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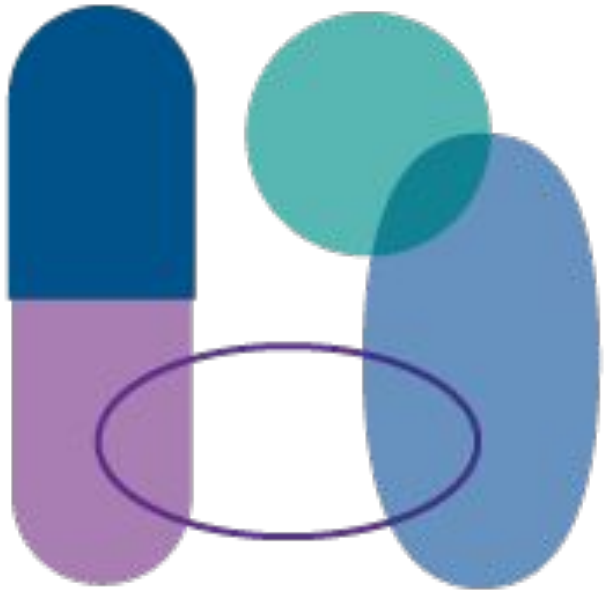

Oral Dosage Form Technologies for Potent Drug Product Development & Commercialization

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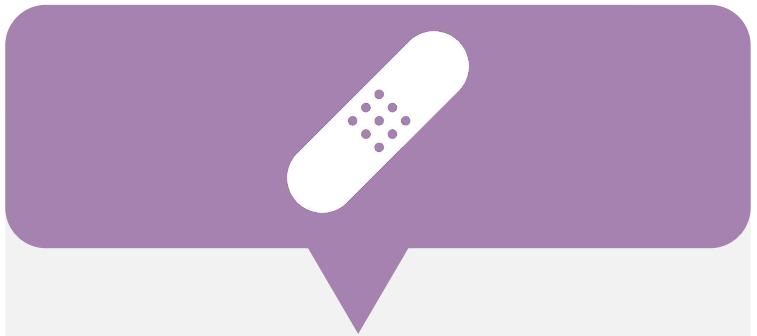
DEVELOPMENT DELIVERY SUPPLY

more products. better treatments. reliably supplied.™

Increased Demand for Complex Potent Handling Capabilities

~30% of development pipeline considered to be potent and share of potent pipeline compounds is growing



~80% oral oncology pipeline compounds estimated to be potent or highly potent

Modified release formulations can improve patient compliance and convenience

Data source: Internal Catalent assessment

What Exactly are Potent Compounds?

WHAT - Molecule that have therapeutic effects at very low doses (≤ 10 mg/day)

EXAMPLES - Cytotoxic drugs, Steroids, Hormones, and select Narcotics

SIGNIFICANCE - Benefits treating disease

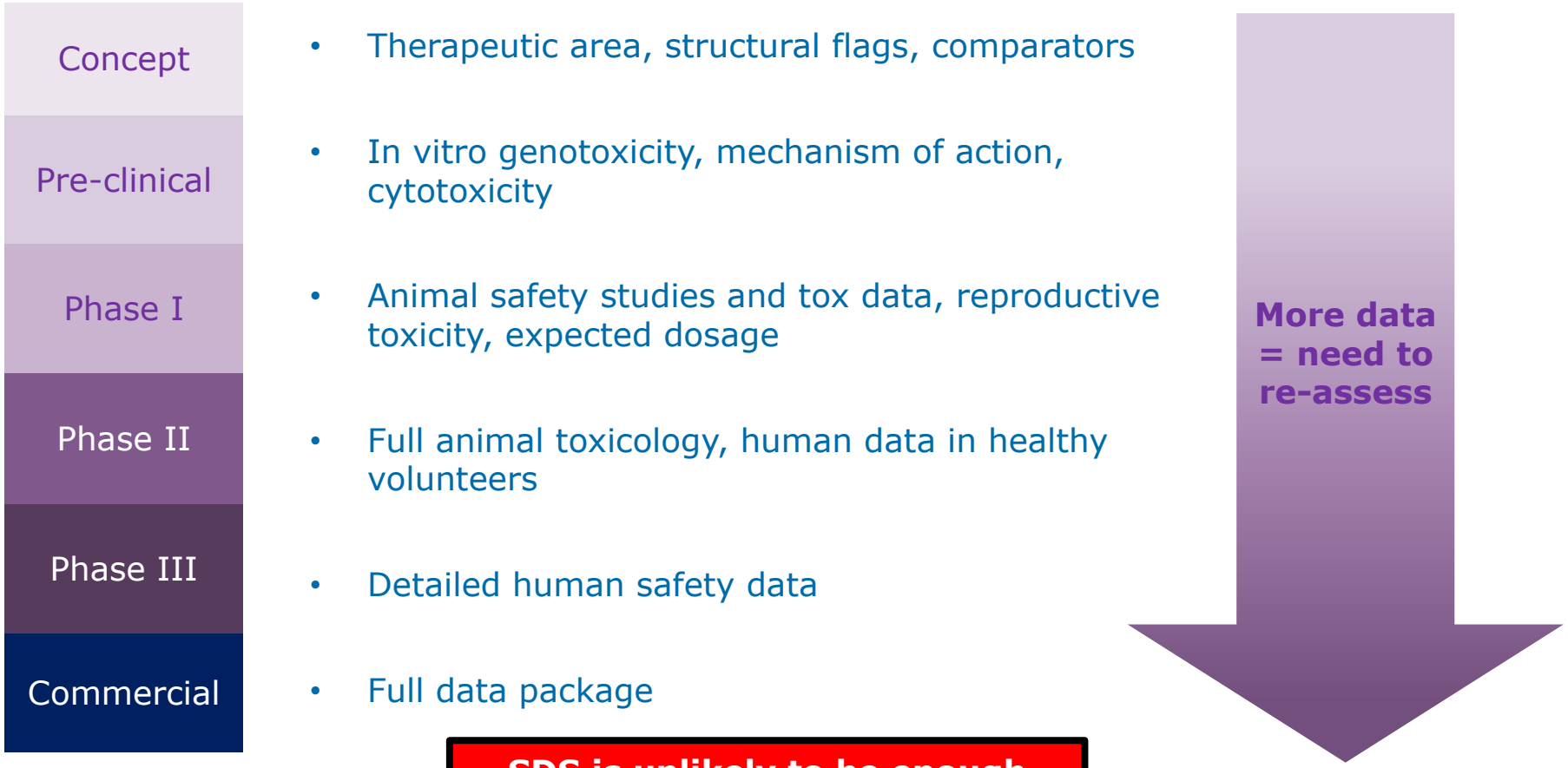
CHALLENGES - Worker safety, cross contamination, dose uniformity

HANDLING - Historically, produced in separate facilities with dedicate equipment

CLASSIFICATION - Systematic process to assign the Occupational Exposure Band/Occupational Health Categorization (OEB/OHC) using OELs & pre-clinical tox data.

PHARMA INDUSTRY STANDARD FOR HPAPI CLASSIFICATION – 20+ banding systems exist with 2–7 bands

Data requirement for potent project

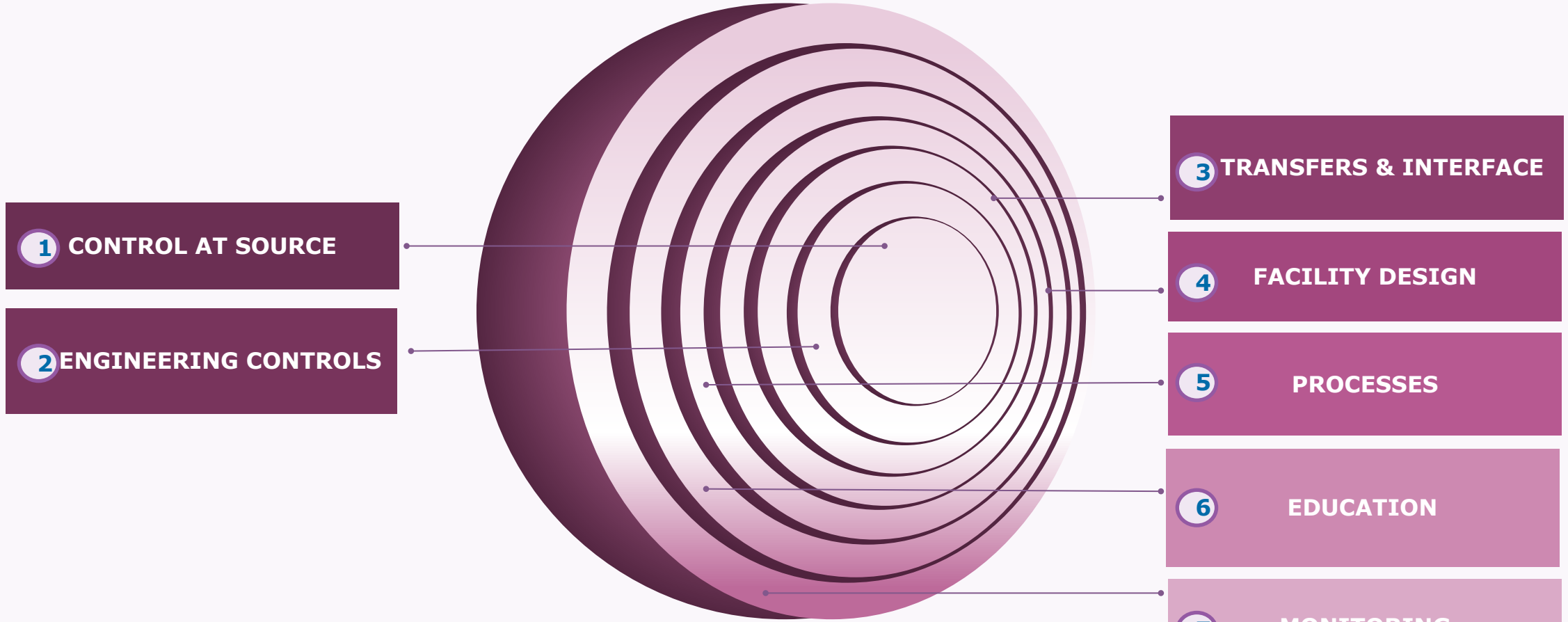


SDS is unlikely to be enough

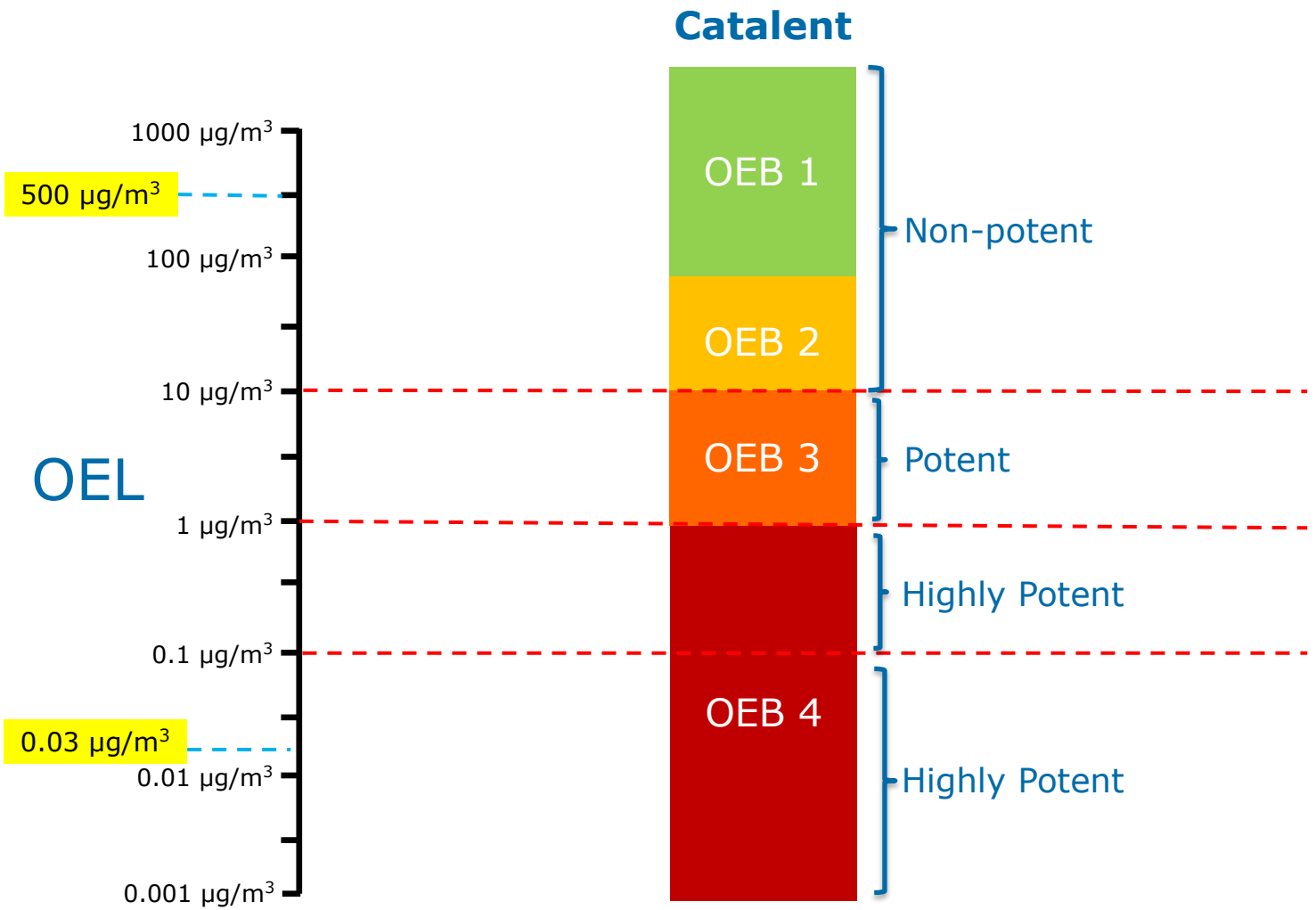
OEB/OEL/PDE report from a toxicologist is excellent

An Investigators' Brochure is excellent

Potent Facility Design Philosophy/Required Elements - "Onion Skin" Approach

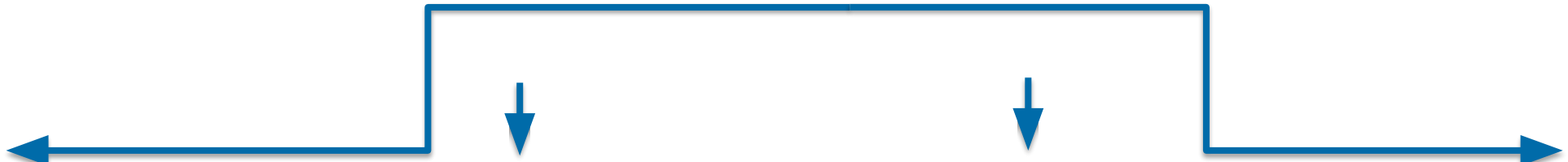


Occupational Health and Safety Classification (OHC)



Challenges in developing & manufacturing potent drug product are rooted in balancing safety with performance of manufacturing procedures

4 Main Challenges Relating to Safety & Development/Manufacturing Activities



Process Containment

- Operator safety
- Cross contamination
- Environmental impact

Processing Capabilities

- Consideration of equipment train
- Manufacturing scale

Formulation

- Dose uniformity
- Consideration of energy and physical state
- Poor solubility

Analytical

- Low level of detection

How to decide right process containment?

Process Containment

API

- **Drug load**
  - Amount of API in formulation
- **Batch size**
  - First in Human, Early phase, Late phase
  - Immediate batch size vs. projected scale up
- **API form**
  - Micronized, Semisolid, Liquid, Low vs. high bulk density

Technology

- **Conventional**
  - API in capsule
  - Simple blend
- **Enabling**
  - Micronization
  - Spray drying
  - HME
  - Lipid based formulation

Unit Operations

- Containment for HPAPI **rich** unit operations
- Containment for HPAPI **poor** unit operations

Meeting HPAPI drug product release profile requirements

How to ensure operator safety & preventing cross contamination?

Process Capabilities

People

- Procedural controls
  - Personal protective equipment (e.g., air-line suits)
- Properly trained personnel

Equipment

- Engineering controls at source
  - Split Butterfly Valves
  - Isolators
- Flexible and/or single-use containment systems are becoming more important in contract manufacturing situations

Room

- Prevent airborne cross contamination w/ properly designed high potent rooms:
  - Airlocks
  - Misting showers
  - Single pass HEPA-filtered air

Working Environment

- Containment performance must be proven via:
  - Industrial Hygiene (IH) air monitoring during commissioning of facilities
  - Equipment must prove Containment Performance Target (CPT)

How to plan for processing scale, process isolation & equipment train?

Process Capabilities

Key Issues

- Manufacturing process is chosen based on containment available for unit operation rather than DS properties
- Potent equipment capacity results in small batch sizes (multiple portions)
- Manufacturing processes are generally manual until registration campaign
- Equipment train between early phase and late phase may not follow SUPAC guidance
- Process development and characterization is limited due to DS availability

Key Considerations

- Ability to work on small scale with limited DS
- Fit for purpose early-stage clinical manufacture
- Integrated approach from manufacturing to packaging and distribution
- Bioavailability enhancement technologies and early formulation development capabilities
- Technically competent and experienced in designing engineering solutions
- Product development facility and resources independent of commercial production

Recommendation

Identify facilities that have:

- Flexibility to support a variety of process demands
- Can accommodate many unit operations
- Can adapt quickly to & scales

How to address content uniformity, solubility & physical state challenges?

Formulation

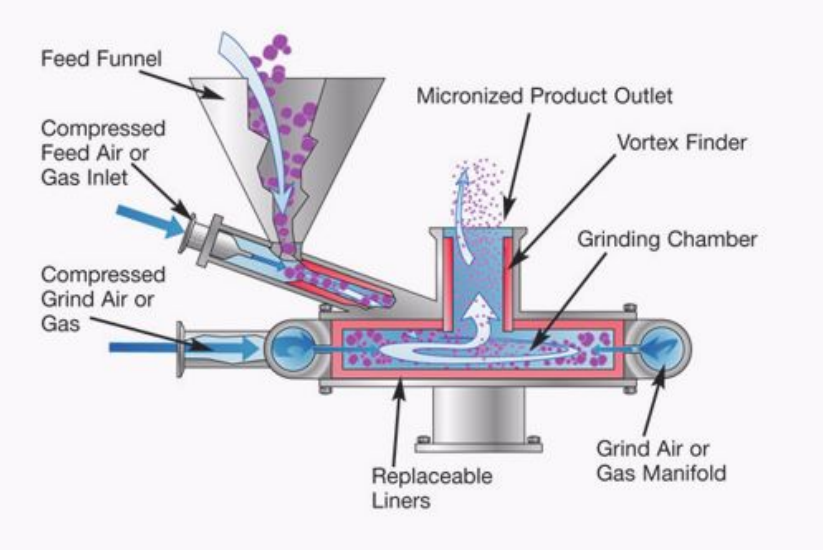
Potent compounds generally:

- Show pharmacological activity at low doses
- Smaller dosage-unit volumes are required
- Additional complexities
  - Poor solubility
  - Issue with physical state

Key Issues	Recommendation	
Blend uniformity, content uniformity does not meet specifications for low dose potent drug products	• API in capsule/bottle • Solution/suspension in bottle • Simple dry fill capsules – manual or automated • Granulation (wet/dry) tablets	Early-stage approaches
	• Drug loaded or layered pellets	Late-stage approaches
Low aqueous solubility can lead to failure to meet dissolution specifications for potent drug products	• Enabling technologies: micronization, solid dispersion, lipid-based formulation	
Batch failures likely due to low bulk density and poor flow for potent drug products	• Roller compaction alone or in combination with enabled technologies	

Micronization can improve poor solubility and bioavailability of potent drug products

Formulation



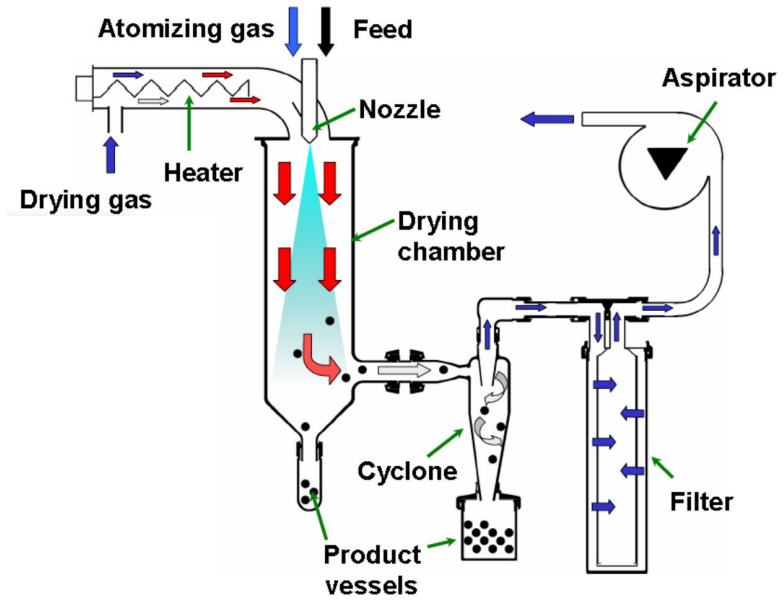
- Micronization provides increased surface area to deliver faster dissolution rate to improve bioavailability
- Micronization provides better content uniformity for low dose potent drug products
- Co-micronization with a surfactant may increase equilibrium solubility, rate of dissolution (typically modest)

Effect on Potent Containment

- Isolators required for weighing API
- Closed manufacturing process employed for potent micronization ensures safety and prevents cross contamination
- Micronized potent API can then be further processed in variety of dosage forms
- Densification technology is typically required for oral solid drug product
- Significant downstream potent handling of micronized API is required for oral formulations

Spray drying can improve poor solubility/bioavailability plus aid in downstream potent containment

Formulation



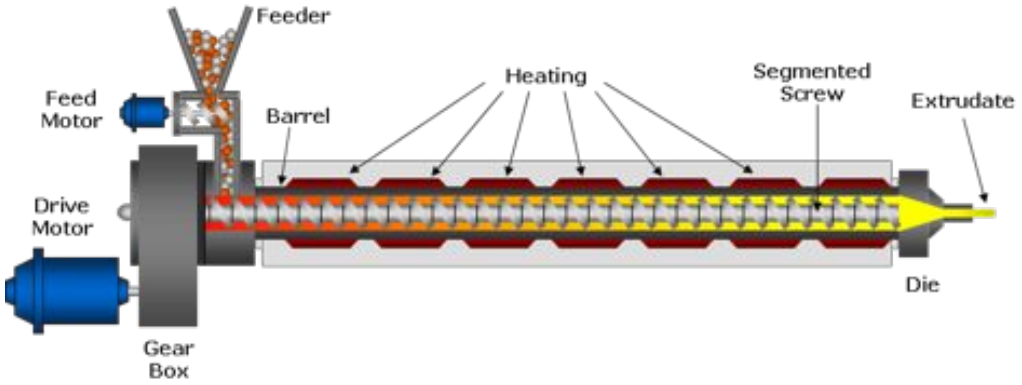
- Enhanced bioavailability of poorly soluble potent compounds
- Long term stability
- Robust and scalable process
- Consistent particle size distribution
- Enables taste masking or controlled release dosage forms downstream

Effect on Potent Containment

- Potent API is dissolved or suspended in appropriate organic solvents with appropriate excipients
- Spray dryer provides a closed manufacturing process
- Downstream densification technology is typically required
- Downstream potent handling easier compared to naïve or micronized API

Hot melt extrusion can provide solubility/bioavailability benefits and resolve potent containment

Formulation



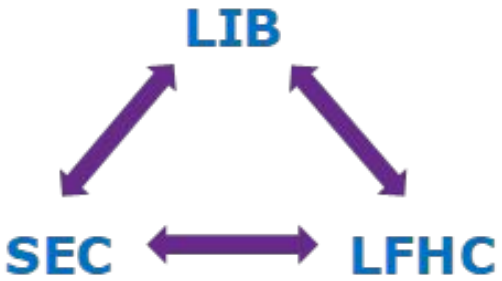
- HME can generate soluble amorphous forms of potent DS that are stable and processable downstream into variety of dosage forms
- Relative high drug loading can be achieved while improving bioavailability
- IR/CR formulations, taste masking, abuse deterrence are possible
- Well suited for thermolabile products
- Solvent free process (advantage over spray drying)

Effect on Potent Containment

- Potent DS handling largely focused on weighing of potent DS in isolator
- Densification technology not required for oral solid drug product
- Downstream potent handling easier compared to naïve, micronized, spray dried API

Lipid based formulation resolve several challenges associated with potent compounds - poor solubility, permeability, physical state and containment

Formulation



- Great benefit for ensuring content uniformity of low dose potent drug products
- Scale up has little or no impact on potent handling
- Compatible with wide variety of excipients for solutions, suspensions and semisolid formulations
- Flexibility converting among the technologies with minimal impact on formulation performance
- Conversion of parenteral to oral delivery of potent compounds is feasible
- Abuse deterrent ability can be employed for potent compounds that are also controlled substances

Effect on Potent Containment

- Containment of potent compounds largely restricted to upstream processes. Isolators required for weighing API
- Potent API suspended or dissolved prevents dust generation in downstream unit operations
- Potent DS challenges due to liquid, semisolid DS, poor solubility and/or permeability, low melting point can be addressed

Roller compaction imparts manufacturability to naïve or enabled intermediates of potent compounds

Formulation

- Suitable for DS/ DPI that has very low bulk density
- Roller compaction can transform these into granules which can result in -
  - Improved powder flow
  - Improved content uniformity
  - Increased bulk density
- Continuous process ensures reduced potent DS handling
- Great for heat sensitive potent DS (advantage over bead coating or melt granulation)
- Containment down to 1µg/m^3 is possible without use of isolator

Effect on Potent Containment

- Isolators generally required for weighing naïve or potent drug intermediate
- Closed manufacturing process for roller compaction ensures safety and prevents cross contamination
- Densification achieved without the use of solvents
- In line milling offers reduction in dust generation
- Challenge exist for containment required for downstream unit operations (blending, compression)

Multi-particulate technology provides advantages of low dose, modified release, containment of potent compounds

Formulation

- Multi-particulates technology has tremendous benefits in terms of achieving desired release profiles
- Dissolving or suspending potent DS prior to coating onto inert bead provides advantages in reduced handling downstream processes
- Dose uniformity is enhanced

Effect on Potent Containment

- Isolators required for weighing API
- Potent API suspended or dissolved prevents dust generation in downstream unit operations
- Closed manufacturing process ensures safety and prevents cross contamination
- Lower level of containment necessary for downstream unit operations (encapsulation, packaging)

Challenges specific to analytical testing of potent products

Analytical

Analytical testing

- Analytical methods are employed for potent compounds for the following:
  - Method development and validation specific to potent API
  - Method development and validation specific to potent drug product
  - Cleaning verification and validation methods for release equipment post-manufacture of potent products

Effect of Potent Containment

- Dexterity to work in isolator with very small quantities of API/product
- Methods developed that involve opening and weighing aliquot of the drug product (e.g., capsule, bottles, stick packs) are challenging for analyst
- Quantitation of API dose to mcg level
- Quantitation of impurities to 0.1% of dose
- Extraction processes and specialized techniques

Summary

- Deciding level of containment depends on a combination of API hazard, technology employed and unit operations
- Solubility and bioavailability enhancement technologies provide containment necessary for potent compounds
- Converting naïve potent API to intermediate (spray dried, hot melt extrudates etc.) aids potent handling downstream
- On-going risk assessment is crucial to understand and incorporate new safety information
- Batch size drives process containment requirements
- “Whole unit” analytical methods avoid sample preparation in the isolator
- Integrated potent dug product development that employs the best technology needed for the drug product vs “what is available”

Robust network of potent capabilities from development to commercial

PRECLINICAL

CHAM, Switzerland
- PBPK Modeling

San Diego, US
- Developability Assessment
- COE Spray Dry
- **OEB 1 - 4**

Beinheim, France
- Developability Assessment
- COE Lipids
- **OEB 1 - 4**

CLINICAL MANUFACTURING

San Diego, US
- Standard Oral Solids
- Integrated Analytical
- COE Spray Dry
- **OEB 1 – 4**

Beinheim, France
- Softgel Capsules
- Liquid Filled Hard Capsules
- Liquid in Bottle
- Analytical Development
- **OEB 1 - 4**

St. Petersburg, US
- Softgel Capsules
- Liquid Filled Hard Capsules
- Liquid in Bottle
- Integrated Analytical
- **OEB 1 - 4**

Greenville, US
- Standard Oral Solids
- Integrated Analytical
- **OEB 1 – 4**

Nottingham, UK
- Standard Oral Solids
- Integrated Analytical
- COE Spray Dry
- OEB 1 -3

Kansas City, US
- Standard Oral Solids
- Integrated Analytical
- **OEB 1 -3**

Winchester, US
- **COE** US Complex Oral/CR
- Integrated Analytical
- Bottling
- Stick Packs
- **OEB 1 -3**

Schorndorf, Germany
- **COE** EU Complex Oral/CR
- Integrated Analytical
- Bottling
- Stick Packs
- **OEB 1 -3**

CLINICAL SUPPLY

PRIMARY | SECONDARY | STORAGE & DISTRIBUTION | SUPPLY MANAGEMENT

Kansas City, US
OEB 1- 4

Philadelphia, US
OEB 1- 4

Schorndorf, Germany
OEB 1- 4

San Diego, US
OEB 1- 3

Bathgate, Scotland
OEB 1- 3

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