From Bench to Clinic – Translating a new therapeutic into a commercially viable product for clinical trial

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5th October 2022

Who are we?

- We provide start-ups, SMEs and researchers with bespoke pharmaceutical drug delivery R&D and manufacturing solutions to help navigate the pathway from concept to first in human trials and beyond.
- The company was founded as a partnership between SLHD, the University of Sydney and ARCS and is supported by the MTPConnect Growth Centre
- Ab Intio is an independent company, agile with respect to partnership, client needs, IP handling and production liability.

We are a young company

- Established in 2019
- State of the art GMP small scale manufacturing labs in PMBC, RPAH Hospital, Sydney, Australia
- ~20 Staff
- Facility completed in 2022
- Full P1-3 manufacturing October 2022

ab initio pharma

R&D

Formulation development of NCE for therapeutic administration.

IP

Enhancing IP position via development of innovative delivery solutions.

TESTING

Commercial product characterisation & testing services .

SUPPORT

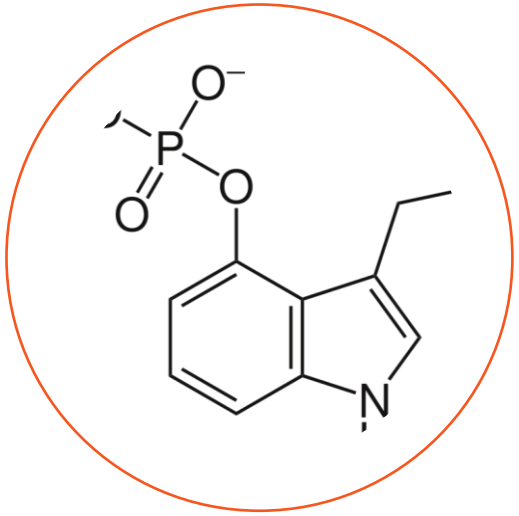
Expert support team & consultancy service.

MANUFACTURE

GMP manufacture for 1st in human and small scale commercial release of final product.

You've done all the hard work discovering your drug, you have an indication and want to conduct a clinical trial

What next?



A few Key things to consider (expertise)

Identify key steps/sections for IND package from day one

Implement GLP pre-clinical studies using API (and dosage form)

Identify Dosage form at an early stage (target, complexity & IP)

PIC/S2 API and Quality materials considerations from day 1

Formulation Development expertise

CMC expertise

PIC/S1 Finished product plan

Clinical trial strategy (Phase 1 ->)

Therapeutic Area	Phase 1	Phase 2	Phase 3	*Phase 1, 2, & 3 Subtotal [d]*	FDA NDA/BLA Review Phase [c]	Phase 4	Total [d]
Anti-Infective	$4.2 (5)	$14.2 (6)	$22.8 (5)	*$41.2 (3)*	$2.0	$11.0 (12)	**$54.2 (10)**
Cardiovascular	$2.2 (9)	$7.0 (13)	$25.2 (3)	*$34.4 (10)*	$2.0	$27.8 (4)	**$64.1 (6)**
Central Nervous System	$3.9 (6)	$13.9 (7)	$19.2 (7)	*$37.0 (6)*	$2.0	$14.1 (11)	**$53.1 (11)**
Dermatology	$1.8 (10)	$8.9 (12)	$11.5 (13)	*$22.2 (13)*	$2.0	$25.2 (7)	**$49.3 (12)**
Endocrine	$1.4 (12)	$12.1 (10)	$17.0 (9)	*$30.5 (12)*	$2.0	$26.7 (6)	**$59.1 (7)**
Gastrointestinal	$2.4 (8)	$15.8 (4)	$14.5 (11)	*$32.7 (11)*	$2.0	$21.8 (8)	**$56.4 (8)**
Genitourinary System	$3.1 (7)	$14.6 (5)	$17.5 (8)	*$35.2 (8)*	$2.0	$6.8 (13)	**$44.0 (13)**
Hematology	$1.7 (11)	$19.6 (1)	$15.0 (10)	*$36.3 (7)*	$2.0	$27.0 (5)	**$65.2 (5)**
Immunomodulation	$6.6 (1)	$16.0 (3)	$11.9 (12)	*$34.5 (9)*	$2.0	$19.8 (9)	**$56.2 (9)**
Oncology	$4.5 (4)	$11.2 (11)	$22.1 (6)	*$37.8 (5)*	$2.0	$38.9 (2)	**$78.6 (3)**
Ophthalmology	$5.3 (2)	$13.8 (8)	$30.7 (2)	*$49.8 (2)*	$2.0	$17.6 (10)	**$69.4 (4)**
Pain and Anesthesia	$1.4 (13)	$17.0 (2)	$52.9 (1)	*$71.3 (1)*	$2.0	$32.1 (3)	**$105.4 (2)**
Respiratory System	$5.2 (3)	$12.2 (9)	$23.1 (4)	*$40.5 (4)*	$2.0	$72.9 (1)	**$115.3 (1)**

EXAMINATION OF CLINICAL TRIAL COSTS AND BARRIERS FOR DRUG DEVELOPMENT

Hui-Hsing Wong & Amber Jessup
U.S. Department of Health and Human Services

Therapeutic Area	Phase 1
Anti-Infective	$4.2 (5)
Cardiovascular	$2.2 (9)
Central Nervous System	$3.9 (6)
Dermatology	$1.8 (10)
Endocrine	$1.4 (12)
Gastrointestinal	$2.4 (8)
Genitourinary System	$3.1 (7)
Hematology	$1.7 (11)
Immunomodulation	$6.6 (1)
Oncology	$4.5 (4)
Ophthalmology	$5.3 (2)
Pain and Anesthesia	$1.4 (13)
Respiratory System	$5.2 (3)

Phase 1

Target Clinic

- Pre-clinical (in vivo) cost upwards of $3m
- Phase 1 trials Respiratory trials have an average cost of US $5.2m
- Costs do not consider trial failures associated with poor formulation decisions, trial design, management of adverse risk profiles.
- Formulation CMC, preclinical and trial design essential for minimising cost and maximising success
- Important to consider Market and Registration (pre IND, IND – FDA, TGA, EMA)

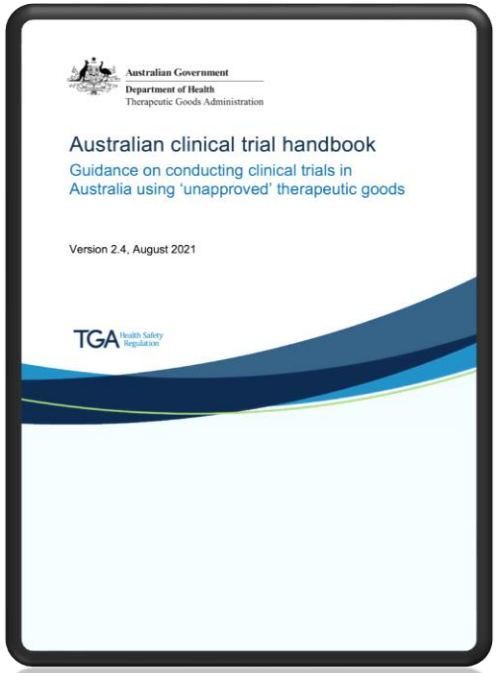
Some Essential skills

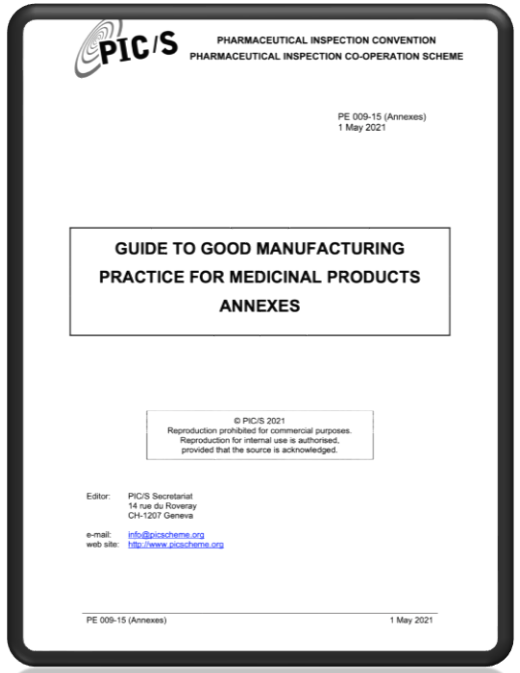
- Quality Management Systems
- Intellectual property
- Regulatory expertise
- TPP
- Pre-clinical expertise (tox/pk)
- Chemistry Manufacturing & Controls
- Industrial chemistry
- Formulation
- GMP
- Scale-up
- Financial & market modelling (COGS/manufacturing reimbursement etc.)
- Business & organizational management
- Corporate finance (VC, License etc.)

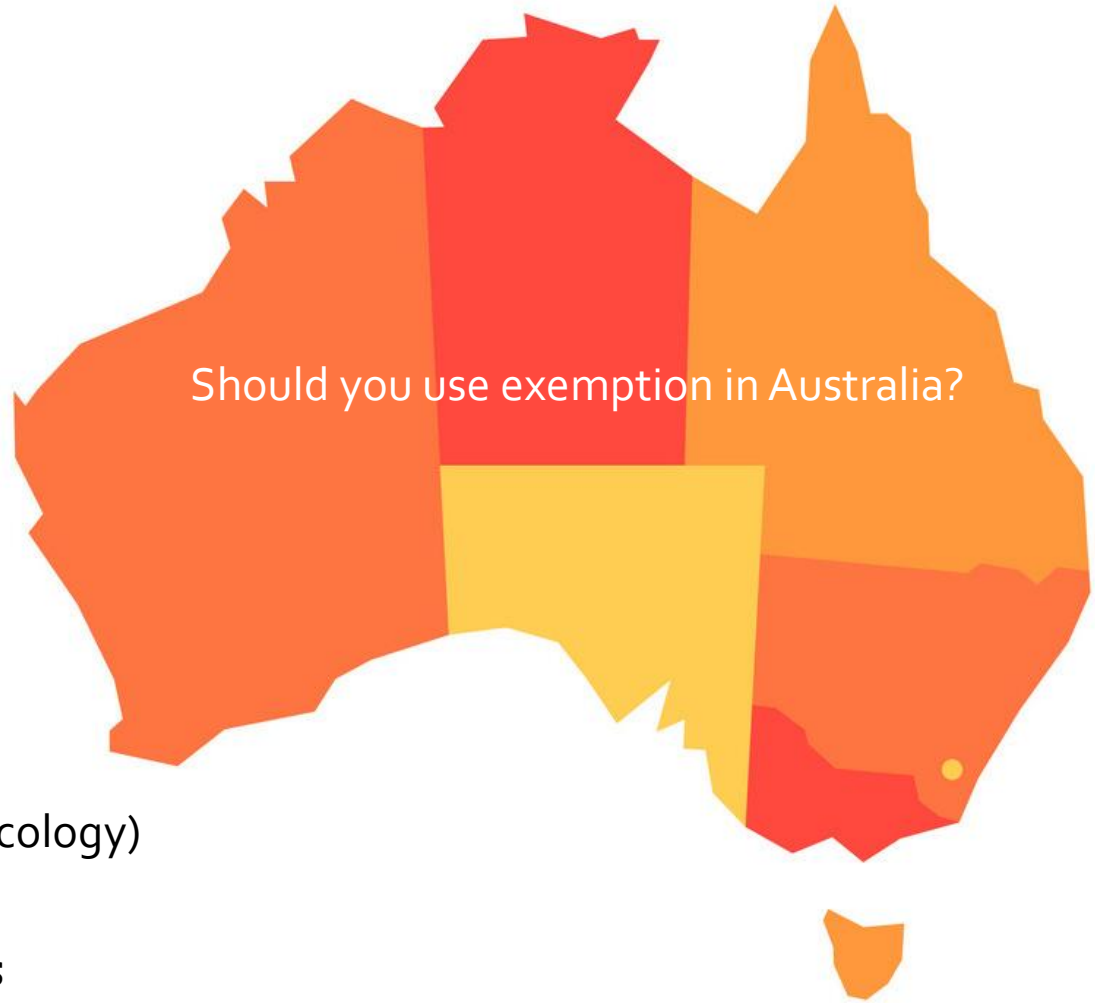
Funding

- NHMRC/MRF
- Government
- Incubation and Accelerators
- VC
- License & partnerships

- Plan ahead!







Phase 0-1 exemptions?

"initial experimental studies in human volunteers" (pharmacology)

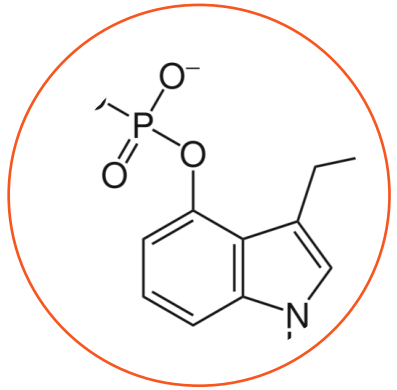
"Trial sponsors should ensure that they have thorough understanding of the principles of GMP in order to assess the quality of the therapeutic goods used in the trial."

"GMP compliance of the manufacturer is recommended to support the acceptance of clinical trial data overseas."

Lack of quality leads to significant exposure to liability for sponsor……

API

- Characterisation of API
- API stability (incl. rel substances)
- Safety and handling of materials with little toxicity data available
- Sourcing and importation PIC/S 2 (Lab vs. GMP is important)
- Identifying safe limits and cleaning validation
- Development of formulation and IP Protection



Quality Control

- Testing of incoming raw materials and packaging components
- Robust sampling plans and testing of finished products to ensure consistency
- Validated analytical methods
- Analytical instruments qualified and calibrated
- Environmental monitoring of cleanrooms

Facility Selection Criteria

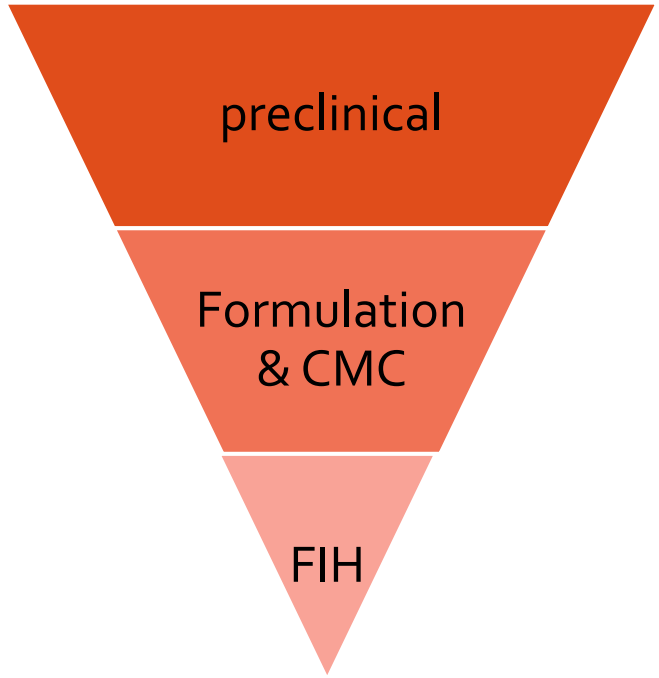
- Dosage form, dictates grade of GMP facility i.e. sterile vs non sterile
- Capability of handling NCE’s and high potency drugs (risk cross contamination)
- Cleaning Validation & equipment history
- Experience and training
- Equipment designed for correct scale (impacts number of batches)
- Site licensing (i.e. scheduled 4,8, 9 etc)
- License for process steps including QC, labelling release for supply, blinding etc

Technology Transfer

- Scaling up from R&D, is API and / or formulation still the same?
- Risk assessments to understand control of critical attributes
- Process validation
- Experience with dosage forms

Case Study (NCE-01)

- Novel small molecule; GMP; good liquid solubility; poor oral bioavailability
- Local pulmonary target (action designed to stay in the lung)
- Acute/ sub-acute indication of “X” (i.e., not chronic)



Challenges with Phase 1

- Inhalation dosage forms are complex
- SAD and MAD studies require controllable lung dosing
- At 10/100 fold safety margin, a 100 µg target dose would require an initial formulation of 1 µg
- Significant formulation challenge!

Solution

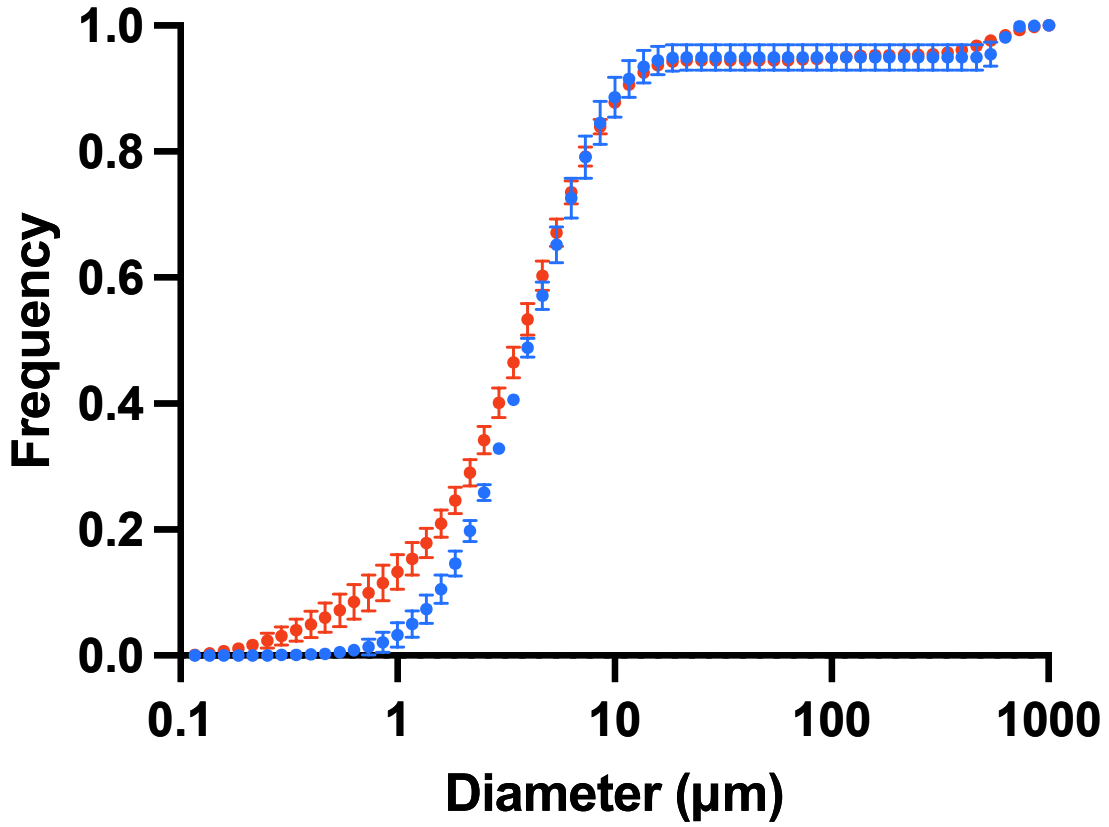
- Develop initial formulation as a nebulizer
- Build in end-to-end solution for formulation-preclinical-trial
- Utilize breath-by breath dosing regime to micro-dose subjects
- First in human trials establish safety/dose range
- Bridging study or simultaneous dual product development.

Human target

- GLP study conducted in small and NHP in GLP environment
- Similar molecules acting on target receptor suggest humans may have heightened response among species; but unknown for NCE-01
- Need for wide potential dose range to target receptor
- Using lung dose in pharmacology model as a guide, clinical human target “low” lung dose (ug) and high dose 100+ fold apart (mg)
- Need for titratable clinical delivery system with flexibility to cover a wide dose range

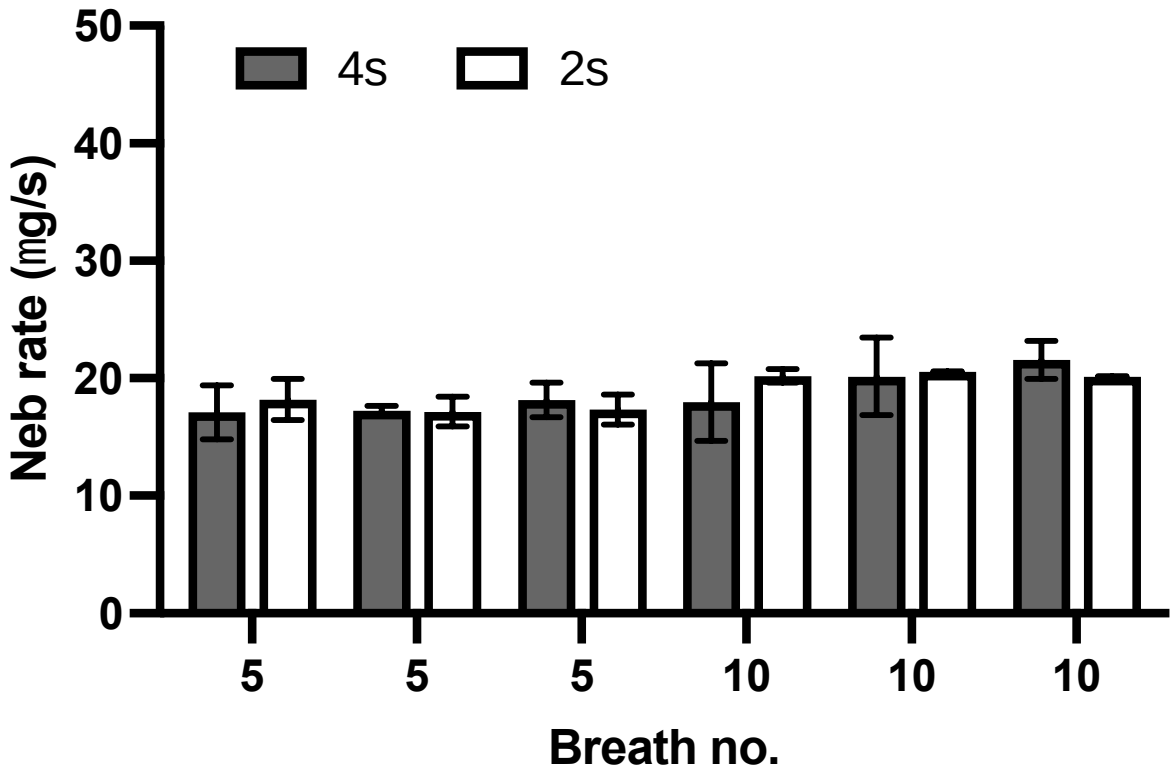
R&D Phase

- Solubility
- PhysChem Props
- Chemical stability
- Prototype formulations
- Initial testing using in line laser diffraction
- Narrowed lead formulations to two
- 0.1 mg/ml & 3.5 mg ml

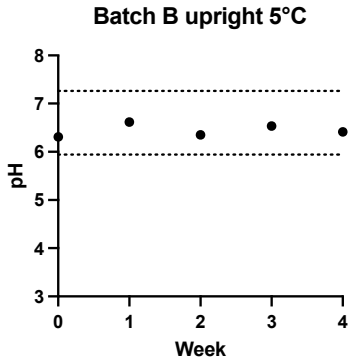


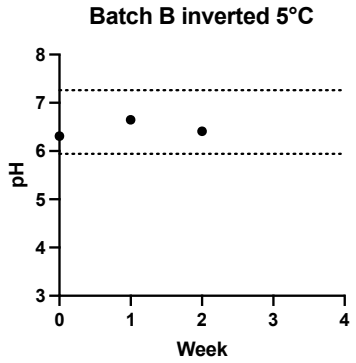
Breath by breath– initial trial concepts

- Consistent dosing through life for breath actuated nebulizer
- Consistent respirable fraction may allow controlled lung dosing from ng to mg



Stability


Batch B upright 5°C
pH
Week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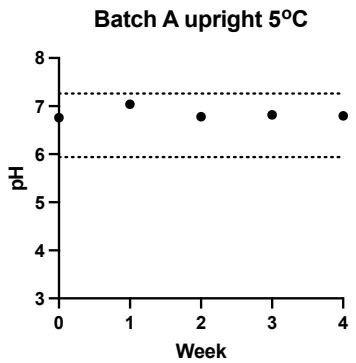
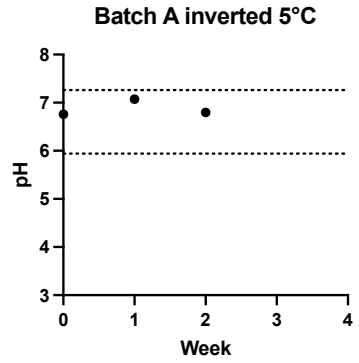
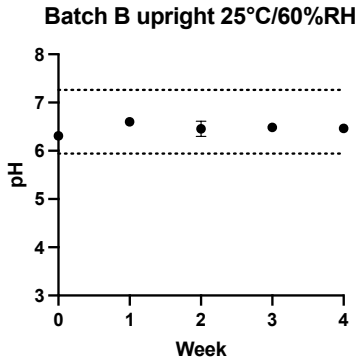
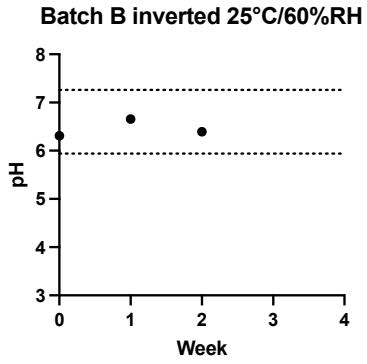
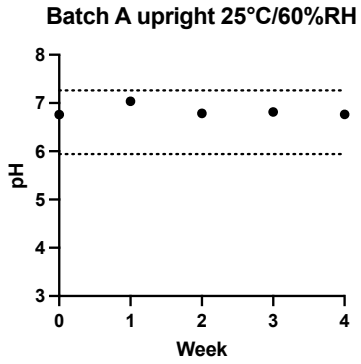
Week

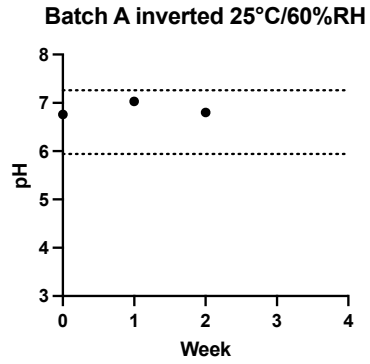

Batch A upright 5°C
pH
Week

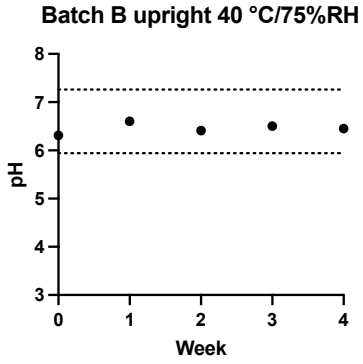

Batch A inverted 5°C
pH
Week

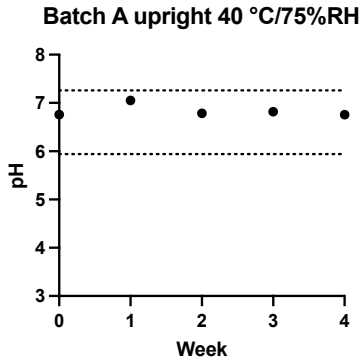

Batch B upright 25°C/60%RH
pH
Week


Batch B inverted 25°C/60%RH
pH
Week

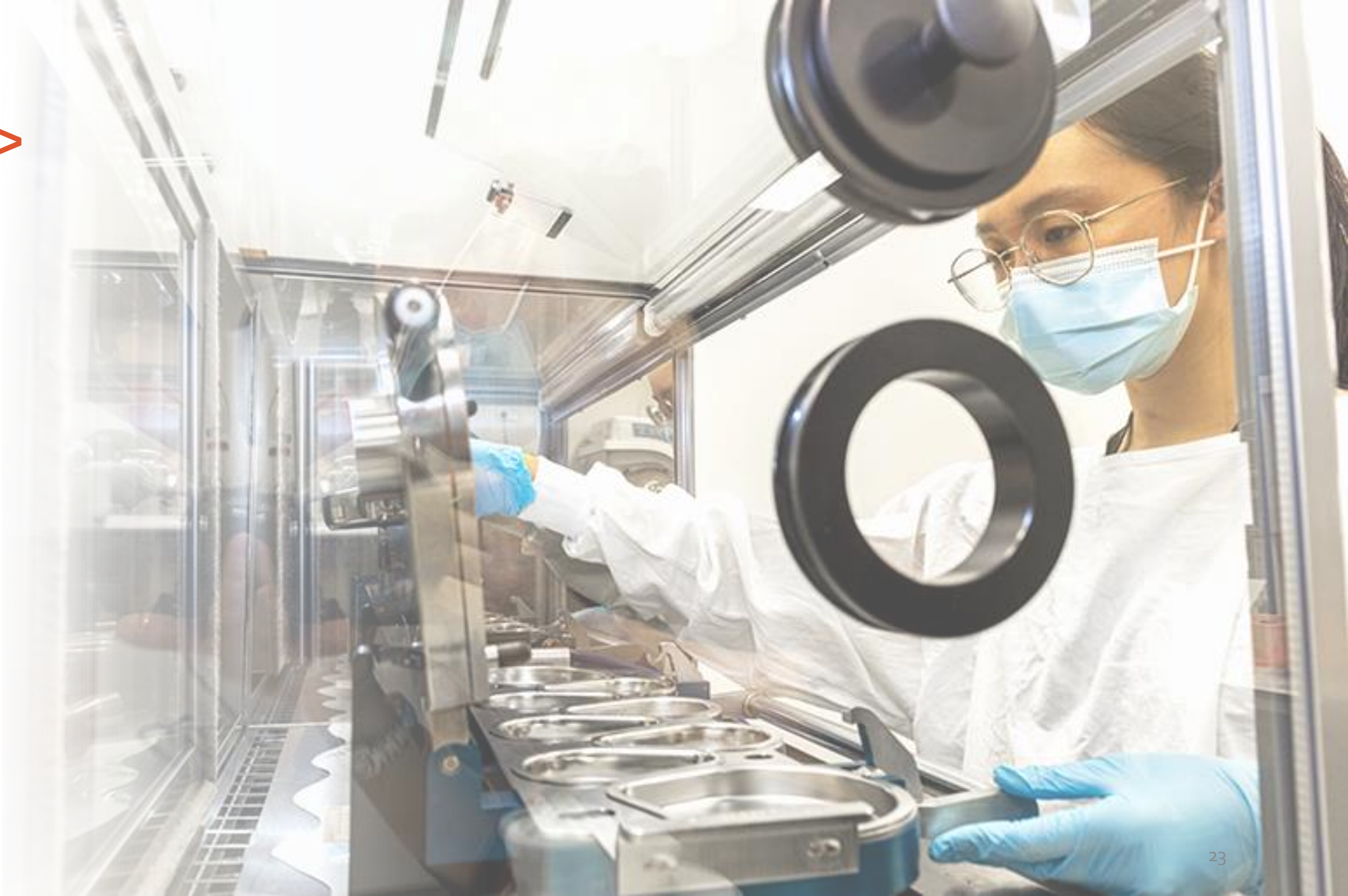

Batch A upright 25°C/60%RH
pH
Week


Batch A inverted 25°C/60%RH
pH
Week

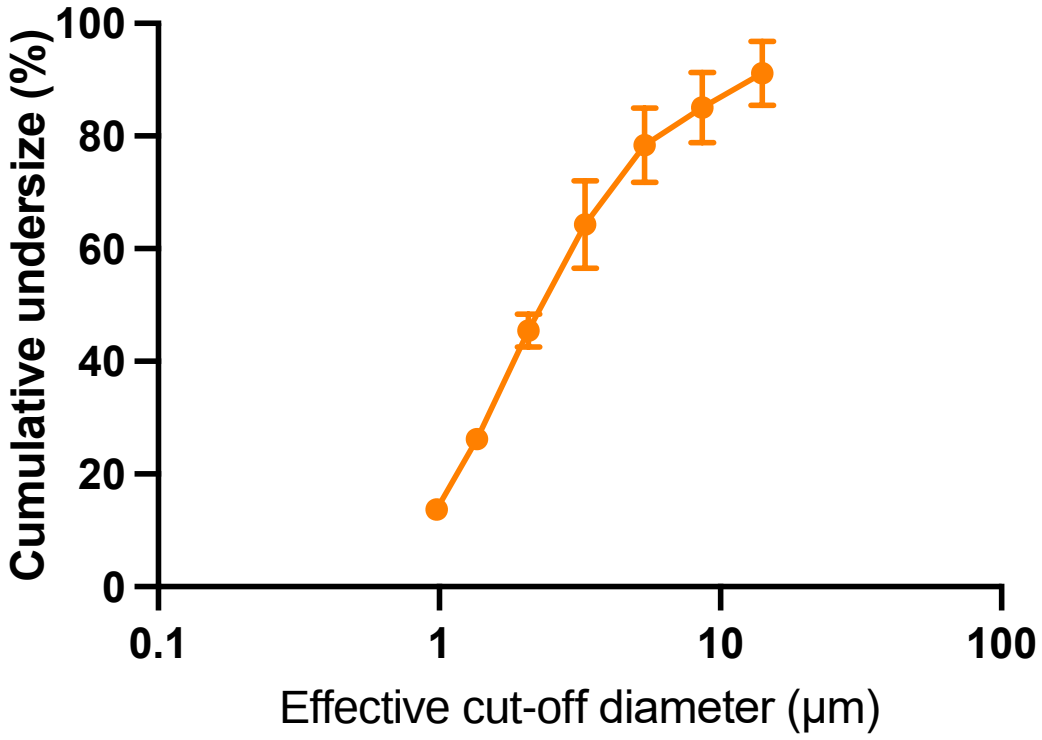

Batch B upright 40 °C/75%RH
pH
Week

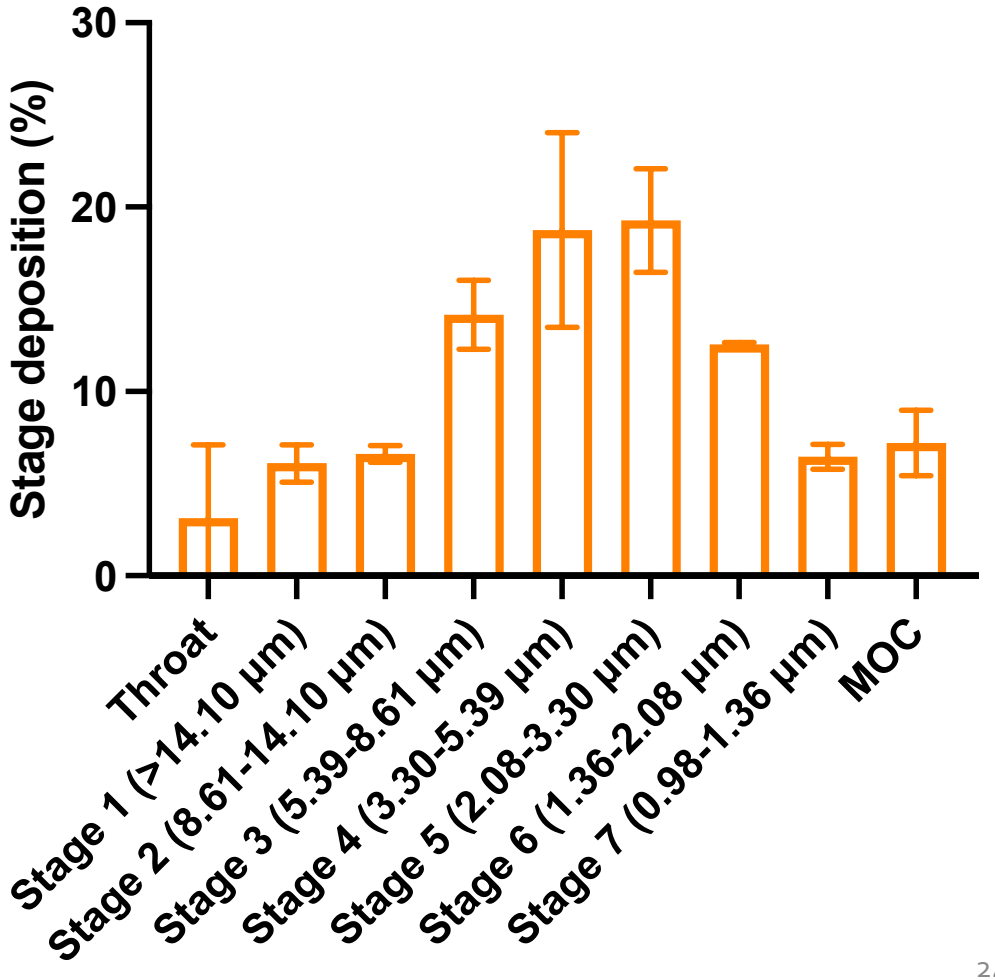

Batch A upright 40 °C/75%RH
pH
Week

APSD <1601>

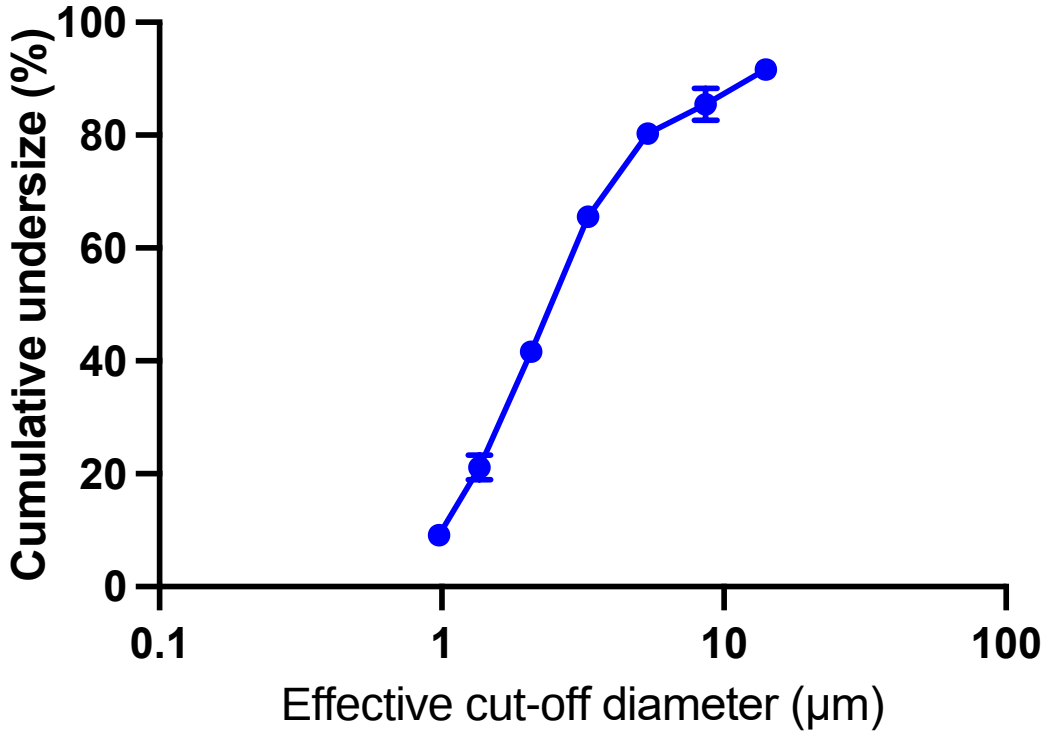


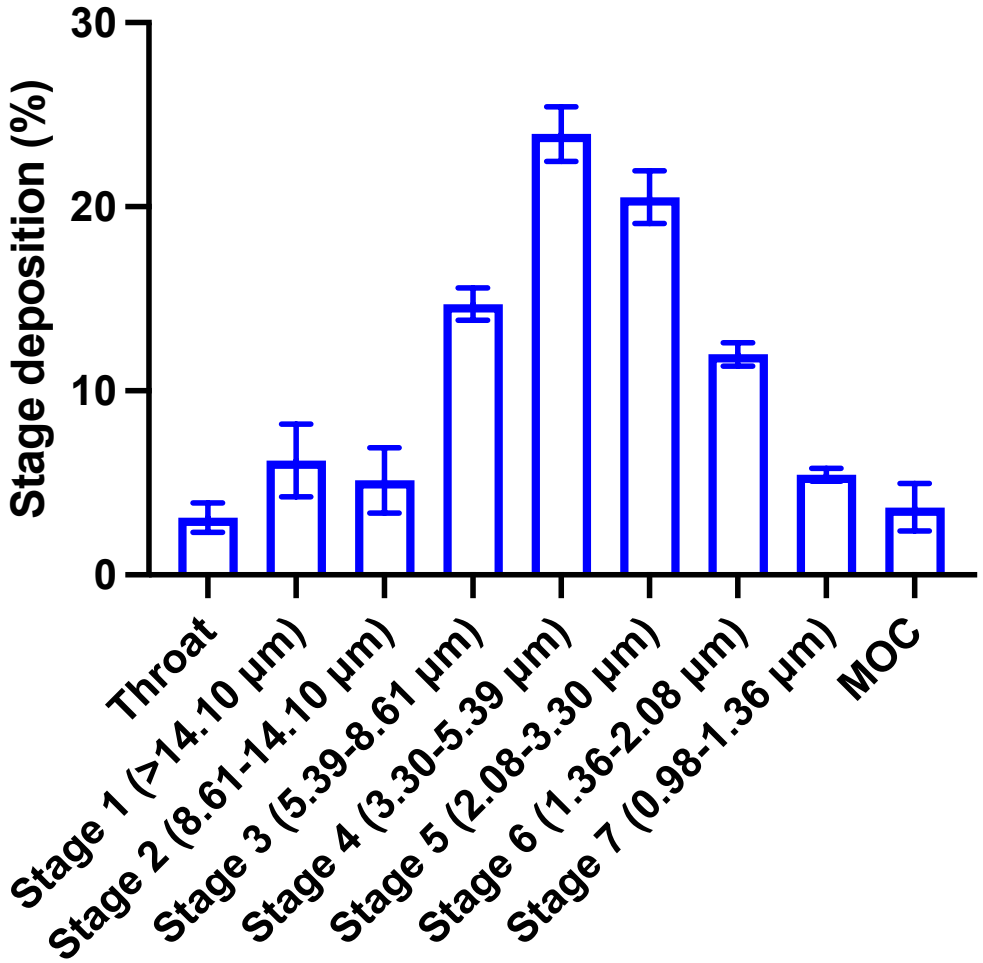
0.1 mg/ml – Next generation impactor <1601>





3.5 mg/ml – Next generation impactor <1601>



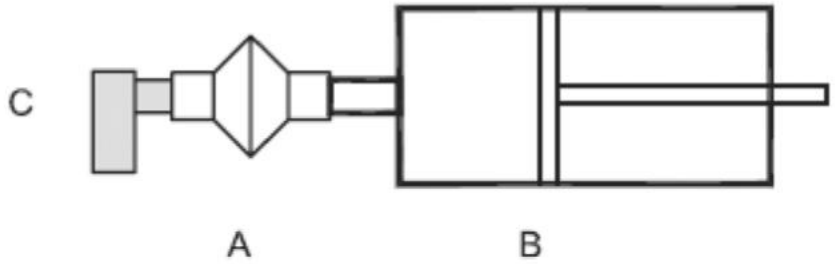


APSD

	0.1 mg/ml		3.5 mg/ml	
Parameter	Mean	StDev	Mean	StDev
Fine Particle Fraction (%<5 μm)	65.3	6.5	65.7	1.6
MMAD (μm)	3.3	0.1	3.6	0.1
GSD	2.4	0.2	2.1	0.1

Breath simulation <1601>

Item	Adult
Total volume	500 ml
Frequency	15 cycles/min
Waveform	sinusoidal
Inhalation:exhalation ratio	1:1

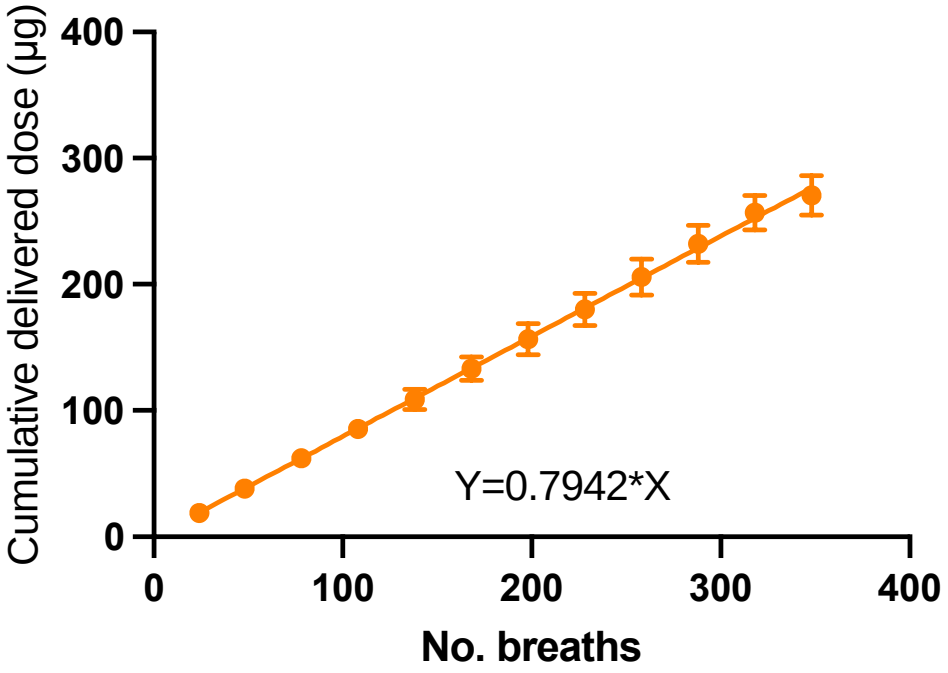


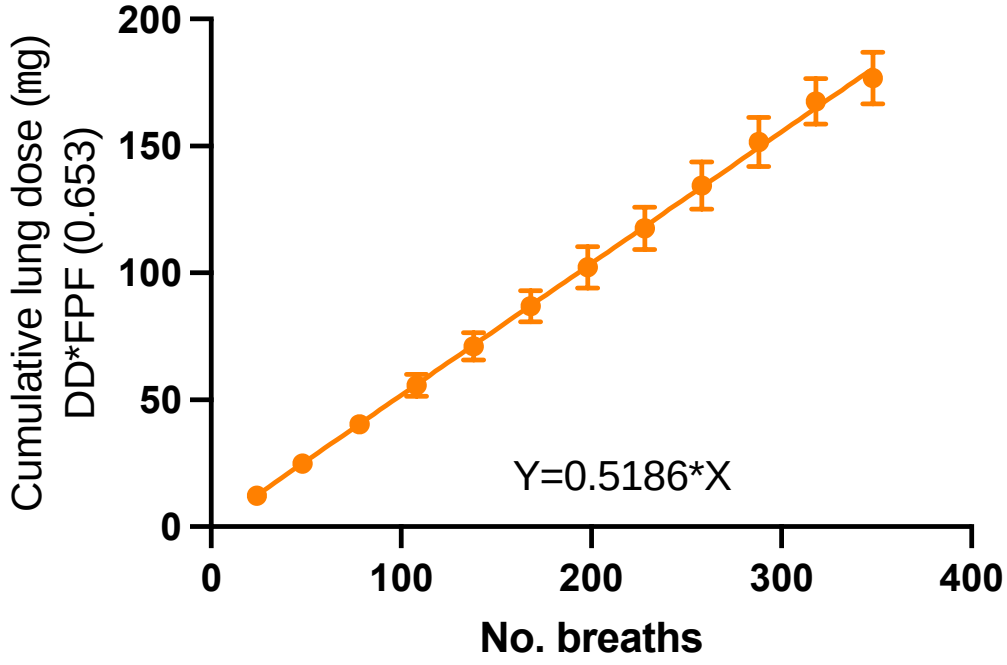
A. inhalation filter and filter holder B. breathing simulator C. nebulizer

Figure 1. Experimental Set-Up for Breathing Simulator Testing.

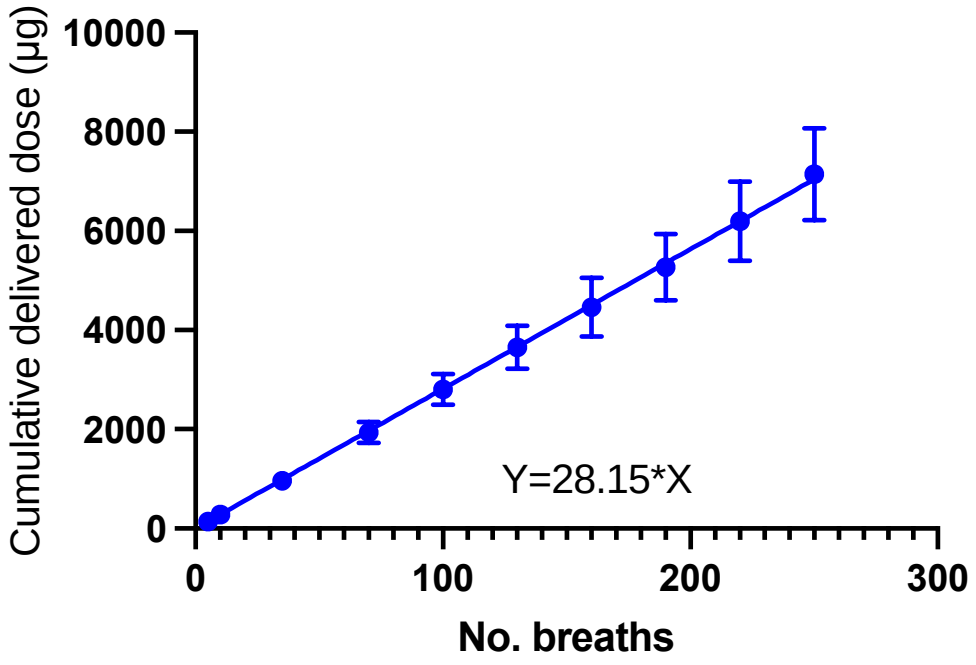
$$\text{Ave Lung dose per breath} = \frac{\text{cumulative delivered doses for n cyclcles x FPF (NGI)}}{\text{n cycles}}$$

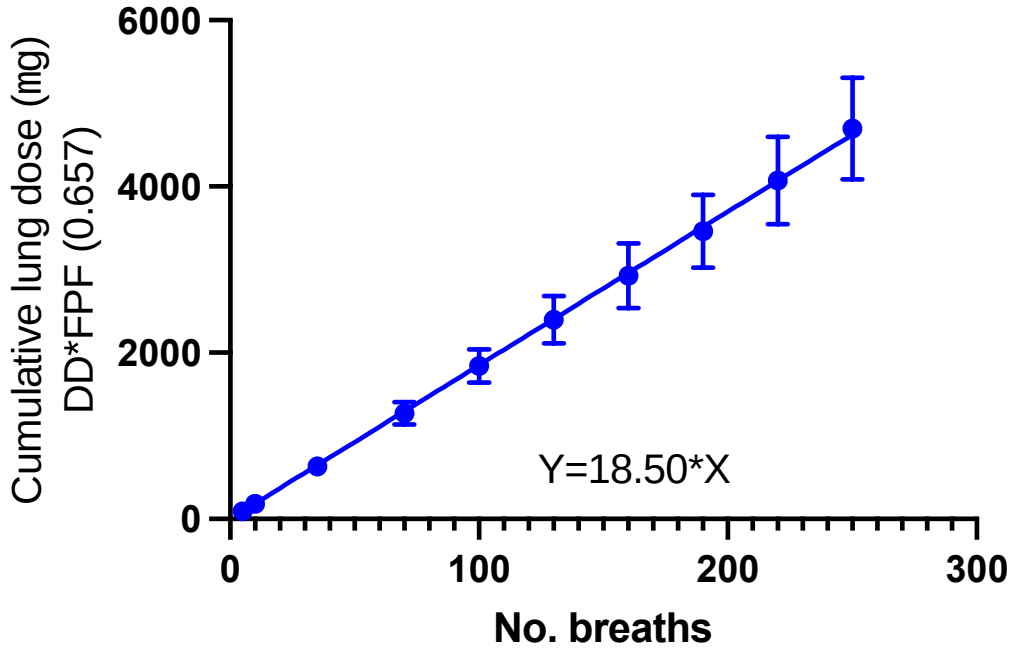
0.1 mg/ml - Breath-By-Breath



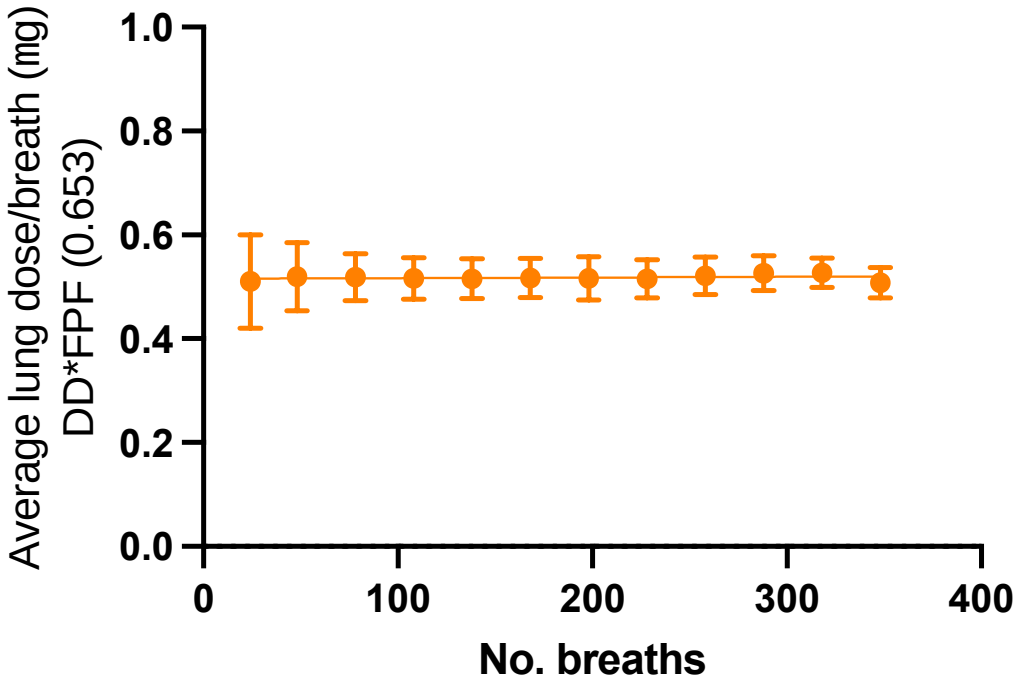


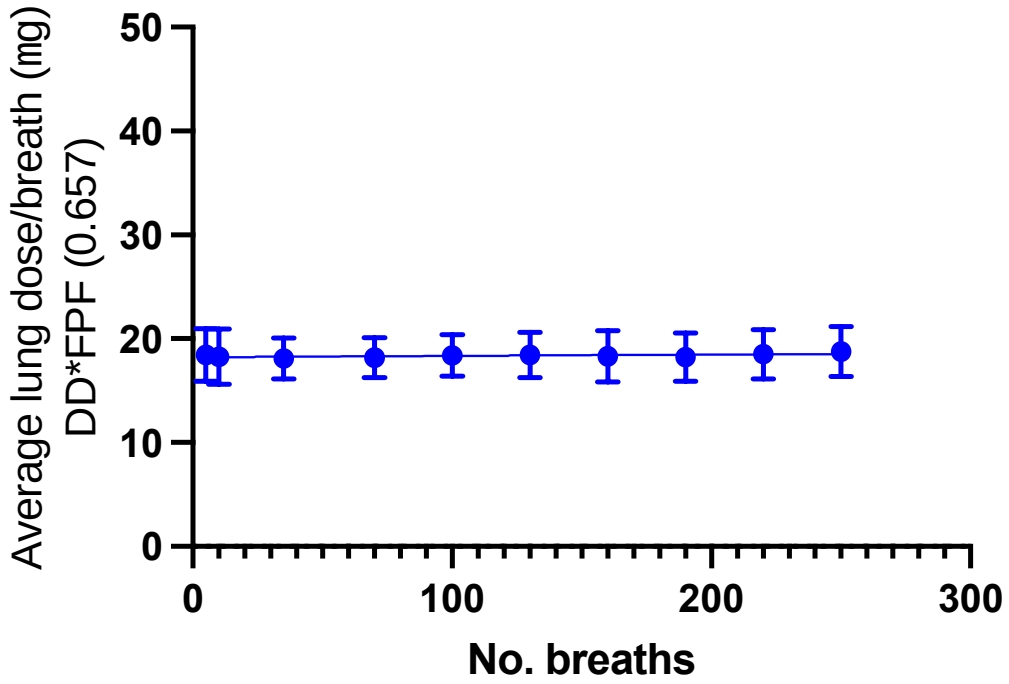
3.5 mg/ml - Breath-By-Breath





Average lung dose per breath





Summary

- Preclinical data package identifies SAD/MAD dose regime
- Formulation and CMC package for robust formulation that can be fast tracked to FIH
- Formulation developed specifically for dose ranging study and nebulizer/bridge
- Phase 1 trial ready

Looking to get clinical trial material formulated and/or manufactured to GMP?

Chat to the team

www.ab-initio-pharma.com