

Systemic delivery of drugs to humans via inhalation

Igor Gonda
Aradigm Corporation

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... and all that
history...

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1946

LAST DOCTORS FROM COAST TO COAST WERE ASKED!

According to 10,000+ Physicians' Survey

MORE DOCTORS SMOKE CAMELS THAN ANY OTHER CIGARETTE!

Physicians and other health professionals are convinced that the healthiest habit is that of a daily Camel.

The Camel cigarette is the only one that is 100% tobacco. It is the only one that is 100% natural. It is the only one that is 100% pure. It is the only one that is 100% delicious. It is the only one that is 100% healthy. It is the only one that is 100% satisfying. It is the only one that is 100% Camel.

SMOKE CAMELS EVERY DAY!

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1942

"GOT A COLD?"
IT'S TIME TO
CHANGE TO SPUDS

NOSE or THROAT
CONGESTED?
IT'S TIME TO
CHANGE TO SPUDS

WHY YOUR COULD BE BETTER BEING
THE ONLY ONE TO GET IT RIGHT!

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THE ONLY ONE TO GET IT RIGHT!

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Medical Marijuana Legalized in California

Senate Joint Resolution No. 8

RESOLUTION CHAPTER 70

Senate Joint Resolution Relative to cannabis/marijuana

Filed with Secretary of State September 2, 1993.;

LEGISLATIVE COUNSEL'S DIGEST SJR 8, Mello:

Controlled substances cannabis/marijuana

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Propellant-driven Metered Dose Inhaler – pMDI: The big breakthrough in inhalation delivery

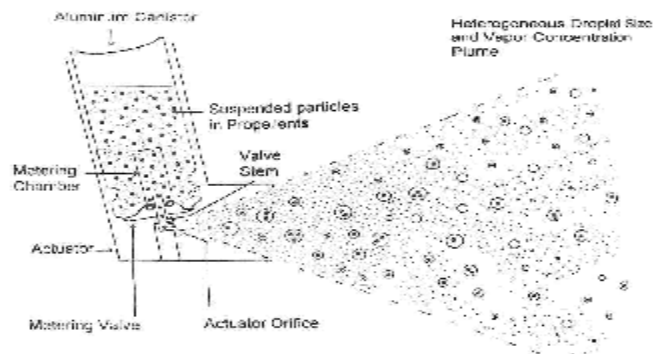
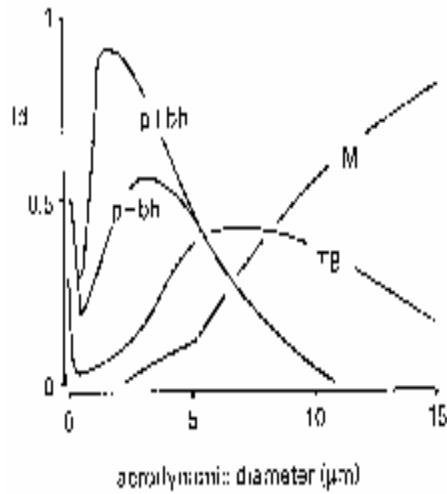


Figure 1 Schematic diagram of the components of a metered dose inhaler and droplet dispersion.

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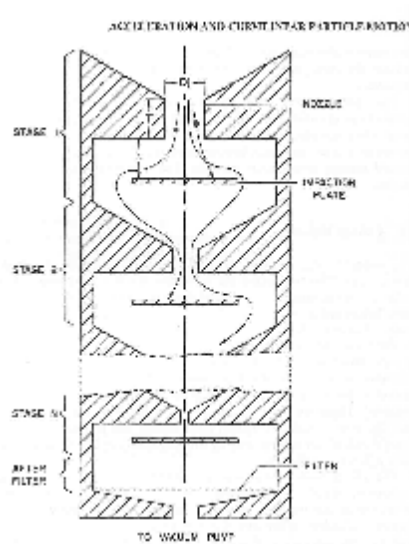
Aerosol Deposition - Gonda 1981, Byron 1986



Mouth (M)
Tracheobronchial (TB)
Pulmonary (P)
With (+bh) and without (-bh) Breath Hold

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Cascade Impaction Measures Drug Distribution in Aerodynamic Size Fractions



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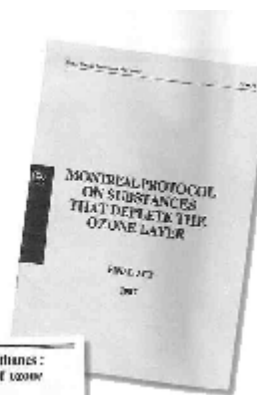
CFCs Destroy the Ozone Layer!

Mario Molina: telling the world

Twenty-five years ago this month, Mario Molina co-authored a paper that he paid to change the face of the chemical industry. Richard Stevenson caught up with him in London recently.

Chemical industry has been told to stop producing high-polluting CFCs and to find alternatives.

Stratospheric sink for chlorofluorocarbons: chlorine atom-catalysed destruction of ozone
Mario J. Molina & F. S. Rowland
Journal of Geophysical Research, 1974, 79, 4712-4716



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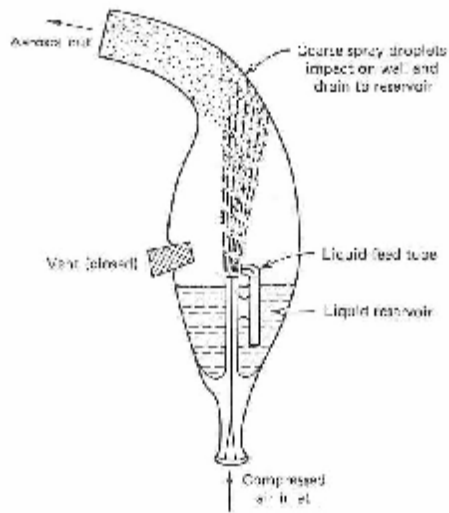
Chemistry in Britain, August 1990:

CFCs RIP

The death warrant for CFCs was signed in London at 9.55 pm on 29 June 1989. The judges were the environmental ministers of 59 nations plus the European Community.

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De Vilbiss Glass Jet Nebulizer



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Spinhaler (Fisons) Dry Powder Inhaler

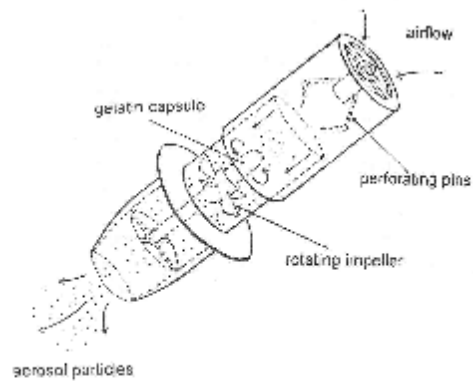
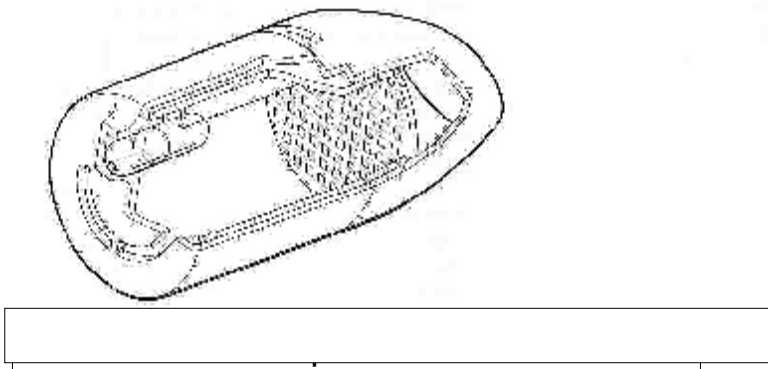


Figure 5 Diagram indicating the essential components of a Spinhaler.

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Rotahaler Dry Powder Inhaler (Glaxo)



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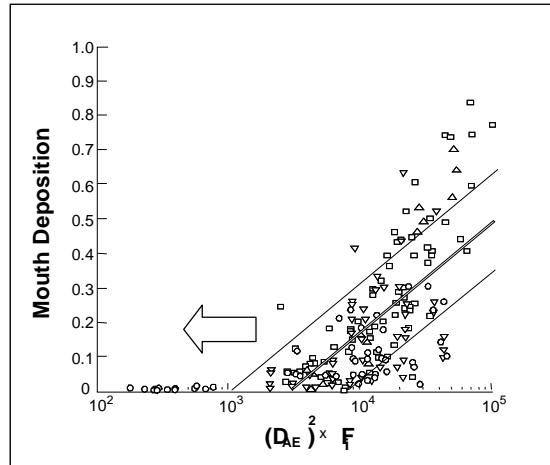
DPI and MDI variability under realistic conditions (Astra-Draco)

	Turbuhaler	pMDI
Lung Deposition (%)	19.5	6.3
Within Subject CV (%)	32.9	64.7
Between Subject CV (%)	28.4	61.8

Borgstroem (1996)

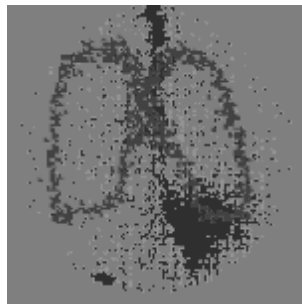
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Oropharyngeal Deposition in Humans is Very Variable and It Depends on Aerodynamic Diameter D_{AE} and Inspiratory Flow Rate F_i (after Morrow and Yu, 1985)

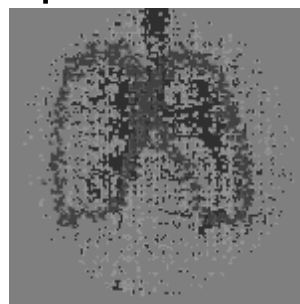


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Incorrect Patient Technique Can Have a Profound Effect on Pulmonary Deposition



Ineffective Delivery



Effective Delivery

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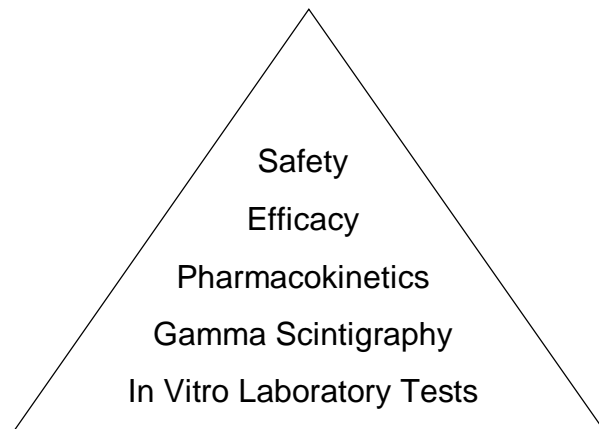
In Vitro Tests vs. In Vivo reality

What is the purpose of in vitro tests:

- During various stages of development
- Post-approval for the “originator” and for generic copies

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Experimental Basis of the Development of Inhalation Products



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November 1999, AAPS, New Orleans

Dr. Jane Henney, FDA Commissioner:

"The Agency will base all of its decisions on the basis of the current, cutting edge science, on data."

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Some of us in IPAC RS thought that this strategic statement from FDA will have a rapid profoundly positive impact on the OINDP industry!

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1990s

Targeting the airways:

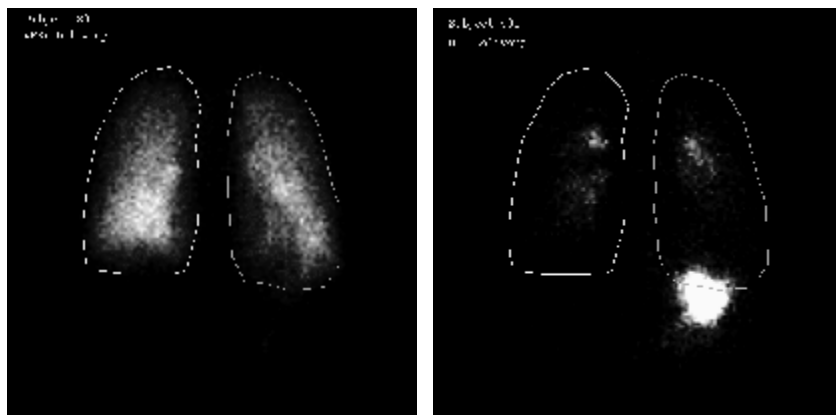
Inhalation drug delivery established itself as the primary method to treat chronic diseases of the respiratory tract - asthma, chronic bronchitis and cystic fibrosis.

Systemic delivery:

Major industrial and academic efforts position inhalation as the most promising method of systemic delivery of peptides, proteins and genes by non-invasive means.

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AERx™, in contrast to MDI, achieves diffuse lung deposition with minimum oropharyngeal drug losses



AERx Delivery

MDI Delivery

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I. Gonda and P. Byron, "Perspectives on the Biopharmacy of Inhalation Aerosols", Drug Dev. Industrial Pharm. 1978

"Inhalation of nebulised insulin solutions in man indicated less than 10% efficiency with poor reproducibility... The response times to this insulin were, however, found to be quite short."

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Who said this and when?

"In *the near future*, it is likely that optimal formulations will be combined with modified aerosol delivery devices to maximize and achieve reproducible values for dose to lung. These will be used as alternatives to parenteral delivery for small through intermediate dose drugs which are not absorbed via the gastro-intestinal tract."

Peter Byron, 1990. Determinants of drug and polypeptide bioavailability from aerosols delivered to the lung, Adv. Drug. Deli. 5:107-132 (*edited by Igor Gonda*)

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Approved pharmaceutical products for systemic delivery via lung

1!

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Use of inhalation route for systemic delivery of Nicotine

Highly effective
Rapid onset of action
Bad excipients!

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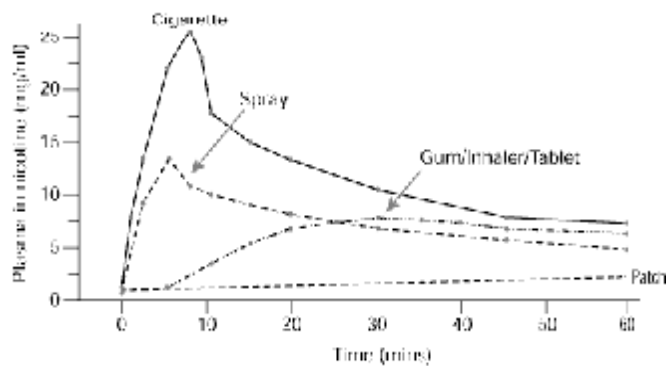
Use of inhalation route for systemic delivery of Nicotine

- Previous attempts to develop inhaled nicotine as a pharmaceutical product unsuccessful – buccal rather than pulmonary absorption
- New inhaled nicotine products in development



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Nicotine pharmacokinetics*



“Spray”: nasal

“Inhaler”: oral

*Royal College of Physicians: Nicotine Addiction in Britain

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Biotech industry discovered pulmonary drug delivery...



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Pulmozyme® : First recombinant human protein approved for administration via inhalation (1993)

- Record approval time - 5 years from cloning
- Orphan drug for cystic fibrosis – key stakeholders involved throughout the development
- Preclinical safety data consistent with immune reaction to a foreign protein
- Good safety record in humans since approval

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Pulmonary Delivery of Insulin

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Pulmonary Delivery of Insulin

Or:

Why did we and others pick the hardest first
product for systemic delivery via the lung?

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Diabetes Epidemic: US Center for Disease Control View October 2005

- ...diabetes has risen by over 14 percent in the last two years. The CDC estimates that 20.8 million Americans – 7 percent of the U.S. population – have diabetes
- The total direct and indirect diabetes costs in the United States in 2002 was \$132 billion.
- Diabetes remains a leading cause of heart disease, stroke, blindness, kidney disease, and amputations.
- Since 1987, the death rate due to diabetes has increased by 45 percent, while the death rates due to heart disease, stroke and cancer have declined.

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Inhaled Insulin – Industrial Developments

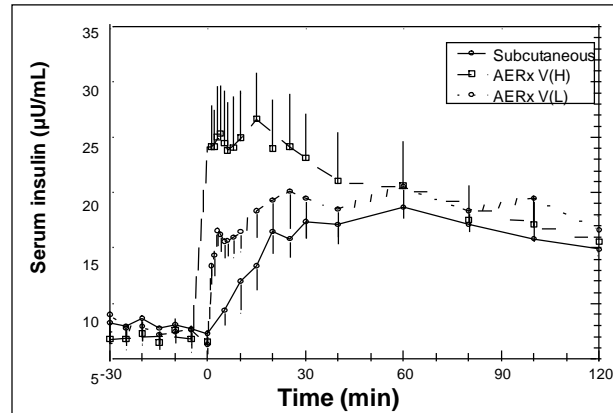
Examples of companies developing and commercializing pulmonary insulin:

- Pfizer/Nektar (dry powder)
- Novo Nordisk/Aradigm (aqueous)
- Eli Lilly/Alkermes (dry powder)
- Mannkind (dry powder)
- KOS (p-MDI)

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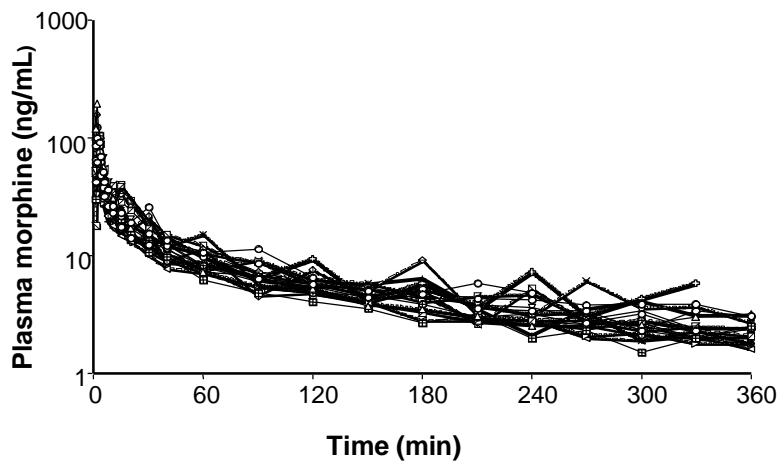
Serum Insulin Profiles Following 2 Modes of Inhalation or Subcutaneous Injection

- Breathing technique changes both time to peak and its value



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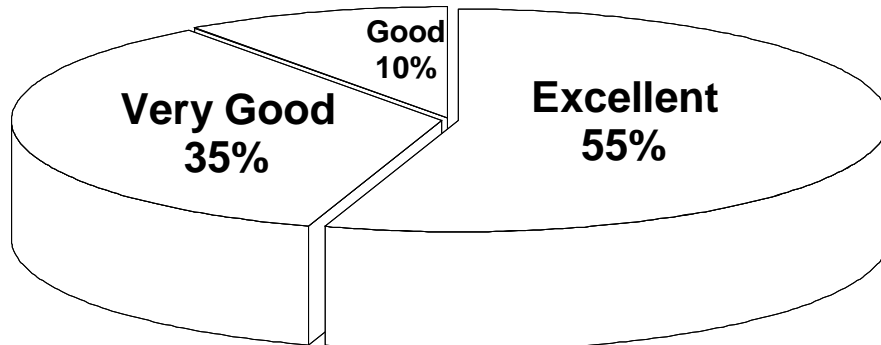
Morphine Pharmacokinetics after Inhaled Delivery using the AERx System (6 subjects, 3 dosing episodes)



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AERx Fentanyl in cancer patients

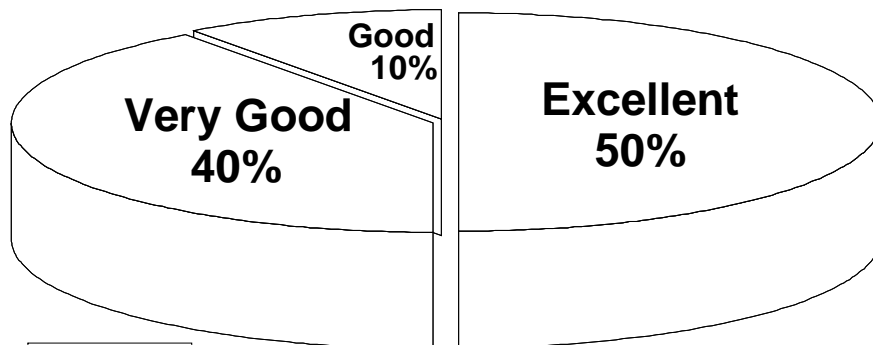
Time for Medication to Take Effect



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AERx Fentanyl in cancer patients

Pain Relief



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PK vs. PD:

Evaluation of the AERx[®] System for the
Pulmonary Delivery of Recombinant Human
Interferon alfa-2b to healthy subjects

Gul Balwani, Brooks Boyd, John Whatley, John Thippawong,
Richard Morishige, Jerry Okikawa, Babatunde Otulana,
Emmanuel Tamchès, Thierry Buclin, Jerome Biollaz,
François Spertini, Igor Gonda

July 23, 2002

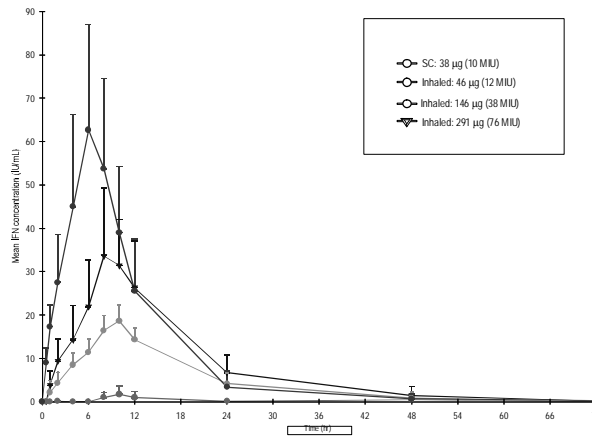
CRS Meeting July 23, 2002
IPAC-RS Conference November 2006

41

- rH Interferon alfa-2b (MW of 19,265 kDa)
- Indications
 - Hepatitis B and C Infection
 - Various cancers (Hairy cell leukemia, Malignant Melanoma, Follicular Lymphoma)
- Therapy
 - Chronic parenteral administration for at least six months

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Pharmacokinetic Results



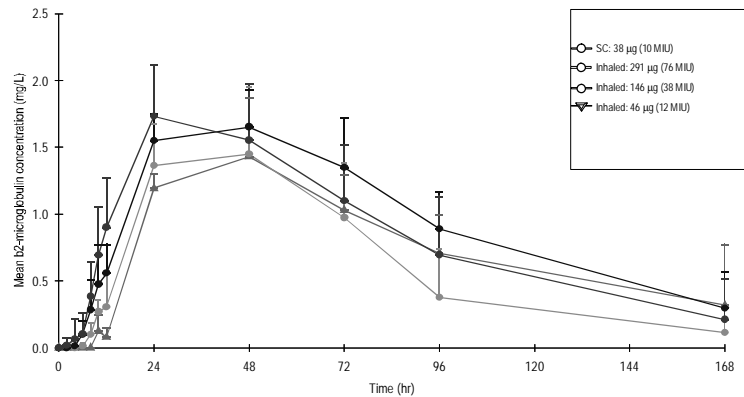
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Pharmacokinetic Results

Mean PK Parameter	SC 10 MIU (%CV) n=13	AERx [®] 12 MIU (%CV) n=1	AERx [®] 38 MIU (%CV) n=3	AERx [®] 76 MIU (%CV) n=8
C _{max} (IU/ml)	64 (37%)	3	19 (20%)	35 (41%)
T _{max} (h)	6.8 (19%)	10	10 (0%)	8.8 (21%)
AUC _{0-inf} (h.IU/ml)	665 (40%)	68	302 (38%)	514 (48%)
F* _{rel to SC} (%)	-	ND	12	10.2

*F = relative bioavailability calculated as loaded dose-adjusted AUC of aerosol vs. subcutaneous administration
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Pharmacodynamic Results – β 2 microglobulin



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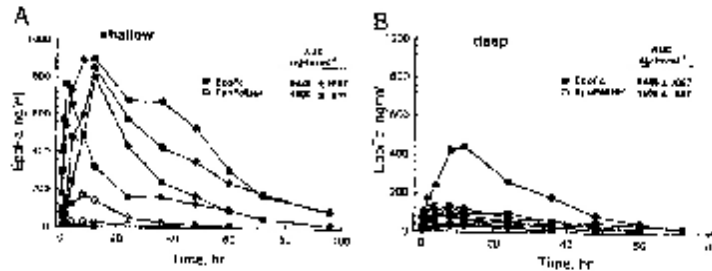
Conclusions

- AERx[®] IFN bioavailability is 10-12 % relative to IFN SC. However, pharmacodynamic response was found to be similar for all the doses of AERx[®] IFN and similar to 10 MIU of IFN given by SC, thereby showing very high bioeffectiveness of the pulmonary route
- Lower incidence and severity of adverse events by the pulmonary route compared to SC
- AERx[®] intersubject variability similar to SC
- Local skin reaction seen by SC can be eliminated by pulmonary route

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Exploiting the IgG1 transport route: Pulmonary delivery of Epo-FC using deep vs. shallow breathing in cynomolgus monkeys

(A. J. Bitonti et al., PNAS 2004 101:9763-9768)



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DEVELOPMENT OF PULMONARY DELIVERY TECHNOLOGY

From:

- CFC pMDIs
- No breath control
- Patient effort- dependent drug delivery from DPI
- Patient education
- PK/PD determined by drug properties
- Local delivery only

To:

- HFA pMDI, DPIs, "soft mists"
- Device-assisted breath control
- Power assisted devices, smart formulations
- Smart devices
- PK/PD determined by delivery: formulation, device
- Local and systemic therapy

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21st Century Pulmonary Delivery

- Treatment of respiratory disease
 - Rapid onset of action
 - Target organ selectivity
 - Convenience for patients
- Systemic delivery
 - Non-invasive route for molecules that are not orally absorbed
 - Avoids first pass
 - Fast and reproducible absorption for small molecules and peptides
 - PK for some proteins similar to subcutaneous injections but lower bioavailability
 - Can have advantageous PD over other routes

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WHAT AND HOW WE MEASURE

From:

- Microscopy, inertial impaction and chemical assay
- Focus on loaded/ED
- Product design for high reproducibility *in vitro*
- End product quality

To?

- *In situ* optical aerodynamic drug size distribution
- Focus on dose to lung
- Product design for high reproducibility *in vivo*
- Process quality

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How do we work together to bring valuable therapies to patients?

<i>From:</i>	<i>To?</i>
Respiratory disease	Pulmonary delivery therapies
Risk/ _{benefit}	Risk/Benefit
Regulation/ _{science}	Regulation/Science
Destructive Criticism	Constructive Critical Path
High late stage product failure rate	High late stage product success rate
High profile catastrophes	High profile public good

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Thanks to the giants on whose shoulders I have walked, and especially...

- Dana, Ellie and Abi
- Peter Byron
- Frank Fildes
- Cheryl Rogerson
- Tony Hickey
- Ahmed Khalik
- Ian Ashurst
- Paul Phipps
- Kim Chan
- Lily Daviskas
- Sandy Anderson
- Dale Bailey
- Steve Shak
- Andy Clark
- David Cipolla
- Terry Sweeney
- Jim Blanchard
- Ron Crystal
- Warren Finlay
- Steve Farr
- Jeff Schuster
- Reid Rubsamen
- Hans Schreier
- Deepa Deshpande
- **IPAC RS**

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