Clinical Gamma Scintigraphy for the Evaluation of Inhaled Medicine

IPI Speaks with Dr. Simon Warren, Research Director at Cardiff Scintigraphics on the benefits of scintigraphic evaluation in respiratory drug delivery.

Q: Cardiff Scintigraphics Limited (CSL) is an Established Provider of Clinical Gamma Scintigraphy Services for the Evaluation of Pharmaceutical Formulations & Devices. Can you tell our readers a brief history of the company, how you started and your growth so far?

A: Cardiff Scintigraphics Limited (CSL, https://www.scintigraphics.co.uk) was formed in 1992, by three distinguished research academics from Cardiff University who had pioneered the application of gamma scintigraphy to the evaluation of pharmaceutical products. One of those founding directors, Prof Glyn Taylor, remains closely involved with the company.

CSL was established as an independent company to provide scintigraphy services to the pharma industry with a particular emphasis on respiratory drug delivery. CSL has for over 25 years performed clinical scintigraphy studies in collaboration with a local full-service contract research organisation (CRO), Simbec Research Limited. Together, in the early 2000's, we established a purpose-built scintigraphy suite and GMP formulation laboratory at Simbec's site and we continue to offer this unique combination of scientific, clinical, analytical, regulatory and project management expertise.

To promote the full range of research and development expertise available from CSL we started trading as i2c Pharmaceutical Services (https://www.i2cpharm.co.uk) to advance research and testing capabilities in pharmaceutical formulation and device development in addition to clinical scintigraphy services.

i2c's laboratory key offerings include small scale manufacture (100's–1000's) of pressurised metered dose inhalers (pMDI's) and dry powder inhalers (DPI's), accelerated stability testing, particle size analysis by inertial impaction, chemical analysis by HPLC, and moisture analysis (Karl Fischer). i2c also performs analysis of oral dosage forms including tablet disintegration and dissolution and has a small-scale single punch tablet machine. Accelerated stability assessments of all types of dosage forms are performed using four environmental cabinets at standard ICH and custom conditions.

In addition to the bespoke service offerings, CSL has developed a novel pMDI formulation & production approach and licencing opportunities are available for this Respitab™ platform technology (www.Respitab.co.uk) which offers affordable & accelerated development for NCE and generic products.

The experienced team of scientists at CSL / i2c provide independent services to global pharma, medical technology companies and emerging clients for the development of pharmaceutical formulations and inhaler devices and has performed studies for more than 30 different pharma companies, including half of the 'Global Top 10'.

Q: You serve as the Research Director at Cardiff Scintigraphics. What does your day-to-day role look like and what are your daily goals and objectives?

A: As Research Director in a thriving R&D company, every day is different and that is what makes my role both challenging and exciting. For scintigraphy studies my day-to-day role involves close liaison with Simbec Research, in particular with the IMP management services group i.e. Research Pharmacist & QP, functions essential in the successful production of small scale batches of radiolabelled product formulated to GMP quality standards.

For i2c studies my day-to-day role is defined by close interaction with the R&D team to achieve our goal of providing excellent customer service by ensuring the integrity and interpretation of laboratory data and ensuring that detailed updates are maintained and provided to the sponsors of external research and development projects.

For all types of study, I interact with sponsor companies to develop and evaluate research proposals and assure the smooth running of projects and allocate internal resources to ensure their timely conduct and reporting.

Q: What is the role of scintigraphic evaluation in respiratory drug delivery.

A: Gamma scintigraphy is a safe non-invasive method for determining the biodistribution of drug delivery systems under physiological conditions, providing critical data early in the clinical development process. This provides information on the efficiency of deposition and the distribution in the lung. It also gives a crucial insight into the inter- and intra-subject variability in the performance of the drug / device *in vivo* and

using this methodology early in the clinical development process gives valuable insights for the design of larger clinical trials.

The radiolabelling processes used by CSL are fully validated. For pulmonary delivery systems this involves standard Pharmacopoeial inertial impaction techniques combined with chemical assay (HPLC) of API and imaging of radiolabel, these processes are performed to demonstrate that the radiolabel is an accurate surrogate for the drug.

Scintigraphy can be used to evaluate all types of respiratory delivery systems, e.g., pMDI, DPI nebulisers, air-jet, electronic and soft mist inhalers, in patient populations and healthy volunteers. Studies can be designed to evaluate device variables e.g., mouthpiece configurations, formulation factors e.g., excipient levels or patient interactions e.g., inhalation flow rate and inhaled volume. Since the clinical end points i.e., efficiency of lung deposition and distribution pattern can be accurately measured relatively small populations can be evaluated to provide critical data in terms of product performance and variability. Study protocols may also incorporate simultaneous PK evaluations.

Q: Understanding the relationship between *in vitro* and *in vivo* data for inhaled drug products is an important goal. *In vitro* aerodynamic particle size distributions (APSDs) are expected to have some predictive power not only for drug deposition, but also for clinical effects. Can you tell our readers about the current needs and trends in inhalation drug delivery field?

A: *In vitro* data can form a critical part of regulatory submission, EMA guidance indicates that in theory, if not practice, *in vitro* equivalence of test and reference products is sufficient for product registration, in the US *in vitro* data forms a part of the weight of evidence approach.

Key *in vitro* data for inhalation products are generated by inertial impaction assessments whereby aerosolised particles are fractionated according to their aerodynamic properties. The Next Generation Impactor (NGI) is the most widely used instrument for this purpose coupled with a sensitive and accurate analytical technique such as HPLC-UV. The data are evaluated to determine key aerosol characteristics e.g., fine particle fraction (FPF), fine particle dose (FPD) mass median aerodynamic diameter (MMAD).

These methods have great utility for QC purposes e.g. determining batch-to-batch consistency. In terms of product development, the impact of formulation variables e.g., ethanol levels in pMDI formulations, on the resultant aerosol properties can be effectively measured thus enabling optimisation of aerosol performance in idealised laboratory testing conditions.

In terms of predicting *in vivo* deposition, however, *in vitro* tests are often poorly predictive tending to overestimate lung deposition. Patient variables such as upper airway geometry, and inspiratory flow profiles contribute to the deviation from *in vitro* data typically generated by impactors using standard induction ports i.e., non-anatomical throats and operating square wave airflows. Methods have been introduced to improve the predictive power of *in vitro* tests, including the use of more anatomically representative throats (inlets) and air flow profiles/volumes derived from patient data.

The industry is attempting to develop *in vitro* models to be more predictive of *in vivo* deposition. Successful models may allow product development to be streamlined reducing clinical data requirements for registration of products. Gamma scintigraphy is a critical tool for validating the predictive power of *in vitro* models used to estimate *in vivo* lung dose and distribution.

We see increased interest in the treatment of diseases such as idiopathic pulmonary fibrosis and pulmonary arterial hypertension and formulations/devices have been refined to maximise the therapeutic efficacy in these disease states.

We have recently been part of a consortium to develop of a novel proof of concept aerosol formulation for the treatment of antimicrobial resistant chronic lung infections. The concept, known as Light4Lungs (https://light4lungs.eu) utilises novel breathable light emitting nanoparticles that kill pathogenic bacteria by photodynamic effects irrespective of multidrug resistance properties. Uniquely, the formulation is being developed so that the nanoparticles are inhaled, deliver the light energy and are then exhaled. We are currently working on optimising the aerosol properties of these nanoparticles.

Q: Reformulation of pMDI's using low global warming potential propellants is underway, how may γ-Scintigraphy help provide data to support the regulatory process? What kind of work are you doing currently, and what are clients wanting from you?

A: Several pharma companies e.g., AstraZeneca, Chiesi and GSK have publicly stated their intention to reformulate pMDI products using low GWP (Global Warming Potential) propellants.

Recent EMA guidance states that when transitioning to the new propellants, whether that be HFA152a or HFO1234ze, an assessment of possible effects on ciliary function, i.e., a mucociliary clearance (MCC) study should be performed. The guidance reports that gamma scintigraphy would be an acceptable option for performing this assessment.

In addition to MCC studies, gamma scintigraphy can also help clients in understanding the performance of their low GWP MDI formulation in the clinical setting. For these types of studies, the active ingredient is surface labelled with Technetium-99m in the case of suspension systems, or a soluble form of Tc-99m is used to radiolabel solution formulations. *In vitro* characterisation of the radiolabelled product is performed to demonstrate the validity of the radiolabel i.e., that the radiolabelled is an accurate surrogate for the active ingredient and that the radiolabelling process has not changed the aerosol characteristics relative to control samples.

Following validation of the process the radiolabelled products are tested in the clinic. The results from the test formulations can be compared with those from radiolabelled reference products to enable assessments of *in vivo* equivalence. As a consequence of accurate end points i.e. dose to lung, distribution within the lung, such studies can be conducted in relatively small populations i.e. 10's of subjects. To ensure accuracy of the procedures Krypton-81m gas ventilation imaging is used to define the lung margins, and Cobalt-57 transmission imaging enables regional tissue attenuation of the radiotracer signal to be accurately determined and appropriate corrections made.

We have recently performed some radiolabelling development work on model formulations prepared in HFA 152a and HFO 1234ze and found we were able to accurately match radiolabel and drug deposition *in vitro*. These data were published at DDL last year (https://ddl-conference.com/ddl2022/conference-papers/accelerated-stability-studies-with-pmdis-of-respitab-hfa-152a-propellant-dispersible-salbutamol-tablets/).

Results from scintigraphy studies we have performed have been included in product registration documents for locally acting respiratory products and other products intended for sustained delivery to the lung.

Q: As a key player in the pharmaceutical industry, I am sure you are governed by the vision of sustainability and circular economy. What steps are you taking to lead in this category, and what commitments have you made and gained from your customers and suppliers?

A: i2c has an established track record in supporting companies in transitioning to sustainable products and reducing environmental impact. In the early 2010's, i2c was part of a consortium that worked with the United Nations Industrial Development Organisation (UNIDO) to help pharma companies in Egypt and Mexico reformulate CFC based inhalers to HFA 134a products thus reducing the use of ozone depleting propellants. Successful technical transfer procedures were implemented at the benefactor companies that resulted in the successful registration and marketing of five products.

Current F-gas regulations mean that there will be a phase down in the use of HFA 134a and HFA 227ea due to their global warming potential. The industry is now focussed on reformulation activities using alternative low GWP propellants such as HFA 152a and HFO 1234ze.

i2c is using its formulation experience and capabilities for small scale laboratory batch preparation using low GWP propellants to assist companies in their research. We have equipment for single- and two-stage filling of small batches of pMDI and environmental cabinets for accelerated stability storage. These facilities are complemented by analytical methods for drug and moisture analysis so that aerosol properties can be fully characterised during stability studies.

Of the new low GWP propellants HFA 152a presents challenges for scale up to commercial manufacturing due to its classification as a flammable gas. Traditional single stage pressure filling necessitates the use of large pressure vessels which have been identified as a hazard. Eliminating pressure vessels and associated operator interventions during propellant filling of the vessel and drug addition and subsequent cleaning of vessels/filling lines will significantly reduce risks.

i2c has a unique solution to these problems in the form of a propellant dispersible tablet i.e., Respitab™ a patented (WO2015121653A1) formulation /manufacturing approach the eliminates the higher-risk steps in production of pMDI using flammable gases. The process also reduces waste and is thereby more sustainable and cost effective. The API in the form of standard micronised material is compressed into a tablet with inhalation grade lactose and an approved dispersant i.e., menthol, both excipients have been used previously in marketed pMDI's. The inclusion of lactose in the formulation enhances product stability and generates high performance aerosol properties.

The Respitab platform technology can be applied to a range of API's to produce single and combination products. Propellant dispersible tablets may be dispensed into canisters and crimped prior to the addition of the propellant. Filling can be performed at any time after crimping and may even be performed at a different site meaning facilities without experience or capability for complex inhaler manufacturing processes could quickly set-up a finishing service for pMDI production.

Q: What is Cardiff Scintigraphic's vision for the future? What projects are you looking forward to?

A: CSL's vision is to enhance its capabilities as a contract research centre of excellence for inhaler development and testing. Capitalising on CSL's unique combination of knowledge, skills and experience of early-stage pharmaceutical formulation/device development and clinical gamma scintigraphy, it is intended that services will be extended into a GMP environment to provide clients with a world-class facility enabling a swift and cost-effective route to first-in-human trials.

We are particularly looking forward to facilitating projects with the development and clinical trials of Next Generation Inhalers with lower carbon footprints and lower GWP. Included in this objective is finding commercial partners for our Respitab™ technology which can provide excellent aerosol performance, stability and will enable rapid and effective transition to Next Generation Inhalers with associated environmental benefits.

Simon Warren

Dr. Simon Warren is the Research Director at Cardiff Scintigraphics. He joined Scintigraphics in 1994 with responsibility for radiolabelling development and validation programs for oral and inhalation delivery systems. He has extensive experience in small scale GMP manufacture of radiolabelled pMDIs, dry powder inhalers and nebulizer systems for use in clinical trials. Dr. Warren is also the co-inventor of several patents describing novel formulation and manufacturing methods for pMDIs using propellants with low global warming potential.

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