Process Development & Scale-Up of the AIR® Technology

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Pharmaceutical Industry

- Delivering needed therapeutics to the market
- Most highly regulated industry in the US
- Many products greater than $1 billion per year in sales
  - smaller volume higher value than most chemicals
- Typical patent lifetime of 20 years
- Average product development cycle of 7 to 12 years
- Manufacturing costs have not been a significant portion of product costs in the past
- Increasing price pressures will raise importance of efficient manufacturing in pharmaceuticals
- Chemical engineers in best position to make contributions in this area

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Pharmaceutical Product Development

- Pre-clinical
  - discovery, toxicology
- Phase 1 Clinical
  - ~ 10 healthy volunteers, tests safety in humans
- Phase 2 Clinical
  - 100's of patients, dose ranging studies
- Phase 3 Clinical
  - 1000's of patients, efficacy and long term safety

- Chemistry, Manufacturing and Controls (CMC) needs to keep pace at all stages of development

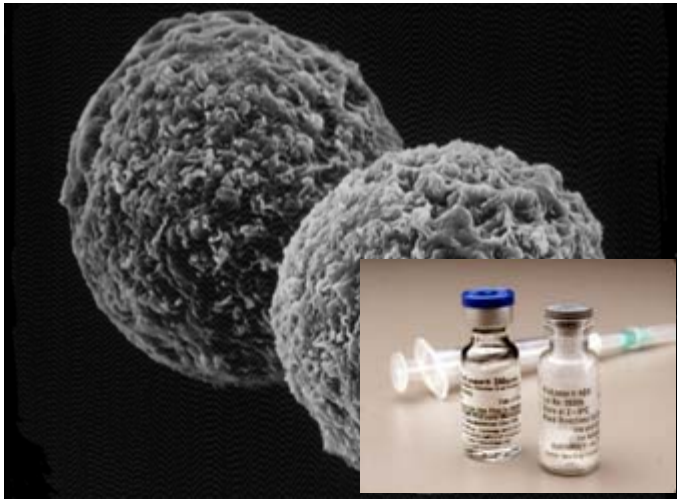
State-of-the-art drug delivery

Effective delivery of highly engineered particles

via

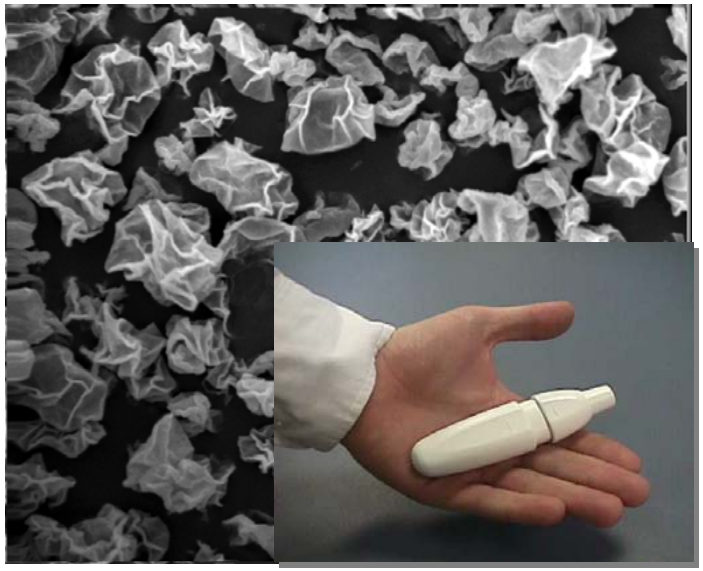
Injectable SR

- **ProLease®**
- **Medisorb®**



Pulmonary

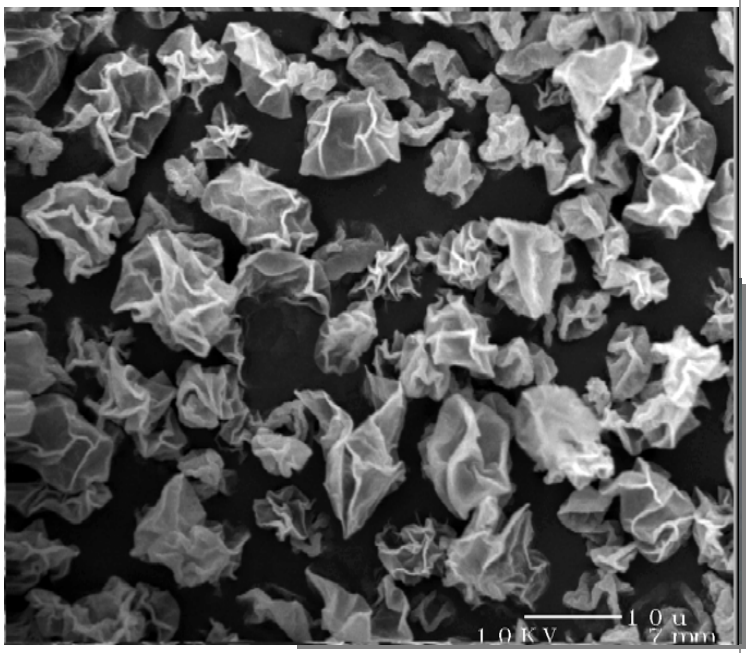
- **AIR®**



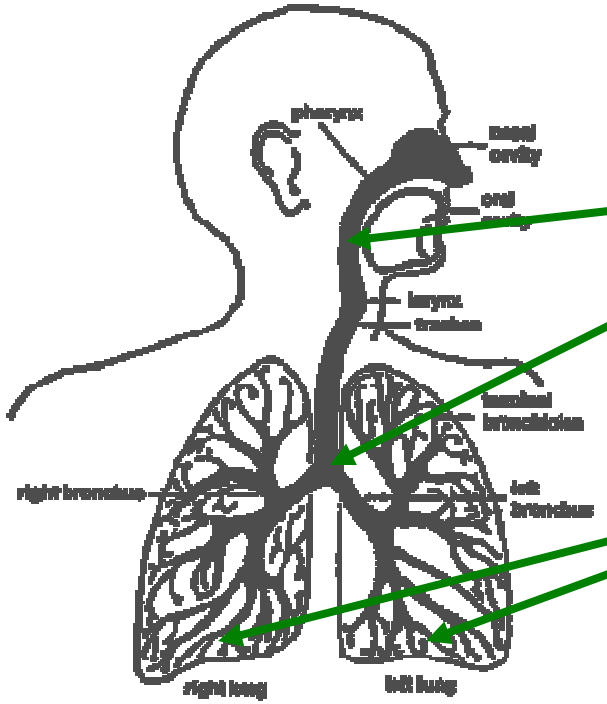
Pulmonary delivery

AIR®

- Local or systemic delivery
- Proteins, peptides, small molecules
- Large porous particles
- Simple inhaler
- Patented and proprietary



The Lung … an Effective Filter



(Greenspan, B. J., 1995)

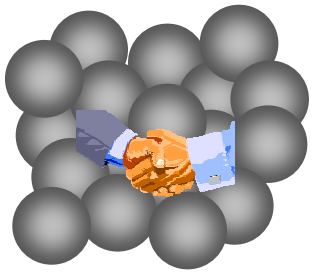
> 5 μm
Mucociliary Escalator

< 5 μm
Phagocytosis

… contingent upon ρ = 1 g/cc

(true in naturally occurring aerosols)

Why the Difficulty?



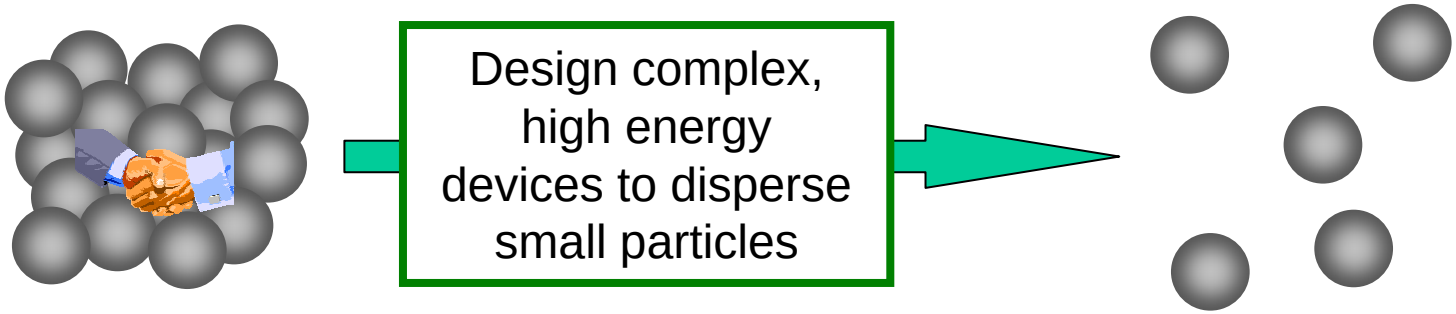
Particles Stick Together

What's Available?

Standard Inhalation Devices

- X low dose
- X low efficiency
- X flow rate dependent
- √ simple device

What Can Be Done?



Engineer the Inhalation Device

Avoid Breath-Actuation

- *more mass, more power*
- *more power, more complexity*

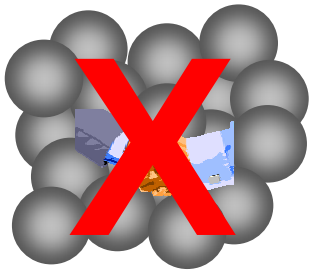
X low-moderate dose

√ high efficiency

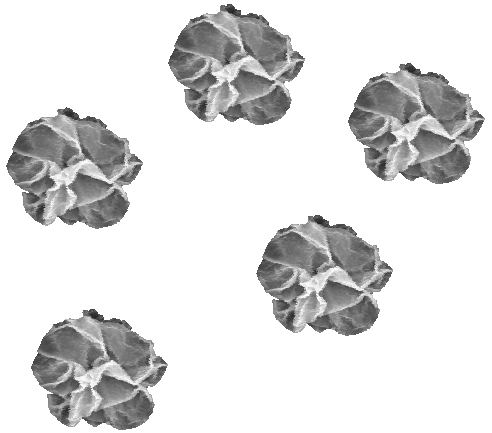
√ flow rate independent

X complex device

Is There Another Way?



Produce Large,
Porous Particles



Decoupled Geometric and Aerodynamic Size

Standard Aerosols

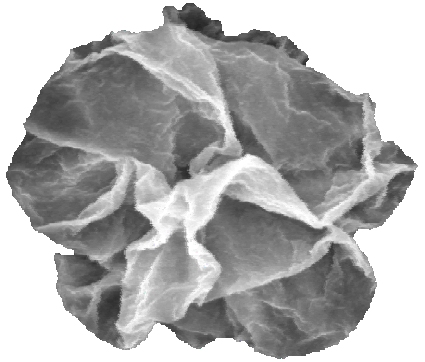
$\rho = 1$ g/cc

$d_g = 3$ μm

$d_a = 3$ μm

$d_a = d_g \rho^{1/2}$

AIR™ Technology



$\rho = 0.03$ g/cc

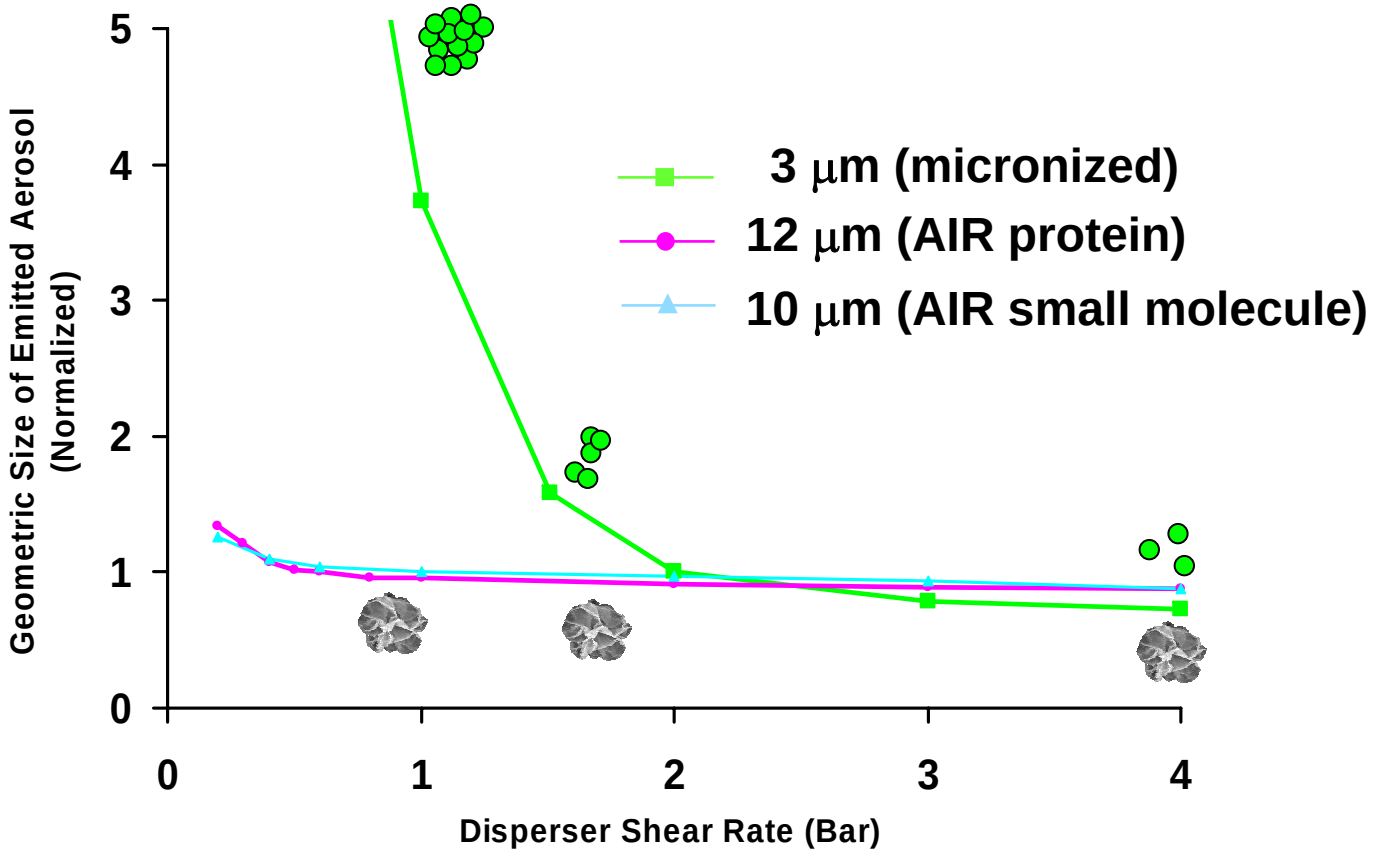
$d_g = 14$ μm

$d_a = 2.4$ μm

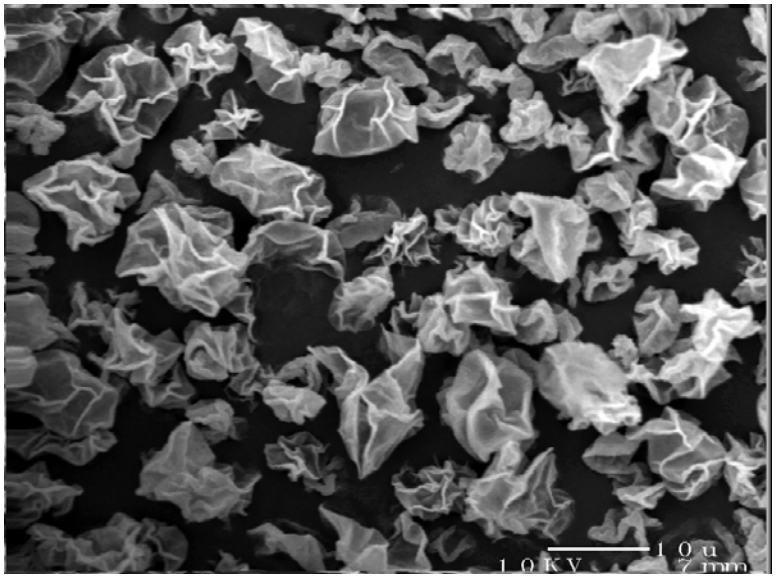
Ease of dispersibility

Targeted Lung Delivery

Dispersibility - Experiment



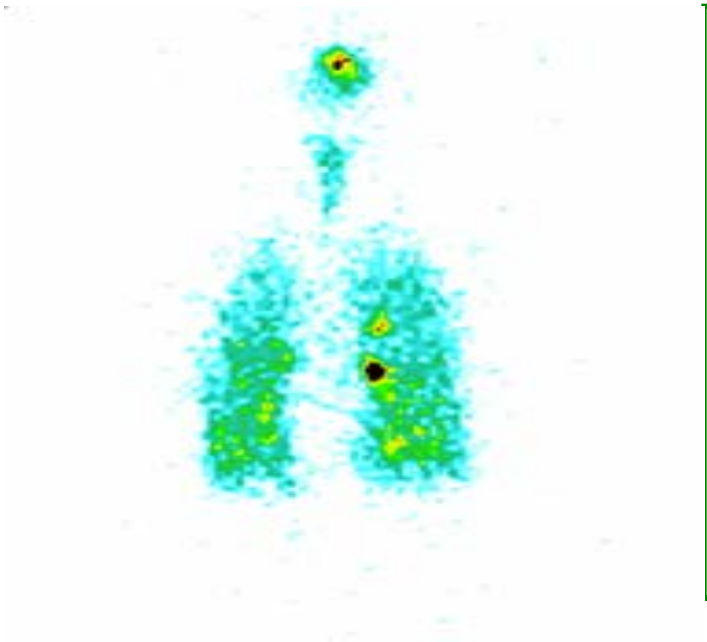
The AIR™ Solution



Large, Porous Particles

- √ low-high dose
- √ high efficiency
- √ flow rate independent
- √ simple device

√ high efficiency



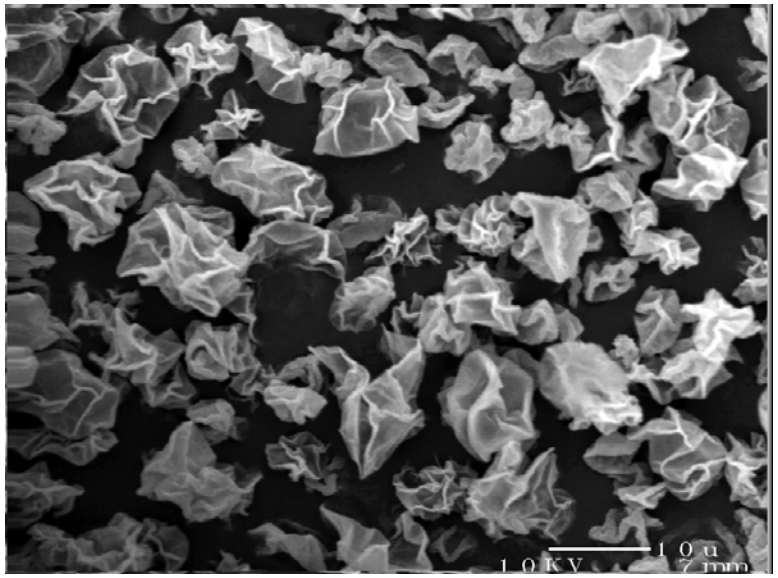
For high efficiency demanding powders

(systemic protein delivery)

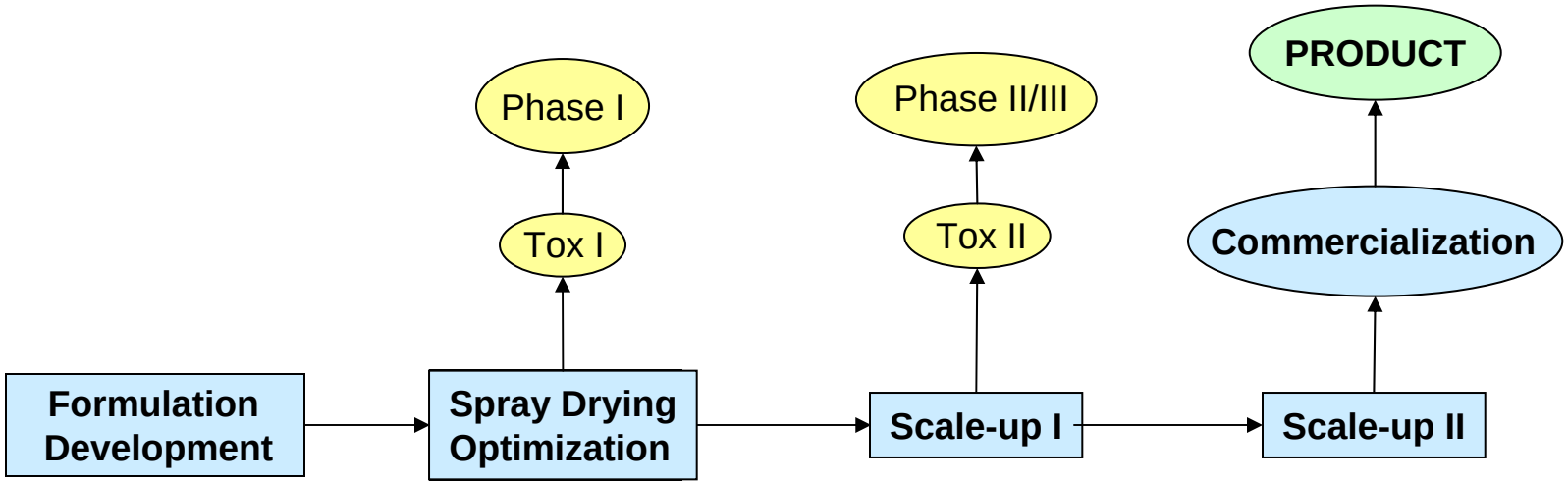
> 70 % of *nominal* dose delivered to the lungs

AIR Technology

High Tech Particles, not High Tech Inhaler



AIR Product Development Cycle



Goals:
1. Large Porous Particles
2. Drug product stability
3. *In vivo* PK/PD Profile

Goals:
1. Geometric size
2. Aerodynamic size
3. Aerosol performance
4. Drug product stability
5. *In vivo* characteristics

Goals:
1. Yield
2. Production rate
3. Maintain product characteristics

Goals:
1. Increase equipment size
2. Yield
3. Production rate
4. Maintain product characteristics

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Process Scale-up

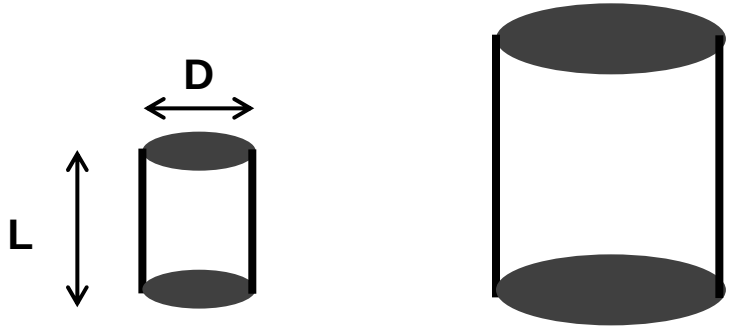
- Scale-up - a working definition
  - "Make a lot more of the same stuff - with a robust, reproducible, reliable process"
- Determine manufacturing targets
  - Too much capacity can be as big a problem as too little capacity
- Determine unit operations
  - Same as research?
  - Ideal to have engineering/manufacturing involved in research phase
  - Use "tried and true" unit operations if possible, even if you use them in a new way
  - Need mechanically robust processes

Process Scale-up

- Build flexibility into processing solutions to accommodate uncertainty
  - Low to high market forecast can vary by 5 to 10 fold
- Determine long term manufacturing strategy
  - Large production train vs. staging multiple trains
- Test scale-up relationships and design ideas at smaller scales
- Use any available similar “scaled-up” test equipment
  - suppliers, contract sites, etc.

General Scale-Up Challenges

- When different attributes of the same system scale differently
  - e.g. Heat Transfer in a cylindrical vessel
    - *Total heat to transfer $\propto$ volume (D^2L)*
    - *Heat transfer area $\propto$ sidewall area (DL)*
    - *If diameter is increased, imbalance between area for heat transfer and total heat to add or remove*



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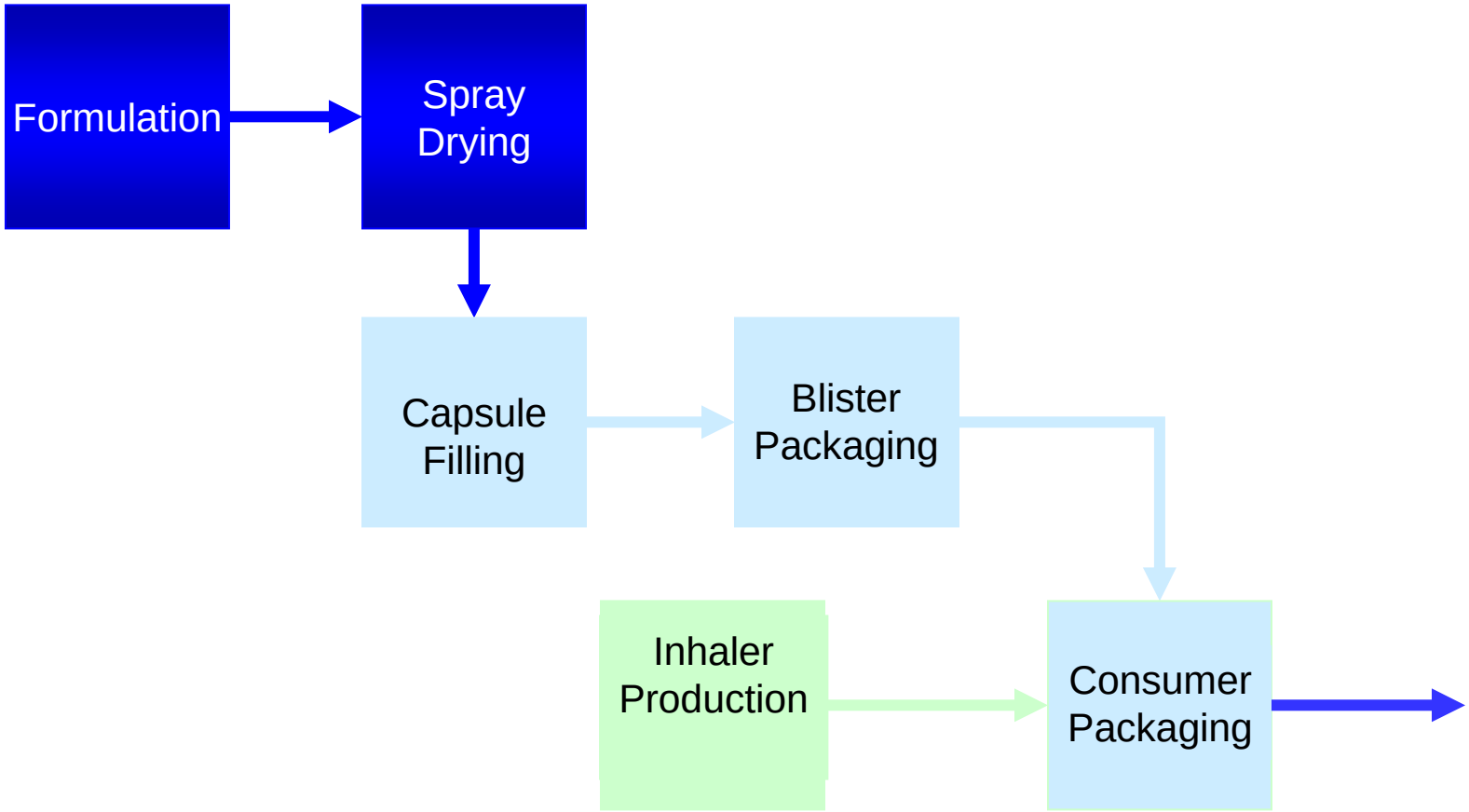
Scale-up Challenges

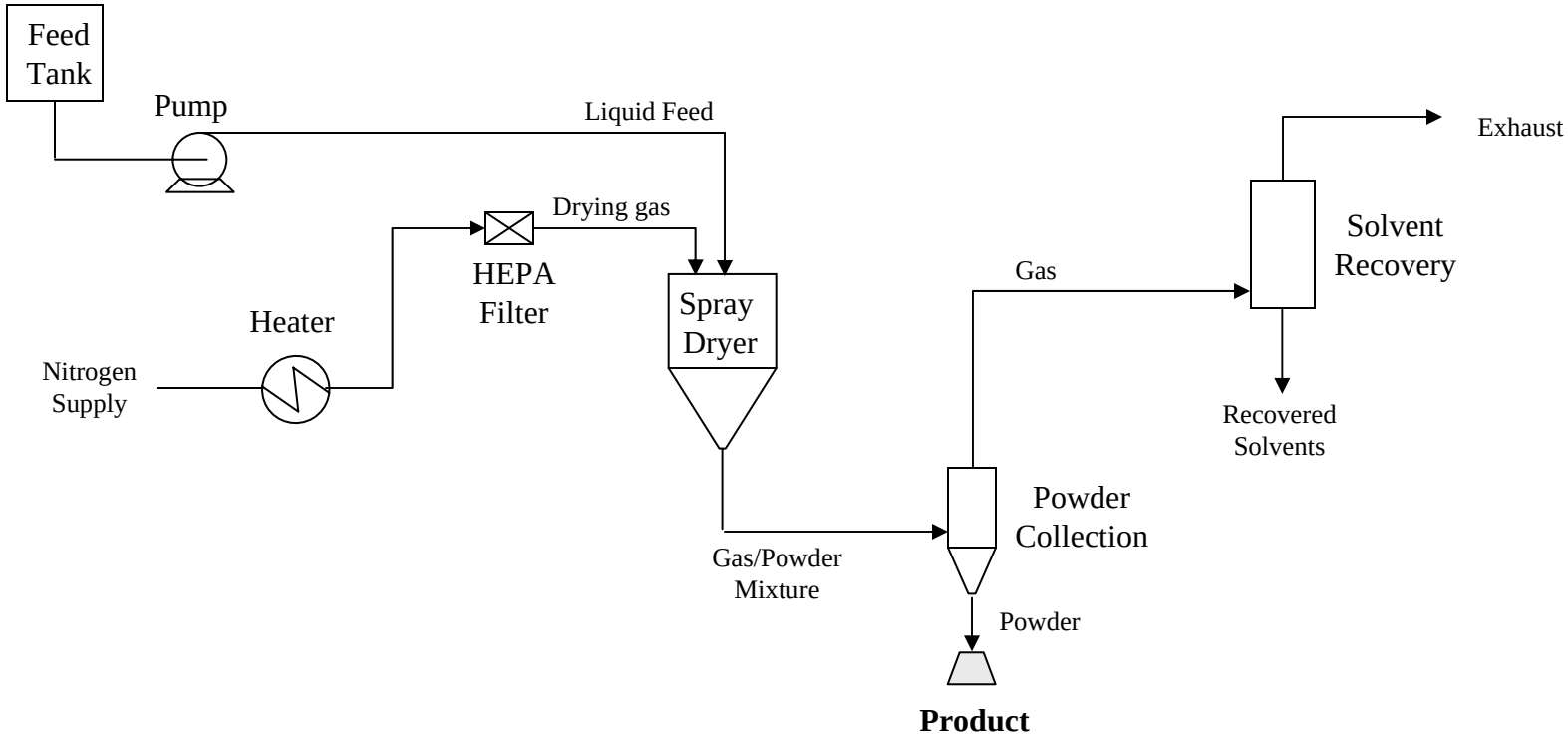
- Safety - increased volumes of hazardous substances
- Cost considerations
  - capital for new facilities
  - cost of increased need for drug substance for experiments
- Time pressure for completing scale-up and manufacturing facilities
  - do not want to spend money for scale-up work and new facilities until new product is demonstrated in clinic
  - once proved in clinic want scaled-up, online manufacturing facilities yesterday
- Pharmaceutical industry regulations limit process degrees of freedom once in pivotal clinical trials

AIR™ Manufacturing Unit Operations



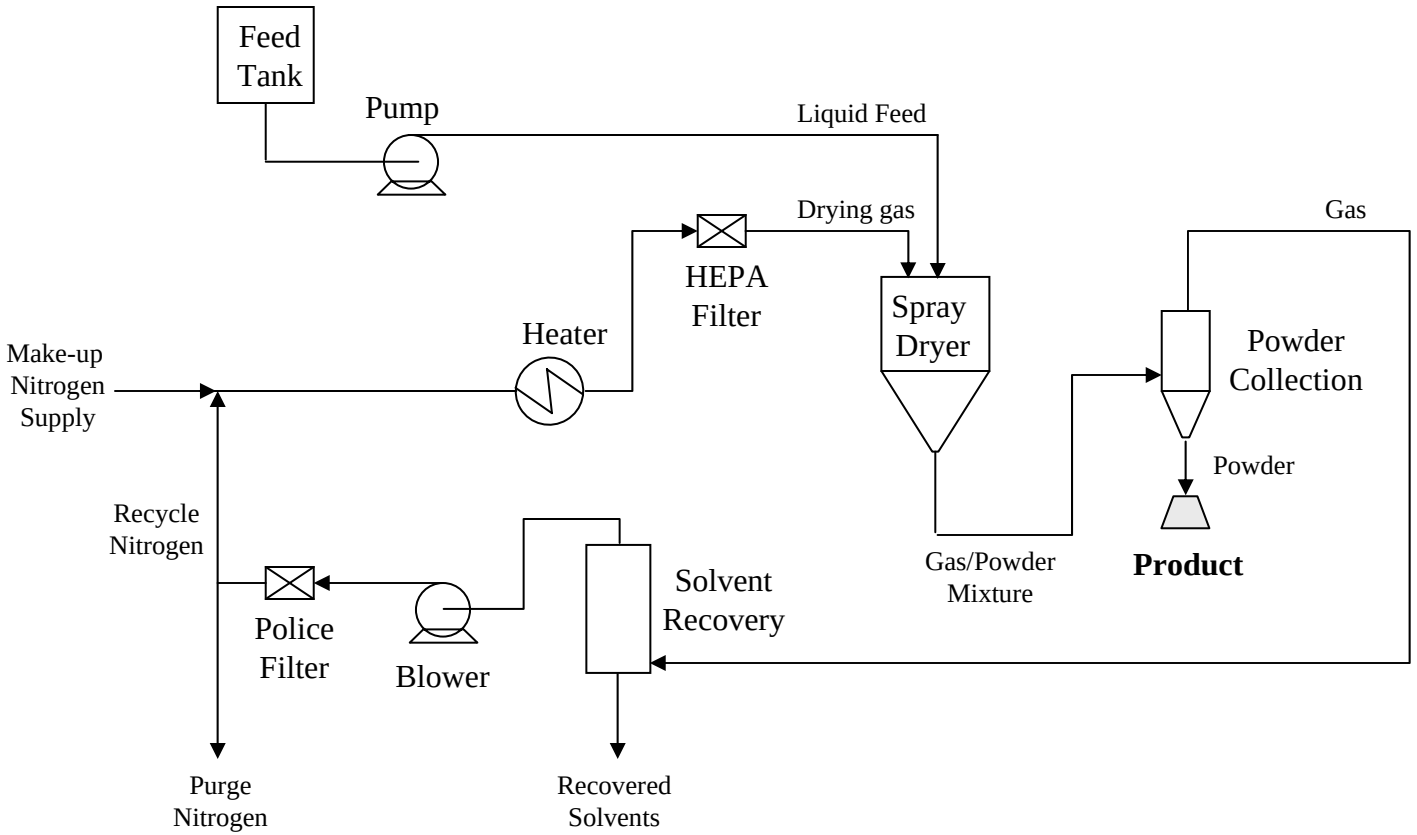
Open System Spray Drying Process

Suitable for small scale production



Closed System Spray Drying Process

Needed for large scale production



Spray Drying Scale-up Modeling

- AIR process scale-up desired result was a particle size, density, morphology and chemical purity
  - no appropriate models for detailed simulation
  - built conceptual models to drive development
- In spray drying scale-up the mixing dynamics of atomized feed and drying gas is crucial
  - spray drying supplier uses sophisticated computer models (computational fluid dynamics) to ensure consistency from small to large scale

Spray Dryer Scale-Up

- Increase batch size
  - Increase process time
- Increase production rate and batch size
  - Concentrate solutions
  - Increase flow rates
  - Increase yield
  - Parallel spray dryers
  - Increase spray dryer size

Focus on maximizing scale in existing small scale equipment

AIR Commercial Manufacturing Facility

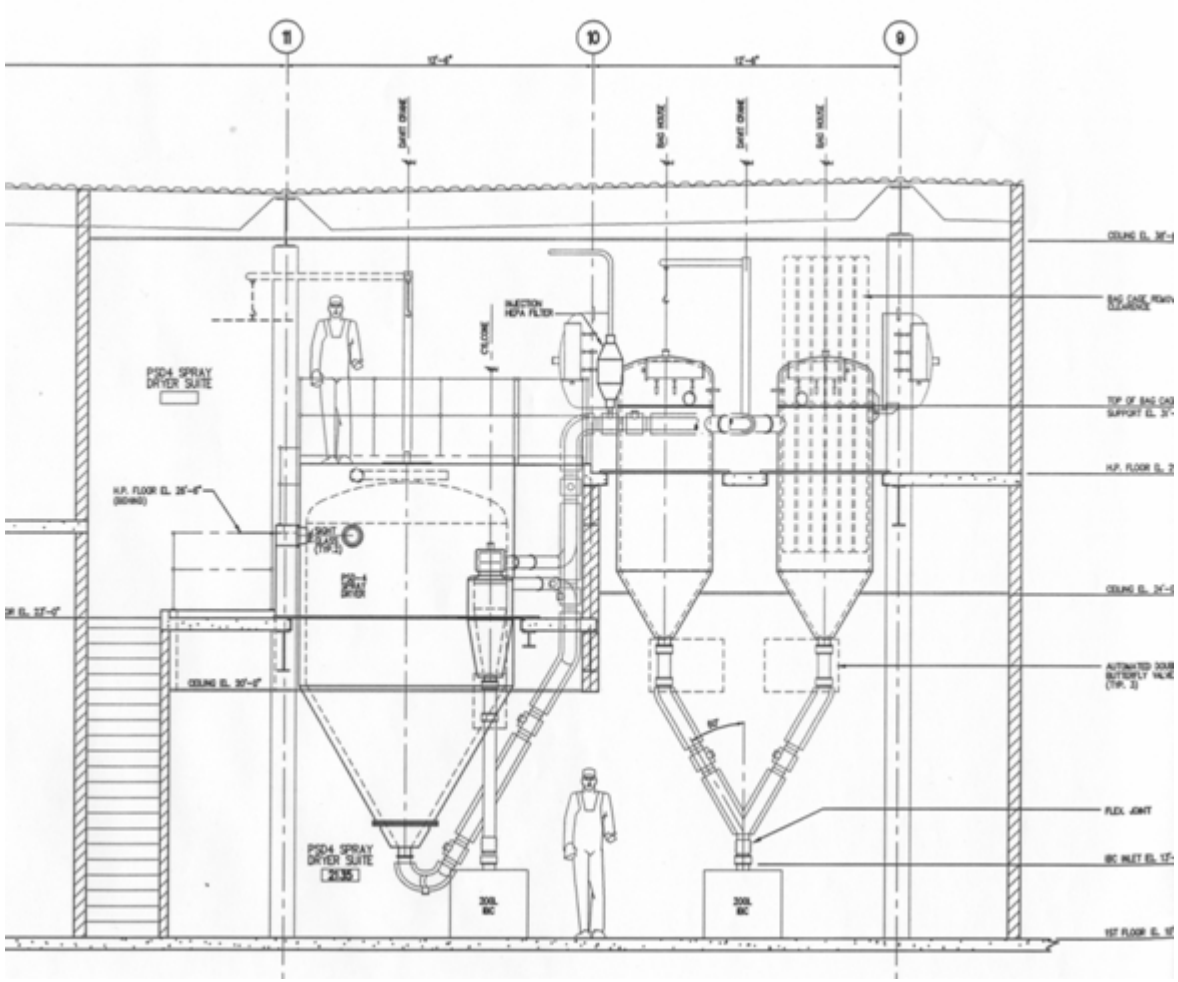
- Alkermes needed a full scale production facility
- 90,000 square foot site in Chelsea, MA
- Complete re-development of existing structure
- $40 million dollar project
- 18 months from start of construction to operation
  - design/build approach to shorten timeline
- Additional 6 months for validation
- Peak workforce of 150 contractors
  - Safety record 16 times better than national average

Facility of the Year Award

- Sponsored by ISPE, INTERPHEX and Pharmaceutical Processing Magazine
- For best pharmaceutical facility to come online
  - Innovation, Technology, Delivery, Project Management, Quality
- 28 entries from 12 different countries
- Alkermes Brickyard Square Facility was selected as one of 5 finalists
  - Only US finalist (from 7 US entries)

Small Scale Spray Drying

Size 4 Spray Dryer Layout



Construction Methods to Keep on Schedule

Construction Methods to Keep on Schedule

Commercial Scale Spray Dryer

Powder Production Scale-up

- Approximately 30 minutes of production each
- Scale-up of powder production by > 100,000 times

Spray Dryer Scale-up Challenges

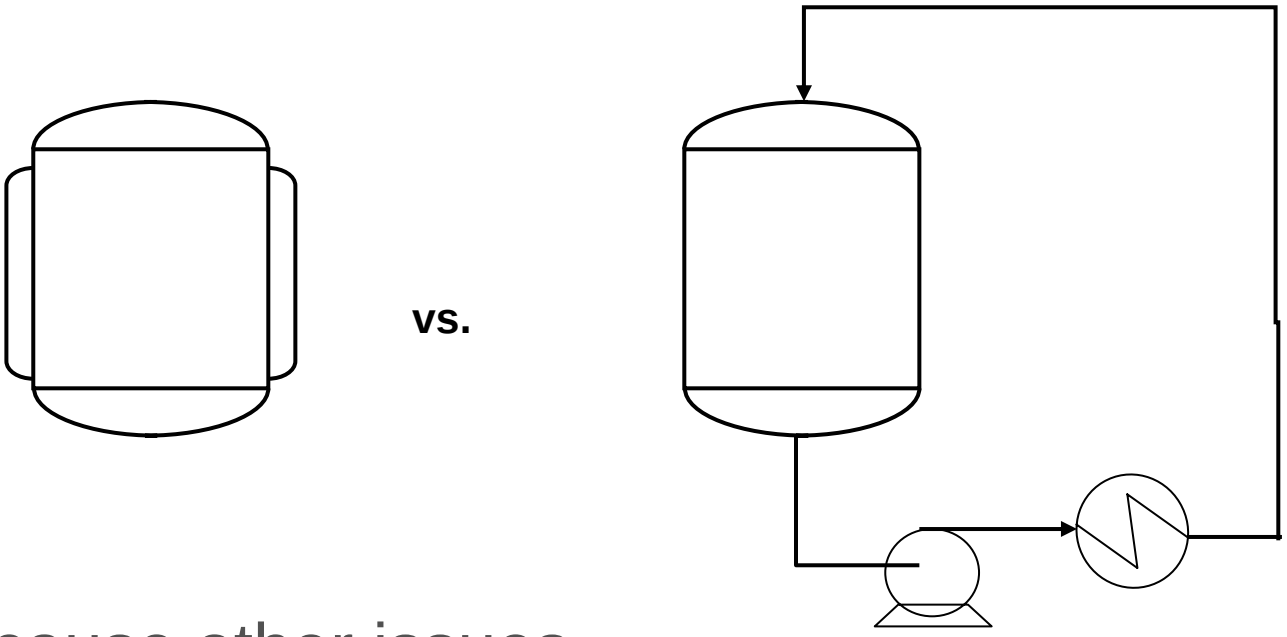
- Increase process time
  - drug stability in process and in collection vessel
- Concentrate solutions
  - solubility issues
  - particle formation and morphology
- Increase feed rate
  - Atomization of liquid feed
    - *keep drop size constant with increased feed rate*
    - *rotary atomization - issues with max achievable rotation*
    - *two-fluid atomization*

Spray Dryer Scale-up Challenges

- Yield
  - powder collection technology
  - minimize adherence of powder to surfaces
  - increased from ~20% to > 90%
- Increase equipment size
  - atomization
  - powder collection
  - equipment cleaning
  - solution preparation and handling
  - feed transfer - dead volumes

Overcoming Batch Scale-up Challenges

- Use steady state unit operations when possible
- Alternate method of heat transfer to a batch tank



- Can cause other issues

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Summary

- Scale-up of a process can be very challenging
- Batch processes have the additional complexity of time
- Use steady state processing tools when possible to reduce complexity of batch process scale-up
- Run a continuous process for longer times to scale-up a batch process
- Pharmaceutical industry has many interesting process challenges that chemical engineers are best suited to handle

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