pharma environment?

As touched upon previously, alternate routes of delivery have gained much attention, especially nasal delivery. It is well known that delivery into the nasal cavity has distinct advantages when one considers the highly vascularised capillary bed which theoretically translates to easy access to the blood stream. This is especially important as it then allows for a compound to avoid first-pass metabolism. Thanks to this direct access to the blood stream

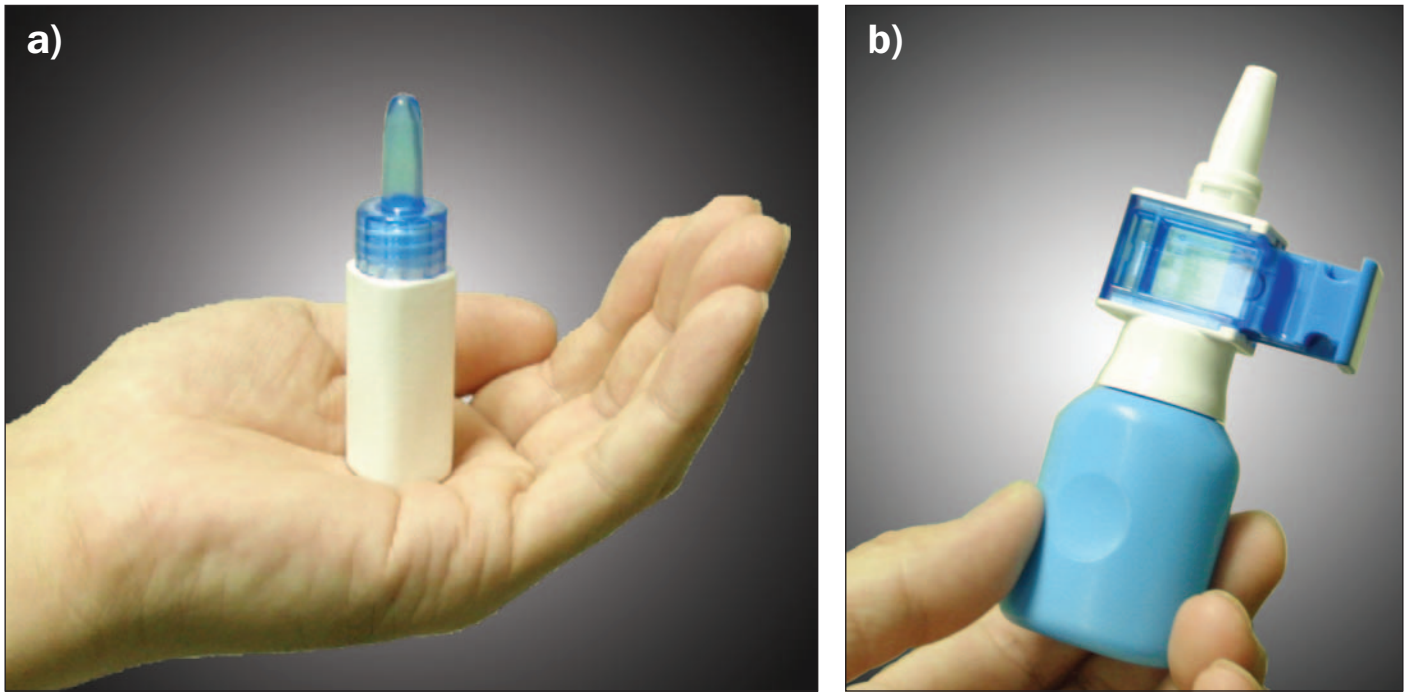


Figure 2: Fit-lizer™ powder delivery devices for use with Muco™ System is offered in a) single-use and b) multiple-use versions.

and loss of metabolism, therapeutic onset is significantly faster.

In recent years, one can see how drug development companies have worked to harness the distinct advantages of nasal delivery. From migraine products to vaccines, nasal products have been able to offer a different route of development to drug companies, along with more patient-friendly products that enable self-administration in the at-home setting. However, the field of nasal products has been dominated by liquid sprays.

THE DIFFICULTY OF LIQUID NASAL SPRAYS

As with every new technology, the beta years of new drug products help to highlight any shortcomings and points out to drug makers the areas where improvement is greatly needed. When it comes to nasal drug products, liquid sprays present a number of areas in need of improvement. To begin, administration of liquid into the nasal cavity is accompanied by an almost immediate running of the liquid from the nasal cavity into the pharynx, eventually making its way into the GI. While a portion of the drug may be absorbed at the site of initial administration, often the majority of the drug is absorbed through the GI. Naturally, the negative impact of running liquids on absorption in the nasal cavity has been acknowledged and developers responded to this problem largely through the use of absorption enhancers, which often results in damaging the nasal mucosa in an attempt to allow for higher absorption. A degree of success has been found with said enhancers, but there is still much room for improvement.

DEVELOPMENT GOALS AND ACHIEVEMENT OF MUCO™ SYSTEM

The inventor of Muco™ System recognised in the late 1990s that there was a significant need to improve nasal drug delivery. Running liquids simply were not taking advantage of the promising aspects of nasal delivery. In response to the shortcomings of existing products, SNBL decided to move in a different direction and explore the benefits of a powder nasal product. As a result, a powder carrier was developed and used in conjunction with granisetron for the purposes of gaining proof of concept. The results have been promising, with the product gaining 100% absolute bioavailability in a Phase I clinical trial (Figure 1).

THE DEFINING CHARACTERISTICS OF MUCO™ SYSTEM

So what is it that sets Muco™ System so far apart from other nasal delivery systems? The first cornerstone is the use of only GRAS ingredients for the powder carrier, which is inactive in the body and causes no nasal irritation.

In two clinical studies to date for a nasal granisetron product utilising Muco™ System, nasal irritation has been neither observed nor reported. The key to the formulation is that the carrier holds the formulation to the nasal mucosa after administration long enough to allow for absorption into the blood stream, without damaging the mucosa. Subsequently, the body's natural mucocilliary clearance removes the remaining inactive carrier from the nasal cavity and it is then expelled naturally.

"IN RESPONSE TO THE SHORTCOMINGS OF EXISTING PRODUCTS, SNBL DECIDED TO MOVE IN A DIFFERENT DIRECTION AND EXPLORE THE BENEFITS OF A POWDER NASAL PRODUCT"

The second cornerstone of Muco™ System is Fit-lizer™, a line of powder delivery devices designed for use with Muco™ System (Figure 2). The line offers both single and multiple use devices with excellent, proven delivery results. SNBL noted that therapeutic effect is not achieved through a good carrier formulation alone, it is also dependent on the formulation being delivered fully. SNBL set out to address this challenge and developed a highly effective device. Delivery characteristic studies have proven that Fit-lizer™ delivers more than 95% of a formulation, every time.

Aside from proof of concept which shows Muco™ System to be a viable technology to replace liquid nasal sprays, Muco™ System also offers a patient-friendly alternative to other traditional therapies. Designed for the delivery of small molecules and peptides, Muco™ System has the ability to give patients a more convenient and controllable alternative to therapies which typically require a hospital or physician setting, namely, injections. Muco™ System can also provide a faster alternative to oral therapies. Two products developed by SNBL using Muco™ System (a granisetron product and a zolmitriptan product) are excellent examples of achievement in high and fast absorption without the use of an injection.

SNBL: A SOLUTION PROVIDER

Through the development of Muco™ System, SNBL has gained an invaluable amount of experience in the development of nasal products. At its core, SNBL is a CRO with over 55 years of experience, with special focus on work with NHPs. Services for nasal drug product development include in-house developed and validated NHP models. Unique to SNBL, these models are offered with both blood and CNS sampling in unanaesthetised animals. Other early development services which help to provide solutions to early development hurdles are also offered, such as assay development and validation, formulation development and optimisation, as well as delivery characterisation and particle size testing.

SNBL can also provide expertise in CMC development of nasal products. In addition to the abovementioned offerings, the nasal drug development team has regulatory experience in taking nasally delivered products through IND approval and into clinical trials, taking full advantage of the 505(b)(2) pathway.

All of this know-how and experience positions SNBL as an ideal solution provider. With the growing need of the pharma industry to outsource work, the ability to choose one outsourcing provider allows for better control and communication throughout the development process. SNBL meets this need, along with the ability to offer fast study starts and competitive timelines.

A Muco™ System nasal drug product coupled with the services by SNBL is a step towards addressing the changing environment of the pharma industry previously cited. Muco™ System allows for high patient compliance and ease-of-use without necessitating a hospital or physician setting. Outsourcing to SNBL the development necessary for nasal products allows pharma companies to work with a solution provider, which is ultimately cost and time saving. The benefits inherent to this pairing are ready for the next challenge.

REFERENCES

1. *EvauatePharma, "World Preview 2018 Embracing the Patent Cliff", 2012. Retrieved from https://www.evaluatepharma.com/wp2018 in October 2012.*
2. *IMS Institute for Healthcare Informatics, "The Global Use of Medicines: Outlook Through 2016", July 2012.*

romeo & juliet

summertime & flip-flops

thunder & lightning

chicken noodle soup & crackers

batman & robin

peanut butter & jelly

movies & popcorn

campfires & scary stories

salt & pepper

baseball & hot-dogs

ken & barbie

tom & jerry

nuts & bolts

hot days & lemonade

rock & roll

wine & cheese

coffee & biscotti

warm cookies & cold milk

yin & yang

lock & key

good friends & belly laughs

golden retrievers & frisbees

μco™ System & (your API)

Great things come in pairs. Have you paired yet?

Impressive preclinical & clinical efficacy
Proprietary powder carrier & devices
Excellent predictive study model
Choice knowledge & know-how

Undeniably better nasal drug delivery
The benefits for your drug product are endless

Find out why our pair works:
info@snbl-nds.co.jp
www.snbl-nds.co.jp/en

μco

by SNBL

DDL23

drug delivery to the lungs 23

EDINBURGH INTERNATIONAL CONFERENCE CENTRE
WEDNESDAY 5TH – FRIDAY 7TH DECEMBER 2012

Drug Delivery to the Lungs is Europe's premier conference and exhibition dedicated to pulmonary and nasal drug delivery

- DDL provides an annual forum for scientists, academics, clinicians, regulatory and industry specialists involved in developing medicines for inhalation.
- DDL attracts a diverse and extensive selection of posters, presentations and our networking Exhibition arena historically attracts full capacity with stands from the Pharmaceutical Industry, Suppliers, Instrument Manufacturers and Contract Research Organizations.

Annual DDL Lecture – 2012
Malcolm Johnson

Respiratory Science Consultant, GlaxoSmithKline Research & Development, UK

"Bronchodilators – the past, present & future"

This year's topics will include:

- Drug Discovery and Development, including new approaches to formulation and product development
- Advances in analytical science for respiratory products
- Targeting drug and formulations to the lungs
- The inhaled market - where is it going?

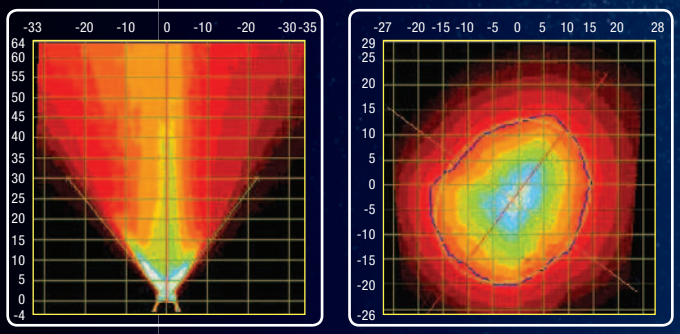
For Sponsorship/Exhibiting Options go to – www.ddl-conference.org.uk
For more information, advice or to reserve your place contact:
Sheila Coates at ddl@aerosol-soc.org.uk Tel: +44 (0) 1275 849019

www.ddl-conference.org.uk

Say Goodbye to Needles
Say Hello to the LMA VaxINator™

Until now there has been no intranasal delivery solution that combines the flexible dosing of a syringe with the cost competitiveness of a needle.

- Compact conical tip is designed for nasal insertion
- Precise 30-100 micron spray
- Low dead space– just 0.1 ml – maximizes drug cost efficiency
- Low activation pressure required for typical fluid volumes
- Attaches to any luer lock syringe
- Perfect for lyophilized and liquid drugs
- Single use means that every use delivers a fresh, maximally effective dose
- Latex Free
- DMF on file with FDA



LMA VaxINator™ particle distribution, plume geometry and spray pattern test results are available upon request.

For free trial samples and more information contact LMA at 1-800-788-7999 or email mlarsen@lmana.com

LMA | VaxINator™
INTRANASAL DRUG DELIVERY DEVICE

LMA™
Better by Design

LMA North America, Inc. 4660 La Jolla Village Dr., Suite 900 San Diego, CA 92122 P: 800-788-7999 F: 858-622-4130

Aptar pharma

AN INTERVIEW WITH MR JEAN-MARC PARDONGE, PRESIDENT, PRESCRIPTION DIVISION, APTAR PHARMA

In this interview, immediately following his very recent appointment as the new President of Aptar Pharma's Prescription Division, Jean-Marc Pardonge, speaks with ONdrugDelivery Magazine about general trends and challenges in the drug delivery market, the wider pharma industry and beyond, describes his vision for the future of Aptar Pharma's Prescription Division, and gives us an insight into the origins of the company's name and its importance in today's changing industry.

Q: Many congratulations on your appointment as President of Aptar Pharma's Prescription Division. You have been with the company for more than 12 years now – a period during which the company has established itself as a world leader in pulmonary and nasal drug delivery, and with the recent Stelmi acquisition it is positioned to become a key player in the injectables market as well. Could you tell us what, personally, first attracted you to join Aptargroup, and describe how you have seen the company change over the years?

Aptargroup is a moderately large US public company (traded on the NYSE: ATR) which specialises in consumer packaging and dispensing systems, with more than 11,000 employees worldwide and operations in more than 19 countries. It's a truly multi-cultural organisation with a unique culture and management style rooted in strong core values.

In addition to that, what has made Aptargroup attractive to me is its strong market focus: each division organises its business according to well-structured application segmentation and this is the cornerstone of a very powerful strategy. It is important to note that innovation and operational excellence are part of Aptargroup's DNA and are the backbone for development of unique solutions meeting or exceeding customers' expectations in all geographical areas.

As you indicated Aptar Pharma worked hard to become the worldwide leader in spray pumps for allergic rhinitis and metering valves for asthma and COPD therapies. Since I joined the Prescription Division, it has more than doubled in size and revenue through organic growth, and expanded considerably with new manufacturing facilities in Asia, the EU and the US. More recently Aptar Pharma also grew by the acquisition of Stelmi, a French company which is leader in elastomeric components for injectable drug delivery devices. We also made an equity investment in Oval Medical, a UK start-up which specialises in auto-injectors.

Q: Can you tell us about your vision for the business direction of Aptar Pharma Prescription Division, both in the shorter term and looking to the coming years and decades?

Well, as you know the short term in pharma could be years, and the long term decades… so we have to be patient, and what is more important, plan, set roadmaps, follow key milestones and monitor performance indicators to deliver consistently against our plan.

Having said that the pharma context is now changing much faster, with challenges such as the patent cliff, generics, biosimilars, emerging countries, and Rx to OTC switches, so we need to adjust our strategy and adapt ('*aptare*' in Latin translates as 'adapting').

You have to seize opportunities as they arise: for instance, the change in pMDI propellants from CFC to ozone-friendly HFA was a game-change for us because we were the only

pMDI player integrated vertically with development and manufacturing of elastomer gaskets. These gaskets are key components of pMDIs and needed to be changed to accommodate novel HFA drug formulations.

On the operations side we need to grow our recently opened Mumbai, India facility. This is an exciting challenge given the dynamics of the Indian market and our strong leadership in this country.

We have also put a lot of emphasis on other emerging markets such as China, Eastern Europe countries and Latin America where we enjoy strong market growth with a majority of new generic drug product launches thanks to the effort of our commercial organisations.

I'm also excited by the recent and upcoming market launches of new products recently developed and promoted. These include our Landmark® pMDI Dose Indicator for asthma, the Twister® DPI, and eDevices, the first electronically-assisted nasal drug delivery devices in their category, used to help manage breakthrough pain episodes with opioid-based drugs.

In the longer term, I'm quite eager to see progress of other patent-protected breakthrough technologies that are in our pipeline, with delivery of strategic projects for customers in Asthma and COPD, Allergy, and Pain Management.

Finally we'll also focus on providing Aptar Stelmi with the appropriate long-term strategy, direction and support, including technical synergies with our legacy Aptar Pharma business.

Q: As the new President, what do you as a person plan to bring to Aptar Pharma Prescription Division following this appointment? What are your goals and hopes?

Now my role is to drive the division towards sustainable growth and success according to our corporate Vision 2030. We have many opportunities, and that is why we have to stay focused

and select appropriate strategies to grow the business step by step, in all selected market segments and territories. At the same time we need to make sure that all our customers are satisfied and our operations remain state-of-the-art and ready to win future challenges. People are at the centre of our success, and so we need to make sure we have the right skills on board.

To summarise, I want to explore new business opportunities, generate successful innovation in all fields, and further develop the Prescription Division of Aptar Pharma on a global basis, including the smooth integration of Aptar Stelmi.

Q: More broadly now, what is your take on the current status of the global drug delivery industry? How are scientific and technological advances, such as the continuing emergence of biotech products, affecting the drug delivery sector? What about the impact of current rapid global geopolitical and economic changes?

In the past decades the drug delivery industry has had its ups and downs. Aptar Pharma has been operating in dynamic market segments such as nasal, inhalation and ophthalmics, with major customer projects that materialised into launched drug products that used our drug delivery devices.

Having said that, the blockbuster era is almost over now and we see more modest customer projects that translate into volumes measured in millions of device units per year, as against tens of millions in the past. As always we need to adapt to this new situation and make sure we allocate our R&D efforts carefully, and provide the right solutions and service to our customers.

An example of this is the recent trend to use pressurised aerosols (pMDIs) for delivery of drug products via the nasal route to treat allergic rhinitis, instead of the gold standard spray pump. This is interesting because it corresponds to a "nichization" of the market based on patient preferences, with some patients preferring dry aerosols to water-based liquid sprays. Given our leadership position in metering valves for pMDIs, this recent evolution has been an opportunity for Aptar Pharma Prescription Division.

Biotech products have become very important in the last few years, making up more than 50% of the R&D pipeline today. As these are mostly large molecules that cannot easily be delivered systemically through the nasal mucosa or via the lungs, this is an area where we are quite active with Aptar Stelmi, and through our partnership with Oval Medical for injectables.

As you pointed out the economic landscape is changing and here also we need to adapt but also anticipate. For instance we were the first drug delivery device company licensed in China more than a decade ago (you need a state license to manufacture in China). Obviously as in other activities, mature markets such as the EU have slowed down while emerging countries keep growing at a double digit rate.

Q: Although the future is looking brighter, the drug delivery industry has had a rough ride over the past decade – pulmonary delivery especially. What have been the particular hurdles that Aptar has faced in this context, and how has the company been able to maintain growth and its strong leading position?

This is very true for systemic delivery via the lungs. The insulin venture to treat diabetes using DPIs and Soft Mist Nebulisers is almost over and left a bitter taste in the mouths of some players. Fortunately Aptar Pharma Prescription Division was not involved in these projects and so we were not affected. Having said that we realise that many "breakthrough projects" that we were involved in did not materialise as planned by our customers. There were many reasons that this happened, such as clinical failure, regulatory hurdles, and pricing/reimbursement schemes. In the meantime the market for asthma and COPD keeps growing steadily in value (with a drug market of more than $30 billion (£18.7 billion)) and annual volumes (more than 600 million pMDIs units and more than 200 million DPI units without counting tens of millions of soft mist inhalers as well). We took market share from our competitors since the major drug products that are marketed successfully worldwide, including generics and branded generics, use our DF 30 technology platform metering valve. We were also successful on the dose counter/dose indicator front with our Landmark® product which hit the market with two new customers this year.

Q: In terms of specific drug delivery products and technologies, what are Aptar's strongest, most interesting offerings a) at present and b) looking ahead to the future?

Well, our key technology platforms are multi-dose spray pumps that are used for nasal and other delivery routes such as buccal/sub-lingual, throat, dermal, and transdermal; one- and two-shot unitdose spray devices for nasal and buccal/sub-lingual routes; metering valves for nasal and pulmonary pMDIs; pulmonary DPIs; and dispensing devices for the ophthalmic route. We also develop innovative add-on systems and technologies such as dose counters and dose indicators, as well as eDevices, which are electronic systems that allow multiple functions including lockout for controlled substances.

On the injectables side we plan to continuously develop the Aptar Stelmi brand and offering, which includes elastomeric components such as vial stoppers, and pre-filled syringe components such as plungers, needle shields, and tip caps. We will also develop disruptive auto-injector technologies as a strategic partner to Oval Medical.

In conclusion, I believe that Aptar Pharma Prescription Division is well positioned to serve the drug delivery market in a wide range of areas that include sprays, aerosols, injectables and many other dispensing systems based on innovative proprietary technologies.

Jean-Marc Pardonge
President, Prescription Division
Aptar Pharma

After graduating from the French ENSAM engineering school (Ecole Nationale Supérieure d'Arts et Métiers), Jean-Marc Pardonge served in various executive positions in the motorcycle and medical device industries, and then joined Aptar Pharma Prescription Division in 2000 as R&D Manager. He was promoted to the position of Vice-President, R&D, in 2003. In January 2010, he became President of Global Market Development of Aptar Pharma's Prescription Division. In this role, he managed and co-ordinated worldwide activities which included scientific and regulatory affairs, business development, communication, engineering, innovation, marketing, project management, and R&D.

Pharmapack EUROPE

13-14 FEBRUARY 2013, PARIS

HOW INNOVATION IN **PHARMA PACKAGING** AND **DRUG DELIVERY TECHNOLOGIES ENHANCE PATIENT SAFETY** AND **COMPLIANCE**

- Annual event in Europe for over 3,000 key decision-makers from the pharmaceutical industry looking for packaging and delivery technologies for their drugs
- Exhibition brings together more than 280 international leading manufacturers and suppliers of packaging and advanced drug delivery technologies
- Two days of cutting-edge technology lectures focusing on the latest international market trends for packaging developments and new drug delivery systems
- NEW! 4 workshops for a deeper insight into current hot topics affecting the industry (Validation of tertiary packaging, Serialisation, Medical packaging sterilisation and validation, Combination product approval process)

Pharmapack AWARDS 2013

- Please visit our website to find out how to participate

www.pharmapack.fr

UBM Canon

24028_FR_PHP13

Malvern

DRY NASAL POWDERS – A NEW ANALYTICAL CHALLENGE?

In this piece, Julie Suman, PhD, President & Founder, NextBreath LLC (Baltimore, MD, US), Paul Kippax, PhD, Product Group Manager, Malvern Instruments Ltd, and Faron Jordan, PhD, Head of Preclinical & Clinical Project Management at Critical Pharmaceuticals (Nottingham, UK), argue that whilst there are sound commercial and technical drivers for adopting dry nasal spray technology, its development relies on identifying suitably supportive analytical protocols. How well do the methods applied to conventional nasal sprays measure up and how can they be applied in accelerating the development of dry nasal sprays to a successful conclusion?

Nasal sprays that deliver active ingredients using droplets are well-established drug delivery vehicles, both for locally acting and systemic therapies. More recently, though, the pharmaceutical industry has started to turn its attention to delivering dry powders via the nasal route, a step that parallels the introduction of dry powder inhalers (DPIs) for pulmonary drug delivery. The current high levels of research activity in the area of dry nasal powder development reflect the potential rewards, which include high patient compliance, good product stability and sterility, and closely targeted drug delivery.

The traditional analytical tools for nasal sprays include laser diffraction particle size analysis, spray pattern and plume geometry measurement. With dry nasal powder technology in its infancy and no regulatory guidance specific to it, it is timely to question how well these techniques support further development and to review any requirements for additional analyses. Moreover, should these powder-based systems be tested following inhalation or aqueous nasal spray guidelines? An optimised analytical toolkit will not only promote the development of efficacious products, but also accelerate their commercialisation within the constraints of the regulatory framework.

The case studies presented here help in understanding the applicability of laser diffraction and plume geometry measurement for characterising dry powder nasal sprays.

WHY USE NASAL SPRAYS?

Rich in blood vessels and presenting a large surface area for absorption, the nasal passages are highly suitable for drug delivery, with systemic therapies already a growing area of application for conventional nasal sprays. For example, the nasal spray route has been commercially exploited for vaccines, which elicit an immune response in the Nasal Associated Lymphoid Tissue (NALT) within the tonsils and adenoids at the back of the nasal passages. A notable success is influenza vaccine, with flu viruses entering the lymphatic system via the same route. Of equal importance is the fact that nasal sprays can be used for other long-chain molecules, proteins and peptides, to deliver large doses of drugs such as antibiotics, or where drug solubility is an issue.

Although the market for nasal delivery systems is dominated by liquid-based formulations delivered using nasal pump sprays, interest is growing in the use of dry-powder devices. Dry nasal powders share the higher patient acceptance (in comparison with intravenous delivery) of conventional nasal sprays and, by avoiding the after taste and nosebleeds associated with some solution- and suspension-based products, may help achieve higher levels of patient compliance. Dry nasal powders have produced encouraging clinical results in trials with both

Dr Paul Kippax
Product Group Manager
T: +44 1684 892456
F: +44 1684 892789
E: salesinfo@malvern.com

Malvern Instruments Ltd
Enigma Business Park
Grovewood Road,
Malvern
Worcestershire, WR14 1XZ
United Kingdom

www.malvern.com

large [1] and small [2] molecules and, beyond this, offer a number of technical and commercial advantages when considered as an alternative to either solution or suspension-based equivalents.

On the stability front, dry formulations are clearly an attractive option for moisture-sensitive compounds and, in addition, present a less hospitable environment for microbe growth than solution or suspension-based systems, making them less prone to sterility problems. Conventional nasal spray vaccines, for example, must be refrigerated at all times to maintain stability but this is not necessary with a dry alternative; no cold supply chain is required, thereby saving considerable cost.

With respect to performance, another attraction of dry nasal powders is that the particle size of the product can be very closely controlled to optimise deposition behaviour. In conventional nasal spray delivery, particles in the sub-ten-micron range are problematic because of the possibility of pulmonary rather than nasal deposition; particles this fine may bypass the nasal passages and pass into the lungs.[4]

It is very difficult to develop a nasal spray pump that efficiently atomises a solution/suspension without producing an uptake range of droplet sizes that includes droplets less than 10 μm but with a dry nasal powder the sub-ten-micron fraction can be removed at the manufacturing stage. It is unlikely that further fine particles will form during actuation because the levels of energy applied are typically insufficient for particle break-up.

In summary then, dry nasal spray technology has the potential to deliver stable products and efficient, highly targeted drug delivery, as well as presenting an opportunity for commercially important patent differentiation. The realisation of these advantages depends on developing an analytical approach that generates sufficient information to understand and optimise this new class of products.

LEARNING FROM LIQUID NASAL SPRAY DEVELOPMENT

It seems likely that dry nasal sprays will share some of the characteristics of both conventional nasal sprays and DPIs, making either area a potentially productive starting point for the identification of relevant analytical techniques. Turning first to conventional nasal spray characterisation brings plume geometry, spray pattern and laser diffraction particle size analysis into focus.

Laser diffraction particle size analysis is highlighted by the regulators for nasal spray testing,[3,4,5] with droplet size routinely used in the assessment of quality, safety and efficacy. During development, droplet size data provide information for the manipulation of critical properties of the formulation, such as viscosity, and support the optimisation of device parameters such as the pump mechanism and geometry of the actuator. Figure 1 shows a typical laser diffraction droplet size profile for a nasal spray event.

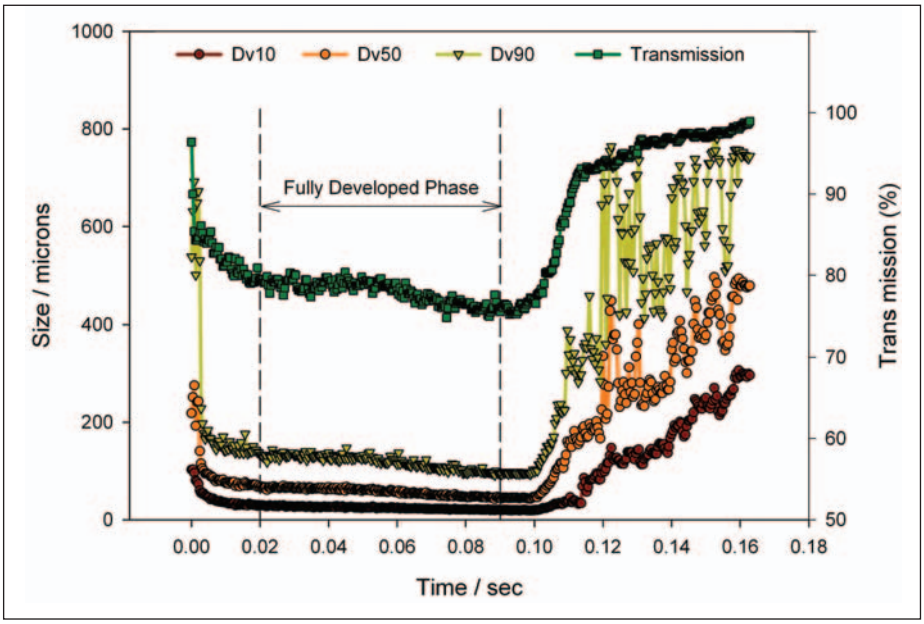


Figure 1: A typical droplet size profile for a nasal spray event.

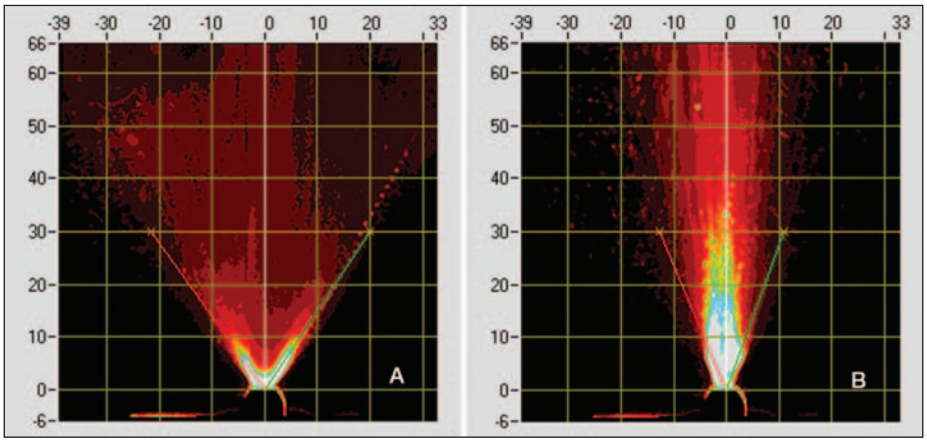


Figure 2: Contrasting plume geometry images for A) water and B) viscous PVP solution.

The measurement rates accessible with laser diffraction – up to 10,000 measurements per second with the best systems – allow capture of the fine detail of the spray event. Larger droplets are produced at both the start (formation phase) and end (dissipation phase) of the event because at these points the pump operates at less than full flow. The central fully developed phase defines the droplet size at which the bulk of the product is delivered, providing data for comparative testing.

For conventional nasal sprays, laser diffraction data is complemented by plume geometry measurements which, as the name suggests, characterise the overall plume rather than the size of the constituent droplets. Plume imaging data allow the nature of the liquid atomisation process to be understood, and can help with formulation and device optimisation. Figure 2 contrasts plume geometry images obtained for the operation of a standard pump system for water with those obtained using the same pump with for a more viscous 1% polyvinylpyrrolidone (PVP) solution. With water, the plume appears as a homogeneous spray sheet having a relatively wide plume angle. Increasing viscosity reduces the atomisation efficiency and changes in the plume reflect this. With the 1%PVP solution the spray emerges as a more jet-like stream, with a smaller plume angle, and there is evidence of individual larger particles; these are the bright streaks that pepper the image.

APPLYING LASER DIFFRACTION AND PLUME GEOMETRY ANALYSIS TO DRY NASAL POWDER PRODUCTS

Dry nasal powder products can be classified either as passive, being driven by the inhalation of the patient, or more commonly as active,

whereby the dose is dispersed by the mechanical action of the device. For active devices, actuation speed, which is a patient-dependent variable, can have a marked impact on dispersion behaviour. The formulations used in dry nasal powders are analogous to those for dry powder inhalation and typically consist of the active drug and other excipients such as lactose. Some formulations may also contain mucoadhesives, dispersion promoters and absorption promoters.

The structure of the powder blend within the device, the device geometry and the actuation method are all key factors in defining whether dispersion to a realistic particle size for nasal deposition can be achieved. In a series of studies, laser diffraction and plume geometry analysis were applied both to lactose and to placebo formulations to assess the applicability of the techniques in understanding the dispersion and delivery processes. Tests were carried out at a range of actuation speeds.

Study 1: Investigating the Behaviour of Lactose Placebos

The technique of laser diffraction exploits the fact that particles in a sample scatter light in a way that is related to their size. A laser diffraction analyser detects the scattered light pattern produced by a sample and uses it to calculate particle size distribution by applying the Mie theory of light. Particle size data is the primary information reported but the transmission of light through the sample is also recorded. As a measure of the amount of light penetrating the sample transmission quantifies concentration.

Figure 3 shows transmission, Dv50 and Dv90 data, averaged over five actuations of the device (Unit dose device, Aptar Pharma, Louveciennes, France) for a lactose placebo formulation, presented as a function of actuation speed. Dv50 and Dv90 are the particle sizes below which 50% and 90% the particle population lie respectively (on the basis of volume).

As the device is actuated, transmission drops instantaneously – indicating a sharp rise in particle concentration – before returning rapidly to a high level. This shows powder entrainment from the device is extremely fast in each case.

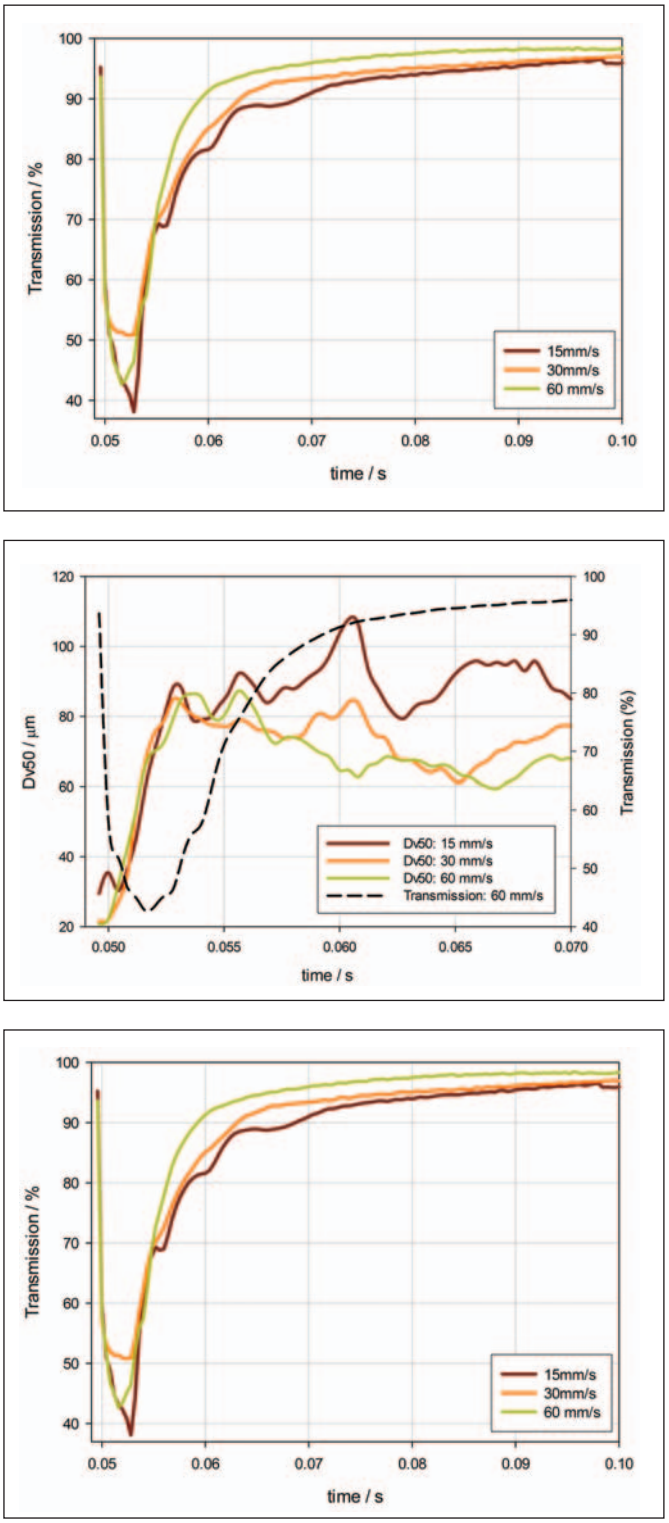


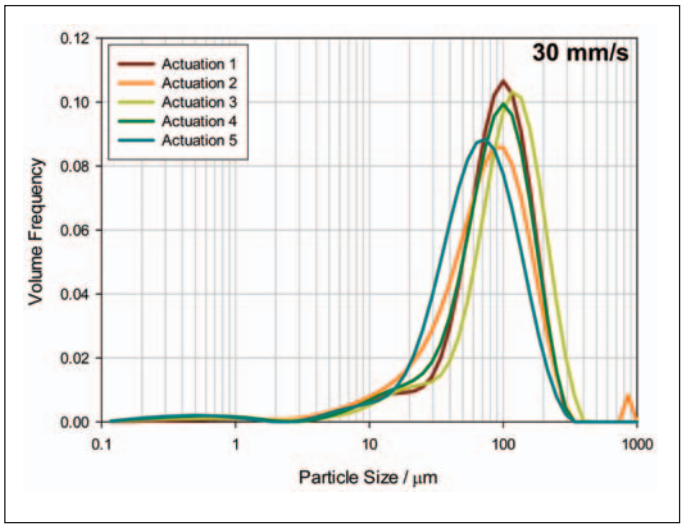
Figure 3: Transmission, Dv50 and Dv90 profiles for a lactose placebo dry nasal spray measured as a function of actuation speed.

The particle size data indicate that at the beginning of the event both small particles and coarse material are released: the Dv90 is high and the Dv50 is low. As transmission reaches a minimum, the point of maximum entrainment, particle size shifts to a narrower distribution, with higher actuation speeds promoting more efficient dispersion of the dose. The difference between the data measured at 15 and 30 mm/s is particularly pronounced, with clear evidence of agglomerated material in the Dv90 data recorded at 15 mm/s. It should be noted that the appropriate actuation parameters representative of a patient should be determined for the drug product being tested. A range of actuation velocities were investigated in this study.

In terms of the particle size profiles, there is no equivalent to the formation, fully developed and dissipation atomisation phases observed with liquids, so comparative characterisation data can be generated simply by averaging the recorded particle size distributions across each event. Detailed comparison of the average particle size distributions measured at each actuation speed confirms that improved dispersion is achieved by increasing the actuation velocity, although even at 60 mm/s complete dispersion is not observed in this case.

While consideration of averaged results calculated across multiple actuations allows the identification of any changes in the state of powder dispersion, more detailed analysis of the results for each actuation provides further insight (see Figure 4). Contrasting the data measured at 30 mm/s with that generated at 60 mm/s shows much greater variability at the lower actuation speed. This suggests that higher actuation velocities are advantageous for reproducible entrainment and dispersion for this device and powder formulation.

Plume geometry data for the three different actuation speeds are shown in Figure 5. These confirm that entrainment and emptying of the device proceed well in each case, and suggest that operation at higher actuation velocities is less variable. The fact that reasonable emptying is observed at all velocities is also reflected in the recorded shot weights, which are similar for each set of conditions. These observations correlate with the particle size and transmission data obtained using laser diffraction, which show the powder concentration to be similar at all actuation velocities, but that improvements in the reproducibility of powder delivery and dispersion are observed at higher velocities.



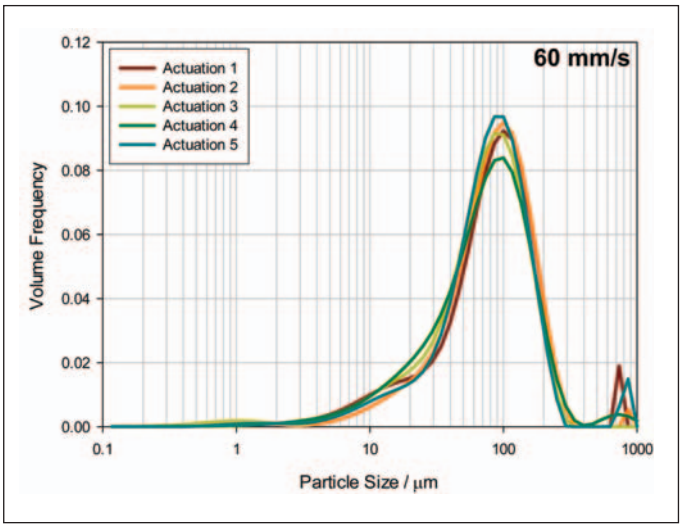
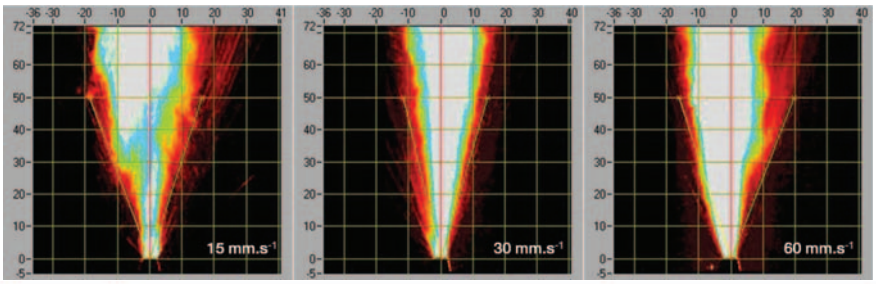


Figure 4: Individual particle size data sets for a lactose placebo.



Velocity mm.s^{-1}	Plume Characteristics				Shot Weight	
	Angle	RSD	Width / mm	RSD	Weight / mg	RSD
15	34.5°	13.1%	31.1	13.8%	10.7	18.2%
30	29.8°	11.7%	26.6	12.1%	10.7	7.1%
60	35.3°	8.9%	31.9	9.5%	10.2	12.7%

Figure 5: Plume geometry data for a lactose placebo measured at a range of actuation speeds.

Sample	Velocity mm.s^{-1}	Plume Characteristics				Shot Weight	
		Angle	RSD	Width / mm	RSD	Weight / mg	RSD
Formulation A	15	31.1°	9.7%	27.9	10.3%	9.5	13.7%
	60	32.1°	10.9%	28.8	11.6%	9.4	6.9%
Formulation B	15	32.7°	7.0%	29.4	7.4%	9.8	8.5%
	60	31.4°	2.9%	28.2	2.8%	10.5	2.6%

Figure 6: Plume characteristics and shot weight for formulations.

Study 2: Investigating the Behaviour of a Placebo Formulation

Similar tests were conducted with two placebo formulations, one containing component functional excipient with a Dv50 of 30μm (A), the other with a Dv50 of 4μm (B). The data obtained show that as with the lactose placebo entrainment of the powder is extremely rapid, with the plume angle similar at each actuation velocity (Figure 6).

Using laser diffraction it is possible to observe differences in the degree of dispersion achieved (Figure 7), with higher speeds leading to a decrease in the observed particle size, especially in the case of formulation B. This relates to the highly cohesive nature of this formulation, caused by the presence of very fine particles, and correlates with an improvement in the reproducibility of powder delivery at higher velocities, as assessed by considering the variability in the plume angle and delivered shot weight (Figure 6).

DRAWING ON DPI EXPERIENCE

The preceding work, which draws on experience from conventional nasal spray characterisation, demonstrates the relevance of laser diffraction in measuring dry nasal powder products. Laser diffraction is a fast, non-invasive, flow-rate-independent technique and its ability to generate precisely resolved particle size and concentration data, in real time during a spray event is valuable. Such information gives insight into the dynamics of dry nasal powder behaviour pointing to areas for performance improvement.

The limitations of laser diffraction, though, are clear, and strictly analogous to its application in the area of DPI development. Laser diffraction cannot be used to predict changes in aerodynamic properties associated with particle shape or density, but most importantly of all it does not differentiate between drug and excipient.

For solution- and suspension-based nasal formulations the inability of laser diffraction to differentiate the active is not so important, as the drug is either dissolved within the liquid phase or milled to a fine enough particle size to ensure that the suspension is essentially homogeneous. The technique therefore provides a realistic means of assessing the likely reproducibility of drug deposition within the nose, which in turn may relate to bioavailability. With a dry nasal powder this assumption can no longer be made, as the drug may be present with large agglomerate particles or finally dispersed as primary particles. This creates an additional requirement for drug specific analysis such as cascade impaction.

In routine DPI testing the dose is size fractionated using a cascade impactor, which separates the sub-ten micron population, the main size fraction of interest for pulmonary delivery. This enables the generation of an aerodynamic particle size distribution specifically for the active. For nasal spray testing, impactors can also be used to study the sub-ten micron fraction3 while larger particles may be analyzed via deposition within a nasal spray cast,[6] which replaces the induction port within the cascade impactor set-up. Analysis of the resulting fractions may be carried out using HPLC or more sophisticated imaging methods that incorporate spectroscopic techniques such as Raman.

Rather than simply producing an averaged figure for active concentration, these techniques generate size, shape and compositional data that together maximise information about the behaviour of the formulation (see Figure 8).

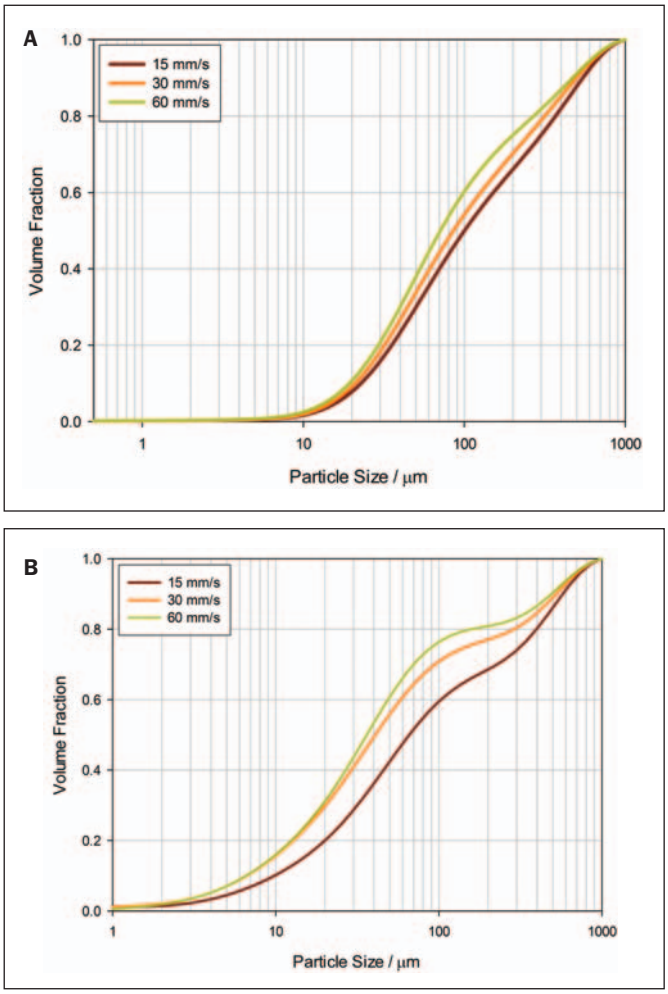


Figure 7: Particle size distributions recorded for formulation A (top) and B (bottom) for different actuation velocities.

THE WAY FORWARD

Dry nasal spray technology offers a number of important technical advantages and is an enticing prospect for commercial exploitation. Its advancement relies on identifying analytical methodologies that can efficiently generate the understanding required for development: techniques that rapidly provide relevant information for formulating an efficacious product and support and streamline commercialisation within the regulatory framework.

The expectation that dry nasal sprays might share some of the features of both conventional nasal sprays and dry powder inhalers, makes the characterisation techniques applied to each of these classes of products potentially valuable.

Early results confirm that laser diffraction particle size analysis, a technique routinely applied to conventional nasal sprays, has value for dry spray characterisation. The particle size and concentration data it provides give insight into the dynamics of dispersion that can be used to tune the performance of both the device and formulation.

Crucially though, as with DPIs, complete dry nasal spray characterisation also requires drug-specific analysis, an understanding of how the active ingredient is distributed across the different size fractions. Here, cascade impaction experience points to the relevance of HPLC analysis for compositional information. However, more sophisticated methods such as automated imaging coupled with Raman spectroscopy may also have a role to play.

By linking size and shape and compositional information, such methods provide a more secure basis for engineering dry nasal spray formulations towards optimum performance.

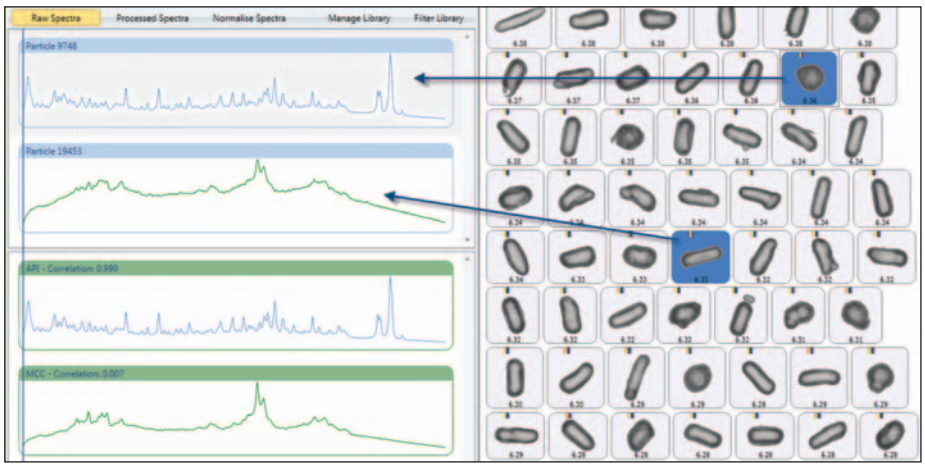


Figure 8: Linking particle shape and composition using automated imaging coupled with Raman spectroscopy. Referencing data for the sample to spectra for the active (upper) and excipient (lower) precisely identifies the nature of individual particles.

REFERENCES

1. *Colombo et al, "In vitro and in vivo study of Desmopressin nasal powder". Proc Respiratory Drug Delivery (RDD) Europe, 2007, Vol 1, pp345-348.*
2. *Luthringer et al, "Rapid absorption of sumatriptan powder and effects on glyceryl trinitrate model of headache following intranasal delivery using a novel bi-directional device". J Pharm Pharmacol, 2009, Vol 61(9), pp 1219-1228.*
3. *US FDA CMC Guidance for Nasal Sprays, 2002. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070575.pdf*
4. *US FDA Draft Bioequivalence Guidance for Nasal Sprays, 2003. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070111.pdf*
5. *EMEA Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products, 2005. http://www.ema.europa.eu/ pdfs/human/qwp/4931305en.pdf*
6. *Coowanitwong, De, Somaraju, Wu, Mclaughlin, Schoenbrodt, Egen, Kohler, Mueller and Schiewe, "Regional deposition of beclomethasone dipropionate powder existing Puvlizer® in a nasal cast connected to a next generation impactor". Proc Respiratory Drug Delivery (RDD) Europe, 2011, Vol 2, pp 373-378.*

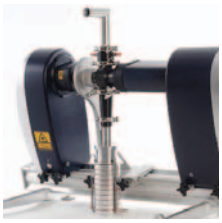
FROM **SPRAYS...**

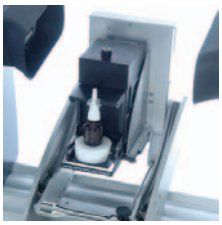
SPRAYTEC:

Dynamic particle and droplet sizing

- Measures concentration and particle/ droplet size during device actuation
- Rapid screening and accelerated optimization of OINDP formulations and delivery device
- Complementary to other analysis methods such as cascade impaction
- Promotes a knowledge-based approach to product development advocated by QbD

www.malvern.com/spraytec





CHARACTERIZE YOUR OINDP IN **DETAIL**

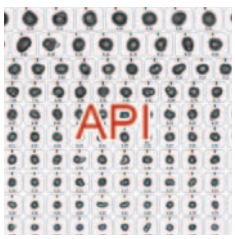
www.malvern.com/g3id

...TO **API SIZE**

MORPHOLOGI G3-ID

Automated, chemically specific particle characterization

- Measures particle size, shape and chemical identity within OINDP formulations
- Simple SOP operation from sample dispersion through to size, shape and chemical analysis
- Provides supporting evidence for in-vitro bioequivalence and CMC studies for nasal sprays
- Promotes a knowledge-based approach to product development advocated by QbD



Malvern | Material relationships

www.malvern.com


We Have Raised the Bar for 2013!
17TH ANNUAL
DRUG DELIVERY
PARTNERSHIPS
Visionaries meet. Challenges are overcome. Innovation happens.
February 6-8, 2013
Hilton San Diego Bayfront • San Diego, CA
www.drugdeliverypartnerships.com

Delivering NEW Content, NEW Speakers, NEW Opportunities

- Full day partnering room, extended breaks and online networking tool
- Increased executive speaker faculty by 20%
- 3 New tracks covering strategies for future profitability
- 40+ Innovative technology companies to help you find your next blockbuster

FEATURED KEYNOTES

HEALTHCARE AND POLICY

Billy Tauzin
Former **U.S. Congressman**,
Former President and CEO
PhRMA

INDUSTRY

David Pyott
Chairman, President and CEO
ALLERGAN

INNOVATION

Myshkin Ingawale
Inventor, co-founder
BIOSENSE TECHNOLOGIES

KEYNOTE PANELS

Where Does Drug Delivery Fit into the Pharmaceutical Pipeline?
PARTICIPANTS FROM **Pfizer · Bayer Pharmaceuticals · Sun Pharmaceuticals · Astrazeneca · Sandoz**

How Has the Political Climate Affected Drug Development and Delivery and How is the Industry Coping?
PARTICIPANTS FROM **Allergan · Phrma · Express Scripts · Johnson & Johnson · Pfizer**

Drug Delivery Devices: How Are Devices and Combination Products Changing the Game?
PARTICIPANTS FROM **Merck · Sanofi-Aventis · Bd Medical - Pharmaceutical Systems · Genentech · Eli Lilly & Company**

VIEW AGENDA

Scan to download the full conference brochure at **www.drugdeliverypartnerships.com**

REGISTER TODAY

15% OFF

Save **15%** when you register with priority code **P1878B**
(discount is off standard rates)

"It's an annual catalyst for getting deals done early in the year. The event attracts an outstanding distribution of companies and functional experts."

– Robert J. Bloder, VP, Business Development, AVEVA Drug Delivery Systems

"DDP accelerates the time it takes to connect with the right person in the right function from the right company."

– Christopher Jordan, Co-Founder and President, JRX Biotechnology Productions, Inc

CI Informatics

Better by Design

WHAT'S IN A GSD?

The basis of this article, from Bob Lott, PhD, Founder of CI Informatics Ltd, comes from his experience trying to specify the Geometric Standard Deviation (GSD) calculation to software developers. Originally, he thought this would be a simple calculation. In reality it transpired to be a minefield of differing opinions and practices. This article is a "tip toe" across the issues Dr Lott encountered and questions some of the most common assumptions made.

Few analytical results can be taken as absolute values, and this is particularly true of a GSD!

WHAT IS A GSD?

The GSD or geometric standard deviation, together with the mass median aerodynamic diameter (MMAD), are the two metrics used to describe the aerodynamic particle size distribution (APSD) both of airborne particles/aerosols and those emitted by orally inhaled and nasal drug delivery devices.

In broad terms, the MMAD can be viewed as the "average particle size" while the GSD represents the spread of particle sizes either side of the "average". So, the smaller the GSD, the narrower the size distribution is, and *vice versa*.

CALCULATION METHODOLOGY

MMAD and GSD are both classically calculated from a Log -Cumulative Mass % plot, such as those shown in Figures 1 and 4. Construction of this plot is well documented not least in the governing guidances.[1,2]

The GSD is determined from the plot according to Equation 1:

$$GSD = \sqrt{\frac{Size\ X}{Size\ Y}} = \left(\frac{Size\ X}{Size\ Y}\right)^{0.5}$$

The Y-axis may be expressed as Cumulative Mass %, Z-Score, or Probits as in Figure 2. Mathematically these are equivalent scales and all three are in common use.

Issues arise around which calculation methodology should be used to process the data. In reality few people use the plot directly in this way, preferring to use some form of computational software to do the job. However the same question remains: what methodology should be used, regression, interpolation, or some other method?

TESTING FOR LOG-NORMALITY

First it must be noted that while an MMAD can be reported for any distribution, a GSD is only valid for Log-Normal distributions. It is therefore necessary to test if this is the case by performing a linear regression and ensuring the data is a good fit.

But what constitutes "a good fit"? The default position of available products is an R^2 >0.95 which is probably too low given the limited number of data points evaluated. The pharmacopoeias do not give any guidance on this.

Then there is the matter of what data to use for the regression. The US Pharmacopeia, USP 601, infers that all the data should be used, whereas ISO 27427 states that only data between 10% and 90% Cumulative Mass should be used. Some software products only use the data between 15.87% (Probit 4) and 84.14% (Probit 6), while others offer all of the above as well as a dynamic approach that ensures the core data is always properly evaluated by a true regression (no fewer than three data points).

Let's look at each in turn. Using all the data can afford too much weight to the extreme ends of the APSD distribution where recovered masses are generally the lowest and error the greatest.[3] Using only data between 10% and 90% Cumulative Mass removes these "extreme ends", but the 90% upper-limit can be counterproductive.

Consider Figure 3, the table containing example data generated from a Next Generation

Dr Bob Lott
Founder
CI Informatics Ltd

T: +44 1235 851 936
M: +44 7890 316 126
E: bob.lott@ciinformatics.co.uk

www.ciinformatics.co.uk

Impactor™ (NGI™; MSP Corporation, Shoreview, MN, US).

Applying the 90 Cumulative Mass % upper limit excludes the data point from Stage 2. However, Stage 2 contains >16% of all the recovered material and more than that found on Stage 5, which would be included. Therefore the argument that this point represents an "extreme end" is hard to justify. Indeed perversely the more material found on stage 2 the less likely the data will be used. This does not make much sense and it could be argued that arbitrary regression limits are not always helpful.

Using only data between 15.87% and 84.13% often renders the available data to just two points. The regression is therefore limited to an interpolation, guaranteed to the linear! In some cases only one point will exist, rendering the regression analysis to a mere assumption.

A dynamic approach that takes the data point immediately below the 15.87% particle population, up to and including to the point immediately above the 84.13% particle population affords the benefits of excluding the extreme ends without applying arbitrary limits and ensures a proper regression is performed.

To sum up so far, there would appear to be a lack of consensus as to how we should decide if a GSD is even to be reported, let alone how it should be determined! For the sake of this article however let's say we are all agreed and a GSD is to be calculated.

REGRESSION

Since we have already performed a regression to determine whether or not a GSD should be reported, it would seem most sensible to use it to calculate the result. The only case the author can think of where it would not be sensible would be when an inappropriate regression methodology was used during the Log-Normal assessment.

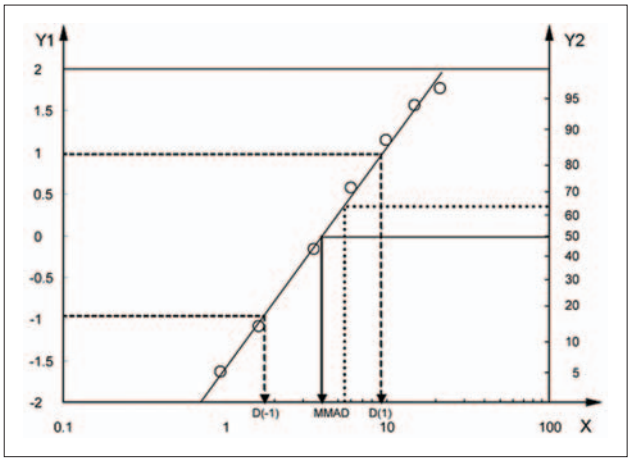


Figure 1: Example Log-Cumulative Mass % plot. *(Reproduced from ISO 27427:2009(E) Figure D.2.)*

INTERPOLATION

Good sound reasons exist why interpolation may be used for the calculation of MMAD, namely that it works well for Log-Normal and non Log-Normal distributions alike and is by far the simplest methodology to use in the latter case.[3] To be clear we are talking here about interpolating the two data points above and below the 50% percentile (Probit 5). Applying these same arguments to calculation of the GSD is questionable, as 1) a GSD is not reported if the APSD is non-Log-Normal, and 2) basing the result on only two data points about the MMAD may bias the result as these data points tend to be the "steepest" portion of the Log-Cumulative Mass % plot so giving a steeper slope and therefore smaller GSD result.

THEORETICAL EXTRAPOLATION

As Size X, Size Y and the MMAD all sit on the same straight line of a theoretically perfect Log-Normal distribution it can be shown that:

GSD = Size X/MMAD (Equation 2) *or*
GSD = MMAD/Size Y (Equation 3)

However these are only true where the arguments of the equation are determined from the same linear regression data. If the MMAD and Size X are determined from independent interpolations there is a risk that the extrapolation to Size Y will not be sufficient to the data, as not all the relevant data has been taken into consideration. This is best seen with the aid an example Log-Cumulative Mass % plot, Figure 4.

Here the MMAD and Size X were found by independent interpolations on data bracketing Z-Score = 0 and 1 respectively. These two points are then themselves interpolated and the resultant line extrapolated to Z-Score = -1 to find Size Y. This is graphically identical to Equation 2.

From the plot it can be seen that Size Y determined in this manner is not representative of the data in that region. This is simply because the method excludes the data point just below Z-Score = -1. Figure 5 contains comparative APSD data calculated from the distribution shown in Figure 4.

Data in brackets were not measured according to the method used, but were back-calculated for illustration purposes.

Note the data point just below Z-Score = -1 is Stage 5 of an NGI @30L/min, resulting in a cut-off diameter of 2.3 μm. Size Y calculated by regression agrees well with this and is the more accurate result.

Consider now if Size Y were interpolated and used with the MMAD to determine Size X (graphical equivalent of Equation 3). Size Y is found to be 2.33 which has good agreement with the nearest stage cut-off diameter mentioned above. However the GSD is determined as just 1.76. This discrepancy originates from a data set with an R^2 >0.99 (based on the four points shown in Figure 4). Applying this methodology to less linear data sets can only result in bigger inconsistencies. So although Equations 2 and 3 are true, they do not produce accurate results when misused in this way.

	Cumulative Mass %	Z-Score	Probit
Size Y / D(1)	15.87	-1	4
MMAD	50	0	5
Size X / D(-1)	84.13	1	6

Figure 2: Table showing Y-Scale equivalence values.

Stage	Mass (μg)	Cumulative Mass (μg)	Cumulative Mass %	Stage Fraction %
MOC	0.00	0.00	0.00	0.00
Stage 7	0.04	0.04	0.76	0.76
Stage 6	0.13	0.16	3.40	2.65
Stage 5	0.60	0.77	15.83	12.42
Stage 4	1.58	2.35	48.43	32.61
Stage 3	1.29	3.63	75.01	26.57
Stage 2	0.80	4.43	91.53	16.52
Stage 1	0.41	4.85	100.00	8.47

Figure 3: Example NGI deposition data.

Using the regression data in Figure 5, Equations 2 and 3 give coherent results. This is because both Size X and Y are determined on an equal basis so there is no bias for one data point over the other.

CONCLUSIONS

If all distributions were perfectly Log-Normal, all the methodologies discussed would give the same result, but this is not that case and a GSD is only ever an approximation. However some approximations have greater mathematical integrity resulting in more accurate results, than others.

Given the variety of practices and regulatory requirements within the global respiratory drug delivery industry, it is important for computational tools to offer the flexibility to meet these varying demands.

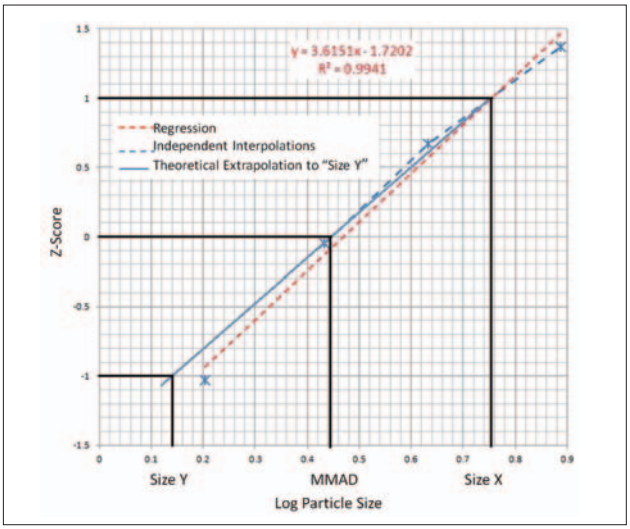


Figure 4: Log-Z-Score plot depicting alternative methods to determine the GSD.

Methodology	MMAD (μm)	Size X	Size Y	GSD
Regression	4.35	8.58	2.21	1.97
Interpolation	4.12	7.96	2.13	1.93
Theoretical Equ. 2	4.12	8.52	*(1.52)*	2.07
Theoretical Equ. 3	4.12	*(7.2)*	2.33	1.76

Figure 5: APSD results obtained from Figure 4 using alternate calculation approaches.

REFERENCES

1. *USP 34-NF 29, Physical Tests and Determinations <601>, "Aerosols, nasal sprays, metered-dose inhalers and dry-powder inhalers".*
2. *ISO 27427:2009(E), "Anaesthetic and respiratory equipment nebulizing systems and components".*
3. *Stimuli to the Revision Process, "Generalized simplified approaches for mass median aerodynamic determination". Pharmacopeial Forum, 2010, Vol 36(3).*

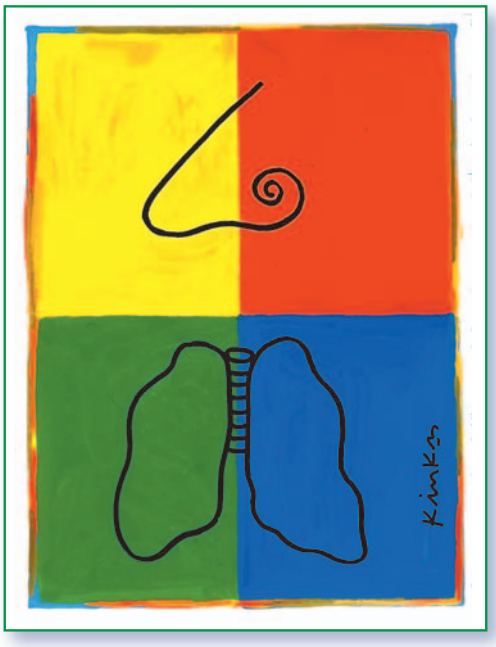
ABOUT THE AUTHOR

Dr Bob Lott is founder of CI Informatics Ltd and has worked closely with S-Matrix Corporation (Eureka, CA, US) to bring Fusion Inhaler Testing (FIT) to the respiratory market place. CI Informatics is the European distributor for all S-Matrix products including Quality by Design (QbD) solutions for respiratory product development. Visit www.ciinformatics.co.uk for more information.

PLEASE MARK YOUR CALENDARS AND PLAN TO ATTEND!

RDD EUROPE 2013

Respiratory Drug Delivery



MAY 21 - 24, 2013

Intercontinental Hotel
Berlin, **GERMANY**

Sponsorship and Exhibition Opportunities
Contact : info@rddonline.com

Call for Scientific Poster Abstracts
Deadline: January 11, 2013

For more information visit www.rddonline.com/rddeurope2013

RDD Europe is a conference jointly organized by

RDD Online
Respiratory Drug Delivery

Aptar
pharma

SINGLE-DOSE INHALERS FOR CAPSULES: A CONSOLIDATED TRADITION WITH AMPLE GROWTH PROSPECTS

In this article, Pierluigi Magni, Group Marketing Manager, Plastiape, describes how the single-dose per capsule dry-powder inhaler is once again finding favour in the pharma market, and introduces the company's latest offering in this space – the Monodose RS01 device.

Until a few years ago, experts in this sector considered the days of dry powder inhalers (DPIs) – in the "single dose per capsule" format – to be numbered. In their desire to find increasingly innovative solutions, as well as to show themselves more technologically sophisticated than their competitors, many pharmaceutical companies had placed their bets on multi-dose inhalers with more advanced engineering and, on the face of it, simpler for the user.

In reality, many of these inhalers proved to be too complex technically and, in certain cases, unreliable, insufficiently user-friendly or too bulky. The well-known failures of various highly sophisticated devices, which were expected to invade the market like blockbusters, brought about a return to favour of simpler, safer and more effective devices such as the single-dose per capsule inhaler.

Although these devices require a new capsule to be loaded before each inhalation, they nevertheless have a number of unquestionable advantages, such as:

- the medicine is pre-dosed and the dose can be checked on the filling-lines
- the patient can easily see, after each inhalation, whether the medicine has been taken
- blister packaging ensures high stability of the medicine.

"RS01 IS NOTABLE FOR ITS COMPACT SIZE, REDUCED NUMBER OF PARTS AND FOR THE SIMPLICITY AND EFFECTIVENESS OF ITS PERFORATION SYSTEM, SUITED TO BOTH GELATINE AND HPMC CAPSULES"

Furthermore, the capsule filling systems are standardised and reliable, thereby calling for relatively low investment from pharma companies and allowing easier transition from the clinical, pre-industrial phase to the industrial.

As is well-known, Plastiape can boast today a thirty-year tradition in the development and industrialisation of inhalers for powders. The producer of the Aerolizer® (Novartis Pharma, Basel, Switzerland), Pulvinal® (Chiesi Farmaceutici, Parma, Italy) and Turbospin® (PH&T, Milan, Italy), it also has several families of inhalers of its own design.

Mr Pierluigi Magni
Group Marketing Manager
T: +39 039 952 981
F: +39 039 587 805
E: pierluigi.magni@plastiape.com

Plastiape SpA
Via 1° Maggio, 8
23875 Osnago (Lecco)
Italy

www.plastiape.com

Figure 1: The Monodose RS01 is the latest generation single-dose per capsule inhaler from Plastiape.

From Plastiape, the latest generation single-dose per capsule inhaler is the *Monodose* RS01, shown in Figure 1.

Compared with the more sophisticated multi-dose and other single-dose inhalers on the market, the RS01 is notable for its compact size, reduced number of parts (see Figure 2) and for the simplicity and effectiveness of its perforation system, suited to both gelatine and HPMC capsules.

The RS01 is created with thermoplastic resins specifically intended for the pharmaceutical sector and which have passed the physical-chemical tests laid down by international pharmacopoeias. With the collaboration of laboratories operating in GLP conditions, Plastiape has also performed extractible tests on its families of single-dose inhalers and biocompatibility tests on the finished product in compliance with ISO10993 regulations.

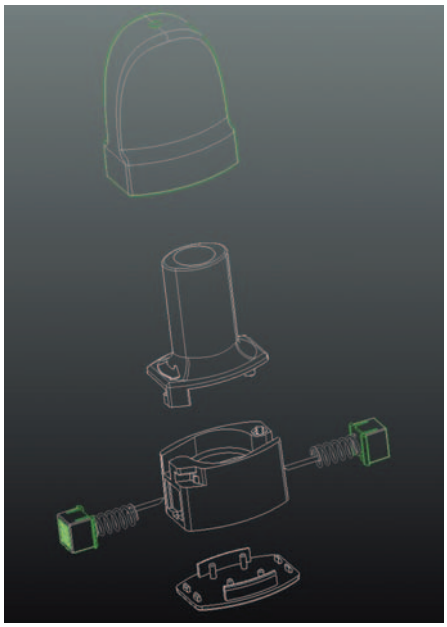


Figure 2: Vertically exploded diagram of the RS01 design, showing the small number of component parts.

"THE RS01 OFFERS A RELIABLE, READY-TO-USE SOLUTION FOR HIGHLY INNOVATIVE FORMULATIONS, WHERE IT IS NECESSARY TO LIMIT THE NUMBER OF VARIABLES AT STAKE, REDUCING RISKS AND COSTS"

In its standard version, the RS01 is a low-resistance device reaching a pressure drop of 4 kPa at c.100 L/min and is therefore suitable for use on a wide range of patients. A high-resistance (4 kPa at 65 L/min) version also exists.

The inhaler is entirely developed by Plastiape and a number of international patents have been taken out for it (including in Europe, the US, Canada, Australia and Japan). Plastiape has also filed a Type III Drug Master File with the US FDA as a support for customers intending to register and trade their medicine in the US market.

The highly compact size, the lesser weight compared with competing appliances, and the complete lack of propellants, make the device particularly environmental friendly and therefore suitable for pharmaceutical companies that, like Plastiape, put respect for the environment at the top of their development strategy.

Plastiape has already developed high capacity moulds and production lines for the RS01 and can therefore provide its clients – even in the case of samples for clinical use – with devices produced in the same conditions as will be applied during industrial production. The highly automated assembly lines are equipped with control stations designed to check all functional aspects of every single inhaler produced.

The device is assembled in IS0 Class 7 cleanrooms (10,000 FED STD) subject to periodical checks for microbiological and particle contamination.

All the above-stated facts make the RS01 an ideal platform for a wide range of inhaled medicines: on the one hand, it may be considered a simple and cheap solution for generic medicines, even those produced in small volumes, while on the other hand the RS01 offers a reliable, ready-to-use solution for highly innovative formulations, where it is necessary to limit the number of variables at stake, reducing the risks and costs of developing a device and thereby leaving researchers free to concentrate their efforts and investments on the formulations themselves.

CONFERENCE REVIEW:
39TH ANNUAL MEETING AND EXPOSITION OF THE CONTROLLED RELEASE SOCIETY 2012

With nearly 1,300 attendees, the 39th Annual Meeting & Exposition of the Controlled Release Society was extremely successful, offering the latest research in the science and once again providing the opportunity to meet colleagues from around the world, connecting again with old friends, and building new relationships.

The meeting began with great science on Saturday, with attendees arriving in beautiful Québec early to attend Educational Workshops covering critical appraisal of EPR effects and intratumoral distribution of nanomedicine, osmotic dosage forms, and *in vitro* testing of controlled release dosage forms. Those newer to the profession arrived early to attend a special Young Scientists Workshop on mucosal drug and gene delivery. Workshops continued with some attendees learning about preserving and enhancing vision through ophthalmic drug delivery, and young scientists learning the important skill of time management.

For the third year, CRS Innovation Sunday helped to encourage and instruct scientists on how to bring their innovative ideas to the market. Companies showcased their newest products and their company's capabilities during the Release Technology Workshops. The ever-popular Soapbox Sessions saw multiple start-ups and established companies presenting new ideas, products, and services. Attendees greatly enjoyed the fast pace of the Soapbox, along with the opportunity to meet one-on-one with those presenting. The Industry Roundtable discussed "Game-Changing Innovation," featuring industry panelists from companies that are known to have had an innovation or two. Julia-Rashba Step of Pfizer and Ronald Smith of Merck & Co offered their perspective on the role of big pharma in innovation in delivery science. Alberto Gabizon, Shaare Zedek MC – Oncology Institute, explained how the entrepreneur brings innovation to the industry.

Monday morning programming got underway early; with the 7:00am "Get Up! Get Educated!" Session, followed by the CRS Opening Session, where President Martyn C. Davies shared the association's activities and accomplishments with a packed room.

The Exhibit Hall was busy, especially during the Exposition Grand Opening and Welcome Reception. Multiple volunteers, including the impressive 2012 Annual Meeting Program Team, were honoured, and Founders Award Winner Yechezkel Berenholz shared his personal voyage in delivery science, followed by Young Investigator Award Winner Cory Berkland describing his personal and professional experiences in the field. The event ended with an entertaining College of Fellows panel on reinventing yourself throughout a career. Monday continued with fantastic scientific sessions, quite a few standing-room only (Figure 1).

Figure 1: Sessions were packed at the CRS Annual Meeting.

Figure 2: The passing of the gavel from past President, Professor Martyn Davies, to the new President, Professor Kazunori Kataoka.

The science presented this year was top-notch. This year's plenary sessions were extremely well-received, with full rooms waiting to hear speakers Donald Tomalia, Molly Shoichet, and Vladimir Torchilin. Tomalia, Founder NanoSynthons LLC, captivated his audience with his research on the dendrimer-based nanomedicine, and the use of abiotic dendrimers in a variety of nanomedical applications. Shoichet, a professor at the University of Toronto, Canada, shared her insights on drug and cell delivery strategies to the central nervous system, describing three regenerative medicine strategies. Professor Vladimir Torchilin ended the meeting on a high note on Wednesday, discussing cell organelles in his address talking about the next generation of drug delivery systems.

Many attendees enjoyed the opportunity to connect with friends and colleagues, and build relationships with people of similar interests. The CRS Annual Meeting offered many chances to do just that. The Young Scientists Mentor/Protégé programme has continued to grow, with a successful Meet & Greet at this year's meeting and outstanding participation by both mentors and protégés, and the Women in Science Luncheon offered the chance for women professionals to learn from some of the leaders in the field on how to navigate the often difficult path of being a woman scientist.

On the final day, the new CRS President, Professor Kazunori Kataoka of the University of Tokyo, Japan, received the official gavel from the immediate past president, Professor Martyn Davies of the University of Nottingham, UK (Figure 2).

Finally, the President's Banquet offered a grand and entertaining opportunity to spend time with colleagues and hear from one the most distinguished and entertaining members of CRS, Kinam Park of Purdue University.

As the meeting came to a close, it was with fondness that we said "Au Revoir" to Québec City and "Aloha" to Honolulu, Hawaii, the ultimate global gathering place, which will be the home for the 40th Annual Meeting & Exposition of the Controlled Release Society next July 21-24, 2013.

CRS is particularly excited to meet in Hawaii as its location in the Pacific makes it the centre of commerce, easily accessible from the Pacific Rim, North America, and Europe. Not only is Honolulu less expensive per day than other major convention cities, but the incredible climate, exotic locate, and genuine hospitality make it the perfect meeting place. **The Call for Abstracts is now open, and will run until January 24, 2013. We will see you in Hawaii! More information is available at: www.controlledreleasesociety.org/meetings.**

The 40th Annual Meeting and Exposition of the Controlled Release Society will take place in Honolulu, Hawaii, US, July 21-24, 2013.

INHALATION MANUFACTURING: COLD FILL, PRESSURE FILL, AND FINDING THE RIGHT PARTNER

In this article, Mr Ross Errington, Business Development Manager, 3M Drug Delivery Systems, explains two pMDI canister filling methods – cold filling and pressure filling. He describes how each method can be applied to meet different formulation requirements, and outlines considerations for pharma companies when selecting an MDI manufacturer.

Both cold-fill and pressure-fill manufacturing methods for pressurised metered-dose inhalers (pMDIs) have existed for quite some time. When considering which route to pursue, pharmaceutical executives should understand the differences between these methods and how they lend themselves to various formulations. Pharmaceutical companies should also be aware of the capabilities they should consider when selecting a manufacturing partner. Finding the right manufacturing partner for an inhalation product can make the difference between a smooth and efficient development process versus one that is expensive and time consuming. Therefore, it is vital to understand the fundamentals of each technology and to examine what a manufacturer has to offer in each.

"PRESSURE FILLING IS THE MOST PREVALENT IN THE MANUFACTURING INDUSTRY BUT CERTAIN FORMULATIONS LEND THEMSELVES BETTER TO COLD FILLING"

UNDERSTANDING COLD FILLING

Cold fill is a method of manufacture in which cold temperatures are used to convert the drug formulation to a liquid phase. The primary propellant in pMDIs is a gas at room temperature; therefore in order to formulate the product, the manufacturer must make that gas a liquid. The process begins with creating a concentrate with the active pharmaceutical ingredient (API) with a solvent or carrier that is a liquid at room temperature. These two components are mixed to form either a homogenous suspension or a solution. In parallel, the bulk propellant, which forms the rest of the formulation, is placed into a pre-chilled vessel; the low temperature ensuring the propellant is in liquid form in the batching vessel. The concentrate is then transferred into the bulk-manufacturing vessel and the entire formulation is mixed. Therefore, a batching vessel will have a formulation containing propellant, solvent/carrier, and the active ingredient, which can either be in solution or as a suspension.

The next step of the cold filling process is to dispense the formulation into appropriate sized canisters. This is achieved by pumping the formulation to a filling head and feeding a predetermined portion of the chilled liquid formulation into an open canister. A valve is placed on top of each canister and then crimped into place. A seal is formed between the top of the canister and a rubber component within the valve. Each completed pMDI is then checked

Ross Errington
Business Development Manager
T: +44 1509 613626
E: rerrington1@mmm.com

3M Drug Delivery System
3M House
Morley Street
Loughborough
Leicestershire, LE11 1EP
United Kingdom

www.3m.com/dds

Figure 1: Example of a pressure fill manufacturing line.

Pressure Fill		Cold Fill
Single Stage	*Two Stage*	• Thicker powder loading suspensions • APIs in which the particle size must be closely controlled during formulation
• Solution with API that easily dissolves in an ethanol/ propellant formulation	• Typical suspension formulations	
• Certain suspensions with very low powder loading and a very small amount of drug relative to the formulation		

Figure 2: Criteria to consider when determining the match for a product.

for weight to ensure the correct amount of formulation is in the product.

Products may then be water bathed to ensure a proper seal has been formed and that there are no gaps through which the propellant may leak. In cold filling, the water bath also serves the purpose of warming the aerosol to room temperature. The formulation in the canister remains a liquid, due to the fact that it is under pressure. After this step the pMDIs will be 100% function tested before batch release testing and final packaging operations are performed.

UNDERSTANDING PRESSURE FILLING

In contrast to cold filling, the pressure fill process uses pressure instead of low temperature to condense the propellant. The propellant is held in a pressurised vessel in liquid form (see Figure 1), and the drug concentrate is typically made in the same way as it is with cold filling, with the API mixed with a solvent or carrier that is liquid at room temperature.

Pressure-fill manufacturing can follow two separate courses. In one, known as two-stage pressure filling, the drug concentrate is placed in an open canister. A valve is then placed on top of the canister and crimped into position to form the seal. The propellant is then driven under pressure backwards through the valve and into the canister. Using this method, the mixing of the concentrate and propellant actually happens in the canister rather than in a bulk formulation tank. In common with the cold-fill process, after this step the unit is checked, weighed, water bathed and submitted for further processing.

The other method of pressure-fill manufacturing is referred to as single-stage pressure filling. In this process, the API and propellant are mixed and held under pressure. An empty canister is then fed onto the filling table and a valve is placed on top and crimped into place. The complete formulation is then fired under pressure into the canister. Following this step, the product is processed similarly to the other methods described.

Both two-stage and single-stage pressure filling rely on a step in which material is driven backwards through the valve, as opposed to the normal patient-use operation in which the valve opens to allow formulation out of the canister. It is therefore important in this filling process for the manufacturer to ensure they are re-sealed in order to prevent the product from escaping after filling.

ADVANCES IN TECHNOLOGY

There was a time when the equipment used in filling pMDIs was only capable of filling one canister at a time, during a process that was manually controlled and which required many manual checks. Today's pMDI filling lines utilise technology that allows the filling of multiple canisters at once, with electronic controls added to manage the filling process, rather than relying on manual intervention. With recipe-driven operating systems, electronic data generation, and the elimination of steps that require manual control, manufacturers are now able to deliver products that are more precise and more cost effective.

DETERMINING THE MATCH FOR A PRODUCT

Both pressure-fill and cold-fill manufacturing methods were developed several decades ago. In today's market, pressure filling is the most prevalent in the manufacturing industry. However, certain formulations of drugs actually lend themselves better to cold filling than pressure filling operations. In order to determine which method of manufacturing to pursue, pharmaceutical companies should examine the properties of their formulations (Figure 2).

A formulation that is a solution, which has an active ingredient that easily dissolves in a solvent/propellant formulation, is ideal for single-stage pressure filling, due to the fact that it can very simply be driven as a liquid backwards through the valve on the canister. Single-stage pressure filling can also be appropriate for certain suspensions that have particularly low powder loading – a small amount of drug relative to formulation as is sometimes found in high potency products.

Two-stage pressure filling is nearly always used with a typical suspension formulation, in which the drug loading of the formulation is too thick for it to be dispensed into the can through the valve with repeatable accuracy.

In the cold-fill process, there are fewer concerns as to whether the formulation is a solution, or a low powder loading or thick powder loading suspension. Cold filling does lend itself very well to thick powder loading suspensions, in that the fully suspended formulation is created in the vessel and the manufacturer is not reliant on the propellant and the concentrate mixing properly in the small canister. For this type of formulation, cold filling is typically preferable to two-stage pressure filling, in which the proper mixing is sometimes not achieved within the canister. Incomplete mixing can prevent a homogenous suspension from being formed and cause inconsistencies in testing.

Cold filling also makes more sense for certain APIs in which the manufacturer seeks to control the particle size closely. With a cold fill process, the chilling of the concentrate can be used to control the crystallisation of the product and therefore the particle size.

WHAT TO LOOK FOR IN A MANUFACTURER

Whether seeking a manufacturer with cold fill, pressure fill or both capabilities, pharmaceutical companies should ask themselves if they need purely a manufacturer, or a manufacturer that provides additional services such as on-site development, access to analytical testing, and regulatory support. In either case, a manufacturer should have a significant track record of inhalation production, preferably with the type of drug in question.

Additionally, a manufacturer should be able to give examples of many different types of formulations it has worked with. As drug com-

Figure 3: MDI components.

bination products increase in popularity, a broad track record will become even more important.

Pharmaceutical companies should consider what a manufacturer's track record consists of and how robust it is, as these factors can help maintain manufacturability over the product's lifetime (see Figure 3). To keep the product's development timeline ahead of competitors, a manufacturer should have the ability to scale-up production quickly from development through commercialisation. At the same time, the manufacturer must be able to meet regulatory requirements and adhere to current good manufacturing practices (cGMP).

The ability to offer guidance in the patent process is another quality that a strong manufacturing partner can offer. Navigating existing patents and finding ways to combine drugs for new patents takes innovation and expertise. In addition, a robust market presence and supply chain are vital. Having manufacturing sites around the world can help increase flexibility and prevent supply issues in critical areas.

As we know, the challenges in the pharmaceutical industry are far from standard, and pharmaceutical companies need partners that have a wide range of tools to meet these challenges. In order to set products up for success, companies should look for manufacturers that have extensive expertise, from the pilot stage to full-scale production. Wide-ranging expertise and long-term experience can go far in helping new inhaler products achieve a successful launch, whether they are pressure-fill or cold-fill devices.

By working with a manufacturer that has experience developing and manufacturing both types of product, as well as expertise in the development and manufacturing process from start to finish, pharmaceutical companies can give themselves an advantage over the competition.

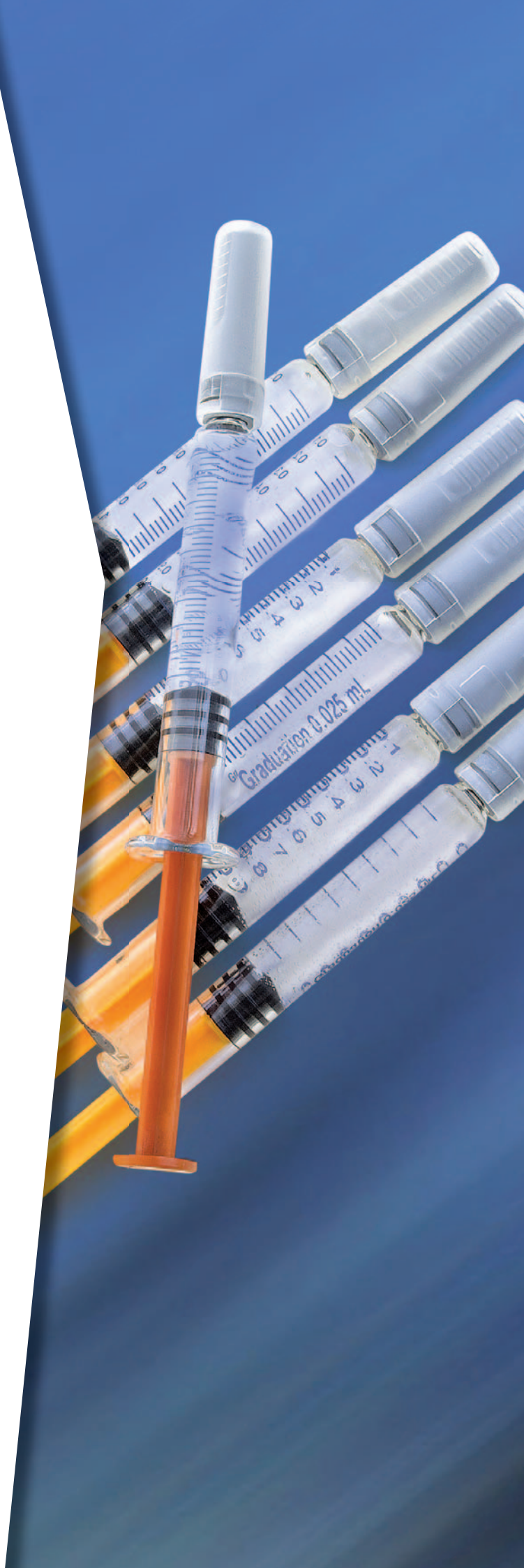
SPECIALTY COATING SYSTEMS™

When it comes to reliability, nothing protects like Parylene.

Parylene is an ideal conformal coating for medical and pharmaceutical delivery devices and components. SCS Parylenes can be applied to virtually any material to provide ultra-thin, pinhole-free coatings with superior extractables/leachables barrier properties and excellent non-liquid, low friction/stiction characteristics. Biocompatible Parylene coatings are USP Class VI certified and ISO 10993 tested.

With 11 locations around the world (6 in the Americas, 3 in Europe, 2 in Asia), Specialty Coating Systems is the leader in Parylene coatings and maintains comprehensive FDA Drug and Device Master Files for customer reference.

Contact SCS today for more information about the ways Parylene coatings can enhance the performance and reliability of your medical or pharmaceutical applications.



World Headquarters (US): +1.317.244.1200
European Headquarters (UK): +44.1483.541000
www.scscoatings.com/medical

REGULATORY ENVIRONMENTAL BIOLOGICAL SCS COMPLIES.COM

To register for upcoming SCS webinars, visit SCSwebinars.com.

CONFERENCE REPORT:
RESPIRATORY DRUG DELIVERY (RDD®) 2012

Here, the RDD Team provides a review of the Respiratory Drug Delivery 2012 Conference, and a taster of what's in store for RDD Europe 2013 in May.

Respiratory Drug Delivery 2012 was held at the JW Marriott Desert Resort & Spa, Phoenix, AZ, US during May 13-17, 2012. Over 600 registrants from all over the world gathered in Arizona to review the latest science and clinical learning from a diverse cadre of presenters. Approximately 54% of the attendees were from the US and Canada, while 35% were from Europe and 8% Australia, India, China and South America. Pharmaceutical industry participants made up the bulk of the audience (38% Research & Development, 20% Sales, Marketing and Business professionals, 10% Management, and 8% Engineers, Process / Packaging, QbD) but we saw increased academic (12%) and regulatory (5%) participation in what continues to emerge as a thriving field of scientific and clinical endeavour.

Figure 1: Andy Clark (centre), recipient of the RDD 2012 Charles G. Thiel Award, pictured with Peter Byron (left), Chairman, VCU School of Pharmacy, Department of Pharmaceutics; and Charles G. Thiel himself (right).

Figure 2: Professor Ian Hall, from the University of Nottingham, UK, presenting the plenary lecture.

The organisers of the meeting and Virginia Commonwealth University (VCU) were honoured to award the 2012 "Charles G. Thiel Award", endowed at VCU by 3M Drug Delivery Systems, for outstanding research and discovery in respiratory drug delivery to Dr Andrew Clark, Site Head and Chief Technology Officer, Novartis (see Figure 1), who pioneered inhaler developments through scientific understanding and publication across disciplines (physics, chemistry, biology and medicine). Andy helped develop some of the most innovative aerosol products of the last two decades including: Pulmozyme®, the first inhaled protein; Exubera®, the first inhaled systemic protein; and TOBI® Podhaler® (tobramycin), the first inhaled dry-powder antibiotic.

Professor Ian Hall, from the University of Nottingham in the United Kingdom, presented the plenary lecture on the topic: "Genetics and Personalized Medicines in Respiratory Disease: How Good is the Evidence?" (see Figure 2). Subsequent sessions addressed advances in asthma, targeting for improved topical effects, respiratory vaccines, emerging markets for inhaled products, debating the dissolution boundaries for inhalation products and science and technology of powder inhalers. Several sessions focused on the importance of the use of inhalers by patients, the impact of adherence on outcomes and patient focused models and devices.

"To (b) or (j) - That is the Question!" was a lively session concerned with the drug approval approaches in the US. This session was audio recorded and will be available online.

As part of RDD's effort to disseminate information from around the world, the presentation by Mr Maozhong Li, Deputy Director of the Chinese SFDA, was simultaneously translated from Chinese to English with both languages included in the Proceedings.

RDD 2012 provided an excellent opportunity for scientific and commercial networking during the meeting's signature Scientific Poster

and Technology Exhibition. Companies, universities and others presented 108 scientific posters with selected contributions shared with the entire audience during Posters on the Podium. The Technology Exhibition brought together representatives of the world's pharmaceutical companies active in the pulmonary and nasal areas with their suppliers and service providers in a relaxed atmosphere.

In response to feedback from previous meetings, delegates at RDD 2012 were able to choose between receiving peer-reviewed abstracts of all podium and poster presentations either in printed or electronic form via a specially designed conference website; with WiFi access sponsored by RDD Online (Figure 3).

The organisers thank all our presenters, exhibitors and sponsors for their contribution to RDD 2012, and we look forward to meeting you all again at Respiratory Drug Delivery Europe 2013, which will take place at the Intercontinental Hotel, Berlin, Germany on May 21-24, 2013.

RDD Europe 2013 will feature sessions on Respiratory / Cardiopulmonary Disease Phenotypes and Improved Diagnostics, Drug Delivery Technologies – User-Focused Approaches, New Drugs and Drug Targets for Aerosol Treatment, Novel *In Vitro* and *In Vivo* Test Methods, and Regulatory Science and Practice in a Global Marketplace; in addition to enhanced networking opportunities during an extended Scientific Poster and Technology Exhibition session.

Figure 3: The RDD 2012 Conference Bag was packed with valuable information resources.

The poster abstract submission deadline is January 11, 2013. The full scientific program, registration information, and sponsorship opportunities are described at: www.rddonline.com/rddeurope2013.

RDD Europe 2013 will be held at the Intercontinental Hotel in Berlin, Germany, on May 21-24, 2013.

novozymes®
Rethink Tomorrow

RECOMBINANT HUMAN ALBUMIN: DELIVERING THE FUTURE OF TYPE 2 DIABETES MEDICATION

In this article, Mark Perkins, PhD, Customer Solution Manager, Novozymes Biopharma, describes the role of recombinant human albumin for extending the half-life of the anti-diabetic protein therapeutic, GLP-1. Without the use of half-life extension technology, the native protein, with a half-life of around two minutes, is not viable as a therapeutic. However, formulations incorporating albumin have significantly extended half-lives, represent promising therapeutic candidates, and are in late-stage clinical trials.

The number of people with diabetes is expected to rise to approximately 300 million by the year 2030; of this number some 90% will have the type 2, non-insulin dependent form of the disease.[1] The major goal in the treatment of type 2 diabetes is to achieve and maintain glycaemic control, since episodes of hyperglycaemia are associated with the risk of microvascular and macrovascular complications.[2] Treatment for type 2 diabetes is typically incremental, starting with the modification of diet and introduction of exercise followed by the introduction of an orally active diabetic medication.[3]

Despite the wide range of available oral medications, many patients fail to achieve appropriate glycaemic control and, in the absence of formulations and devices on the market that can deliver insulin via non-injectable routes, will ultimately require the introduction of injectable insulin.

"DESPITE THE WIDE RANGE OF AVAILABLE ORAL MEDICATIONS, MANY PATIENTS FAIL TO ACHIEVE APPROPRIATE GLYCAEMIC CONTROL AND, IN THE ABSENCE OF FORMULATIONS AND DEVICES ON THE MARKET THAT CAN DELIVER INSULIN VIA NON-INJECTABLE ROUTES, WILL ULTIMATELY REQUIRE THE INTRODUCTION OF INJECTABLE INSULIN"

A particular focus area research for the treatment of type 2 diabetes is the development of alternative and supportive therapies to oral diabetic agents that reduce the need for the introduction of insulin. In particular, analogues of the natural GLP-1 peptide have become important class of molecules in this area.[3]

GLP-1 is a 30 amino acid peptide that belongs to the incretin family. It is secreted in direct response to the ingestion of food and acts to both stimulate insulin secretion and decrease glucagon production providing an effective mechanism for glycaemic control. In addition, the peptide also acts to increase satiety and decrease gasticic emptying which in turn lead to moderate weight loss. Taken together these factors have led to

Dr Mark Perkins
Customer Solution Manager
T: +44 115 955 3355
E: mrpk@novozymes.com

Contact
Niklas Andersson
Global Communications Manager
T: +44 115 955 3355
E: NLAN@novozymes.com

Novozymes Biopharma US Inc
One Broadway, 14th Floor
Cambridge
MA 02142
United States

T: +1 617 401 2500
(US Sales Office)

T: +45 4446 2896
(EU Sales Office)

E: biopharma@novozymes.com

www.biopharma.novozymes.com

Short Acting				Long Acting			
Product	**Half-Life (h)**	**Dosing**	**Status**	**Product**	**Half-Life**	**Dosing**	**Status**
Exenatide	2.4	Twice Daily	*Approved*	Bydureon	2.4 hours	Once weekly	*Approved*
Liraglutide	Nov-15	Once Daily	*Approved*	Albiglutide	6-8 Days	Once weekly	*Phase III*
				CJC-1134	6-8 Days	Once weekly	*Phase II*

Figure 1: Summary of current and developmental GLP-1 analogues utilising human serum albumin for half-life extension.

considerable interest in using this molecule as an anti-diabetic therapeutic.[4]

A half-life of native GLP-1 is around two minutes; a significant issue when considering this molecule as a therapeutic. The short half-life of GLP-1 is caused by specific clearance by a peptidase enzyme (DPP-4) and by renal clearance due to its relatively small size. The therapeutics that have reached the market or are currently achieving success in the clinic are based on GLP-1 analogues or mimics that have been designed to overcome the issues observed for the native GLP-1 molecule.[2] These can be divided into short and long acting and a summary of these is detailed in Figure 1.

A common feature in the advances in dosing regimen made by Liraglutide (short-acting), Albiglutide and CJC-1134 (long-acting) is the utilisation of the extended plasma half-life of human serum albumin to achieve an extended therapeutic half-life. Here we discuss the application of human serum albumin as a half-life extension technology for GLP-1 therapeutics and how further developments in recombinant human albumin technology may further change the dosing paradigm.

GLP-1 HALF-LIFE EXTENSION USING HUMAN SERUM ALBUMIN

Human serum albumin is the most abundant plasma protein that has a number of interesting physicochemical properties that can be used in a pharmaceutical in context. In particular, it has been demonstrated that therapeutic candidates can be attached to the protein can take advantage of the naturally extended half-life (approximately 19 days) of this protein to avoid rapid clearance from the body.[5]

Liraglutide, the short-acting GLP-1 analogue was the first of the GLP-1 analogues to reach the market using human serum albumin as a half-life extension technology. This molecule contained a short fatty acid "tag" attached to glutamic acid at position 26 on the peptide. Once in the plasma this "tag" can reversibly associate with fatty acid binding sites on circulating human serum albumin, preventing rapid renal clearance. This peptide had a half-life of around 11-15 hours and was the first once-daily treatment using a GLP-1 peptide.[6]

The next generation of GLP-1 medicaments are targeting once weekly dosing to both improve patient compliance and efficacy of the therapy. In the context of albumin-based therapeutics this concept has been demonstrated in the clinic by both albiglutide (GlaxoSmithKline, London, UK), which is in Phase III trials, and CJC-1134 (Conjuchem, Los Angeles, CA, US), which in Phase II trials.

These products use a covalent attachment of the GLP-1 peptide to the albumin molecule and achieve significant increase in half-life compared with the in vivo association used by liraglutide. This covalent attachment of the therapeutic target is achieved by either genetic fusion or chemical conjugation of the peptide to the albumin.

GSK's albiglutide was developed in collaboration with Human Genome Sciences (Rockville, MD, US), which GSK acquired earlier this year, and uses albumin fusion technology licensed from Novozymes Biopharma (Figure 3). The process of albumin fusion involves the insertion of a contiguous piece of DNA that encodes for both the albumin and the GLP-1 peptide into a yeast-based expression system. Using this technology, a functional protein is expressed that has both the properties of albumin and the GLP-1 peptide.[4]

In contrast, Conjuchem's CJC-1134 is an engineered GLP-1 peptide, synthesised with an albumin binding group attached to a short linker molecule from the N-terminus of the peptide. This albumin binding group is then reacted with the free cysteine residue on the albumin molecule to form the conjugate.

Despite these two methods of attachment being technically very different in terms of the product design, they both achieve very similar results clinically in terms of half-life and efficacy. The decision of whether to a chose a fusion or conjugation route can be based on many different factors and both the albumin fusion and conjugates have their own benefits. For example, CJC-1134 uses a peptide containing a non-natural amino acid and would not be amenable a fusion route using the existing technology.

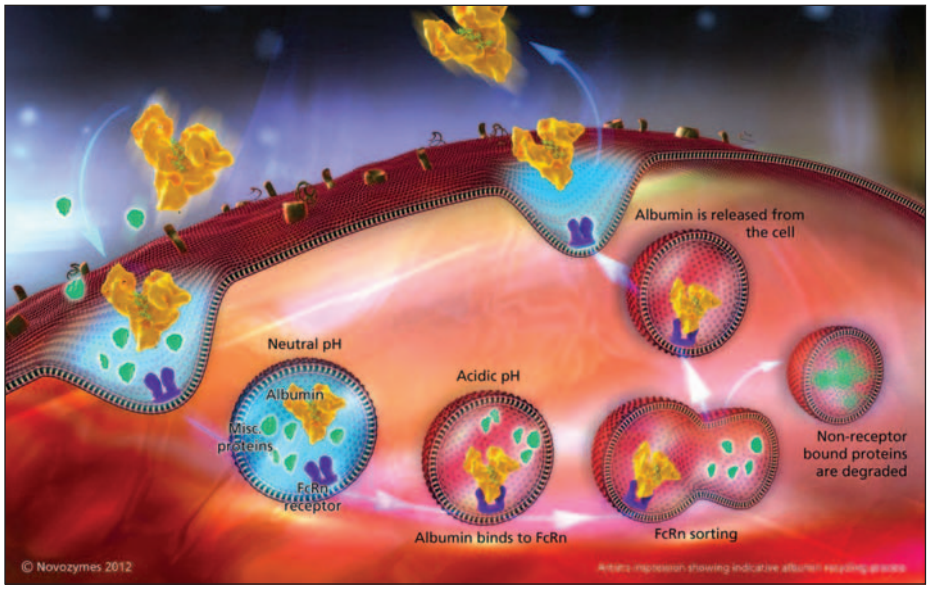


Figure 2: A schematic of the FcRn mediated albumin recycling process.

Figure 3: Novozymes' recombinant human albumin.

NEXT GENERATION OF ALBUMIN BASED ANTI-DIABETIC THERAPEUTICS

As treatment of type 2 diabetes with GLP-1 analogues and other peptide drugs develops, and the notion of longer-acting formulations becomes more accepted by both the regulatory authorities and patients, it is likely that the future goals for diabetic treatments will shift further to monthly treatments and beyond. To meet these changing market demands Novozymes Biopharma is developing the next generation of recombinant albumins for half-life extension. To understand how these molecules are designed its worth taking a look at how the half-life of albumin is regulated.

The half-life of albumin mediated in part by its size but also its pH-dependant interaction in the endosome with the FcRn receptor. A schematic of this process is illustrated in Figure 2. Plasma proteins are taken up by vascular endothelial cells through non-specific pinocytosis. As the endosome is formed and the internal pH falls, albumin binds to the FcRn receptor. The albumin that is bound to this receptor is rescued from intracellular degradation is taken back to the surface of the cell and released back into the circulation. The FcRn recycling system is saturated and as a consequence not all albumins contained within any endosome will be recycled. If the albumin lost to intracellular degradation is also one that has the therapeutic molecule attached then this will also be degraded. It was considered that an understanding of the interaction between albumin and FcRn and the impact of this process and albumins half-life may ultimately lead to the ability to design therapeutics with designed half-life.

Novozymes Biopharma, in collaboration with scientists at the University of Oslo, have identified specific regions within the structure of the albumin molecule that are important for albumin FcRn binding.[7] Subsequently, numerous albumin variants have been generated with single amino acid substitutions that display both increased and decreased binding to the FcRn receptor. A number of the variants have been tested in in animal PK studies where a correlation between FcRn binding affinity and albumin half-life has been established.

In particular, one high-affinity variant demonstrated double the half-life of native sequence human serum albumin in rodent models. Ultimately, these changes in albumin half-life will translate to the therapeutic target and allow the drug development scientist to control the half-life of a target protein. In the context of GLP-1 peptides this technology could allow the shift from weekly, to every two weeks, to monthly dosing. To maintain the full flexibility of the application of this technology Novozymes has applied its extensive experience in recombinant albumin manufacture to ensure this technology is available to albumin fusion and conjugation applications.

SUMMARY

GLP-1 analogues have become an important class of therapeutics in the treatment of type 2 diabetes, offering an alternative therapy where oral diabetic medications have failed. A major factor in the translation of this peptide from an un-druggable natural peptide to successful therapeutics is the application of human serum albumin as a carrier molecule. In particular, the development and expected launch of albiglutide, the first commercial albumin fusion therapeutic will only further enhance the growing pedigree of this technology. The success with GLP-1 is likely to lead to the technology being applied with other therapeutic candidates in the anti-diabetic field.

To ensure that albumin half-life extension technology continues to meet the demands of innovative drug design, Novozymes has developed the next generation of albumin half-life extension technology. These albumin "variants" will open the door to longer dosing regimens for peptides such as GLP-1.

REFERENCES

1. *Verspohl VJ, "Novel pharmacological approaches to the treatment of type 2 diabetes". Pharmacol Rev, 2012, Vol 64, pp 188-237.*
2. *Bush M, Matthews JE, De Boever EH, Dobbins, RL, Hodge RJ, Walker SE, Holland MC, Gutierrez M, Stewart MW, "Safety, tolerability, pharmacodynamics and pharmacokinetics of albiglutide, a long acting glucagon-like peptide 1 mimetic, in healthy subjects". Diabetes, Obesity and Metabolism, 2009, Vol 11, pp 498-505.*
3. *Efendic S, Alvarsson M, Brismar K, Wagner H, "Pathophysiology and treatment of patients with type 2 diabetes exhibiting failure to oral drugs". Acta Physiologica, 2008, Vol 192, pp 117-125.*
4. *Baggio LL, Huang Q, Brown TJ, Drucker DJ, "A recombinant glucagon-like peptide (GLP)-1-albumin protein (Albugon) mimics peptidergic activation of GLP-1 receptor dependent pathways coupled with satiety, gastro-intestinal motility and glucose homeostasis". Diabetes, 2004, Vol 53, pp 2492- 2500.*
5. *Chuang VT, Kragh-Hansen U, Otagiri M, "Pharmaceutical strategies utilising human serum albumin". Pharm Res, 2002, Vol 19, pp 569-577.*
6. *Knudsen LB, "Liraglutide: The therapeutic promise from animal models". Int J Clin Practice (Supplement), 2010, Vol 167, pp 4-11.*
7. *Terge Andersen, J, Dalhus B, Cameron J, Bekele Daba M, Plumridge A, Evans L, O'Brennan S, Stoen Gunnarsen K, Bjoras M, Sleep D, Sandlie I, "Structure-based mutagenesis reveals the albumin-binding site of the neonatal Fc receptor". Nature Communications, 2012, Vol 3, p 610.*

Overlooked something?

Remember when it comes to reducing drug dosing frequency, the natural choice is albumin.

Extend the half-life of your drug from "days to weeks" using the only technology based on albumin, a natural non-immunogenic plasma protein with a proven and safe regulatory profile.

Differentiate your drug with Novozymes' Albufuse® Flex and Novozymes' Recombumin® Flex - a broadly applicable and easily assessed platform with patent life beyond 2030.

Designed by Nature. Improved by Novozymes.

www.daystoweeks.com

novozymes®
Rethink Tomorrow

Aptar pharma

www.aptar.com/pharma

APTAR PHARMA IS YOUR GLOBAL SOLUTION PROVIDER FOR INNOVATIVE AND PROVEN AEROSOL, SPRAY AND DISPENSING SYSTEMS.

Our products and services add value to your products in the fields of biotechnology, healthcare and pharmaceuticals.

Aptar Pharma has two divisions: Prescription and Consumer Health Care.

Delivering solutions, shaping the future.