Aptar pharma

PRESCRIPTION DIVISION

Understanding Regulatory Global Requirements for Nasal Drug Products

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AGENDA

- NDA vs ANDA
- Regulatory Approaches for Bioequivalence (BE)
- FDA Drug Specific Guidances
- FDA, EMA and ANVISA Pharmaceutical Equivalence(PE) Comparison
- Improving BE Outcomes
- Chemistry, Manufacture and Controls (CMC)

Regulatory Pathways-US Perspective

- NDA: 505(b)(1)
  - Way most new drugs are approved
  - Full pre-clinical and clinical study
- NDA: 505(b)(2)
  - New formulations of existing drugs
  - Relies on previous studies or references published information
- ANDA: 505(j)
  - Generic drug submission
  - Same as the Reference Listed Drug (RLD)
- OTC Switch
  - FDA approval required
  - Treated as an ANDA
  - No OTC monograph issued (yet)

Why 505(b)(2)?

- Faster route to market
- Branded generic—exclusivity
- Sales force needed

	DISCOVERY	NONCLINICAL RESEARCH	CLINICAL STUDIES
505(B)(1)	2-5 YEARS	1-5 YEARS	8-15 YEARS
505(B)(2)	<1-3 YEARS	<1-2 YEARS	2-5 YEARS

505(b)(2) vs. ANDA

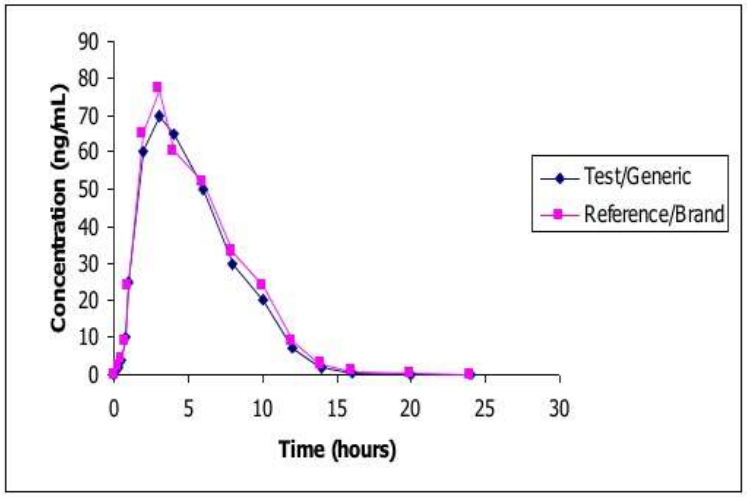
Test	505 (b) (2)	*ANDA
Scientific Studies	Partial	Bioequivalence
New Active Moiety	No	No
New Chemical Entity (Ingredient)	Yes/No	No
New Indication	Yes	No
New Formulation	Yes	No
New Dosage Form or Strength	Yes	No
Patented	Yes	No
Market Exclusivity	Yes	No**

** Except against other generics. * Abbreviated New Drug Application (ANDA)

Global Regulatory Perspectives: Generics

- FDA and Brazil (ANVISA) have issued guidances for bioequivalence (BE) of nasal and pulmonary drug products
- Europe (EMA) had issued a BE guidance on pulmonary products
- China releasing updated pharmacopeia
- Different approaches to bioequivalence
  - EMA applies step wise approach to BE
  - FDA applies weight of evidence
  - Brazil appears to follow FDA approach
  - Required tests and statistical approaches vary between regions

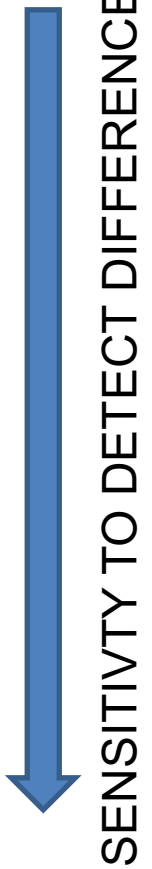
Definition of Bioequivalence



- Generally defined as the same rate and extent of absorption as the Reference Drug Product
- EU, US, Brazil and Canada all require bioequivalence
  - Common goal: Determine the effectiveness of the proposed generic's active ingredient[s] at the primary site of action.
- Requirements for chemical "sameness" of the active and non-active ingredients vary among regions
  - In US, *formulations* are expected to be quantitatively and qualitatively the same (within 5% of reference drug)
- FDA recommends device designs be as close as possible in all critical dimensions to those of the reference product.

FDA Approach for Bioequivalence

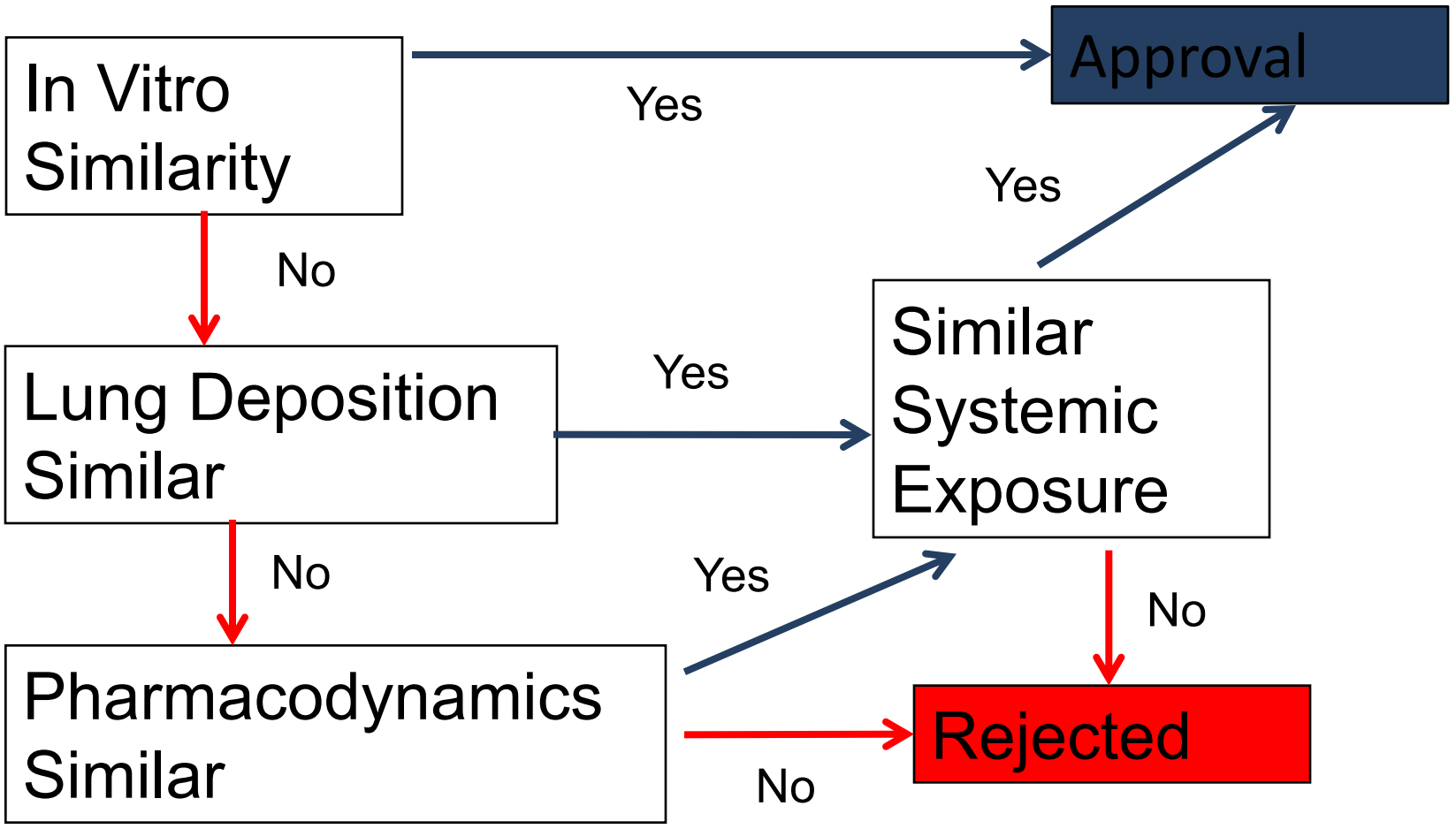
- Clinical endpoint
  - Same as a clinical study
  - Measure survival rate
- Pharmacodynamic (PD) endpoint
  - More sensitive than a clinical study
  - Measure lipid lowering
- Pharmacokinetic (PK)
- In Vitro Tests
- **Nasal and respiratory drug products place special emphasis on in vitro tests for ANDA applications**



EMA Approach

- Generic vs Hybrid
  - Generic establishes bioequivalence by PK
  - Hybrid established by PD, CE or other means
  - Many inhalation products are hybrids
- Prescribable vs Interchangeable
  - Prescribable determined at EU level
  - Interchangeable determined at National level

EMA Step Wise Approach**



**Applied to Inhalation Products Only

ANVISA Approach

- Generic nasal product
  - Contains same active pharmaceutical ingredient (API)
  - Uses similar excipients and polymorphic profile
  - Uses the same dosage form with similar device handling characteristics
  - Demonstrates in vitro equivalence
  - Demonstrates in vitro equivalence

ANVISA

- Technical note explains in vitro requirements
- No final guidelines issued
  - Decisions made on a case by case basis
- Therefore, each company seeking generic approval should submit proposals to Coordination and Therapeutic Equivalence Committee to establish relevant in vitro and in vivo studies

FDA Nasal Spray BE Requirements

- **Locally Acting Solution**
  - In vitro only
- **Systemically Acting Solution**
  - New guidances for Sprix, NasalFent and Imitrex
  - In vivo: if not qualitatively (Q1) and quantitatively (Q2) the same

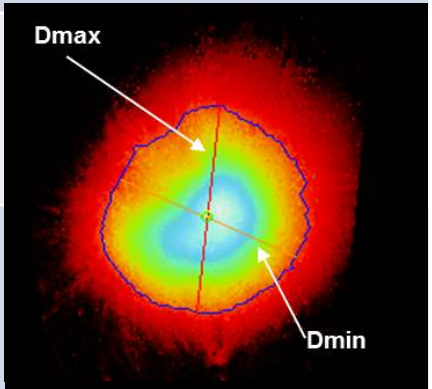
    OR
  - In vitro: Q1 and Q2
- **Suspensions**
  - In vivo
    - Clinical endpoint to assess local delivery +
    - Clinical endpoint to assess systemic exposure

      OR
    - Clinical endpoint +
    - PK study for systemic exposure

    AND
  - In vitro
  - *Particle size removed for mometasone*

In Vitro BE Statistical Analysis Per FDA Guidance
Nasal Spray Example

In Vitro Test	Statistical Process
Single Actuation Content Uniformity • Drug mass per actuation	Population Bioequivalence (PBE)
Droplet Size • Dv50 • Span	PBE
Spray Pattern • Ovality Ratio • Area	PBE
Plume Geometry • Width • Angle	Point Estimate
Particle Size by Microscopy	N/A
Drug in Small Particles by Cascade Impaction (Sprays)	Comparison of means by PBE
Prime Reprime	Point Estimate



Spray Pattern (SprayVIEW, Proveris Scientific)

ANDA Expectations (FDA)

- Q and Q

- Q1– Qualitative Sameness
  - Active & inactive ingredient the same as Reference Label Drug (RLD)

- Q2 – Quantitative Sameness
  - Inactive ingredients ±5% RLD

Statistical Approach for IVBE (FDA)

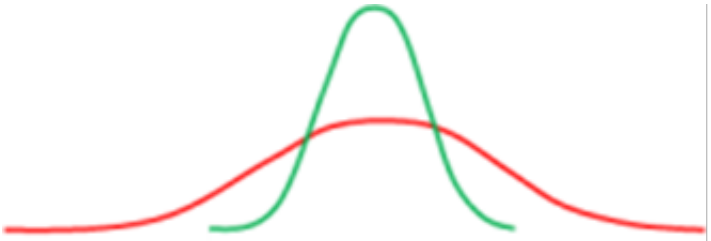
- Applies to both Nasal and Inhalation!!
- Defined in the Budesonide Inhalation Suspension Draft Guidance (September 2012)
  - **All FDA applications will be evaluated using this guidance**
  - **Ignore the examples in the 1999/2003 Nasal BE Drafts**
- ANVISA requires PBE
- EMA PBE and/or ABE

In Vitro BE Across Regulatory Bodies for Nasal Sprays

FDA	Brazil (ANVISA)	EMA
Droplet Size	Droplet Size	Droplet Size officially
Single Actuation Content Uniformity	Single Actuation Content Uniformity	Other in vitro tests appear to be used
Spray Pattern	Spray Pattern	
Prime Reprime	Prime Reprime	
Particle Size	Number of Metered Doses	
Plume Geometry	Pump Delivery	
Particles < 10µm		

Approaches for Increasing Success for In Vitro BE

- Evaluate RLD and Test during method development
- Perform pre-screening studies
- Avoid the temptation to compare averages and standard deviations to judge equivalence
- Sample variance is factored into the PBE equation



Pre-BE Studies—Nasal Spray Study

- Investigate likely hood of a successful outcome
- KEY TEST METRICS
  - Innovator and Generic Pumps tested with Innovator formulation
  - Hand study determined actuation parameters
  - All units acutated using Proveris Scientific platform
  - Droplet size (DSD) measured at beginning and end of unit life using a Malvern Spraytec
  - Spray pattern (SP) meaured using SprayVIEW
  - Plume geometry (PG) measured using SprayVIEW
  - Statistical analysis by population bioequivalence (PBE) and point estimates

IN VITRO BIOEQUIVALENCE: INNOVATOR VS GENERIC

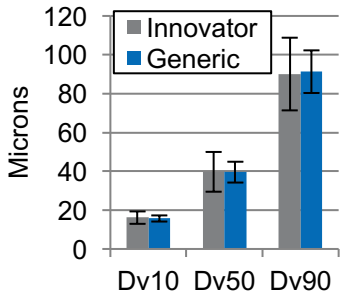
RESULTS

- All results show as average of 15 bottles

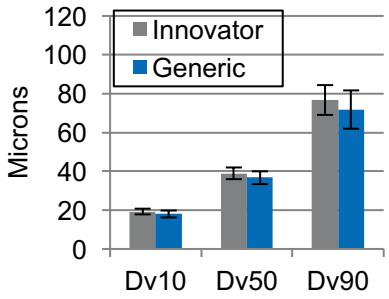
Average Spray Pattern Results

	Dmax (mm)		Dmin (mm)		Ovality Ratio		Area (mm²)	
	3 cm	6 cm	3 cm	6 cm	3 cm	6 cm	3 cm	6 cm
Innovator	21.2	34.6	25.4	47.1	1.204	1.364	437.5	1297.7
Generic	21.1	35.9	24.8	43.5	1.181	1.200	418.4	1252.8

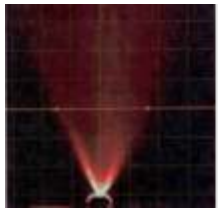
Droplet Size Distribution - 3 cm

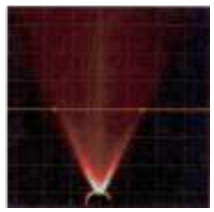


Droplet Size Distribution - 6 cm



	Innovator	Generic
Spray Angle (°)	51.0	52.0
Plume Width (mm)	28.9	29.3





IN VITRO BIOEQUIVALENCE SUMMARY

	DSD - 3 cm		DSD - 6 cm		SP - 3 cm		SP - 6 cm		PG	
	Dv50 (µm)	Span	Dv50 (µm)	Span	Ovality Ratio	Area (mm²)	Ovality Ratio	Area (mm²)	Plume Angle	Plume Width
Innovator	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Generic										

Outcome of Population Bioequivalence (PBE) Statistics reported for Beginning of Life (BOL) and End of Life (EOL)

FDA Chemistry Manufacturing and Controls Stability Studies

- Three registration batches required for both NDA **and ANDA** applications
- 24 to 36 month stability program
- Stability storage of drug product in multiple orientations, e.g. upright and inverted
  - Expands the scope of stability significantly
- Additional stability studies to assess foil overwrap, pouching or specialty packaging

FDA **CMC** Specifications for Nasal Sprays

- Appearance
- Identification
- Assay
- Impurities and degradation products
- Particulate matter
- Microbial limits
- Net content
- Leachables
- Weight loss on stability
- pH, osmolality, viscosity
- Pump delivery
- Spray content uniformity
- Spray pattern
- Plume geometry
- Droplet size distribution
- Particle size distribution

Release Testing

Stability

Support IND or NDA

Refer to CMC guidance—not all tests required on stability

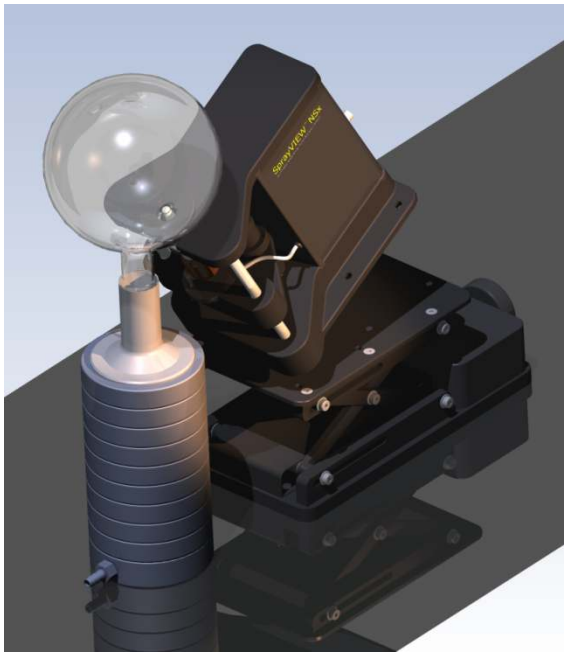
One Time CMC Studies

- Cascade Impaction
  - If for BE, not a CMC study
- Robustness
  - Drop & Vibration Testing
  - Cleaning
- Temperature Cycling
- Photostability
- Prime/Reprime Studies
  - Two orientations required
  - If for BE, one orientation for BE, second for CMC purposes

Short stack Andersen Cascade Impactor

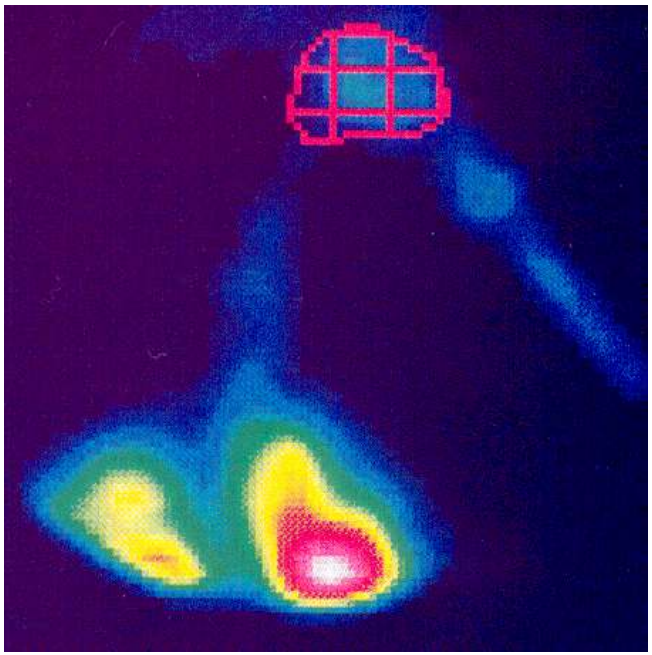
Amount of Small Particles by Cascade Impaction

- Not a measure of aerodynamic diameter
- Mass of “small droplets”
- FDA BE requirement

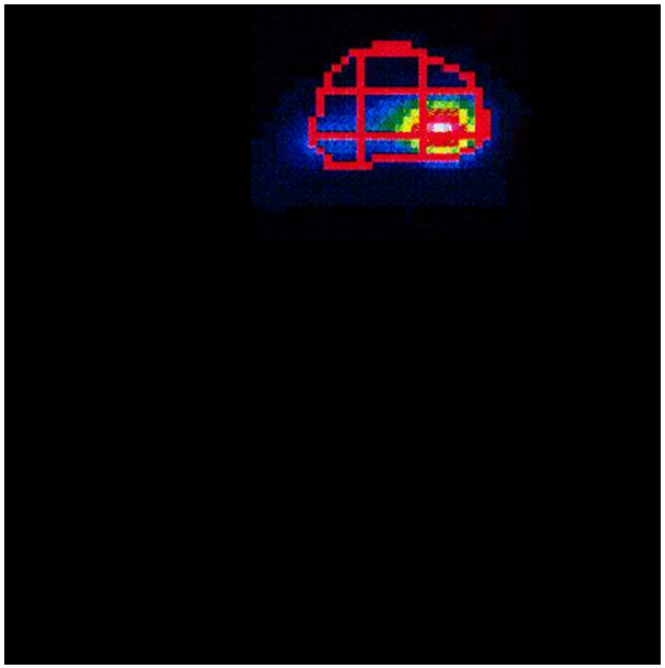


Lung Penetration Via the Nose?

No lung deposition was demonstrated following administration of radiolabeled saline by spray pumps



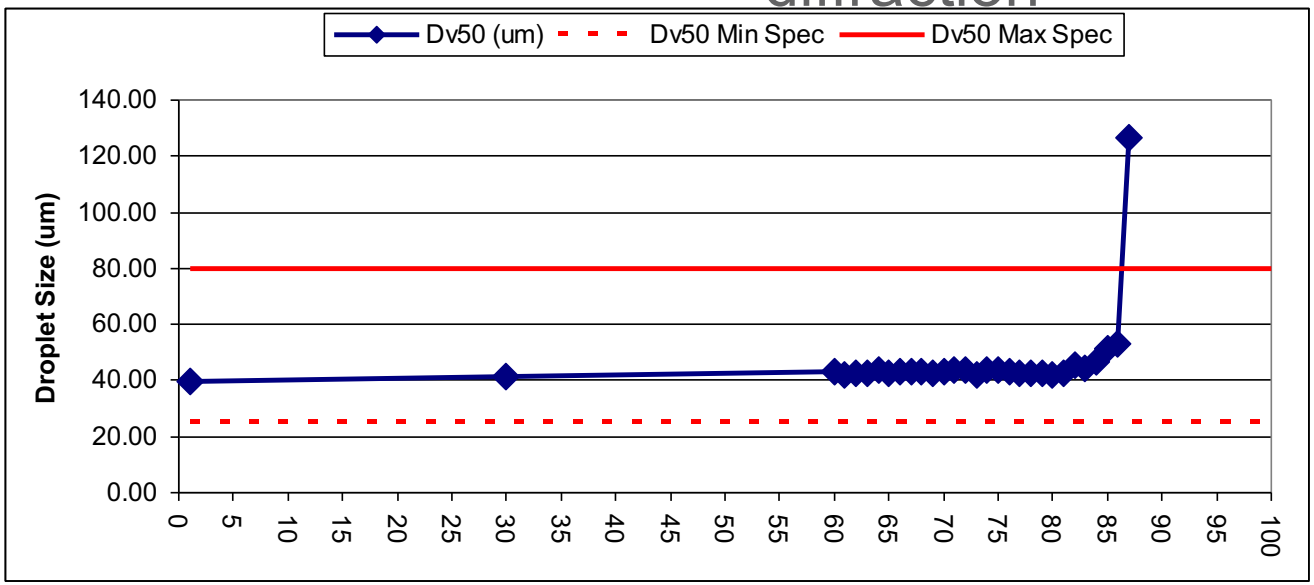
Ventilation scan showing radioactive gas penetrating the lungs and nasal cavity



Nasal spray scintigraph from a typical volunteer

One Time CMC Studies

- Tail-off (Profiling)
- Effect of Dosing Orientation
- Studies may include
  - Pump delivery
  - Spray content uniformity
  - Droplet size by laser diffraction



Example Tail-off Study Graph with Droplet Size Component

Release Tests: Regulatory Differences

Study	FDA	EMA/HC
Spray Pattern	X	
Plume Geometry	X	
Droplet Size	X	X

J. Suman, The Role of In Vitro Spray Characterization in the Development Cycle of a Nasal Spray Product, Inhalation Magazine, June 2009

- Thank you for your attention
- Questions????

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