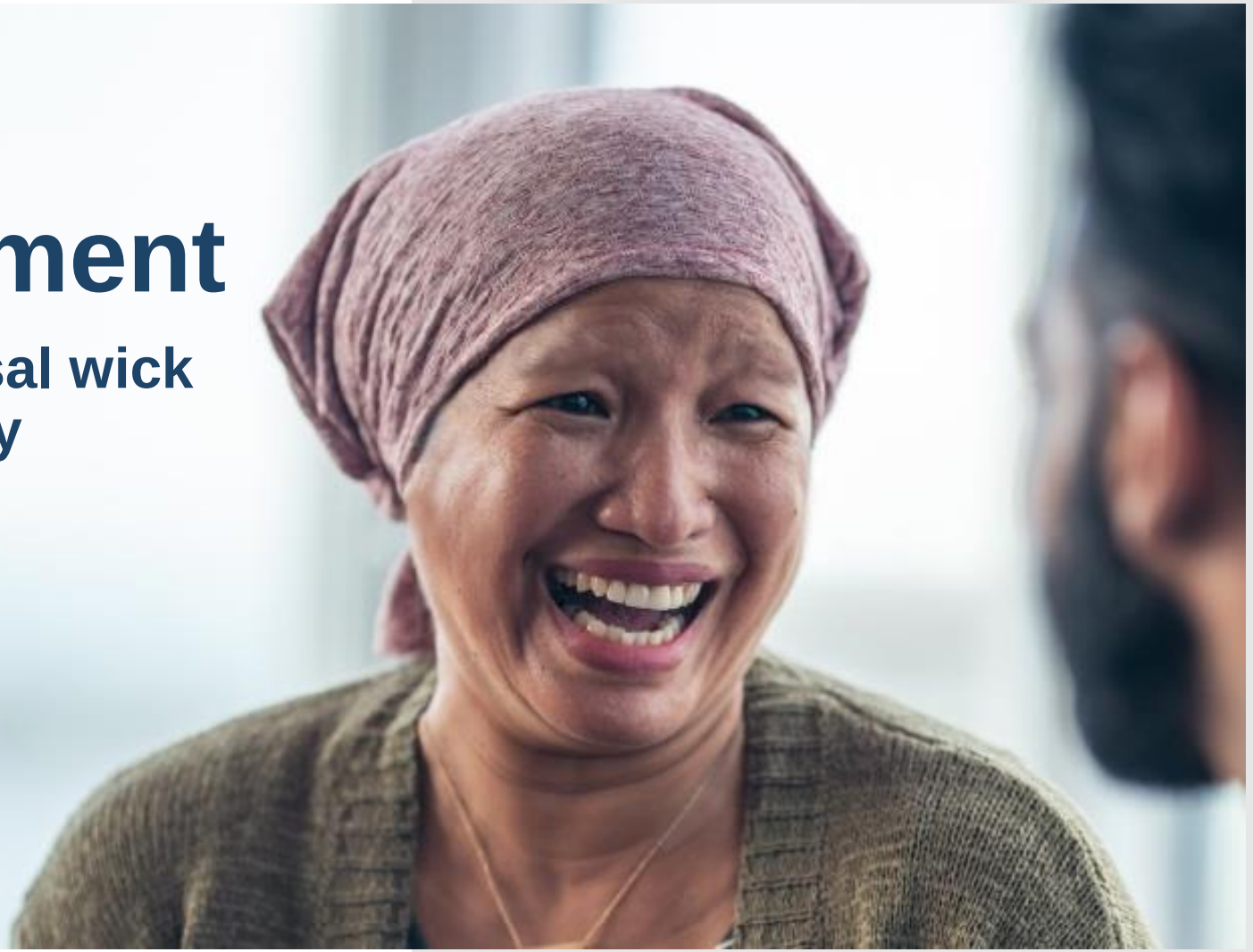
Quotient Sciences

Molecule to cure. Fast.™

Clinical development

Scintigraphic imaging and nasal wick tools to evaluate nasal delivery



Chris Roe, Quotient Sciences

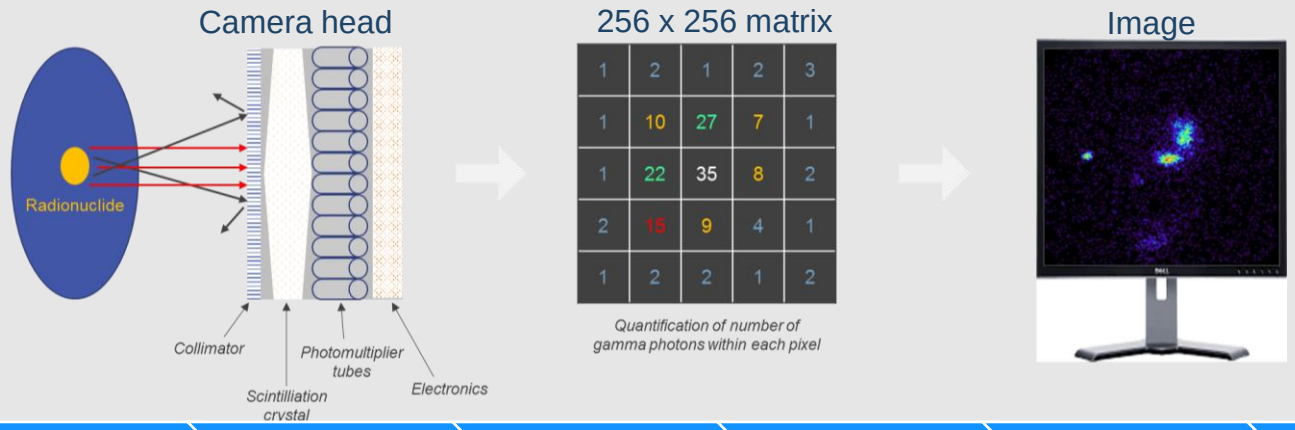
APS Nasal Biopharmaceutics Workshop

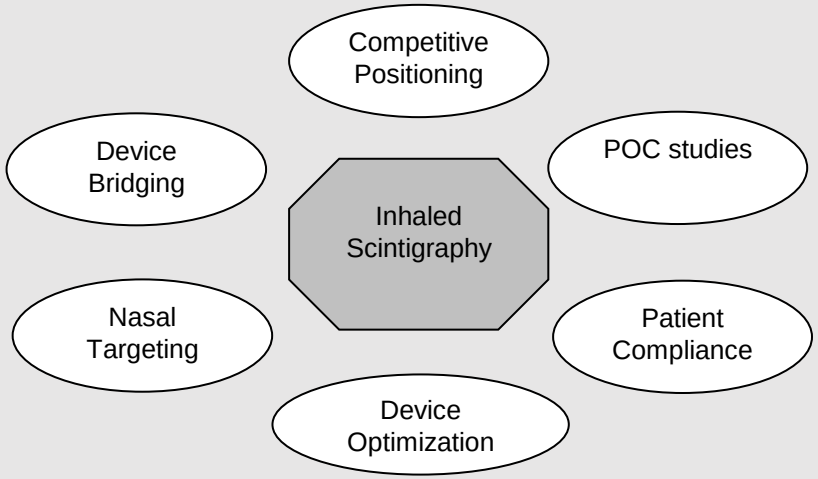
DDL, December 2022

Use of Gamma Scintigraphy in clinical programs that assess efficiency of delivery, efficacy, dose and safety

- The global nasal drug delivery market size stood at $42.38 billion in 2018 and is projected to reach $73.84 billion by 2026. https://www.fortunebusinessinsights.com/industry-reports/nasal-drug-delivery-market-100415

- Quotient have performed 13 nasal clinical studies using scintigraphy over the last 20 years
  - Local or systemic administration applications
  - Combination with PK measurements
  - Understand location of deposition over time
  - Gamma scintigraphy limited to 2 dimensions (SPECT / PET offer 3D)



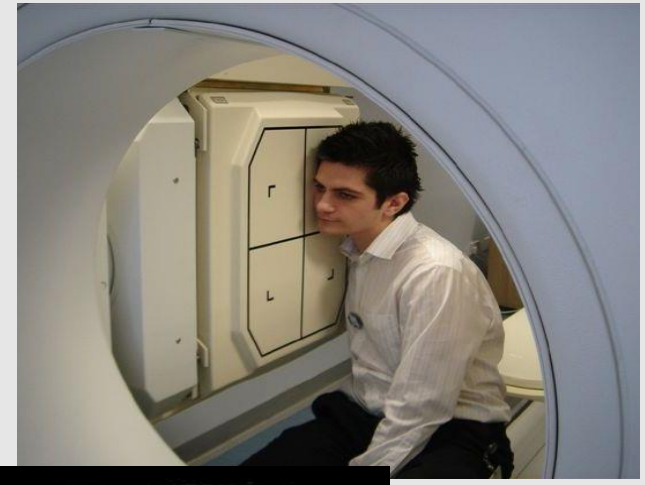


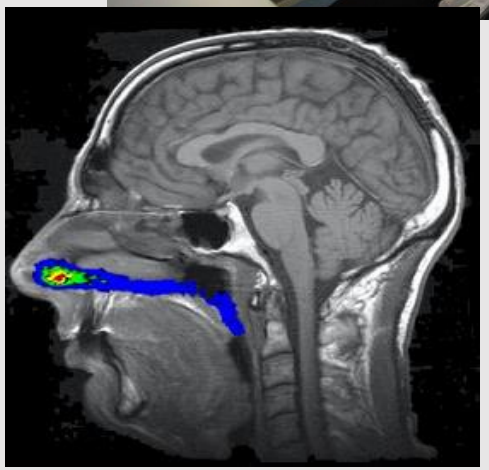
SUBJECT: Gamma photon emitted → COLLIMATOR: Parallel rays enter camera → CRYSTAL: Conversion to light photon → PM TUBES: Amplify / convert to electronic → ELECTRONICS: Digital (location / energy) → IMAGE: Matrix and colour scale

https://doi.org/10.2165/00137696-200402020-00003

Scintigraphic imaging and analysis of nasal delivery

- **Gamma emitting radionuclide is incorporated into the test article/formulation (usually technetium-99m (99mTc), half-life = 6 hours) administered and gamma camera used to visualise and quantify the radioactivity**
- **Following administration of radio-aerosol or drops, images acquired with gamma camera**
- **Co-registration with MRI to define shape of nasal cavity**
- **Quantification of deposition in:**
  - Nasal cavity (whole, regional)
  - Nasopharynx / swallowed
  - Lungs
  - Device
  - Nasal wipes (tissues)



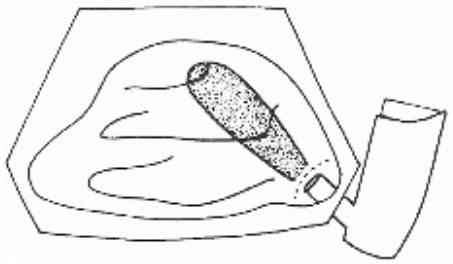


***** Typically radiolabel the product, <u>not</u> the drug *****

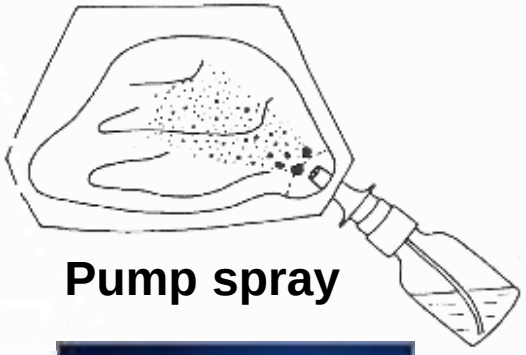
Radiolabelling Methodologies with 99mTc Techniques

- **Formulation spiking**
- **Solution pMDIs**
- **Nebuilisers**
- **Soft Mist Inhalers**

- **Surface labelling of Drug Particles**
  - Suspension MDIs, DPIs
    - Technically challenging
    - Historical non-solvent method
    - Potential to affect particle properties
- **Technecoat™ technology no longer in use at Quotient**



Pressurised MDI



Pump spray

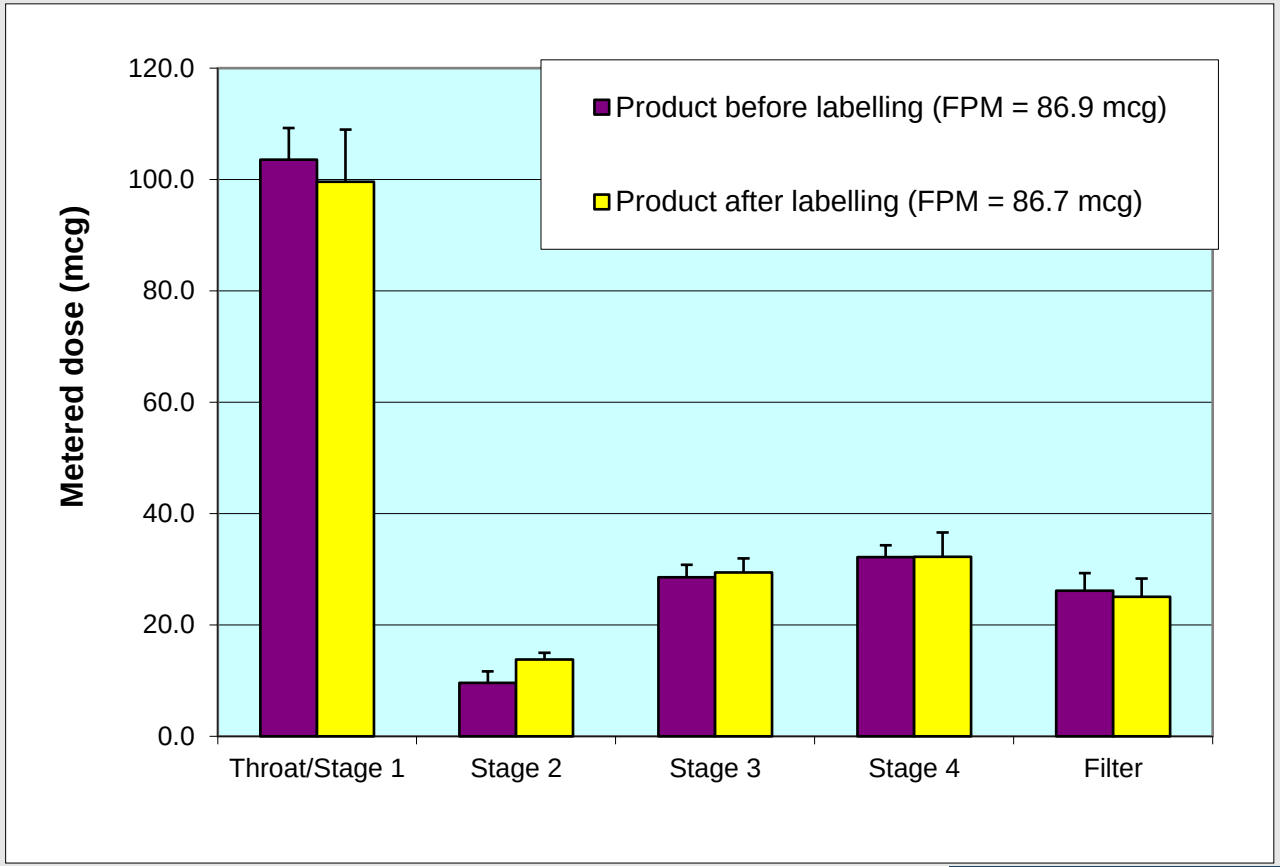
Nasal drops

Powder inhalers?

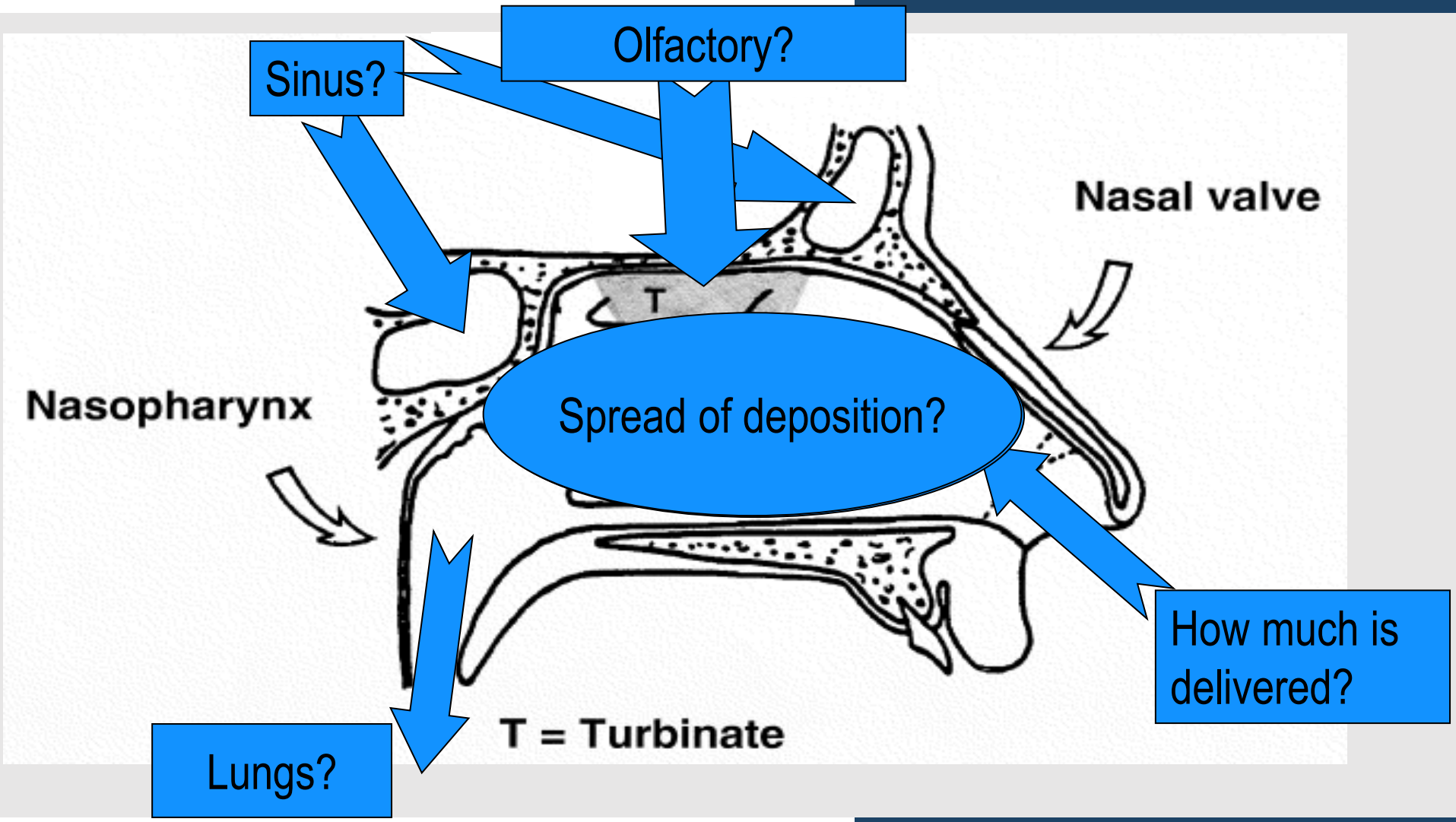
Radiolabelling Validation Data

Does the radiolabelling process alter the product?

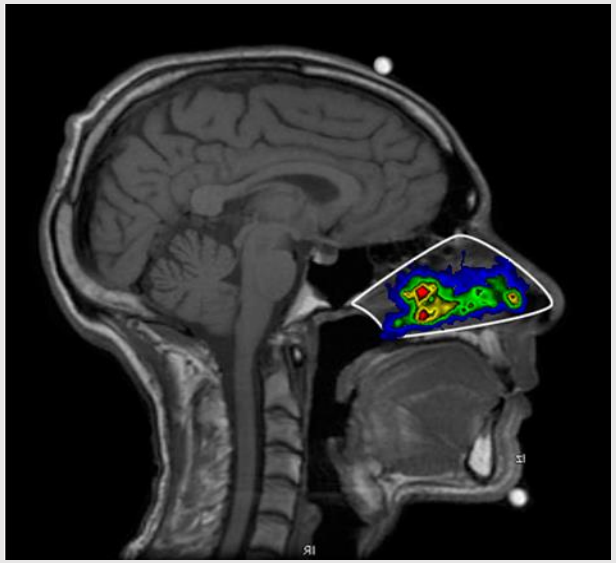
Is the radiolabel a good marker for the drug?

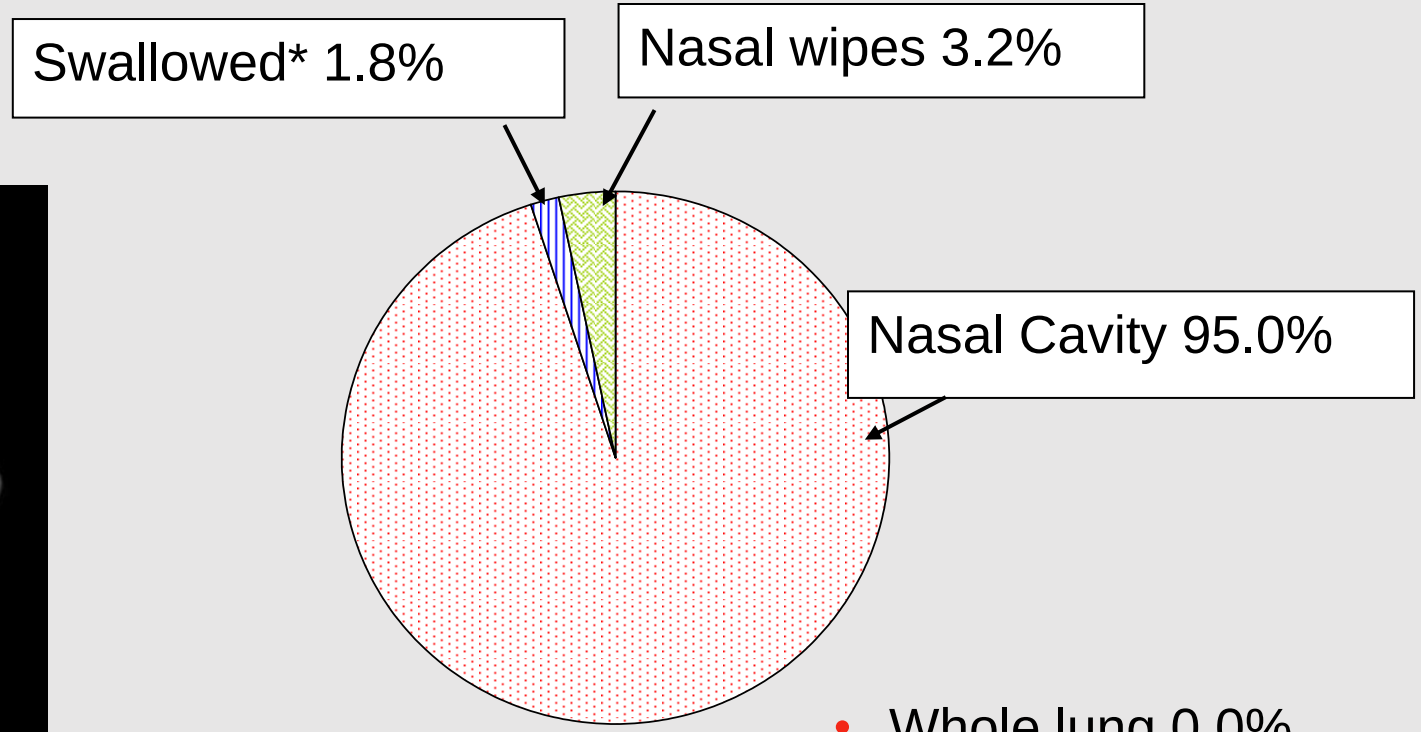


Key questions in nasal delivery in vivo addressed by gamma-scintigraphy in conjunction with MRI



Case Study: Comparing nasal delivery from different devices

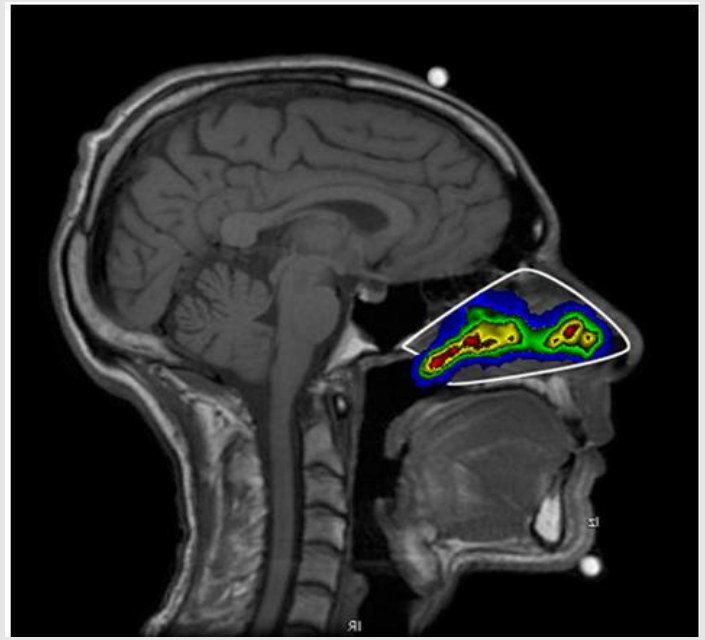


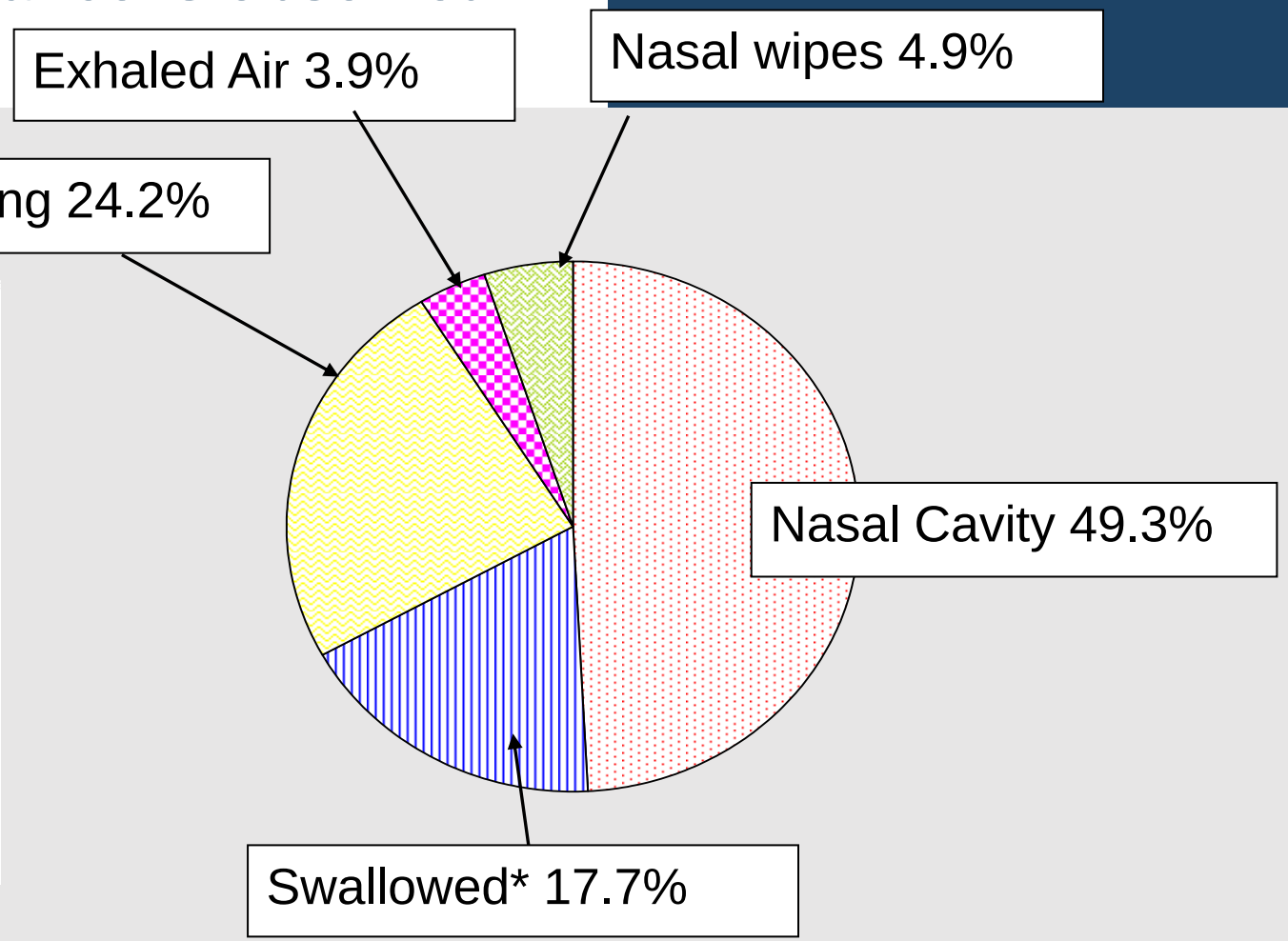


- Whole lung 0.0%
- Exhaled Air 0.0%

Delivery from a conventional pump spray is largely retained in the nasal cavity

Different in vivo performance is observed from nebulised delivery

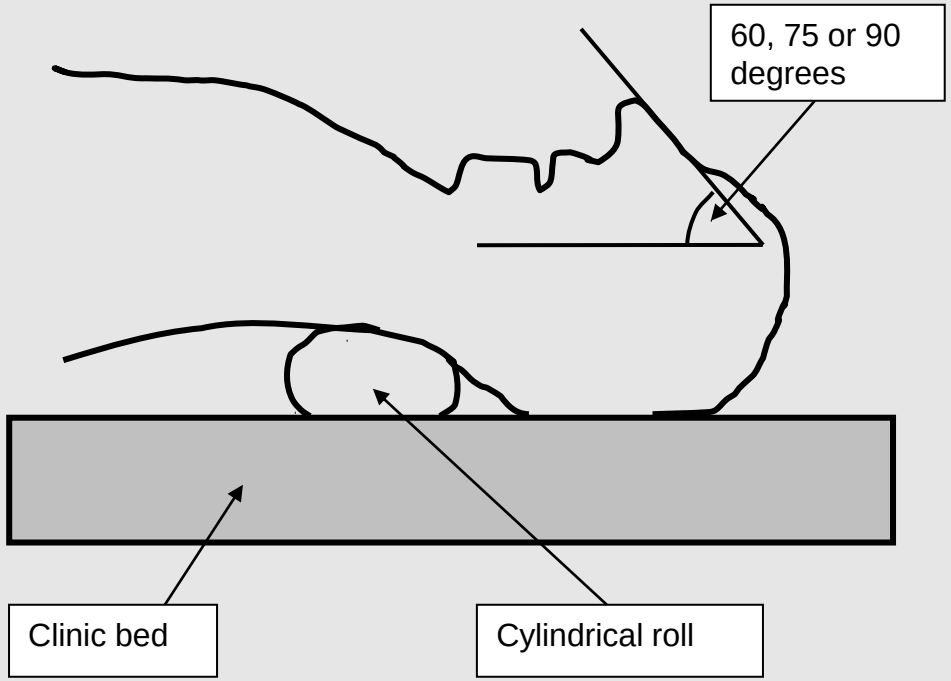




Increased deposition in lung indicates this device is less suitable for local delivery

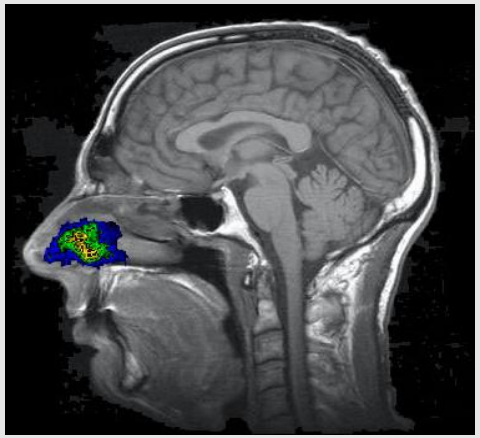
Case study: quantifying olfactory delivery via nasal drops

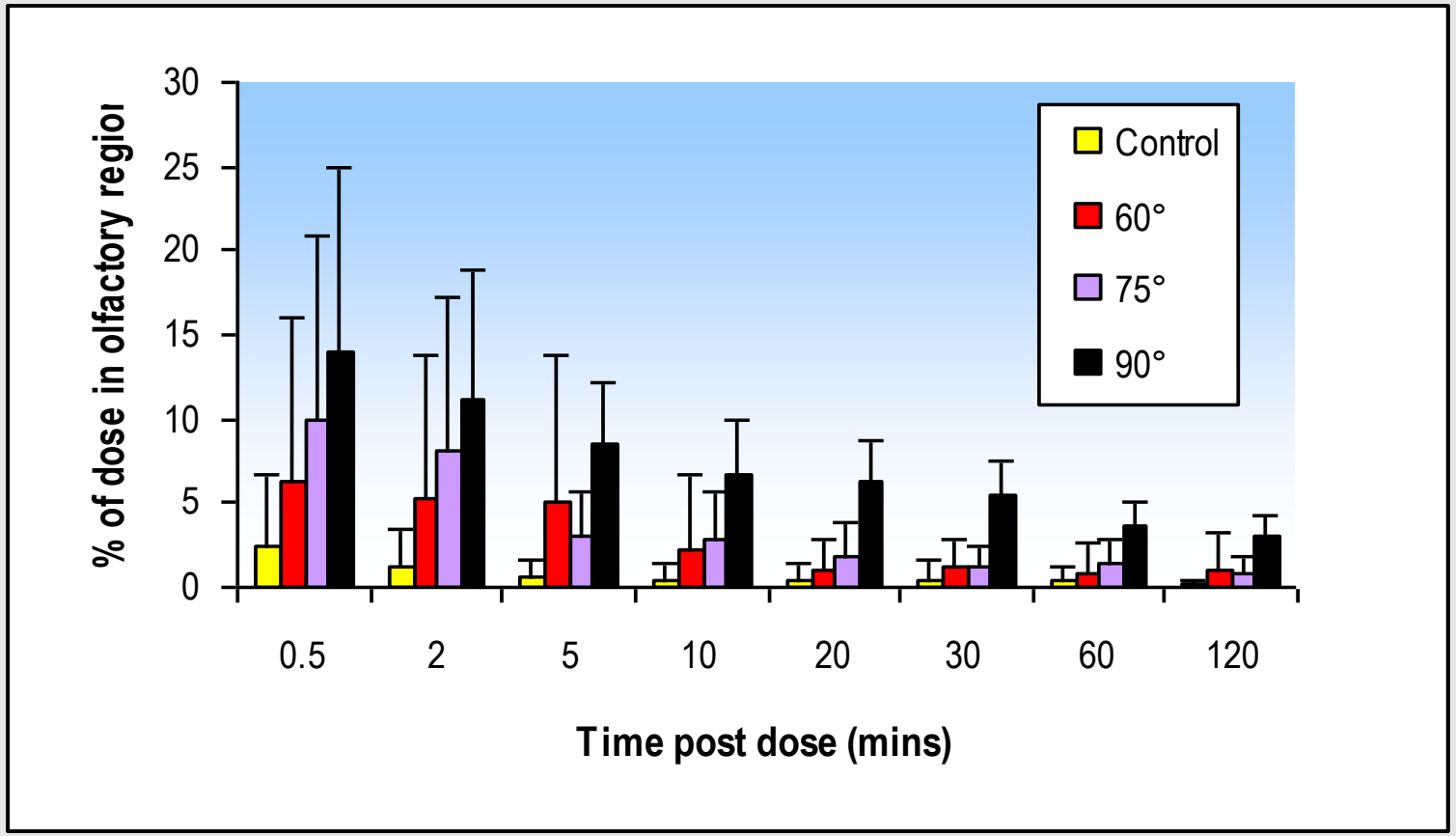
- 100µL placebo solution given via syringe & cannula
- 4-way cross over in 8 healthy volunteers
- 4 dosing positions; head flat on bed (control) and 3 positions where head held such that angle of the nose was:
  - 60°
  - 75°
  - 90°
- Images acquired over 2 hours



Scintigraphy results indicate how delivery will affect olfactory deposition

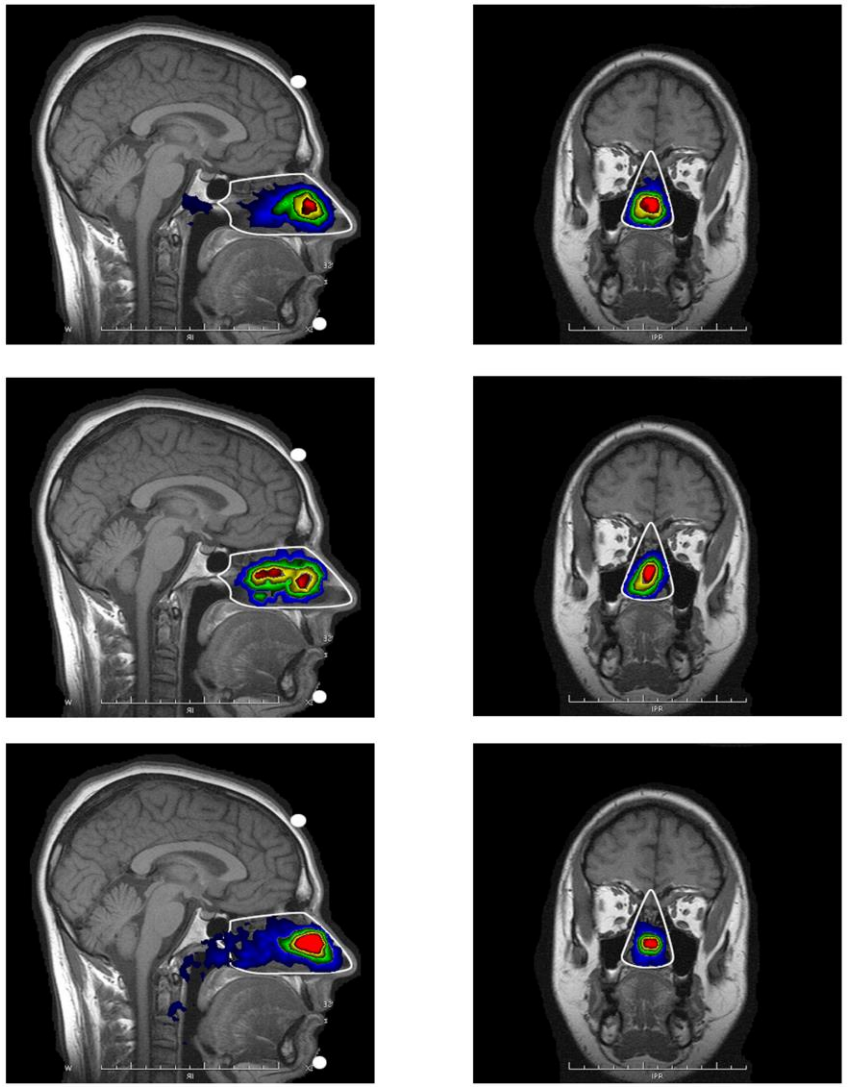
Position D (head tipped right back) reduces variability and achieves best olfactory deposition with this device





Case Study: Assessment of Sinus targeting

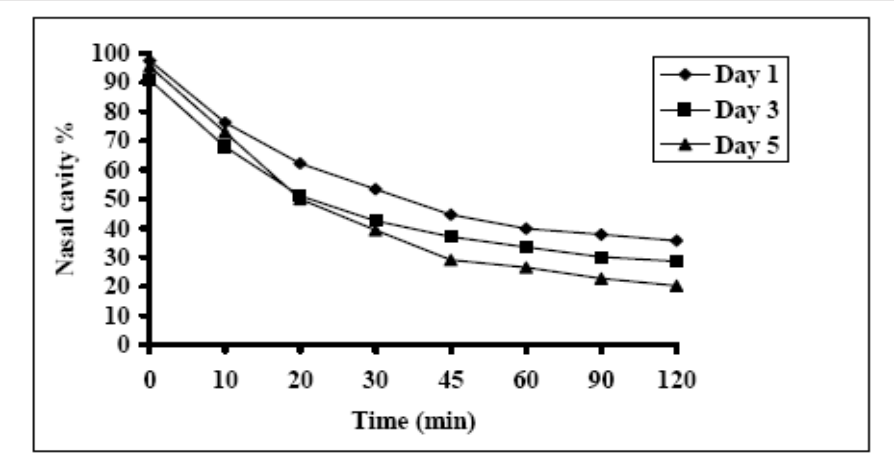
- **Quantification of delivery to sinus regions is also possible**
- **Opportunity to select or optimise device for regional targeting of local indications**



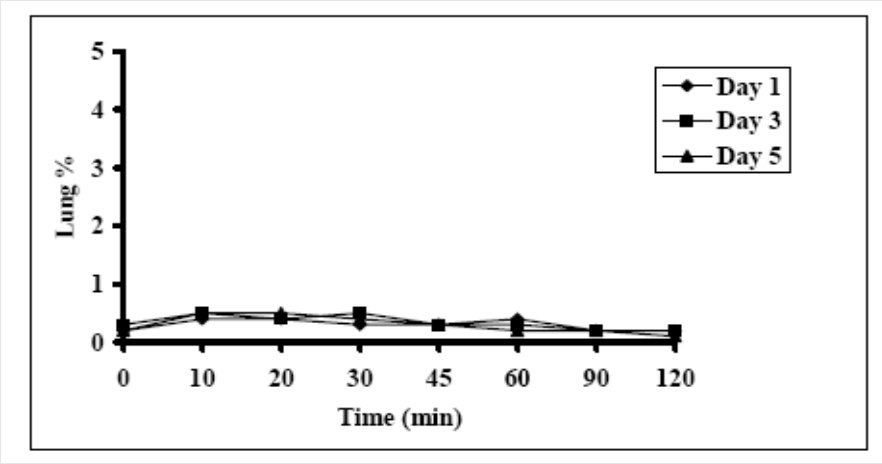
Case study: chitosan formulations for nasal retention and avoidance of lung delivery

- **Evaluation of lung and nasal drug deposition of a chitosan formulation from a Pfeiffer unit dose pump spray**
- **14 healthy volunteers tested at the same time on five successive days, variability data obtained**

Data shows drug retained in nasal cavity

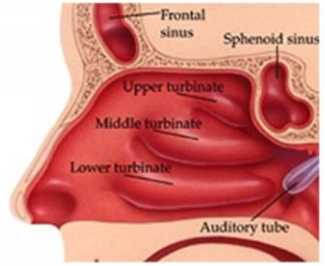


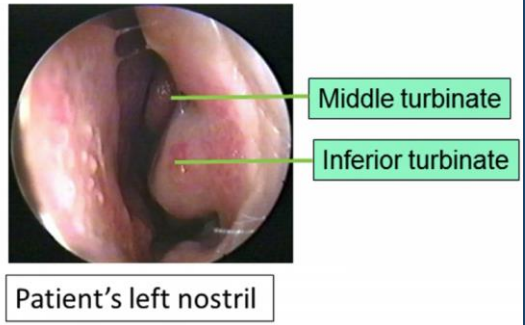
…and negligible amounts reach the lung



Nasal wick evaluations

- Potential benefit vs e.g. nasal wash in terms of sensitivity and variability
- General points / procedures
  - Careful examination of nasal anatomy performed initially
  - Weight of the wick (or wick plus tube) measured before and after sampling
  - Nose tip pushed gently back and up and wick introduce carefully and precisely orientated horizontally backwards and not upwards
  - Flat surface of the absorptive matrices placed gently on the lateral wall of the nasal cavity, onto the lateral/inferior surface of the inferior turbinate.
  - The aim is fresh clear mucosal lining fluid (not lumps of mucus or congealed matter)
  - Typical nasolacrimal reflex: slight watering of the eyes.
  - Subject's own index finger used to apply slight pressure to absorb nasal secretions typically for 60 accurately timed seconds.
  - Wicks typically stored at -80°C before elution procedure in suitable vehicle and centrifugation prior to relevant bioanalysis

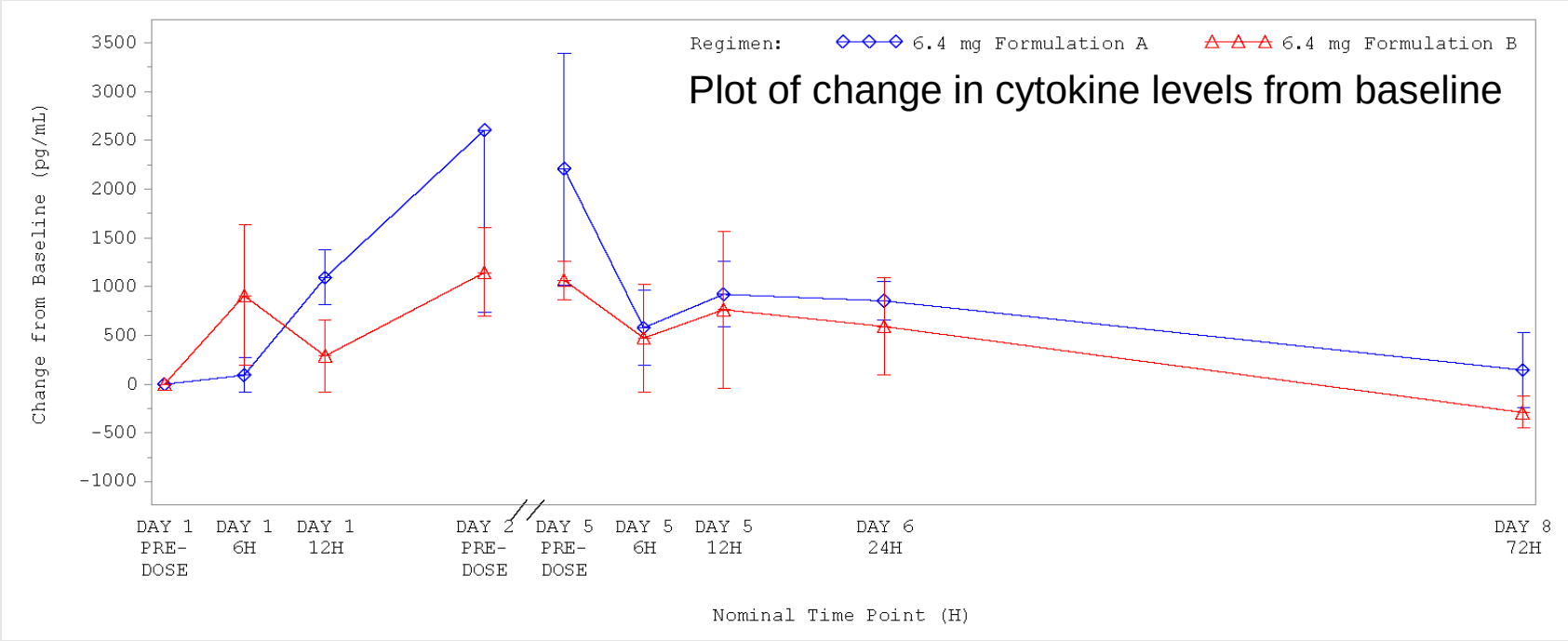




Case study – PD cytokine evaluation for two different formulations using nasal wicks

- To reduce the number of sprays/dose a subject would be required to administer a clinically relevant dose and to facilitate scale of manufacturing process, a novel nasal formulation (formulation B) was developed and evaluated in vivo vs reference nasal formulation (formulation A) over 5 days of dosing using nasal wicks

- Cytokine increased significantly by 24 h post dose for both Formulations A and B, with no loss of response following 5 consecutive doses before levels appeared to decline to baseline levels by 72 h following the last administration.



- Most frequently reported TEAEs were procedural haemorrhage (90% subjects), nasal mucosal disorder (85% subjects) and nasal crusting (75% subjects). These however were considered minor and AE similarity between placebo and active formulations indicated AEs may be related to either formulation excipients or the sampling.

Summary

Nasal drug delivery may be assessed in vivo to:

- Compare different delivery devices
- Investigate delivery to nasal regions
- Assess if pulmonary deposition occurs from nasally administered products
- Assess residence & clearance
- Assess drug and biomarker levels in mucosal lining fluid
- Can support a clearer understanding of the changes in in vitro parameters that are important for predicting differences in in vivo performance

Some Questions:

- Which clinical nasal product development / evaluation methods are key to enabling improved model development for prediction of in vivo performance?
- What next steps should/could be taken to enhance our holistic understanding of the interrelationship of the physicochemical properties of the drug, the dosage form and device performance characteristics on the robustness, rate and extent of drug deposition, residency, clearance and absorption for nasal products?
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Thank you

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