# Clinical Relevance of Aerosol Quality Attributes: EXUBERA® Case Study

IPAC-RS Conference
September 2008

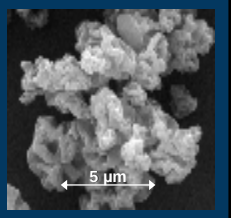
Nancy Harper, PhD
Research Fellow,
Parenteral Center of Emphasis
Pfizer Global R&D

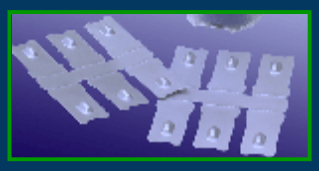
EXUBERA

## EXUBERA®

EXUBERA

- DPI for systemic delivery of human insulin (rDNA origin)
- Re-usable Exubera® Inhaler
- Spray-dried powder from aqueous solution of Insulin, Na Citrate, Mannitol, Glycine
- 1 mg, 3 mg unit dose blisters



IPAC-RS 2008 Conference

# EXUBERA®

## Application of QbD

- Development in parallel with evolution of QbD concepts
- Many QbD elements incorporated naturally, due to novelty and complexity of the system
  - FMEA's and other risk analyses on a variety of focus areas
  - Elaborate characterization programs, multivariate DOE's
  - Control systems, PAT
  - Change control process (development as well as commercialization)
  - Proactive life cycle planning / continual improvement
- Criticality assessments continued to evolve after commercialization
  - Aerosol quality attributes (today's focus)

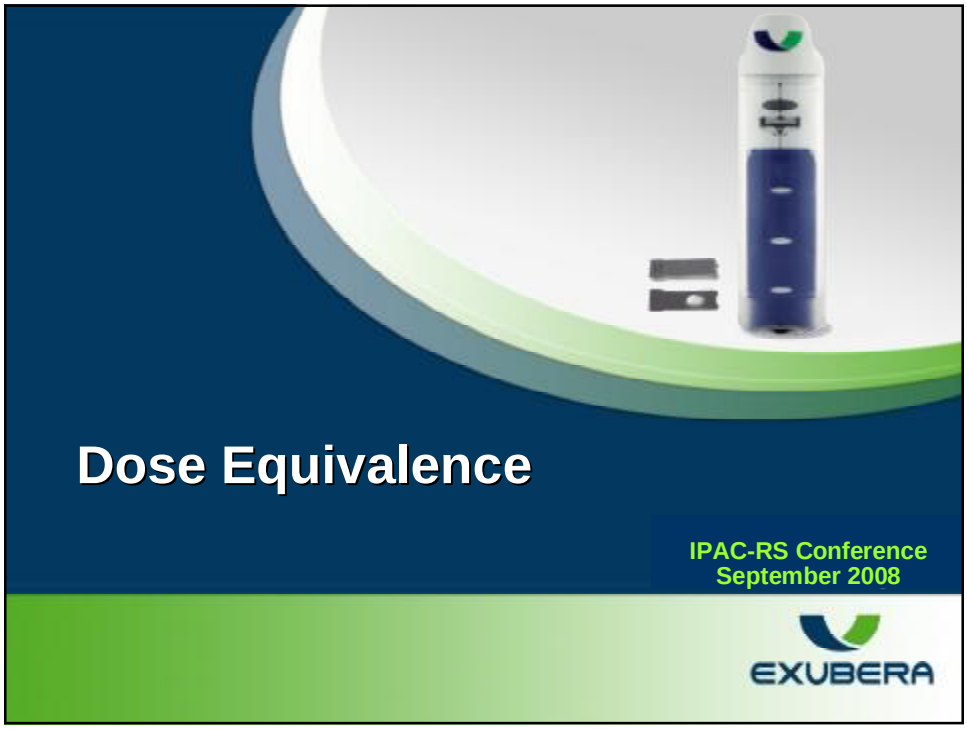


# Challenges and Opportunities

- Systemic Delivery
- Opportunity to conduct standard PK/PD studies
- Opportunity to explore *in vivo* / *in vitro* relationships
- Challenges: Dose Equivalence and Label Claim

| Nominal Dose (mg insulin) | Emitted Dose (mg insulin) | Fine Particle Dose (mg insulin) |
|---|---|---|
| 1.0 | 0.53 | 0.4 |
| 3.0 | 2.03 | 1.0 |

Source: EXUBERA® US Package Insert



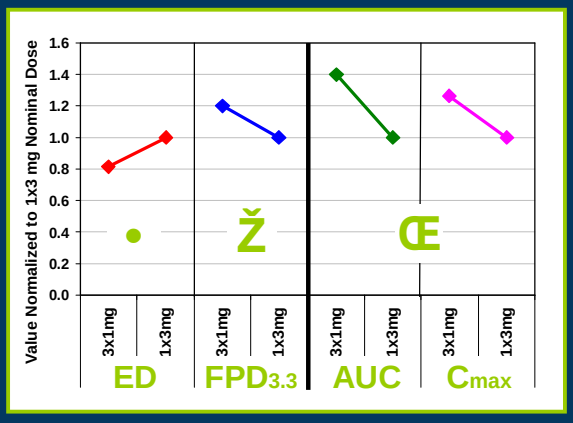
# Dose Equivalence

IPAC-RS Conference
September 2008

EXUBERA

## Dose Equivalence: 3 x 1 mg vs 1 x 3 mg

EXUBERA



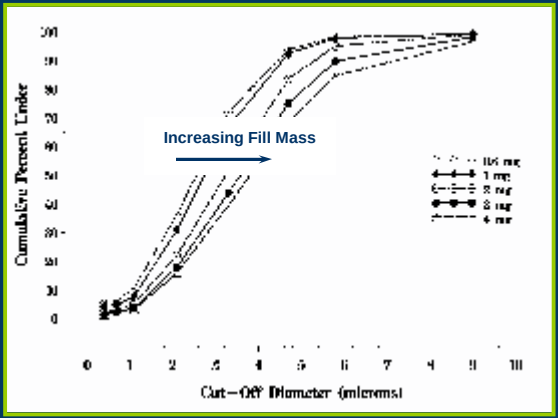

Œ Higher systemic exposure from 3 x 1 mg blisters relative to 1 x 3 mg

- ED would have predicted the opposite

Ž FPD in line with PK results

IPAC-RS 2008 Conference

## So what's different between 1 mg and 3 mg blisters? Fill Mass !



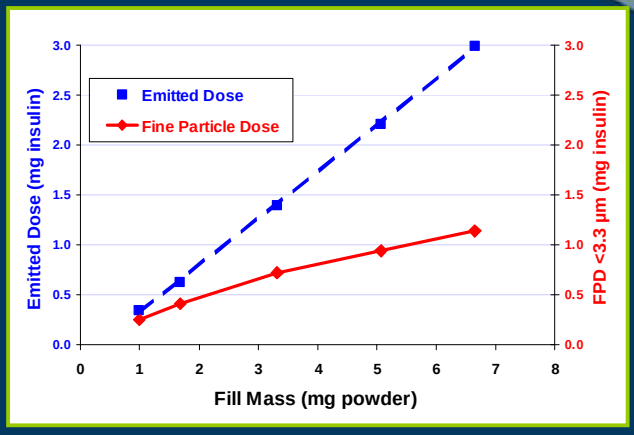

| Nominal Dose (mg insulin) | FPD <3.3µm (mg insulin) | FPF <3.3µm (%) | MMAD (µm) |
|---|---|---|---|
| 0.6 | 0.25 | 72 | 2.5 |
| 1 | 0.41 | 67 | 2.7 |
| 2 | 0.72 | 52 | 3.2 |
| 3 | 0.94 | 44 | 3.5 |
| 4 | 1.14 | 40 | 3.7 |

As fill weight is increased:

- Aerosol particle size increases
- Percentage of fine (respirable) particles decreases

IPAC-RS 2008 Conference

## Effect of Blister Fill Mass



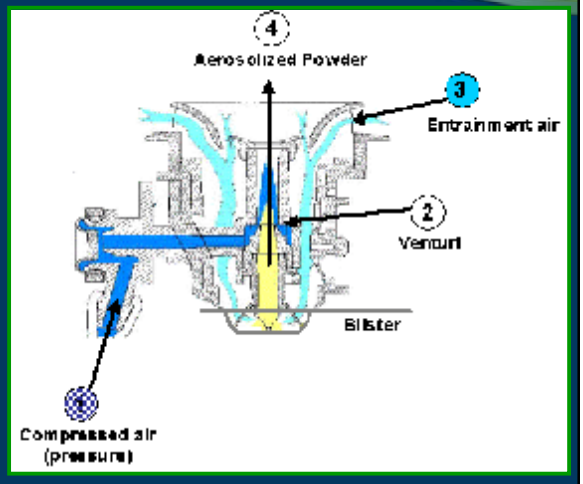

- FPD response to fill mass is more shallow than ED, and non-linear

IPAC-RS 2008 Conference


## Product Understanding: Design Features Contributing to Aerosol Performance

EXUBERA

1. Compressed air (fixed volume) is generated as the energy source
2. Air travels through small orifice forming two jets, creating a venturi effect
3. Entrained air flows into the blister to sweep powder into the feed tube
4. Powder undergoes high acceleration as it interacts with the sonic air from jets

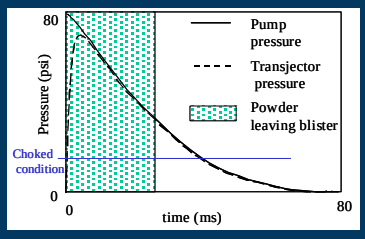



IPAC-RS 2008 Conference

# Powder Extraction and Dispersal

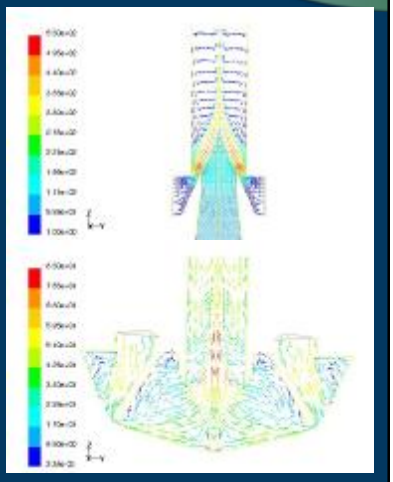
## Extraction of powder from blister:

- Accomplished via entrainment air flow
- Flow profile is constant; sufficient to extract majority of powder (slightly greater percentage as fill mass increases)




## Powder Dispersion:

- Accomplished via powder interaction with jets
- Fill mass will determine energy coupling with powder, since energy is constant
- Energy per mg of powder is greater for 1 mg than 3 mg, therefore producing greater dispersion and deagglomeration, and APSD shift to smaller particles

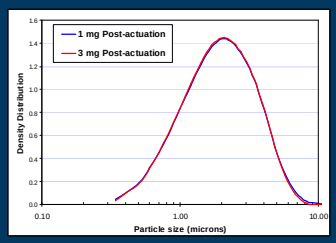


Shuler et al, CRS, Honolulu, June 2004

IPAC-RS 2008 Conference

# Confirmation of Mechanism

- Demonstration that residual powder in the blister (post-actuation) has identical primary PSD for both 1 mg and 3 mg blisters.
- Confirms that the inhaler is not preferentially extracting smaller particles from lower fill mass blisters.



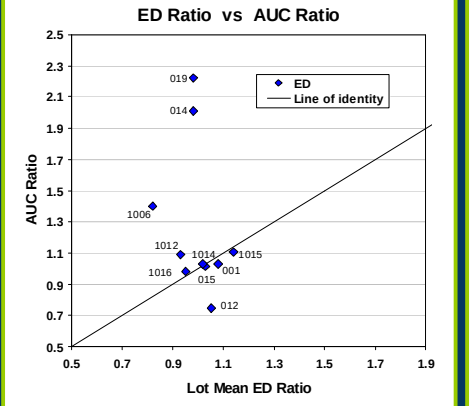

IPAC-RS 2008 Conference

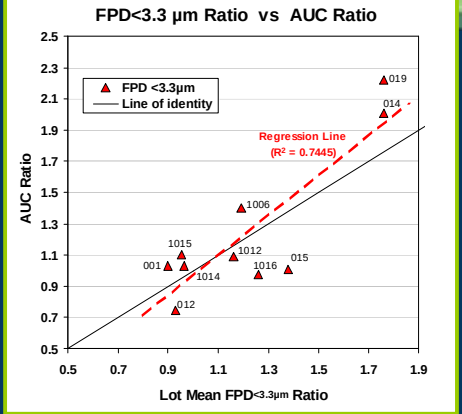
# Clinical Relevance of Aerosol QA's

- Solid understanding of the *in vitro* performance differences between 1 mg and 3 mg blisters adds confidence in exploring correlation between aerosol attributes and *in vivo* exposure.
- Conducted a retrospective analysis of various biopharm studies
- Evaluated studies that involved drug product variables in discrete treatment arms.
- Drug product variables included:
  - Different formulations (API/excipient ratios)
  - Different fill mass (eg, 1 mg and 3 mg)
  - Different spray drying conditions (intentional differences in primary PSD of the spray dried powder)
- Within-study response ratios were calculated (Treatment A/B) for PK parameters and lot-specific aerosol attributes.



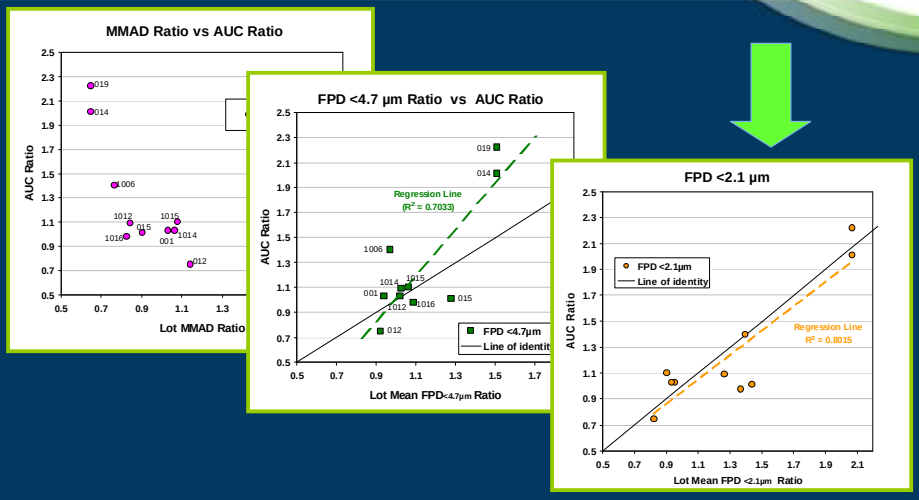
# *In vivo* / *in vitro* correlations




- No apparent correlation between ED and AUC
- FPD <3.3 µm shows a trend (higher FPD → higher AUC)
- FPD <3.3 µm trend is relatively close to a 1:1 relationship

# *In vivo* / *in vitro* correlations: Other Metrics

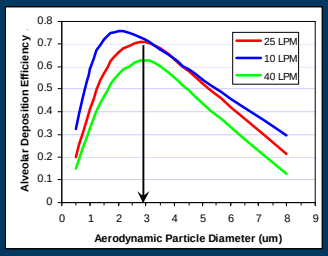


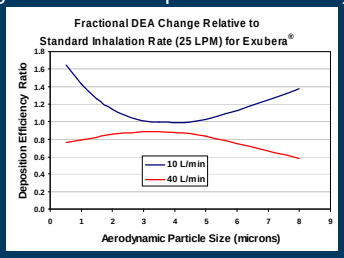

- Correlation appears to improve for lower particle size cut-off for FPD



# Quality Attribute Selection

- **FPD <3.3µm was selected as a critical quality attribute**
  - Consistent with literature and modeling for alveolar deposition efficiency



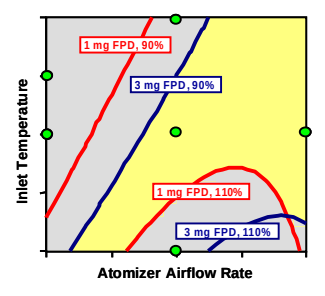




  - Reasonable correlation with in vivo exposure
  - Captures more of the emitted powder than lower ACI stage cut-offs (analytical reproducibility)

- **ED maintained as a quality attribute, but non-critical**
  - Absence of correlation with PK parameters
  - Large particles (swallowed) are not active for insulin

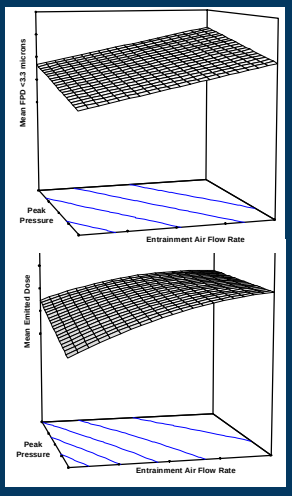
# Applications of FPD as CQA During Development

- Spray-drying scale-up




Harper et al, RDD EU, April 2007

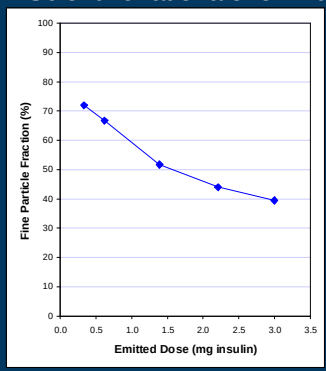
- Inhaler attribute controls




IPAC-RS 2008 Conference

# Dose Uniformity – An Opportunity

- **Functionality of the Exubera system allowed opportunity to look at dose uniformity in a different way:**
  - Consider uniformity of FPD rather than ED? **L**
  - Scientific rationale for wider EDU limits **J**




- Blister-to-blister variations in ED are muted in FPD, particularly for low ED
- Low ED **è** smaller particles **è** less change in FPD
- "Self-correcting"
- Uniformity based on ED is an over-estimate of clinically relevant dose delivery variability

IPAC-RS 2008 Conference

## Conclusions and Key Learnings

- Technically successful product.
  - Benefited greatly from the application of QbD concepts.
- Non-criticality of ED.
  - Unique situation for an inhalation product
  - Possible applicability to other products, particularly systemic delivery / non-orally active (eg biologics).
- Definition of respirable (absorbable) dose will be product-specific.
  - Thorough characterization (in vivo and in vitro) is immensely valuable in defining development strategies and rational control approaches.
- Opportunities in optimizing APSD testing.
  - According to only truly relevant particle size measures.
- Expression of Label Claim vs. Nominal Dose may need to be approached differently.
  - For Exubera, "1 mg" and "3 mg" was essentially irrelevant. Dose equivalence would not have been an issue if blisters were stamped with "FPD"!
  - What would need to be addressed to accommodate this change in labeling approach?



## Acknowledgements

Thanks to the entire Pfizer/Nektar Exubera team.

SPECIAL THANKS TO:
Jackie Schumacher, Eileen Bohler, Bob Fountaine, Marty Mikelsons, Greg Larner, Greg Steeno, Kevin Jenkins, Sangita Seshadri, Jim Spavins

IPAC-RS Conference
September 2008