CROS & CMOS OFFERING DRUG DELIVERY SOLUTIONS

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"CROs & CMOs Offering Drug Delivery Services & Solutions"

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EVOLVING INDUSTRY NEEDS REQUIRE EVOLVING PARTNERS: WELCOME THE SOLUTION PROVIDER *VERSUS* THE CMO

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In this article, Steven Hamlen, Group Product Manager, Modified Release Technologies and Rao Tatapudy, PhD, Vice-President, Scientific Affairs, R&D, both of Catalent Pharma Solutions, and Thorsten Schmeller, PhD, Head of Global Marketing, New Products, Pharmaceutical Ingredients & Services in the Nutrition & Health Division of BASF (Ludwigshaven, Germany), discuss how companies that previously followed the traditional CMO model are increasingly moving toward becoming solution providers. They describe the drivers that have led to this innovation, as well as how solution providers have integrated technologies and innovative business partnerships into efficient solution offerings in place of historic sole contract manufacturing. A case study of this evolution to a total solution provider business model is discussed in relation to solubility enhancement, resulting in better treatments for patients and increased efficiency, as well as differentiated products for the pharmaceutical industry.

DRIVERS OF EVOLUTION TO SOLUTION PROVIDERS FROM CMOS – MARKET DYNAMICS

Contract manufacturing organisations have experienced a good deal of success in recent years. However, a pure CMO model is no longer effective in solving many of the pharmaceutical industry's challenges, and successful companies have evolved into solution providers.

> "A PURE CMO MODEL IS NO LONGER EFFECTIVE IN SOLVING MANY OF THE PHARMACEUTICAL INDUSTRY'S CHALLENGES, AND SUCCESSFUL COMPANIES HAVE EVOLVED INTO SOLUTION PROVIDERS"

Two key factors are driving increased focus in solution provider business models. First, the introduction of innovative medicines has slowed in the branded pharmaceutical industry over the past decade, leading to significant generic erosion and pressure on innovator company revenues and profit margins. At the same time, the level of competition has increased. Companies of all sizes are under pressure to differentiate their products – not only to convince regulators and clinicians of a drug's superiority, but also to ensure that payers are willing to reimburse.

These market dynamics are driving companies to strive to achieve improved therapeutic profiles earlier in development in order to maximise their return on investments. In many cases, the use of full solutions providers can assist them in achieving this goal.

SOLUBILITY ENHANCEMENT: A CASE STUDY IN MEETING CUSTOMER NEEDS

One challenge where this is very evident is in the need to optimise the bioavailabilty of compounds, with respect to solubility enhancement. Estimates have varied over the years, but at least 40%,[1] and as many as 70%,[2] of new chemical entities are considered poorly soluble in water, leading to low bioavailability, high intra- and inter-patient response variability, and variable dose proportionality. When BCS Class II (high permeability, low solubility) and BCS Class IV (low permeability, low solubility) are combined, the percentage of poorly soluble NCEs is approximately 90%.[2] Amongst approved drugs, 30% are considered poorly soluble. Comparing the percentage for drugs in development with that for approved drugs shows a clear trend towards the development of an increasing number of molecules with poor solubility.

BCS Classification of new molecular entities in development is shown in Figure 1.[3]

The number of molecules on market that might benefit from further differentiation is significant. Moreover, the number of compounds in development that become shelved or are launched with suboptimal product profiles as a result of low solubility represents a very large lost opportunity for pharmaceutical industry investment.

SOLUBILITY ENHANCEMENT IS MULTI-FACTORIAL - UNDERSTANDING THE FACTORS:

Solubility, and thus bioavailability, can be enhanced in four main ways:

1. Optimising the API form itself
2. Optimising the Formulation
3. Optimising the Processing
4. Optimising the Dose Delivery

On many occasions, optimising solubility requires iterations across the above four factors.

Catalent has recently invested, both internally and in the form of alliances, to deliver a complete solution across these parameters, without clients having to deal with time- and resource-constraining discussions across multiple companies or teams.

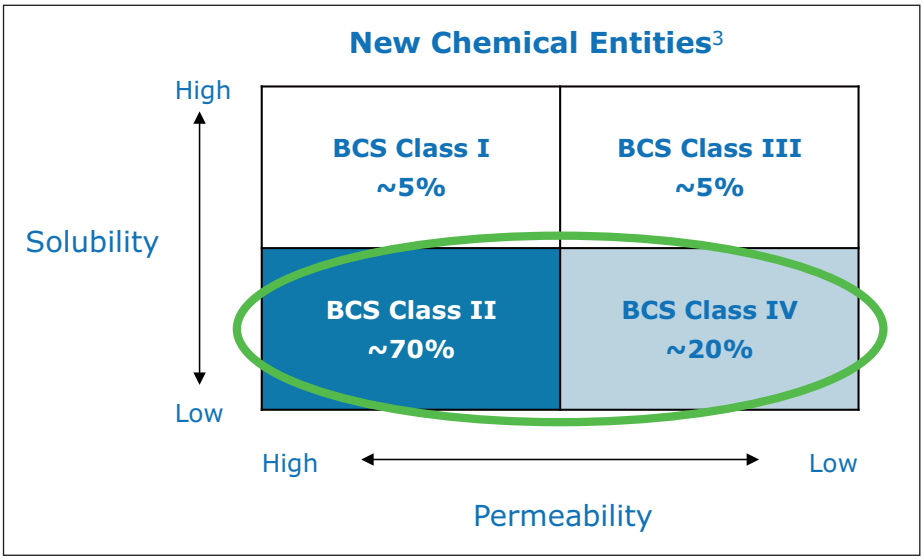

Figure 1: Molecules in Development BCS Classification.

THE EVOLVED SOLUTION MODEL

As a complete solution model solving bioavailability, Catalent expanded its reach in both technology offerings and scientific expertise to provide clients with a single, integrated partner. Following are the innovative building blocks that Catalent offers to address the four main factors mentioned above and best meet the needs of the pharmaceutical industry customers.

1. Optimising the API itself

Catalent offers OptiForm® salt screening to optimise molecule form selection and maximise solubility potential. Additional clinical, analytical, supplies, and packaging services expedite trials.

2. Optimising formulation

Catalent has expert formulation scientists who have helped bring molecules from lab to market for 90 of the top 100 pharmaceutical companies, 44 of the top 50 biotech firms, and hundreds of smaller innovators. Catalent offers RP Scherer Softgel and OptiShell™, a non-bovine based capsule, both of which are optimal for lipid formulations.

3. Optimising the process

For solid dispersions, RP Scherer is the industry leader, with 75 years of experience addressing solubility issues. Understanding that hot melt extrusion is an additional solution for solid dispersions for certain molecules, Catalent has expanded to offer OptiMelt™ hot melt extrusion pilot, lab, and commercial capabilities in a global footprint.

COMBINING WORLD-LEADING TECHNICAL EXPERTISE

For a complete solution offering for solubility enhancement, Catalent needed to offer raw ingredient solubilisers and excipients. However, this was a missing component. Therefore, in April 2012, realising a mutual combined benefit to customers for solving the same need, BASF and Catalent entered into an innovative open alliance to fill this gap.

The fact that the companies entered into an open alliance means that they collaborate in cases where it serves their customers best, but would liaise with someone else with a more tailored offering for a specific customer need or at a customer request. The main rationale for this open alliance can be summarised as follows:

- Provides customers with a unique range of seamless solutions
- Complementary offerings to enhance solubility and permeability
- A full solution for development - from molecule to market

"IN APRIL 2012, REALISING A MUTUAL COMBINED BENEFIT TO CUSTOMERS FOR SOLVING THE SAME NEED, BASF AND CATALENT ENTERED INTO AN INNOVATIVE OPEN ALLIANCE"

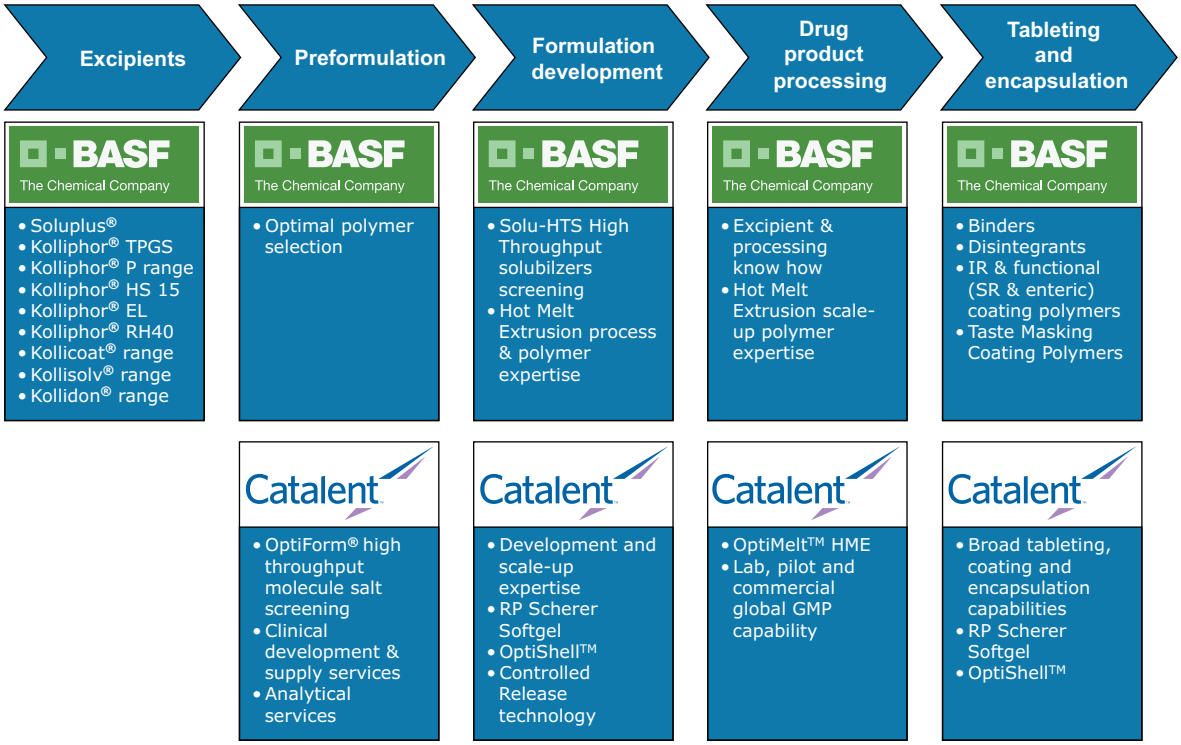

Figure 2: BASF-Catalent Open Bioavailability Alliance – Combined Solubility Solutions.

The combined solubility enhancement capabilities from the BASF-Catalent open alliance are shown in Figure 2.

4. Optimising the Dose Delivery Form

Selection of the appropriate dose delivery form provides a variety of options to enhance bioavailability and solubility. Catalent has offered RP Scherer Softgel and the most advanced controlled release capabilities to the market for decades, including a complete range of granulation, tablet, capsule, bead and also coating options. Wurster fluid bed technology is also available in both the US and Europe to produce desired release profiles.

Catalent has also launched OSDRC® OptiDose™ optimised dosing technology to advance innovation in controlled release. This novel delivery technology enables the design of single or multi-core tablets, with a variety of core numbers, shapes, sizes and placement within the tablet, offering the broadest range of controlled release designs for drug formulators in a one-step, solvent-free manufacturing process.

The flexibility of OSDRC® OptiDose™ controlled release formulations is able to improve therapeutic profiles to meet a variety of patient needs, including:

- Control API plasma release profiles
- Improve target delivery
- Optimise patient dosing
- Enhance patient convenience

A final offering that Catalent includes in its comprehensive bioavailability solution technologies is its Zydis® platform, including Zydis® ODT (orally disintegrating tablets), Zydis® stick packs, and Zydis® nano. For some APIs, an ODT can be absorbed buccally (through the oral mucosa) and lead to increased bioavailability and/or improved safety profiles by greatly avoiding first-pass metabolite formation.

This was the case when Catalent partnered with Valeant Pharmaceuticals (Montreal, Canada) to develop Zelapar®, a formulation of selegiline for Parkinson's Disease, using Zydis® ODT. The improved therapeutic profile of the Zydis® ODT formulation is shown in Figure 3.

An additional benefit from the improved product profile achieved by using Zydis® ODT to formulate Zelapar®, beyond increased bioavailability and improved safety profile, was a significant increase in patient medication compliance. This was demonstrated in a longitudinal one-year, blinded, patient-record-analysis study, which compared the compliance rates for the standard pill and Zelapar®. In US Medicare patients, a compliance rate of 98.5% was achieved with Zelapar®, compared with 81% with the standard oral tablet. This data, and data from other cohorts, is shown in Figure 4.

CONCLUSION

The global pharmaceutical industry has faced unprecedented challenges, because of a reduced number of innovative drugs, increased competition, and heightened pressures from regulators and payers. These dynamics have increased the need to maximise product differentiation not only as part of lifecycle manage-

	Selegiline (traditional tablet/capsule)	**Zelapar** (Zydis ODT formulation)
Lower Dose and Less Frequent Dosing	5-mg doses, taken twice a day (BID). Pill or capsule that must be swallowed.	1.25-mg or 2.5-mg doses, taken once a day (QD). Tablet that dissolves in mouth within seconds, without water.
Increased Bioavailability/ Faster Onset of Action	T_{max} = 1 hour. Digested in the gut, absorbed through the small intestine, processed by the liver.	T_{max}=15 minutes. Innovative transmucosal drug delivery absorbed rapidly through the lining of the mouth directly into the blood.
Lower Side Effect Potential	Processed through the liver, producing undesired metabolites.	Significantly bypasses the liver, producing lower undesired metabolites.

Figure 3: Therapeutic profile of standard selegiline table compared with Zelapar® formulated with Zydis® ODT.

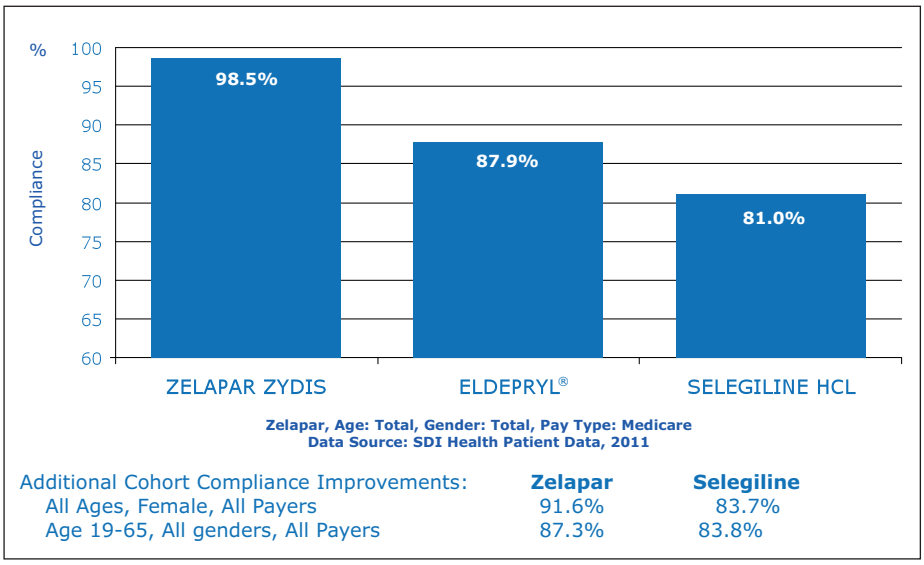

Figure 4: Zelapar® formulated using Zydis® ODT technology shows improvement in patient compliance compared with standard selegiline tablet.

ment strategies, but early in the development process as well. This has led to the need for CMOs to adapt and modify both their technology offerings and their business models. The historic model of a pure CMO is not viable if the evolved needs of the pharmaceutical industry are to be met. True solution providers will be required in the future to help solve the current challenges facing our industry.

Catalent has already adapted to these changing industry needs by understanding that solubility plus equipment is not the answer. A true partnership with expert scientists able to bridge the integrated complexities from molecule to market with the best technologies and partnerships is the way of the future to deliver better treatments to our customers and – most importantly – to the patients who will ultimately benefit.

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DEVELOPMENT AND BIOEQUIVALENCE TESTING FOR INHALED THERAPEUTICS

Here, Stephen Dodds, Manager, Regulatory Affairs, Wesley Hicks, PhD, Senior Medical Director, Global Product Development, and Bill Schachtner, Associate Director, cGMP Labs, all of PPD, describe the regulatory requirements for bioequivalence testing of inhalables, and explain why it is important to select a service provider with capabilities across the board in this regard.

With most orally inhaled products delivering only 10-30% of a drug to the lungs, coupled with the complexity of developing delivery systems for inhaled products,[1,2] we need to remind ourselves why this seemingly inefficient route of delivery remains an attractive clinical proposition.

- For respiratory indications, inhalation of the drug may be the only route of administration to achieve sufficiently high levels of the drug at the site of the disease. For drugs whose mechanism of action is targeted within the lung, the ability to deliver drugs topically allows for a dramatic reduction in systemic exposure and associated systemic adverse events.
- For other therapeutic indications, the large surface area of the lungs provides rapid and greater absorption of a drug into the systemic circulation, especially when the drug is delivered deep into the lung, potentially providing rapid symptom relief.
- For patients who are afraid of injections, this method of delivery may provide an effective and easy-to-use alternative.
- Inhalation may even offer the most effective method of achieving good absorption of many protein and peptide therapeutics because they are less likely to undergo degradation in the lung.[3]

In addition to these clinical benefits, innovator companies also may gain a degree of product protection through patents and data exclusivity associated with the inhaled formulations and unique delivery device itself.

> "FOR INHALED PRODUCTS, EQUIVALENCY OF THE DELIVERED DOSE THROUGH DOSE CONTENT UNIFORMITY TESTING AND THE POTENTIAL LUNG DEPOSITION … ARE CRITICAL COMPARISON PARAMETERS"

In developing generics for inhaled formulations and devices, there can be challenges demonstrating equivalence. Different formulations and device technologies can have a significant impact on the lung deposition characteristics of the drug and potentially on efficacy.

IN VITRO TESTING OVERVIEW

US Center for Drug Evaluation and Research (CDER) [4,5] and European Medicines Agency (EMA)[6] guidances outline the testing that is involved for the comparative testing of generic inhalers to reference products. Even though the guidances are for specific products or drafts, the evaluation criteria still are considered appropriate today. For inhaled products, equivalency of the delivered dose through dose content uniformity testing and the potential lung deposition—measured via particle size distribution by inertial impaction testing—are critical compari-

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Manager, Regulatory Affairs

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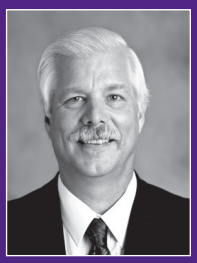

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son parameters. Additionally, for DPIs, when comparing devices for aerosol performance, additional testing should be performed under various flow rates and pressure drops, mimicking expected differing patient inhalation ranges.

In addition, for pMDI products, spray pattern and plume geometry testing is performed as well to characterise the performance of the valve and actuator combination to demonstrate equivalence of the spray between the generic and reference products.

All of the comparative testing needs to be performed on each strength of product being considered as the performance of each product can be influenced by changes in drug substance and excipient concentration changes or mass of formulation delivered.

Figure 1: Delivery systems used in the adult programme may not be suitable for younger children and reformulation may be required.

DEVICE PERFORMANCE

For inhaled products, not only should the drug product ingredients be formulated within 5% of the reference article, *in vitro* equivalency only can be achieved if there is equivalency between the devices for aerosol delivery performance. Therefore it is imperative that the generic (test) article matches the delivery system of the reference article as closely as possible. For pMDI products, selecting commercially available valves for equivalency of the valve delivered volume and equivalency of the actuator delivery system with regards to spray pattern and plume geometry in the early product development stages is critical.

For DPIs, the device selection is extremely challenging when considering both the *in vitro* equivalency requirements, and taking into account the patient interface. It must be remembered that product/device equivalency is the goal. Improved device performance for any measured parameter will not show equivalency and will not meet with regulatory approval.

MATERIAL SUPPLY, RESERVES AND SAMPLING REQUIREMENTS

The CDER guidance,[7] coupled with the aforementioned inhaler guidance, directs all material requirements and handling for the sampling and reserve storage requirements for all bioequivalence testing. All samples for *in vitro* testing and retained storage should be sent to the testing facility as a single shipment. The testing laboratory should randomly select the *in vitro* and reserve samples from the shipment, thus ensuring that the reserve samples are representative of the samples tested. Ten units per lot from three lots each of generic and reference material should be tested for bioequivalence.

It is recommended that the quantity of reserve samples of both the test and reference materials should be sufficient to perform release testing five times. For inhalation products, the number of reserve samples for release testing can be quite large, so the US FDA allows that at least 50 units per batch be retained. This recommendation applies to products that deliver 30 or more doses per unit. The reserve samples must be retained at the study site for five years.

BLINDING AND TESTING DESIGN

For *in vitro* testing, the identity and lot number of the samples tested should be blinded from the analytical testing personnel. Overlabelling of product to obscure the product name and lot number should be performed. Additionally, full randomisation of the testing—not only by test and reference article, but also by lot number—is recommended and adds further confidence that the *in vitro* data is an accurate representation of each product. Often test *versus* reference devices are visually different. Therefore, it is recommended that one analyst should perform the sample collection while a second analyst should process the data. This is particularly important for analytical methods requiring subjective analysis of the data such as manual processing of plume geometry. Manual integration of chromatograms for *in vitro* testing should be avoided.

CLINICAL DEVELOPMENT CONSIDERATIONS FOR INHALED PRODUCTS

A low systemic exposure with inhaled drugs provides clinical benefit, but also can cause development challenges. Defining the pharmacology *in vivo* is difficult if bioanalytical assays are not sensitive enough to detect low concentrations of parent compounds or key metabolites. In early pharmacological studies, administering higher exposure may be achieved with higher-strength formulations or by delivering multiple inhalations, although increasing the number of inhalations may increase variability in the dataset. Exquisitely potent molecules may have clinical dose ranges so low—especially if lower doses are required for children—that they are impossible to manufacture on a commercial scale.

Companies with little experience in developing inhaled products need to be aware of unique studies in the development plan. For example, charcoal block studies will be required for new active substances, while device handling studies will be required for new devices whether or not the drug is a known or a new active substance.

BIOEQUIVALENCE *IN VIVO* IN THE DEVELOPMENT PROGRAMME

Clinical bioequivalence can be split into two approaches: 1) lung deposition as determined by pharmacokinetics (PK) or imaging studies; or 2) therapeutic equivalence evaluating a pharmacodynamics (PD) outcome measure.

PK is the most common way to determine lung deposition and has the advantage of being relatively easy to conduct with conventional endpoints and avoids exposure to radiation. The validated bioanalytical methods required for PK analysis must be highly selective and ultra sensitive using state-of-the-art instrumentation to provide reliable results. PK's major limitation is that it lacks detail regarding the distribution of the drug within the airways (central *versus* peripheral), a detail that is important since receptor distribution is not uniform throughout the lung. Imaging studies provide this detail, but

are challenging to conduct and interpret. Their greatest limitation is that they are not widely accepted as validated, and tend to be regarded as supportive rather than definitive.

For the development of generic compounds against a reference product, care should be taken to maximise the quality of the *in vitro* and lung deposition data because it can reduce or obviate the need to demonstrate therapeutic equivalence. Reducing the volume of PD studies will have a major impact on programme timelines and cost. Clinical studies for therapeutic equivalence will vary depending on the class of compound. Inhaled beta-agonists can demonstrate therapeutic equivalence on both safety and efficacy parameters against a reference product with a relatively small and short crossover study. Inhaled corticosteroids are more challenging due to the shallow dose-response relationship. A study powered for non-inferiority on routine clinical outcomes will be slow and costly.

The need to demonstrate bioequivalence for new active substances is also relevant. As longer-term stability data become available and commercial upscaling of the manufacturing process is undertaken, reformulation with different blends of excipients may be required. Additionally, if adverse effects such as cough or pharyngitis are reported in significant numbers of patients in early development, reformulation may be required with an alternate salt. Demonstration of equivalent *in vitro* and lung deposition data between formulations may allow bridging to the existing clinical data package rather than repeating studies at considerable cost and time.

If spacers are intended for use with a pMDI, additional bioequivalence studies are required.

HEALTHY VOLUNTEER *VERSUS* PATIENT STUDIES

Early studies with inhaled compounds are normally undertaken in healthy volunteers rather than patients with underlying respiratory disease. Patients with airway hyperactivity may be at greater risk of life-threatening bronchospasm if exposed to a novel entity or formulation. In addition, patients with moderate or severe airflow obstruction may show lower systemic exposure through reduced lung deposition.[8] In small PK studies, even patients with mild airflow obstruction may introduce additional variability into the data and affect the precision of estimates. This becomes more challenging in repeat-dose patient studies due to the day-to-day variability in lung function even in patients with relatively well-controlled asthma. Selection of a healthy volunteer or patient population will depend on the objectives of the study.

"IT IS IMPORTANT FOR PHARMACEUTICAL AND BIOTECHNOLOGY COMPANIES TO SEEK OUT AND WORK WITH SERVICE PROVIDERS THAT CAN ADDRESS ALL ASPECTS OF DRUG DISCOVERY, DEVELOPMENT AND LIFECYCLE MANAGEMENT SERVICES"

PAEDIATRIC CONSIDERATIONS

Delivery systems used in the adult programme may not be suitable for younger children and reformulation may be required (Figure 1).[9] For drugs absorbed from the lungs, modeling systemic exposure in children based on adult data is challenging and can theoretically exceed the maximum exposures that have been evaluated in adults. Modelling does not typically allow for differences in the paediatric oropharynx, breathing patterns and reduced inhalation efficiency.

LOOKING AHEAD

Orally inhaled products should continue to remain an attractive clinical proposition. Although a potentially lucrative market, different formulations and device technologies can have a significant impact on the lung deposition characteristics of the drug and potentially on efficacy. At the same time, establishing bioequivalency of an inhaled therapeutic can be a challenging proposition. For example, the number of inhaled drugs targeting phosphodiesterase type 4 (PDE4) pathways currently in development may be a reflection of the number of systemic PDE4 inhibitors that have failed in development due to systemic toxicity and tolerability issues over recent decades

There is no one-size-fits-all programme. *In vitro* equivalence may not predict PK equivalence, and non-equivalent PK might not translate into PD differences. Programmes are designed individually based on regional regulatory requirements, the class of compound under evaluation, and other clinical and pharmaceutical considerations. Companies need to be able to adapt as bioequivalence data in the programme evolves, and they must be able to incorporate additional *in vitro* or *in vivo* studies depending on the strength of the data package and agency feedback.

That's why it is important for pharmaceutical and biotechnology companies to seek out and work with service providers that can address all aspects of drug discovery, development and lifecycle management services. Doing so will help them accelerate the delivery of safe and effective therapeutics like orally inhaled products, and maximise the returns on their R&D investments.

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SPECIAL CRO SERVICES GENERATED THROUGH R&D OF PROPRIETARY NASAL DELIVERY SYSTEM

In this article, Shunji Haruta, PhD, Executive Officer, SNBL Ltd and General Manager, NDS Division, describes how the history of SNBL – Japan's first CRO – has provided the company with the particular know-how and experience to offer world-class contract research services for nasal drug delivery.

As the pharmaceutical industry continues transforming the drug development business model to reduce costs and improve performance, there is an opportunity for contract research businesses to face these challenges as partners with pharmaceutical companies.

Particularly for a preclinical CRO there is value in offering specialised assessments or study models that can aid in early decision making, and/or provide early proof of concept for a drug product, in addition to offering the normal battery of GLP safety and toxicology studies.

SNBL, a full-service CRO, offers specialised contract services which have been generated and complimented by the experience acquired through development of SNBL's own novel nasal drug delivery system (μco™ System).

HISTORY: CRO BUSINESS AND SPECIALISED DRUG DELIVERY TECHNOLOGY DEVELOPMENT

Shin Nippon Biomedical Laboratories, Ltd (SNBL) was founded in 1957 as the first contract research organisation (CRO) in Japan. Since then, SNBL has developed a solid business foundation in preclinical research operation and subsequently has become a global CRO providing a full range of drug development services including pharmacokinetic analyses, clinical studies and site management services.

Fifteen years ago SNBL Group established a new business unit to research and develop nasal drug delivery technologies (part of the growing translational research activities at the time). Traditionally, dogs have been the accepted model for non-rodent PK studies for nasal drug delivery technologies. However, nasal drug PK studies in dog models routinely show poor correlation with that of humans. This is easily attributed to significant differences in nasal anatomy and physiology between dogs and humans.

The nasal anatomy and physiology of NHPs, on the other hand, are very similar to those of humans. Having made this observation, SNBL recognised that its extensive expertise with NHPs accumulated by SNBL's CRO business would be advantageous in the research and development of nasal drug delivery technologies.

After determining to move forward with the development of a nasal drug delivery technology and drug products utilising said technology, SNBL established many capabilities specific to the development and evaluation of nasal delivery. Validated by development of SNBL's own nasal products, these useful evaluation/development capabilities are now offered to pharmaceutical companies as contract services.

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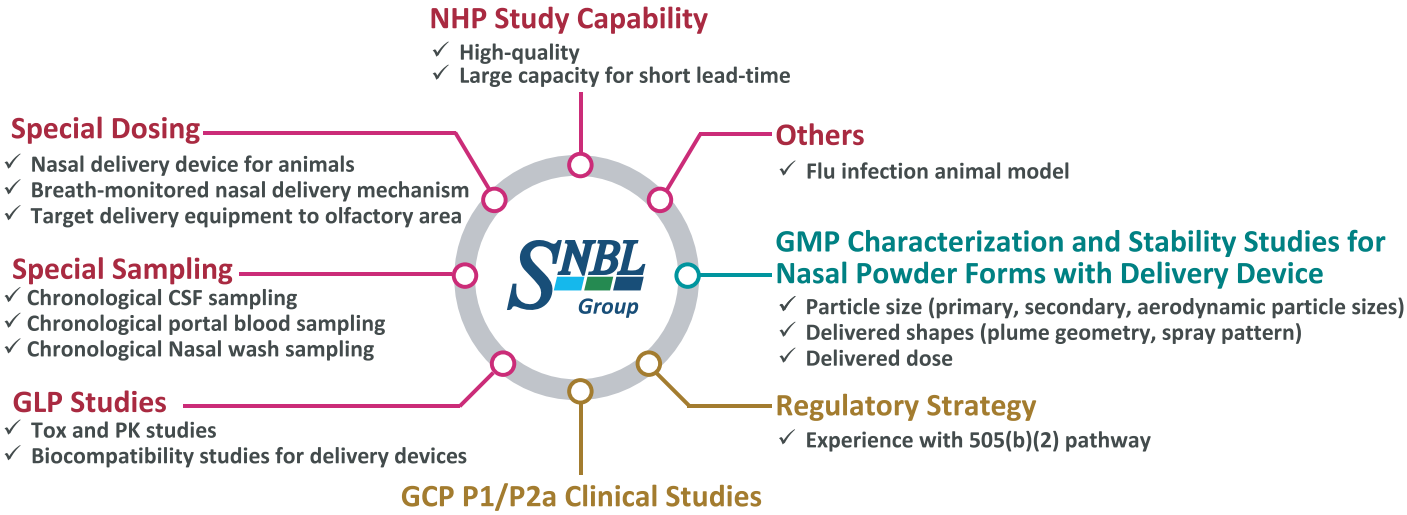

Figure 1: Nasal Drug Delivery Technologies and Know-How Generated through R&D of the µco™ System.

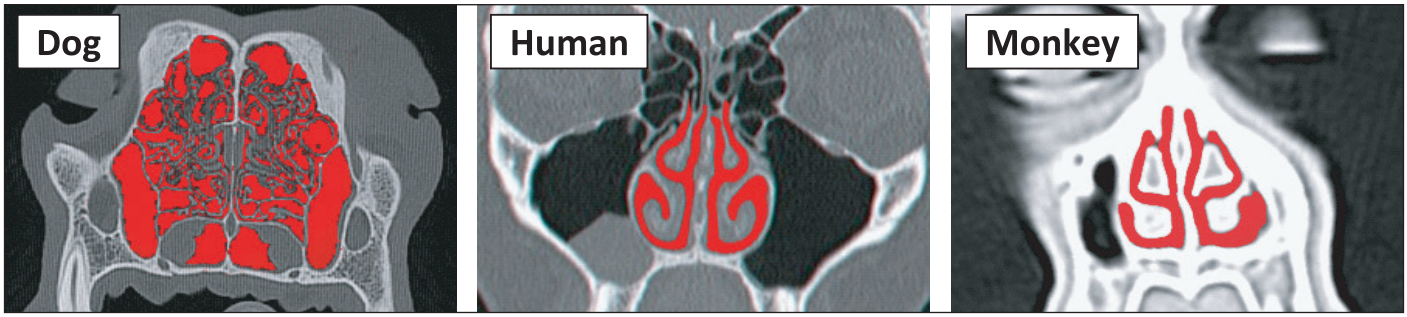

Figure 2: Anatomy of the Dogs, Human and Monkey Nasal Cavities.

SPECIALISED SERVICES FOR NASAL DRUG PRODUCTS

Our NDS Division has developed the following testing services for nasal drug delivery evaluation (see Figure 1).

Predictive NHP PK model

As with any drug product, it is of paramount importance that pharmacokinetics (PK) and pharmacodynamics (PD) are estimated accurately in an early stage of development and species selection for predictive PK/PD data is crucial. As previously noted, the industry norm has long perpetuated rats and dogs as the standard for nasal drug delivery studies, only to have the compounds fall short after reaching the expensive milestone of Phase I data. This shortcoming can be attributed to the lack of physiological similarities in the nasal cavity between humans and rats and/or dogs. The importance in the parameters of comparison for the human nasal cavity cannot be overemphasised when determining why Phase I results have so often been lacklustre.

First, the nasal surface area per kg of weight is vastly different; dogs have massive surface area allowing incredibly high absorption which is not seen in humans (Figure 2). Second is the rate of mucocilliary clearance; rats and dogs provide a mucocilliary clearance distinct to that of humans which cannot provide accurate predictive results.

In contrast, NHPs provide excellent similarities in these respects; nasal cavity structure is similar, the ratio of surface area to body mass is close to that of humans, and they model a close mucocilliary clearance. Thus NHPs are truly the best predictive species to evaluate nasal delivery.

Structural and physiological similarities are not enough for a predictive model though, especially when dealing with NHPs. The use of unanaesthetised animals, with minimal stress during dosing, is also an important factor as this minimises any spurious signal. SNBL provides such testing.

The ability to offer these studies is due to proprietary procedure cages, decades of excellence in NHP handling, and a specially designed nasal delivery device specifically for delivery to animals. Designed, engineered and validated all in-house at SNBL, this device is a breath-monitored nasal delivery mechanism for use in both systemic and local delivery. The nasal administration mechanism monitors the breathing cycle of the animal and automatically synchronises

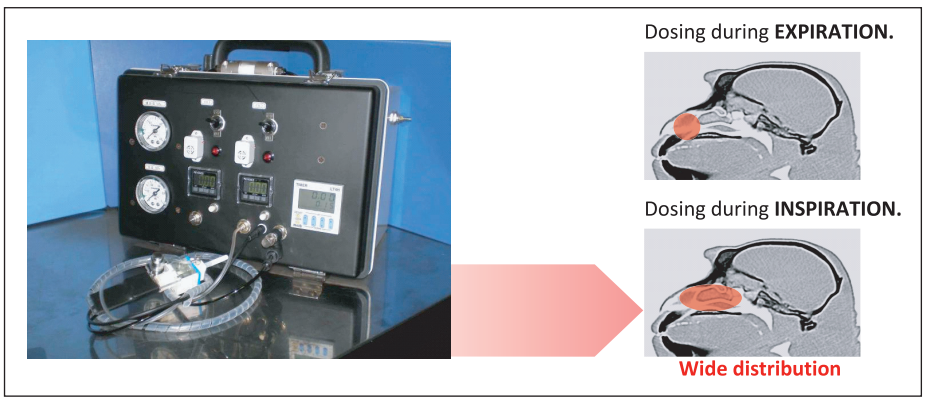

Figure 3: Breath-Monitored Nasal Delivery Mechanism.

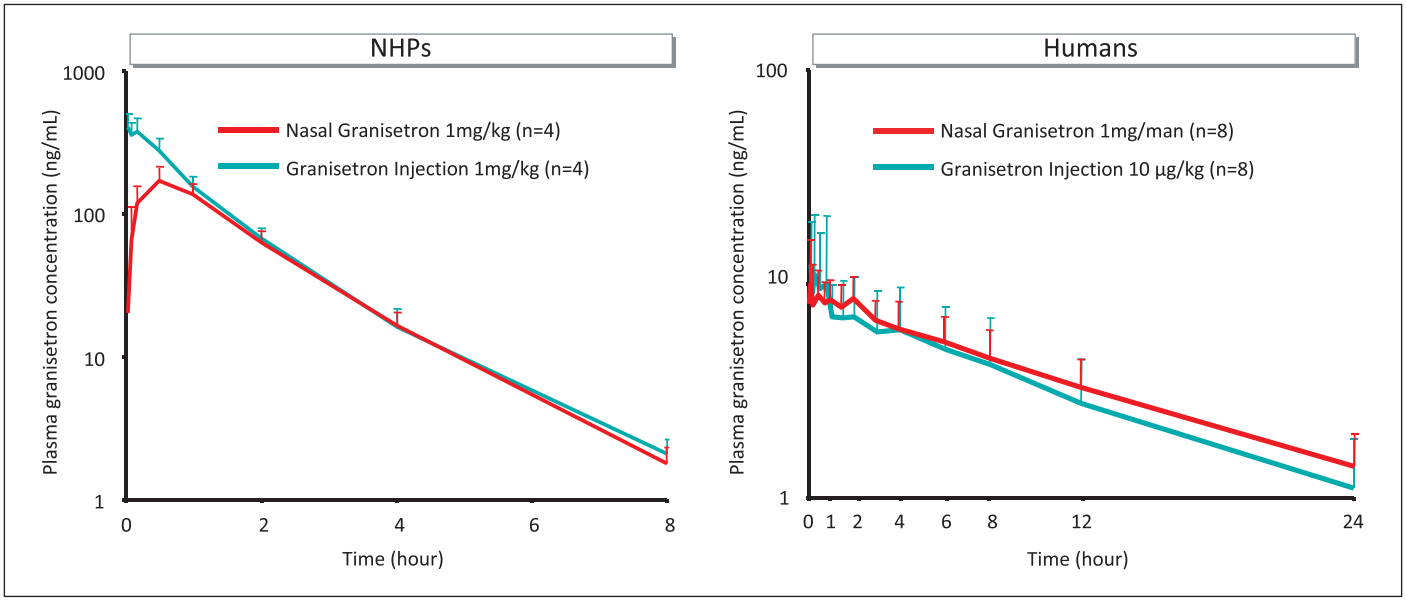

Figure 4: Plasma Granisetron Concentration – Time Profiles of Nasal Granisetron Delivered Using µco™ System in Humans and NHPs.

the administration with the inhalation phase. Not only does this ensure that the drug is making it fully into the nasal cavity, but it also closely mimics administration in humans (Figure 3).

As a result, SNBL has achieved robust reproducibility to the extent that three animals per dose is often sufficient to generate statistically predictive results. SNBL utilised this model for the development of a nasal granisetron product. As shown in Figure 4, the PK profile shown in this model accurately estimated the clinical PK profile.

In addition to this unique nasal delivery service, SNBL also offers target dosing to the olfactory area using specialised equipment for companies looking to measure the effects of nose-to-brain delivery.

It is important to note that SNBL has experience with nasal delivery in dogs, rats, mice and ferrets. Nasal delivery in such models is offered because certain efficacy studies require specific species for dosing (other than NHPs), and SNBL recognises the need for companies to compare nasal dosing in other species with already existing background data.

Sampling

Along with the typical battery of sampling offered by CRO's worldwide, SNBL has developed specialised sampling methods for CSF, including a method for the chronological sampling of CSF in unanaesthetised NHPs. For the most valuable and physiological relevant results in CSF sampling, unanesthetised animals are crucial and, as previously stated, SNBL specialises in such requirements. Lastly, for nasal vaccine analysis, chronological sampling of nasal wash for evaluation of nasal mucosal antibody production is available.

Delivery Characterisation Studies

For two nasal compounds taken into clinical trials, SNBL conducted CMC work including delivery characterisation studies. Having conducted these studies in-house, SNBL owns and has experience and know-how with special equipment for device pump actuating and a cascade impactor for nasal delivery; both secondary and aerodynamic particle size can be measured. For delivery shape studies, SNBL can measure both plume geometry and spray pattern using special equipment and the aforementioned device pump actuator. Lastly, delivered dose is able to be measured using the device pump actuator and a trap bag.

***In vitro* evaluation**

As pharmaceutical companies continue to seek cost savings at the earliest stages of development, SNBL has recognised this need and has established an *in vitro* drug permeability test system using a human cell line monolayer, which promises to be a useful tool in the prediction of nasal drug absorption *in vivo*. This cost-effective, high-throughput system is able to provide information about optimal formulation design to achieve higher absorption while minimising cytotoxicity. Furthermore, this system reveals the molecular mechanisms of drug absorption; that is, the effect of cellular tight-junctions and mucus barriers, and the involvement of a specific absorption or excretion transporters.

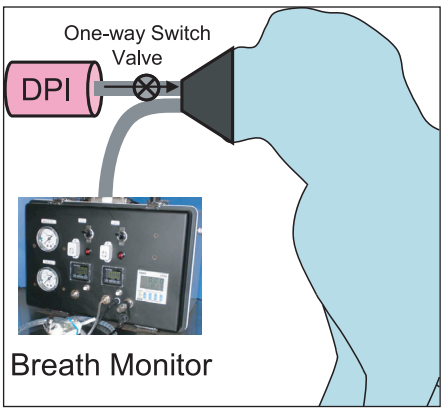

Figure 5: Breath-Monitored Oral Inhalation System.

Regulatory Consulting

Having successfully taken two novel nasal delivery device/drug combination products through IND and into clinical trials in the US, SNBL has acquired regulatory know-how for nasal drug products. Recognising the incredible value of this knowledge and its benefits, SNBL can offer this acquired insight and experience to help biotech and pharmaceutical companies with their regulatory strategy and submissions. This creates a relationship in which SNBL is not only a service provider, but a partner in drug development.

Preclinical and Clinical Studies

Aside from specialised studies supporting nasal drugs and nasal delivery, preclinical GLP studies are the bread and butter of SNBL; a full battery of standard GLP, IND-enabling studies are offered and conducted on a regular basis. In fact, this extensive CRO experience is what has enabled the speciality services to be developed.

Over the past 55 years since establishment, SNBL was the first to rise in NHP testing excellence and innovation and continues to be a world leader in such research.

Additionally, SNBL provides the standard clinical studies required for registration of nasal

Continued on Page 16...

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?

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

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...continued from Page 14

formulations using µco™ System, as well as other nasal delivery systems. The life sciences industry is ever-evolving and as such SNBL continues to look forward and innovate, and is currently developing a breath-monitored oral inhalation mechanism for NHP testing (Figure 5).

CHOOSING SNBL AS A NASAL DRUG DEVELOPMENT PARTNER

As the business model of pharma and biotech changes, partnerships with experienced and valuable service providers grow increasingly pertinent. SNBL makes an ideal partner in the drug development process for nasal drugs by utilising the services and experience described here.

These enabling services allow for early, critical decisions; comparisons of nasal drug delivery technologies; and provide optimisation of drug products. An example programme which provides these services is the feasibility study for µco™ System, which is ideal for determining the applicability of the system to a compound. Additionally, invaluable know-how of navigating regulatory requirements for IND filing is available and, should µco™ System be a good fit, licensing is offered to partners.

µCO™ SYSTEM AND ITS CLINICAL APPLICATIONS: NOVEL NASAL DELIVERY SYSTEM

SNBL's NDS Division has developed an innovative, proprietary novel nasal delivery system, µco™ System, consisting of a muco-adhesive powder drug carrier and a user-friendly nasal delivery device. This system is absorption enhancer-free, with no clinical irritation to date.

Nasally delivered zolmitriptan (TRZ) using µco™ System completed Phase I clinical trials and demonstrated higher absorption than the marketed products (both oral and liquid nasal spray) with relative bioavailability of 182% compared with the commercially available nasal spray. More importantly, TRZ demonstrated significantly faster absorption than the nasal spray and its relative bioavailability in the first 120 minutes after administration was 333% compared with the nasal spray.

Also utilising µco™ System, nasally delivered granisetron (TRG) demonstrated 100% absolute bioavailability, rapid absorption with maximum concentration (C_{max}) achieved by 20 minutes (70% of C_{max} reached within five minutes) post administration and low variability observed between patients.

Both compounds in clinical studies have proven excellent safety profiles in more than 200 human subjects combined.

µco™ System also represents an effective platform for delivering vaccines locally to the nasal mucosa. Due to the muco-adhesive carrier's prolonged retention time, the platform enables efficient delivery of vaccines to the nasal mucosa, resulting in the generation of an effective mucosal immune response. Given these promising properties, SNBL is using µco™ System actively to pursue the development of a number of nasally-delivered vaccines.

As demonstrated by the examples described above, µco™ System rapidly and effectively delivers drugs via the nasal cavity into the bloodstream with consistently high efficiency. NDS Division currently offers a feasibility programme to companies with compounds in early development to determine if µco™ System is a good fit.

Technomics

THE NEW i-pen②

- All plastic reusable pen
- Dose increments from 0,01ml to 0,6ml
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HASELMEIER

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HASELMEIER

Haselmeier is dedicated to meeting the self-injection needs of pharmaceutical manufacturers and patients.

In 1920, Wilhelm Haselmeier established a medical device company in Stuttgart, Germany. Since that time, Haselmeier has continued to develop and create injection devices designed for patient comfort and ease-of-use.

Today, Haselmeier is one of the leading designers and manufacturers of pen and auto-injector systems. Many of these systems feature Haselmeier's patented hidden needle system, which is designed to help patients overcome the fear of self-injection, provide a more comfortable injection and help increase compliance of the patient's medication.

PRODUCT DESIGN

Our capabilities include design and development from concept to finished device using Haselmeier's strong IP portfolio or tailoring of existing Haselmeier designs to meet customer and therapeutic needs.

All designs undergo comprehensive testing, in addition to risk management, risk analysis and FMEA design review. Three-dimensional CAD designs are utilised for creation of customer-specific concepts or customisation of existing designs.

MANUFACTURING AND QUALITY

As a specialist in the manufacture of complex system assembly, product integrity is assured by Haselmeier's manufacturing processes. All new device concepts are created with an "Integrated Design Approach" which focuses on both, the device and the efficiency of manufacture and assembly.

All manufacturing is within compliance with applied standards EN ISO 13485:2003 and Annex ll, Section 3 of the European Directive 93/42/EEC on medical devices. CE certification is certified by TÜV SÜD Product Service (Munich, Germany).

PLATFORM & PRODUCTS

Axis Pen System: variable-dose injection device

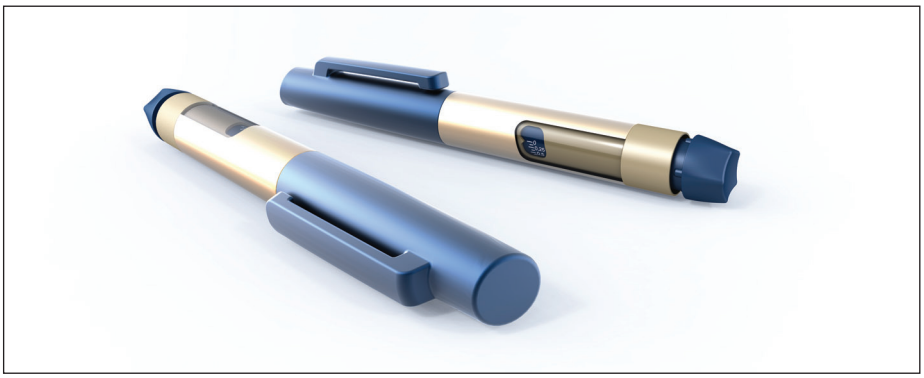

Figure 1: Axis Pen System – variable-dose injection device.

The Axis Pen System is a variable-dose injection device for manual injection. It is available in a disposable or re-usable presentation. The Axis-D and Axis-R Pen Systems (Figure 1) provide a new, unique technical function.

Figure 2: i-pen: re-usable – variable dose injection device.

Figure 3: i-pen²: re-usable – variable dose all-plastic injector device.

The Axis pens feature:
- No or minimal priming
- Accurate dose reading with sliding window
- No rotating outer components
- Protected dose scale

i-pen: re-usable, variable dose injection device

The Haselmeier i-pen is a re-usable, variable-dose injection device for use with a standard 3 ml cartridge. The i-pen (see Figure 2) features an elegant non-medical design which is the result of extensive research and patient testing.

The i-pen is available as a standard Haselmeier design or can be customised to your specific requirements. It features:
- Dose adjustment from 0.01-0.6 ml per injection
- Compact size enables easy handling and portability
- Large, easy-to-read dose indicator
- All metal outer body

i-pen²: re-usable, variable dose all-plastic injector device

The i-pen² (Figure 3) is a reusable, variable dose injection device for use with a standard 3ml cartridge. The i-pen² was specifically created to provide a high-quality pen at economic cost.

The i-pen² is available as a standard Haselmeier design or can be customised to your specific requirements. It features:
- Dose adjustment from 0.01-0.6 ml per injection
- Compact size enables easy handling and portability
- Large, easy-to-read dose indicator
- All plastic components

Softpen – reusable injection device

The Softpen (Figure 4) is a fully automatic, re-usable injection device featuring Haselmeier's patented hidden-needle design. Upon depressing the clip on the pen, the needle automatically enters the subcutaneous tissue followed by delivery of the solution. The Softpen features:
- Fully automatic needle insertion and injection
- Needle is hidden prior to and during injection
- Multiple injections from single 3 ml cartridge

Figure 4: Softpen – a fully automatic, re-usable injection device featuring Haselmeier's patented hidden-needle design.

Figure 5: The disposable Penlet is a fully automatic, fixed-dose injection device designed for use with a standard 3 ml cartridge.

Penlet – disposable, fixed-dose injection device

The Haselmeier disposable Penlet is a fully automatic, fixed dose injection device designed for use with a standard 3ml cartridge. Upon depressing the clip on the pen, the needle automatically enters the subcutaneous tissue which is followed by delivery of the solution. The Penlet features:
- Ready for use by the patient and no dose adjustment required
- Fully automatic needle insertion and injection
- Needle is hidden prior to and during injection

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MEDICATED CHEWING GUM DRUG DELIVERY SYSTEMS

In this piece, Lene Jorsal, MSc (Pharm), Formulation Scientist, and Bo Tandrup, MSc (Pharm), Chief Executive Officer, both of Alkalon, and Liisa Vartiainen Lauenborg, Journalist, describe the industry's growing acceptance of chewing gum as a drug delivery system, and outline their company's contract research and product development offering in the field of medicated chewing gum.

THE MARKET FOR MEDICATED CHEWING GUM

Medicated chewing gum has gained increasing acceptance as a drug delivery system since the first medicated gum product, Aspergum® (acetylsalicylic acid), was launched commercially in 1928. In 1991 the European Pharmacopoeia defined the intended use of medicated chewing gum as the local treatment of mouth diseases or for systemic absorption through the oral mucosa or from the gastro-intestinal tract.[1]

Medicated chewing gum has become the first choice for nicotine replacement therapy and over the past decades the perception of chewing gum drug delivery systems has changed from cautious scepticism to general appreciation. Today, several active pharmaceutical ingredients are available in medicated gum formulations.

Most medicated chewing gum products are launched as line extensions to existing OTC medications. The format is often chosen by category managers not because of its pharmacokinetic properties but because chewing gum is easily recognised by consumers and stands out from all the common formats such as lozenges and chewable tablets.

ALKALON'S BUSINESS MODEL

Alkalon's first product was a generic nicotine gum based on an extrudable gum base. The development work was completed in 2011 and Alkalon recently received regulatory approval for a portfolio of the gums (2 mg and 4 mg nicotine with various flavours) in a number of European countries. Commercial launch is anticipated by the end of 2012.

The company managed to complete development, up-scaling, bioequivalence and stability studies as well as pan-European registration in less than 30 months, an achievement which was possible only because overall responsibility for all disciplines was kept in-house at Alkalon. The organisation is small and flexible, and the company can easily draw on expertise in regulatory affairs, clinical trials, analysis and other areas, not just from the company's own advisory board but also from closely connected partner companies with whom Alkalon has worked for many years.

The company's development laboratory is equipped with all the machinery needed to develop medicated chewing gum formulations based on various technologies, and its technical staff have comprehensive and in-depth experience in the field.

Alkalon currently focuses on the development of line extensions and the continued marketing of its own product portfolio, and is also managing several formulation development projects for large pharmaceutical companies on a contract development basis.

The competitive advantage of Alkalon is not just technology driven. The company is able to compete with Big Pharma through a large number of licensing and supply agreements with generic companies across the world. Pooling the demand from several companies who use new distribution channels for own-label or own-brand products enables Alkalon to supply products at competitive prices.

Alkalon is currently the only independent contract development company with a proven track record which focuses entirely on medicated chewing gum.

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SOURCING OF MEDICATED CHEWING GUM

Medicated chewing gum can be manufactured by extrusion or tableting, but until recently only extruded gums have had an acceptable texture and release profile, and all the major nicotine gum brands on the market are still extruded gums.

Manufacturing extruded gums requires highly specialised equipment and, as the market for medicated chewing gum is relatively small, very few CMOs were available until recently. However, the quality of compressible gum bases has increased significantly in the last few years, and today it is possible to manufacture very good tableted gums.

From a sourcing perspective, this has increased the pharmaceutical companies' freedom to choose CMOs because compressed gums can be manufactured using any tableting machine.

Nonetheless, finding technical staff with sufficient experience in pharmaceutical gum manufacturing remain a challenge.

WHERE TO USE MEDICATED CHEWING GUM

New oral drug delivery systems often compete on fast onset of action and ease of administration.

Medicated chewing gum offers a number of advantages. Importantly, these advantages are not limited to instances where a local effect in the oral cavity or throat are required, where the advantages are obvious, but also apply in systemic delivery applications.

In general, medicated chewing gum is good for convenient administration on demand. There is no need for water and, unlike for example taking tablets or using an inhaler, chewing a piece of gum is not readily associated with illness. Gum is also an obvious choice for children and patients who have difficulty swallowing tablets.

Chewing gum has advantages for the systemic delivery of substances that readily cross the oral mucosa. This provides rapid onset of action and avoids first-pass metabolism and breakdown in the gastro-intestinal tract.

The dissolution rate can be controlled via the quantity and type of gum base in the formulation, as illustrated in Figure 1, making medicated gum suitable for controlled drug release.

The safety of a drug formulated as chewing gum is high, as extreme doses can be ingested only by chewing extensively. The release of drug from the gum if swallowed is very low.

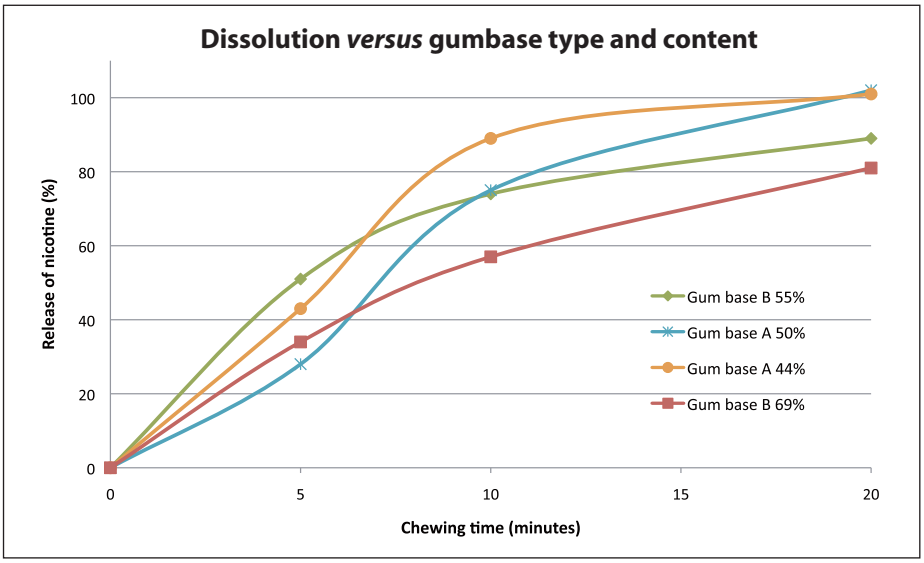

Figure 1: Release of nicotine over time from chewing gum formulations with various contents and types of gum base.

The taste must be appealing and there are a number of ways of masking the unpleasant taste of an API, although extremely bitter drug substances or high dosages might be difficult to work with. Very fat-soluble active ingredients might have such a low dissolution rate though that use of a chewing gum formulation is not possible.

Medicated chewing gum is ideal for:

- Nicotine replacement therapy (NRT)
- Treating pain and inflammation in the mouth and throat
- Gastro-oesophageal reflux disease (GORD)
- Prophylaxis of tooth decay
- Buccal absorption of drugs

PRODUCT DEVELOPMENT

The development of a medicated gum formulation from first lab trials to product launch can be described in terms of the phases shown in Figure 2.

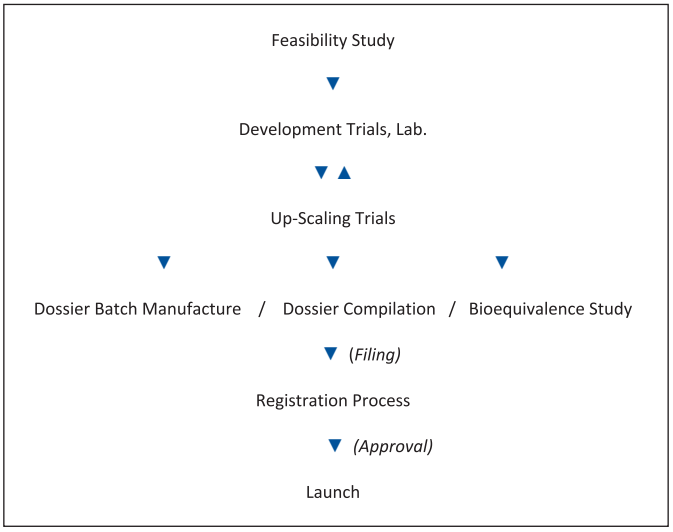

Figure 2: Stages of a typical development project at Alkalon.

Being a small company Alkalon is able to maintain an overview of the project in its entirity, from the start of the feasibility study to filing. This makes it possible to compile all relevant technical data for the registration file in parallel during the development and upscale phases, resulting in a very fast and flexible process. In a recent case, Alkalon succeeded in writing the registration dossier in seven months while the bioequivalence study and the ICH stability study were performed, and had it ready for filing just one month after receiving the last clinical data and six-month stability data.

Alkalon works in close collaboration with industry experts who have the widest experience of the development and full-scale production of both extruded and compressed gums. By working with Alkalon, its customers gain access to this strong network of experts, which ensures that a new medicated gum project's progress through development, up-scaling and registration is rapid and unproblematic. Alkalon offers a one-stop shop as a medicated chewing gum solutions provider (see Figure 3).

FEASIBILITY STUDY

When a new development project is started at Alkalon, an initial feasibility study is performed. This provides valuable information at an early stage about important properties such as taste, dissolution and stability of the API in the gum formulation. This is done using a simple test setup and early prototypes to understand the most relevant results quickly and at low cost. A feasibility report can be completed in 6-8 weeks.

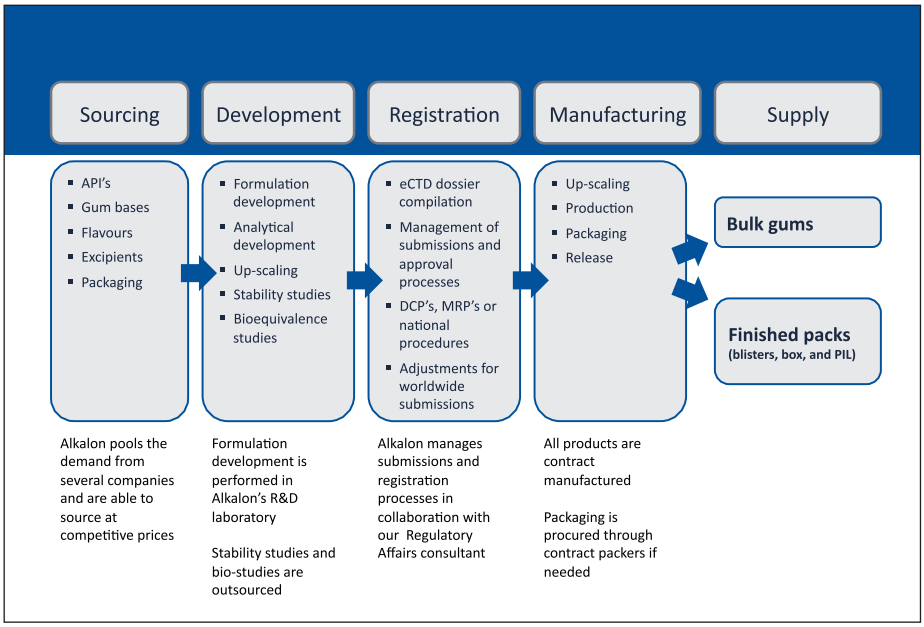

Figure 3: Alkalon offers an easy one-stop medicated chewing gum solution.

The report provides the relevant technical information about possible challenges in the further development and forms a solid basis for a go/no-go decision.

In Alkalon's in-house development laboratory all relevant equipment for the production of medicated chewing gum samples is available for both extruded and compressed products. The most important analyses can also be performed in-house, which makes it possible to move the project forward in the minimum amount of time.

An internal tasting panel of trained tasters make taste evaluations of the chewing gum samples. If relevant a consumer test can also be arranged.

Figure 4: The chewing apparatus used in the development laboratory.

Dissolution testing is performed using a chewing apparatus (*Ph Eur 2.9.25 Apparatus B*), as shown in Figure 4, and measures the amount of API released from the gum into a chewing solution after chewing for, typically, 10, 20 and 30 minutes.

A good indication of stability is provided by stress testing early prototypes by comparison with well-known dosage forms such as tablets. Stress tests are chosen according to what is relevant to the individual API, heat, humidity, oxidation etc. Comparative accelerated climatic studies at 40ºC/75% RH are initiated in-house at a very early stage to predict whether any challenges with degradation of the drug substance can be expected.

IMPORTANT PARAMETERS

The most important parameters to control when formulating a medicated chewing gum product are taste, dissolution and stability.

Since the API is released from the chewing gum by mastication, the product remains in the mouth for a period of 10-30 minutes and so it is critical to obtain a pleasant taste. This is achieved by various means such as selecting the right type and level of flavours and sweeteners and if necessary applying a number of special taste-masking techniques. The release rate of the flavours and sweeteners can also be matched to the release rate of the API so that they peak at the same time and give the best overall taste profile.

The dissolution rate of the API will depend on its solubility: the more water soluble it is, the faster it is released. If the drug substance has poor solubility, release can be improved by choosing the right type of gum base, reducing the amount of gum base and by adding a solubiliser.

As discussed here, chewing gum can be produced by two different techniques, extrusion or compression, and the choice of technique also plays a major role as regards taste, dissolution and stability. The traditional method of producing chewing gum is by mixing at approximately 50-60ºC, then extruding, rolling and scoring gum cores and subsequently adding a coating layer. In recent years, new techniques of producing compressed gum tablets based on a directly compressible gum base powder have been optimised and today gum products manufactured by compression virtually equal extruded gums in quality.

A compressed gum can offer faster release than extruded gum and, by formulating a two-layer gum tablet and adding the API in the layer without the lipophilic gum base, release can be increased still further if necessary.

The stability of a medicated gum formulation can also be improved by choosing the right excipients. Screening of the compatibility of the API and the relevant flavours and gum bases is advisable, since these are potentially the most aggressive ingredients. It is an advantage for the stability of a chewing gum formulation that it contains no water. The stability of a gum product can be improved by adding a coating layer, as with a regular tablet.

REFERENCE

1. *Rassing MR et al, "Chewing gums as a drug delivery system". Adv Drug Delivery Reviews, 1994, Vol 13, p 89.*

ABOUT ALKALON

Alkalon is an independent, privately-owned contract research and product development company based in Denmark. The company specialises in the development of medicated chewing gum formulations and is working in partnership with pharmaceutical companies on dosage form development projects and the supply of finished products. Alkalon's in-house R&D activities take place in a small non-GMP laboratory and all non-core activities are outsourced.

The company has recently developed and registered a portfolio of new, improved nicotine polacrilex chewing gum and is currently the only company which offers licensing and the supply of high quality nicotine gums to the generics industry in Europe and elsewhere.

ALKALON

Test your product in a Medicated Chewing Gum formulation

Alkalon offers to prepare prototypes and a technical report which will give you valuable information about properties, release, and stability of your molecule in a medicated chewing gum formulation.

Meet our team at the CPhI Finished Dosage Zone Booth 9A08

Alkalon is a Scandinavian company specialised in formulation development and supply of medicated chewing gum.
The company has recently received EU regulatory approval of a new portfolio of nicotine gums.


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