



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^{TM} 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 pharmacoki-

netic 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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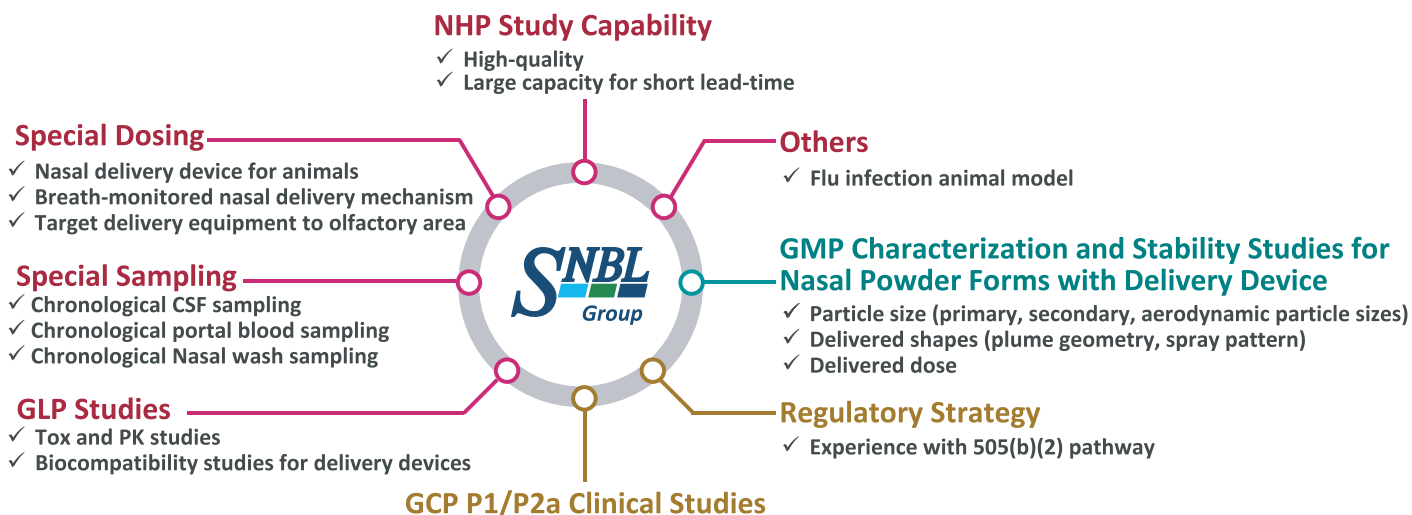


Figure 1: Nasal Drug Delivery Technologies and Know-How Generated through R&D of the μco^{TM} System.

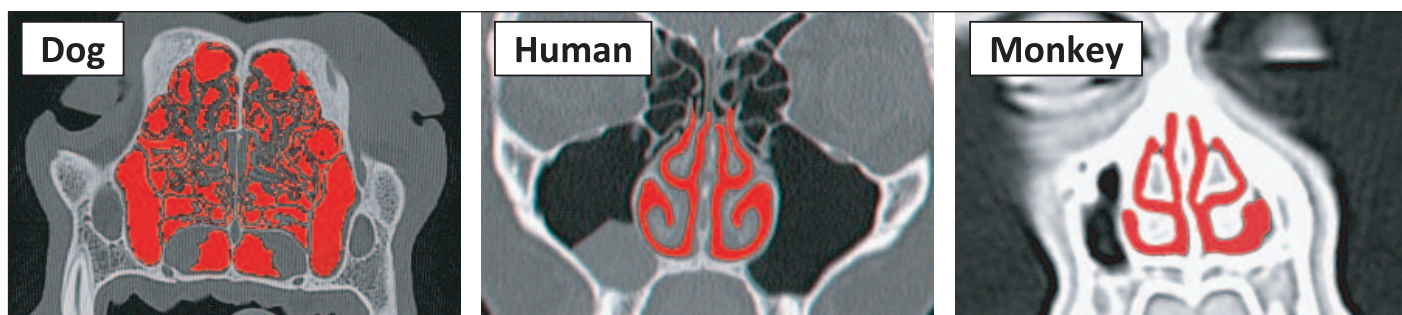


Figure 2: Anatomy of the Dogs, Human and Monkey Nasal Cavities.

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 over-emphasised 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 mucociliary clearance; rats and dogs provide a mucociliary 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 mucociliary 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

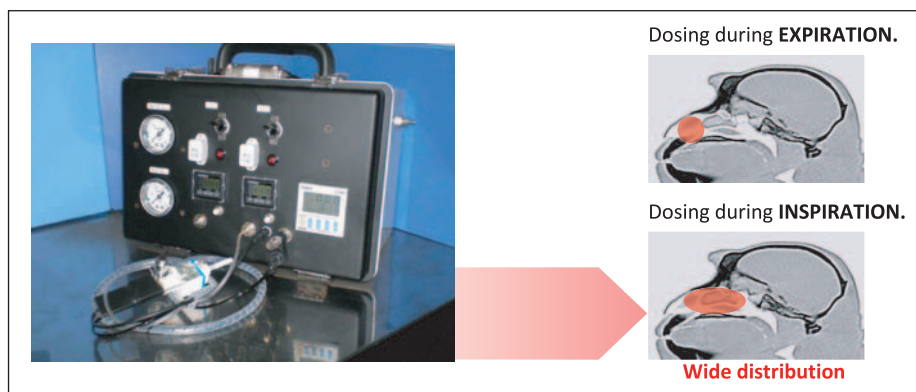


Figure 3: Breath-Monitored Nasal Delivery Mechanism.

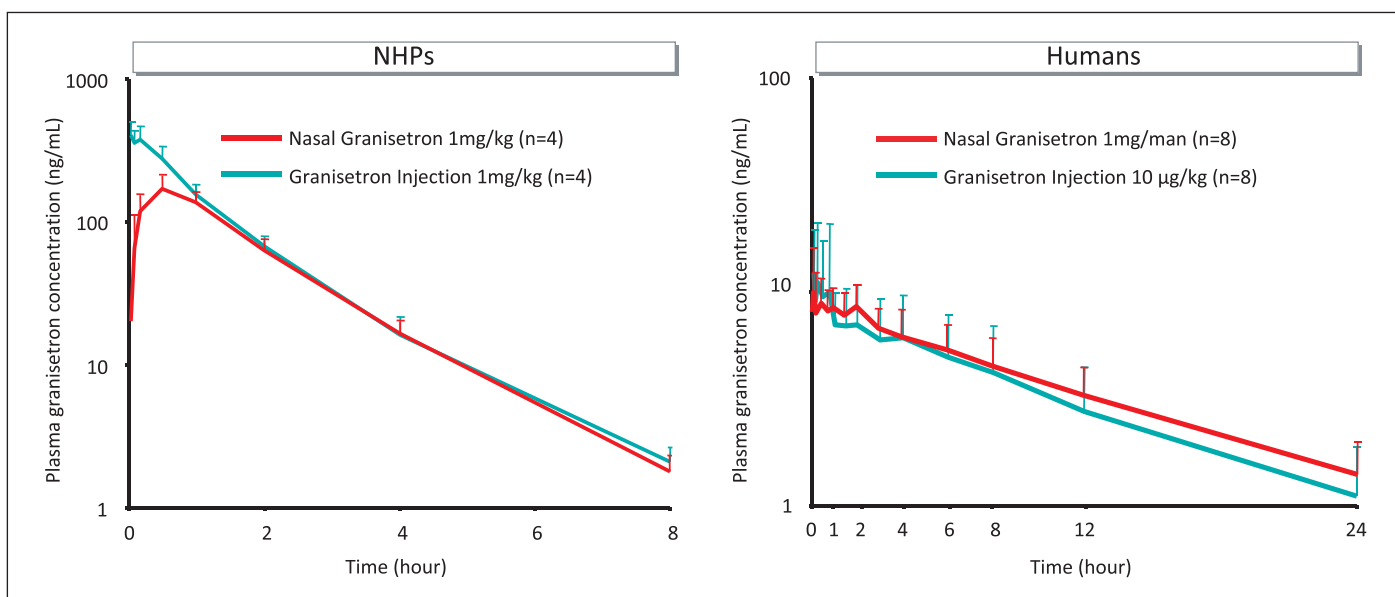


Figure 4: Plasma Granisetron Concentration – Time Profiles of Nasal Granisetron Delivered Using µco™ System in Humans and NHPs.

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, unanaesthetised 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.

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

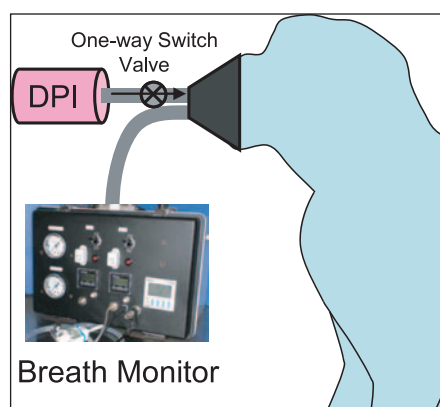
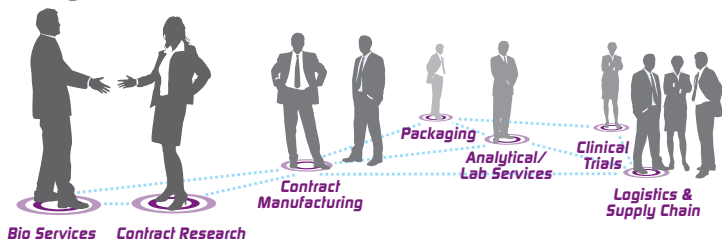


Figure 5: Breath-Monitored Oral Inhalation System.

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formulations using μco^{TM} 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^{TM} 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^{TM} System be a good fit, licensing is offered to partners.

μCO^{TM} SYSTEM AND ITS CLINICAL APPLICATIONS: NOVEL NASAL DELIVERY SYSTEM

SNBL's NDS Division has developed an innovative, proprietary novel nasal delivery system, μco^{TM} 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^{TM} 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^{TM} 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^{TM} 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^{TM} System actively to pursue the development of a number of nasally-delivered vaccines.

As demonstrated by the examples described above, μco^{TM} 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^{TM} System is a good fit.

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
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