An acute regulatory challenge: The need for SimInhale and better *in vivo* predictions

SimInhale, Athens, Sept. 30, 2019.

Anders Fuglsang, PhD
Fuglsang Pharma
anfu@fuglsangpharma.com

Our paradigm

COPD and Asthma are highly prevalent diseases and a huge burden on healthcare systems globally.

Treatment options are numerous. Many common drugs are highly profitable and off patent.

= Generic developments.

But where are all the generics?

At least 9/10 projects are failing.
Zero info in the public domain about all the failure.

No publications.

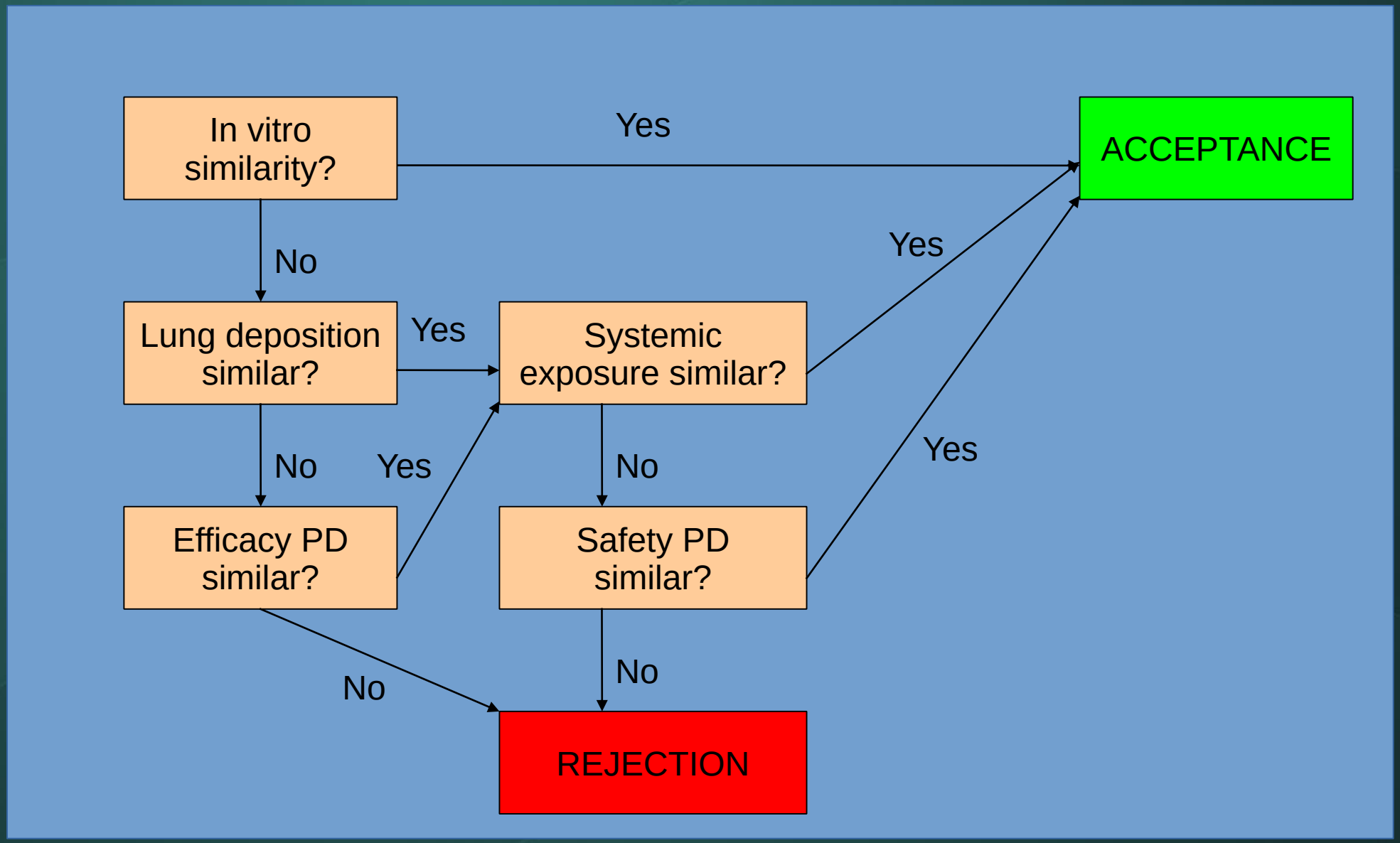
This is a talk....

...about a scientific field facing big trouble. About the steps generic as well as originator companies often take and which generally lead to failure. About frustration due to the lack of obvious alternatives.

And therefore also about opportunity. Opportunity for developing the alternatives.

Development of 'generics'

- for example the EU stepwise approach



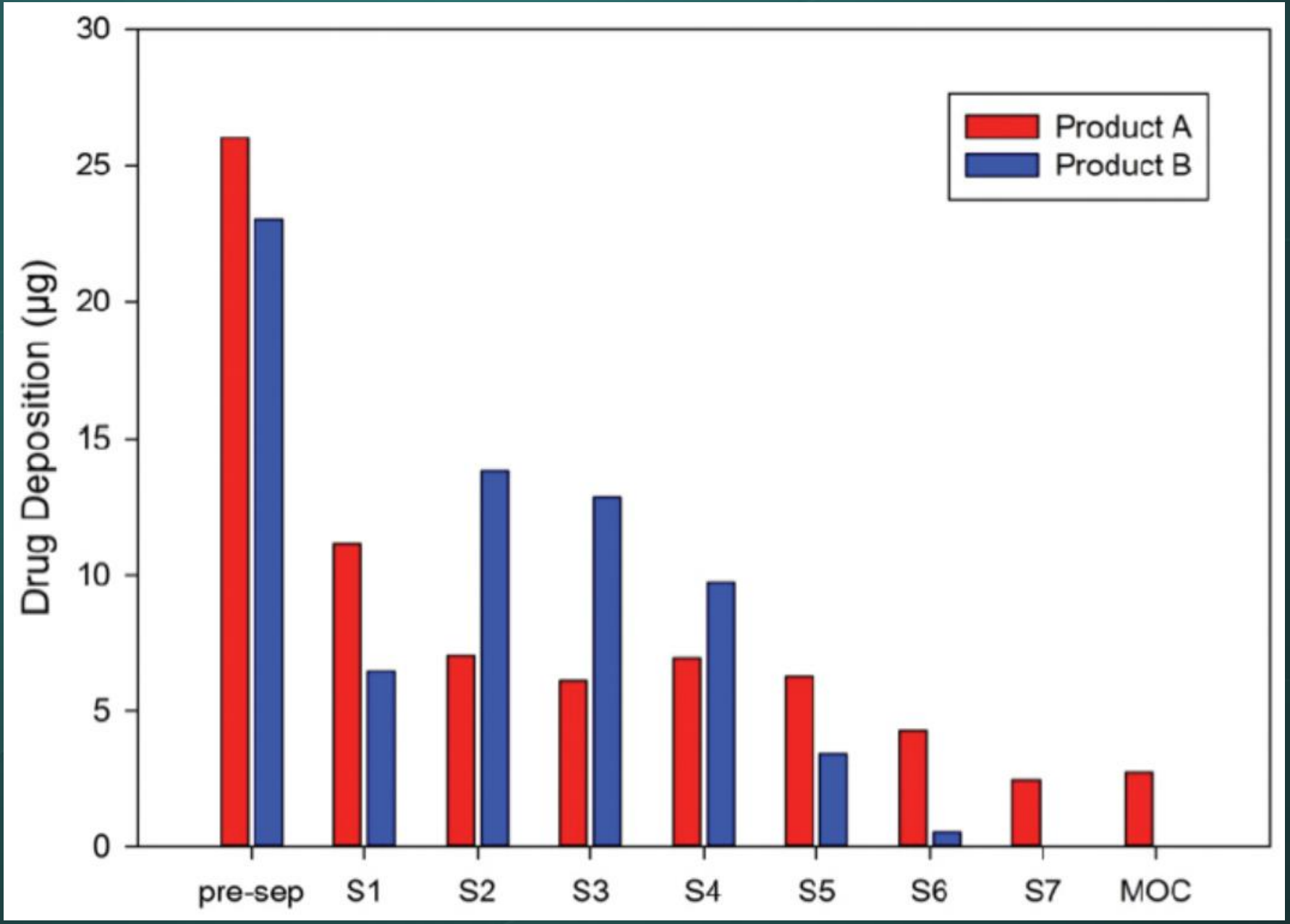
Challenge #1

In vitro approvals are almost non-existing.

Companies cannot match each others particle size distributions (e.g. as measured by NGIs).

There are a million techniques available from jet milling to ultrasono-crystallisation, but none of these techniques are understood to a level where one can, say, increase NGI Cup#3 and decrease NGI Cup #4,5.

Remember: different flow rates= different cutoffs etc.



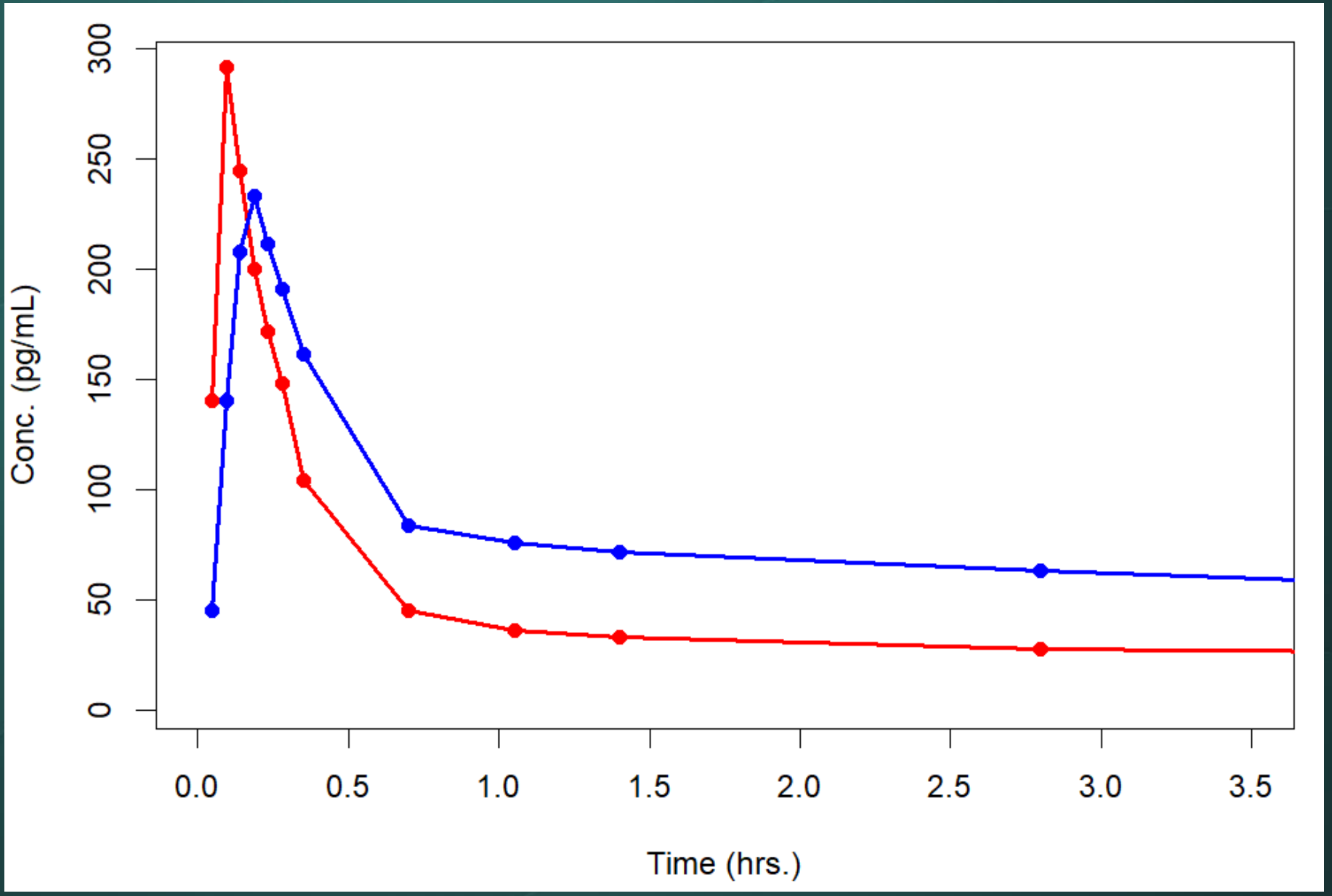
PK comparisons

We compare Cmax and AUCt of these plots.

90% Confidence intervals for T/R ratios must lie within 80.00%-125.00%.

(T is the generic, R is the originator)

Pharmacokinetic comparisons



Challenge #2
Typical example, N=24

For AUCt you have a quite OK match, e.g. the 90% CI is 94.05% - 118.73%.

For Cmax it is 56.83%-86.72%.

How would you increase Cmax and keep AUCt the same? If you could, would you be sure that would be the solution?

How good is our understanding?
Do we really get the IVIVCs?

Usmani et al. 2003

J Appl Physiol 95: 2106–2112, 2003.
First published August 1, 2003; 10.1152/japplphysiol.00525.2003.

translational physiology

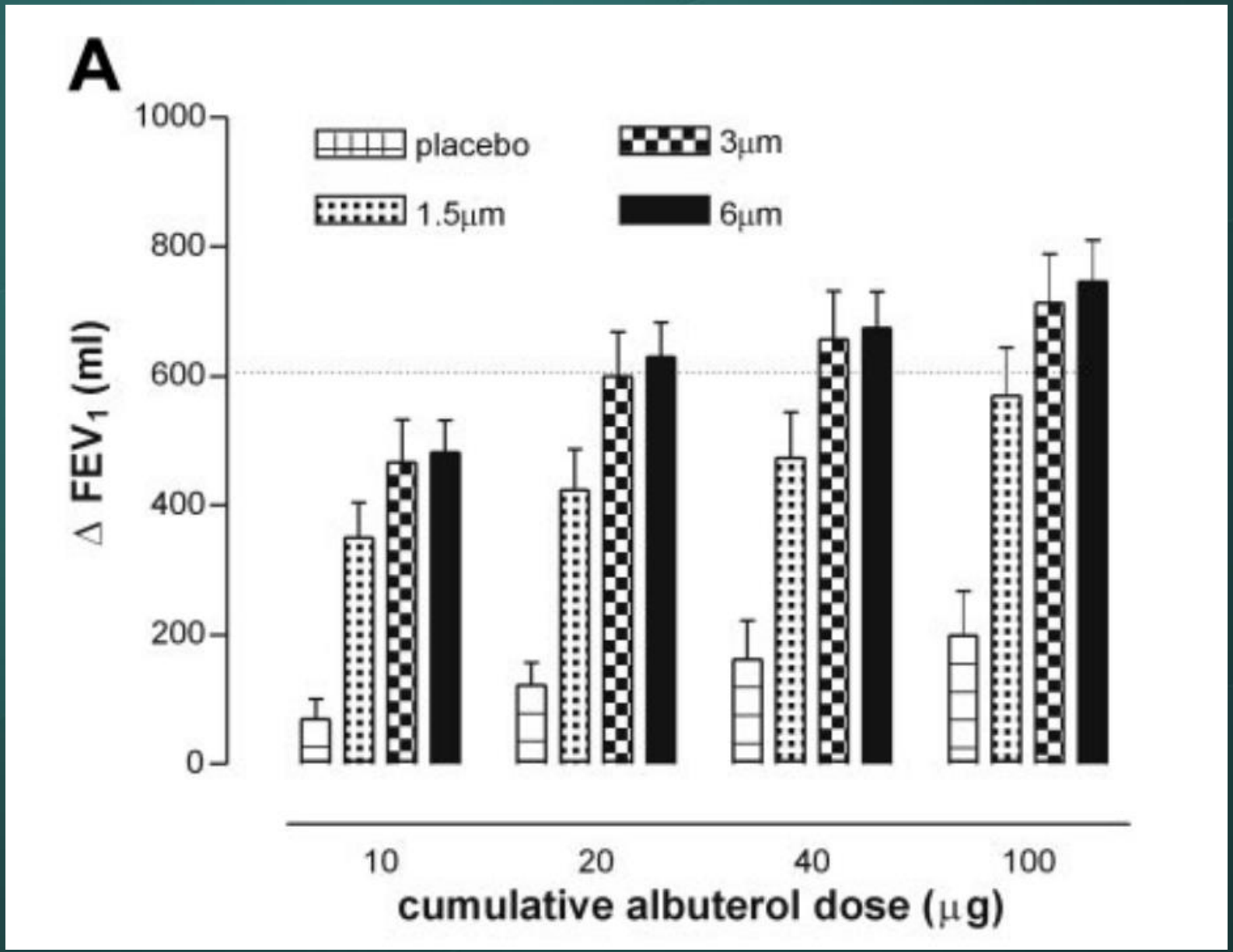
Effects of bronchodilator particle size in asthmatic patients using monodisperse aerosols

Omar S. Usmani,[1] Martyn F. Biddiscombe,[2] Julia A. Nightingale,[1] S. Richard Underwood,[2] and Peter J. Barnes[1]

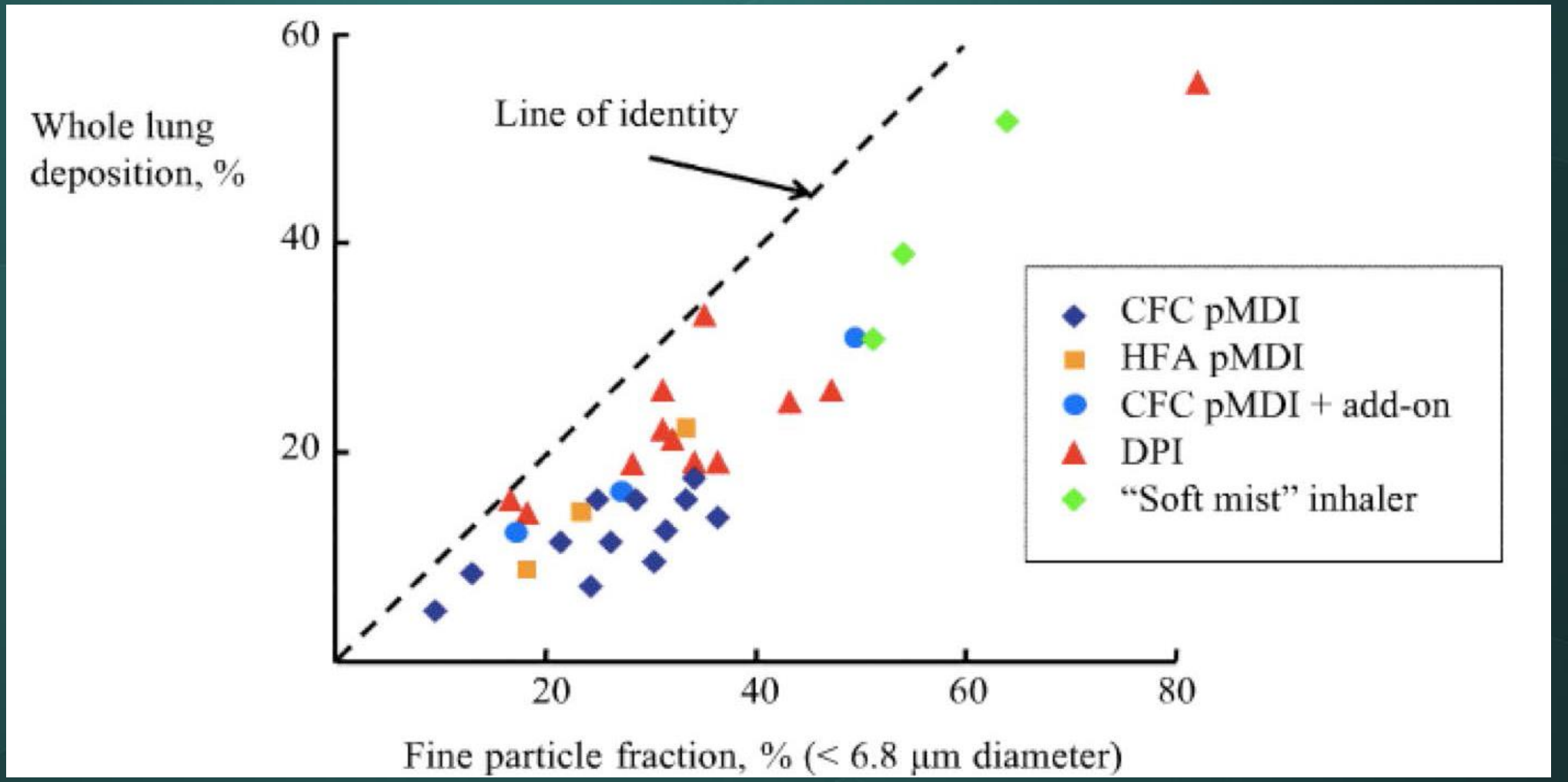
[1]*Department of Thoracic Medicine, National Heart and Lung Institute, Imperial College, and* [2]*Department of Nuclear Medicine, Royal Brompton Hospital, London SW3 6LY, United Kingdom*

Submitted 16 May 2003; accepted in final form 30 July 2003

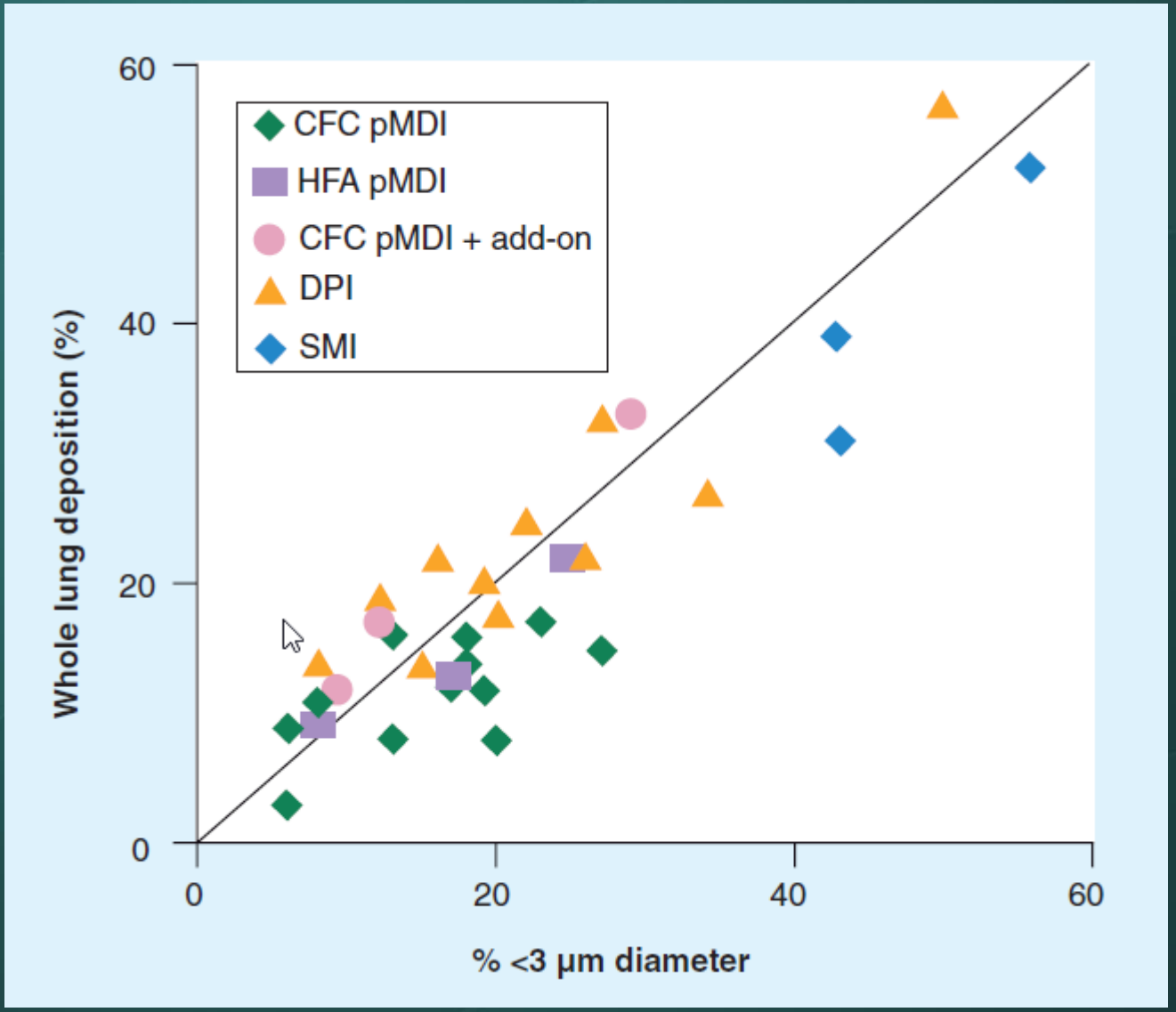
Effect vs. particle size



Particle size versus lung deposition Newman & Chan, 2008



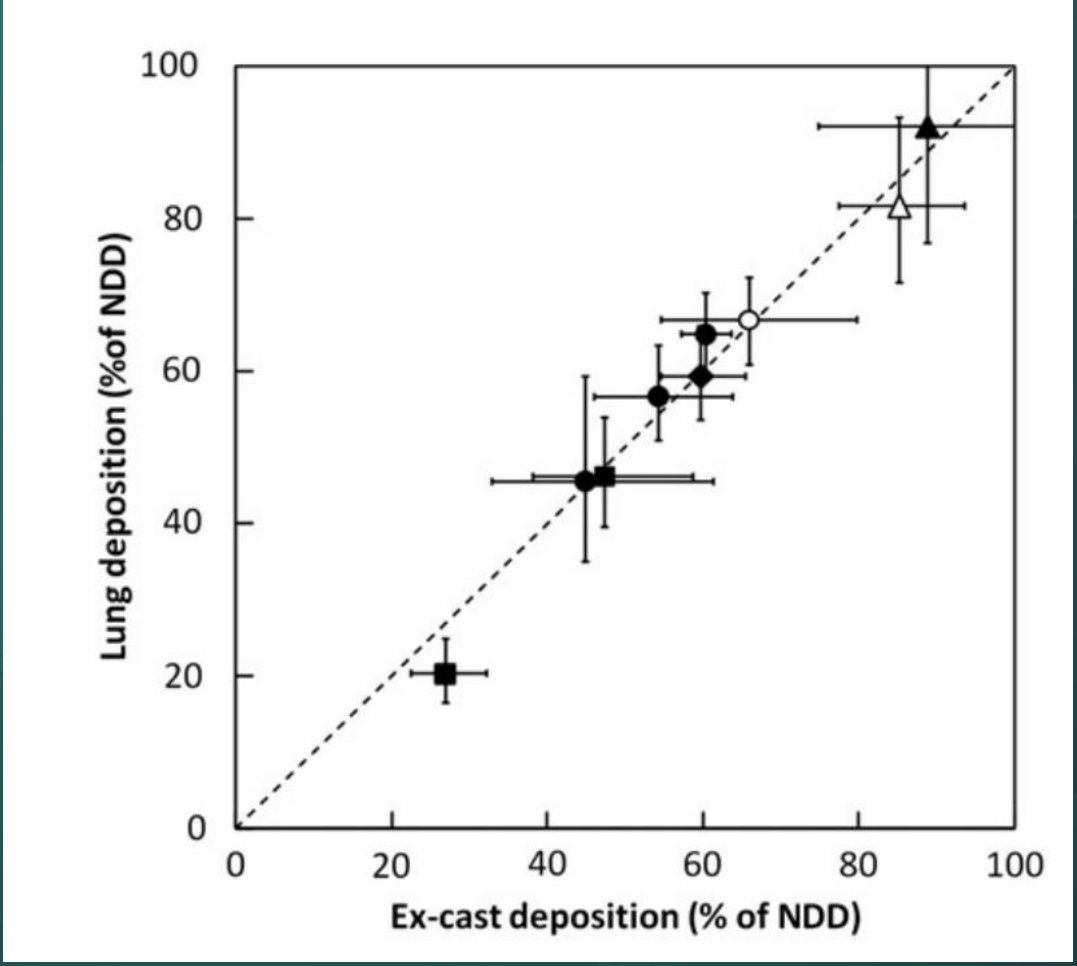
Newman & Chan, 2008



And the work above them all:
Olsson et al. 2013.

NGIs
Anatomical throats
Breathing profiles

Olsson et al., 2013.

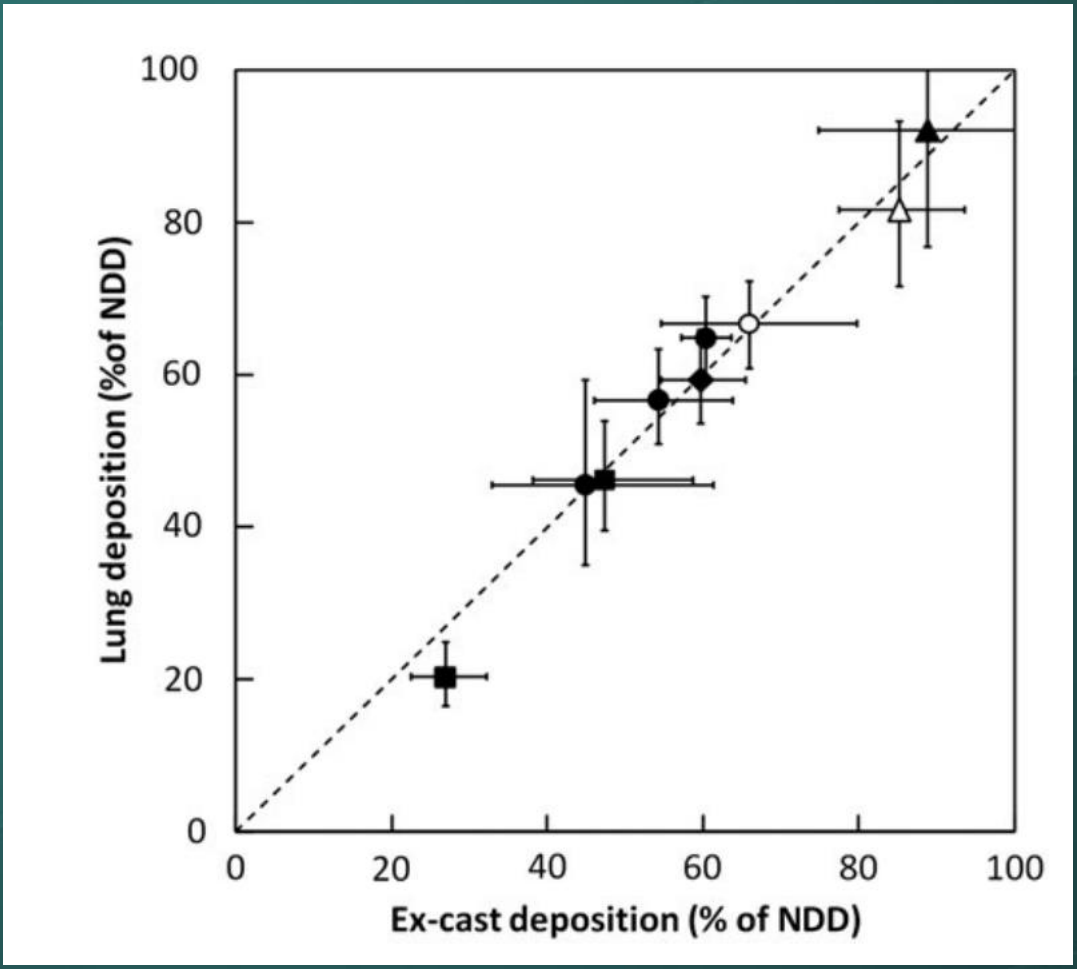


As a result of this great paper…

…the industry collective switched off the brain and collectively concluded:

We can use the Olsson model to screen for optimal formulations.
A good in vitro match must mean a good in vivo match!

Look at the error bars (SE)

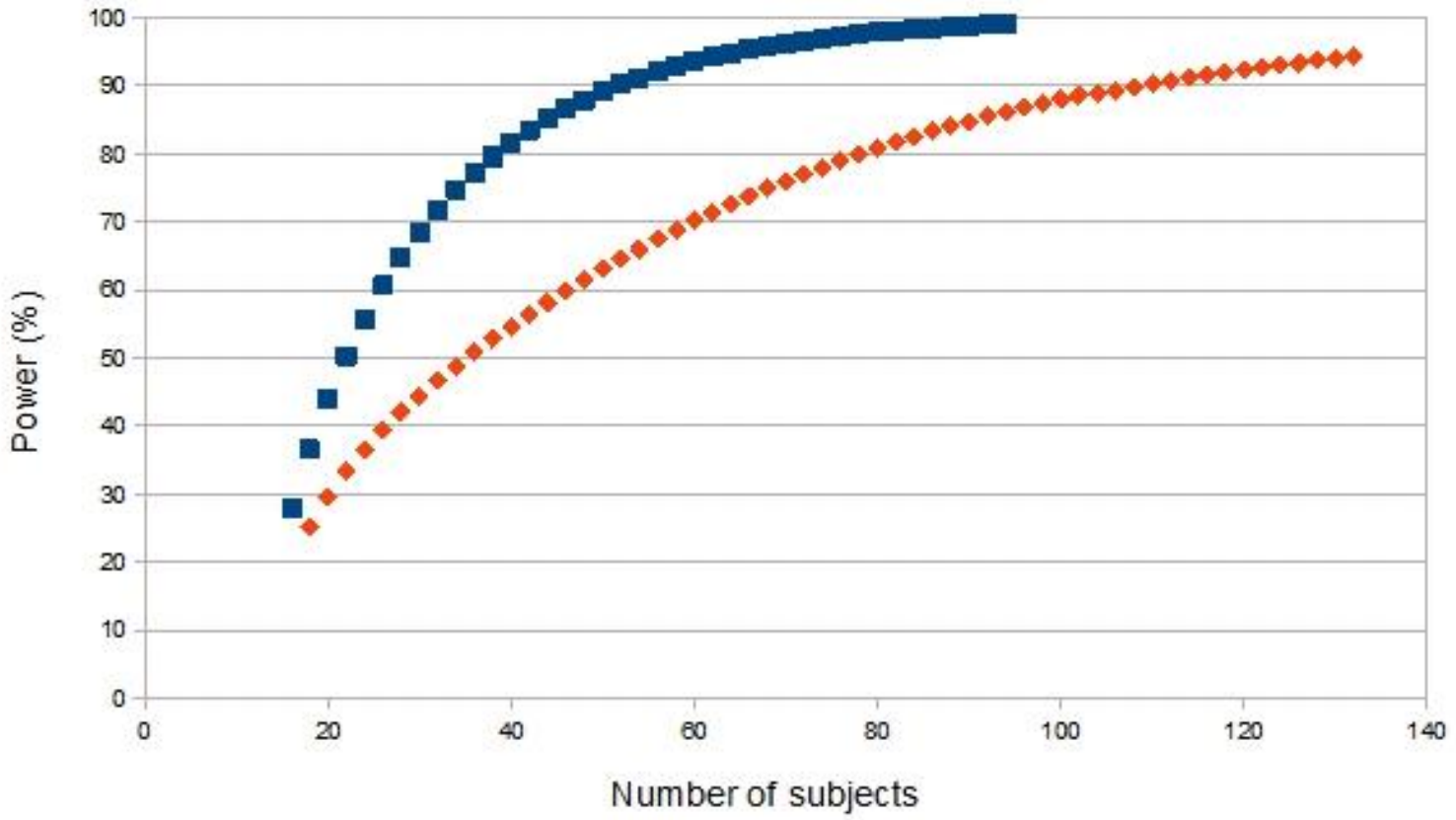


- they are way, way, **way** too large in order for a comparison to make any sense.

Why is that?

Let us take one step back to PK comparison. Usually this is a 2-treatment, 2-sequence, 2-period BE study. Samples sizes for a given level of power (like 80% or 90%) require us to guess/predict the degree of match (in vivo!) and the variation (in vivo!) associated with that match.

Power example: 2,2,2-design (1 API)



NB!

Blue: T/R=0.95, CV=30%. At N=52 power is 90%.
Red: T/R=0.90, CV=30%. At N=52 power is 65% ! N>100 needed for 90% power.

The sad realities

We need to hit our target with an accuracy of 5% (points) or so.

i.e. if we have two candidate formulations A and B that have a true in vivo match of 90% and 95%, respectively, then we need to be able to see that difference in vitro.

We need to be able to pick B over A with certainty.

With the Olsson model the figures I have seen are like marginally above 50%.

Here's a roughly equally effective screening method for A vs B

Where is the problem then?

No-one really knows, and the industry has not yet accepted the facts.

My own guess: Lung deposition

Impaction

Sedimentation

Brownian motion

Sedimentation vs impaction

Impaction: Not the way aerosol deposit.

But the basis for all currently used predictions.

Everything today starts with an NGI

(plus anatomical casts, rate constants, breathing profiles, a pinch of physiologically relevant this, permeation principle that...)

Sedimentation: The way aerosols deposit.

There is no cascade sedimentor. There are no models starting with sedimentation or trying to work on its basis.

Get me right please:
Olsson's paper is a great publication.

I am not in any way saying there is anything wrong about Olsson's paper, but there is everything wrong with the industry's way of using the information in it.

Bottom line

Most pivotal comparative PK-trials are still failing and that's why we are not seeing so many generics (or hybrids).

I see failure whenever someone tries to predict something about comparative in vivo performance on basis of impactor testing.

Ethical concern?

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE (ICH)

ICH HARMONISED GUIDELINE

INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE

E6(R2)

Current *Step 4* version

dated 9 November 2016

Some canonical clauses

2. THE PRINCIPLES OF ICH GCP

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

Impactors + anatomical throats + physiological rate constants
+ realistic breathing profiles + N-compartment models
+ supercomputers (+ CFD, + neural networks)
= no particular anticipated benefit.

Conclusion

We need much, much better models.
We don't just need correlations, we need predictions.

- To establish a roadmap to realistic computer simulations that will provide quantitative data to designers of aerosolized medicines and inhalation devices.
- To describe patient- and disease-specific biological interaction of inhaled particles within the lung.
- To promote advanced imaging technologies for patient monitoring, delivery verification and simulation validation.
- To promote integration of particle/formulation engineering with inhaler design for optimal lung delivery.
- To contribute to developing specifications and standards for aerosolized medicines that will accelerate and streamline transition from the R&D stage to approval.
- To identify and evaluate emerging technologies in the field and publish critical reviews that will be disseminated to end users (scientists, medical professionals, pharmaceutics companies).
- To identify commonalities with issues in inhaled pollutants.
- To promote the multidisciplinary / multisectorial training of Early Career Investigators (ECIs) in order to overcome fragmentation of knowledge in the field now, but also in the long term.
- To directly involve ECIs in outreach activities.
- To directly involve ECIs in the scientific deliberations of WGs.
- To generate new collaborations and ideas that will lead to new (independently funded) research projects.
- To deliver best-practice advice to practitioners and disseminate unbiased perspectives of scientific knowledge to decision makers, public authorities and other stakeholders.

Regardless of whether we see it from a patient, scientific, ethical or industry perspective,
the SimInhale initiative is much needed.

Thanks for listening.