Potent Compound Processing in the Merck Rahway FLEx Center

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Rob O'Connor

- Senior Scientist at Merck & Co., Inc., Rahway, NJ, USA
- Pharmaceutical Operations, Oral Solid Dosage
- Support FLEx equipment and facility design, system commissioning/qualification, facility operations, and formulation and process development

Agenda

Merck High Potency Classifications

FLEx Center Overview

Types of Processing Areas

Unit Operations/Products for Sterile Formulation

Unit Operations/Products for Oral Formulation

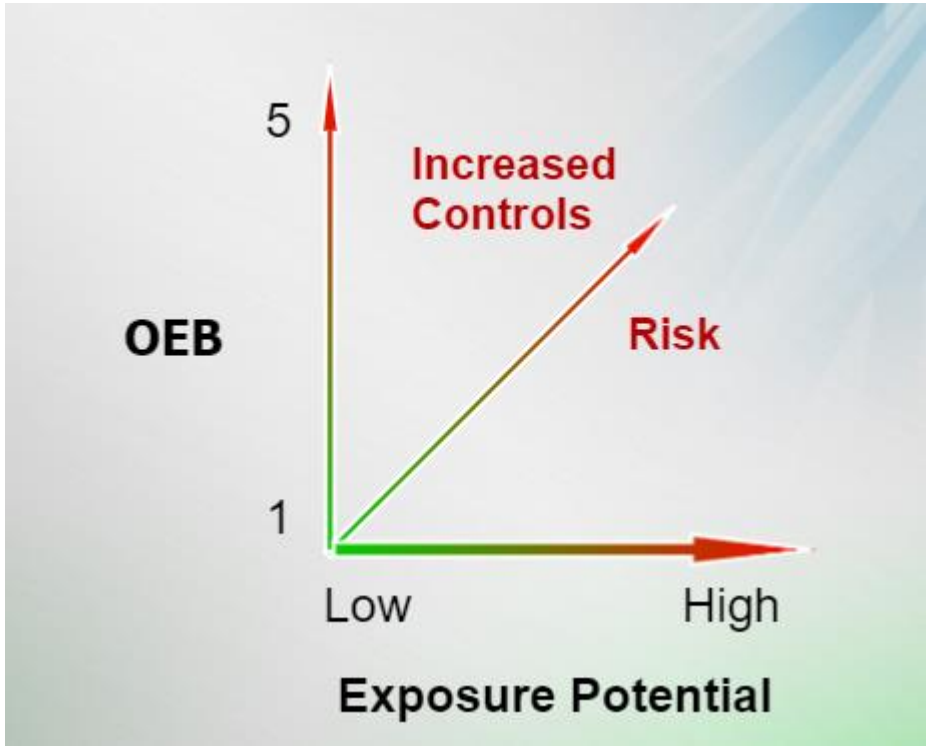
Processing Technology for Containing OEB4/5

Containment Verification Strategy

Occupational Exposure Banding and High-Potency API's

OEB	1	2	3	4	5
Potency (mg/day)	<100	10-100	1-10	0.1-1	<0.1
Potential Exposure Effect	None to Minor	Minor to Moderate	Moderate to Serious	Serious	Serious
Handling	GMP/PPE	GMP/PPE	Containment	Containment	Containment
OEL range (µg/m^3) (8-hr TWA)	>1000	<1000 to 100	<100 to 10	<10 to 1	<1
Example Compound	Lactose	Naproxen (ALEVE)	Pembrolizumab (KEYTRUDA)	Mometasone	Ethinyl Estradiol

- Merck OEL/OEB Strategy:
  - Potent APIs have OELs <10 ug/m^3
  - OEB 4s are compounds with OELs 1-10 ug/m^3
  - OEB 5s are compounds with OELs <1 ug/m^3
  - Default highly potent, toxic and potentially genotoxic compounds (e.g. small molecule oncology, hormones, etc) as OEB 4/5
  - **Target for OEB 4 containment designed for 1ug/m^3 for the duration of the task (not an 8 hour average)**
  - **Target for OEB 5 containment designed for 10ng/ m^3 for duration of task**
- The ranges of OELs that OEBs span can vary from company to company as well as the number of bands / categories, but there is alignment on the definition of potent compounds and effective engineering controls



Merck's FLEX Center (Formulation, Laboratory, and Experimentation Center)

- Clinical and Developmental Drug Product Pilot Plant spanning multiple modalities
- Oral Solid Dosage, Sterile, and Animal Health co-located within one drug product pilot plant facility
- Create flexible, compliant research capabilities that can **adapt to shifts in pipeline and technologies** quickly and provide line-of-sight to our commercial facilities
- Remain at the forefront of quality, regulatory and safety compliance

$450M Facility
Rahway, NJ
Open 2022

Flexible Manufacturing Space: *Modular Clean Rooms*

Modular Clean Room Opportunities:

- Allows for facile reconfiguration of walls and ceilings based on process needs
- Walls can be fitted with glass panels for maximum light and viewing of the manufacturing space
- Manufacturing space can be expanded into fallow space with additional modular walls
- Utilities/HVAC located on walkable ceiling above cleanrooms

Flexible Manufacturing Space: *Podular Clean Rooms*

- Prefabricated biopharmaceutical cleanroom environment
- Flexible and mobile due to integrated air bearings
- Utility connections are made external to the POD at manufacturing facility, allows for potential relocation from site to site
- Not necessary to build a new lab into infrastructure, can leverage moving PODS

Potent Compound Processing Areas

- Designated material and personnel airlocks for potent compounds (MAL and PAL)
- Visible and audible alarms on all equipment for containment breaches
- Pressure gradients utilized across processing areas
- Processing areas equipped with safe change exhaust HEPA filters (BIBO)
- Containment verification studies conducted on all pieces of equipment
- Wipe testing of both equipment and processing area conducted post processing to confirm area is free of contamination

Strategy for Flexible High-Potency Sterile and Aseptic Manufacturing in FLEx

FLEx Capabilities

- A totally sterile environment with minimal human intervention (isolated)
- Use of robotics to reduce the need for human intervention and reduce difficult to clean conveyor belts and star wheels
- Ability to handle highly potent compounds + BSL-2
- Containment control for personnel safety and cross contamination
- Ancillary equipment is being designed as either movable or portable; will be “flexed” depending on batch needs

Unit Operation / Technology	OEB 3	OEB 4/5	BSL-1	BSL-2
Compounding	✓	+	✓	+
Aseptic Fill / Finish	✓	+	✓	+
Blast Freezing	+	+	+	+
Lyophilization	✓	+	✓	+
Lyosphere	+		+	+
Lipid Nanoparticle	+	+		
Dry Powder Inhalers	✓	✓		
Long-Acting Parenterals	+	●	●	
Cell Therapy			●	●
Alternative Drying	●	●	●	●

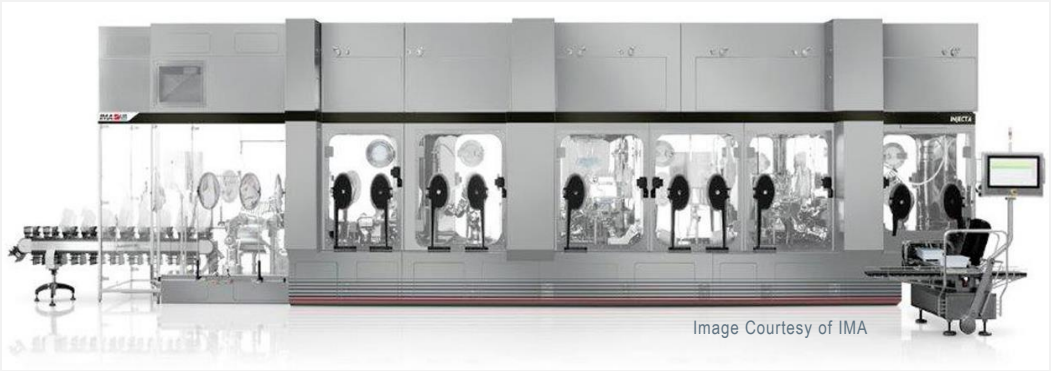
+	New capability	✓	Existing capability	●	Designed capability

Process and Product Flexibility in Sterile & Specialty Products

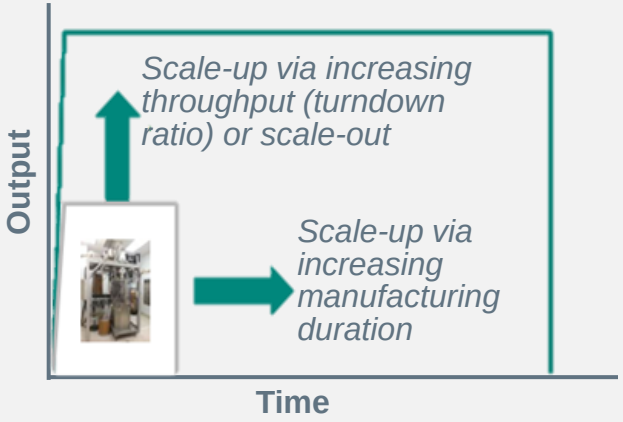
Process Flexibility

Single Use Systems

Robotics and Isolators



Continuous Manufacturing



Product Flexibility

Sterile Injectables

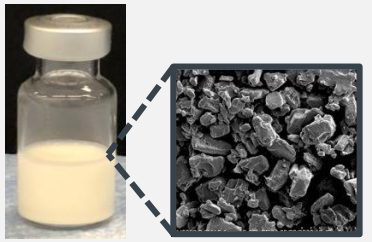
Metered Dose + Dry Powder Inhalers

Alternative Drying Technologies

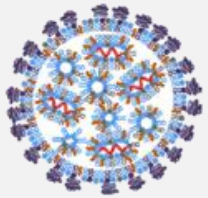
(e.g., Lyosphere, microwave drying)

Long-Acting Parenterals

(e.g., implants, suspensions, controlled release particles)

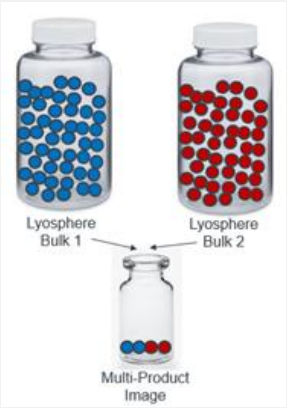


Lipid Nanoparticles + Novel Adjuvants



Co-Formulations in Sterile

(liquid and lyophilized)



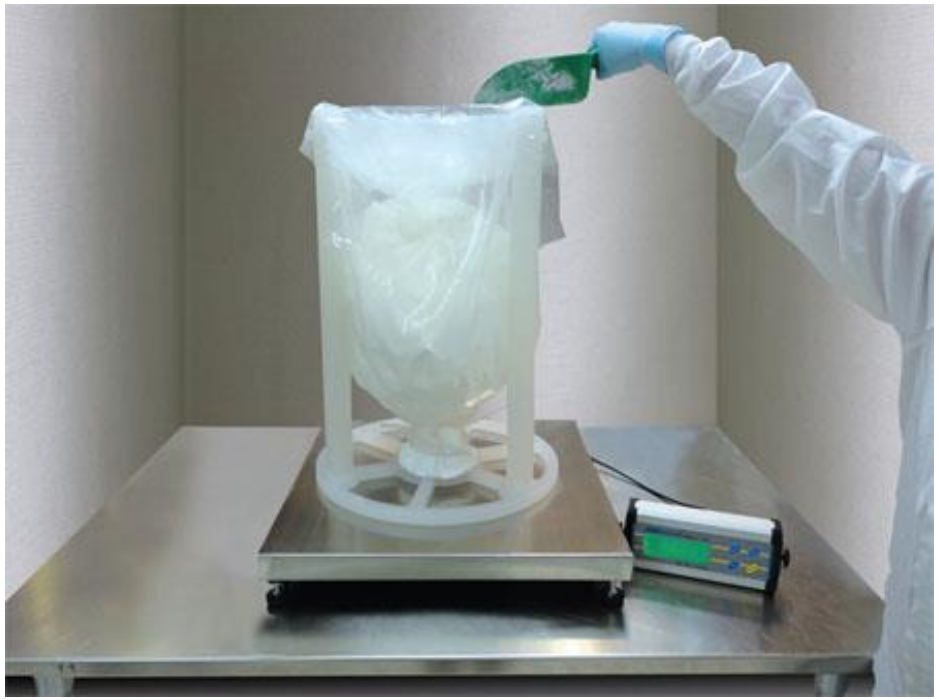
Strategy for Flexible High-Potency Oral Formulation Manufacturing in FLEx

- Equipment is being designed as either movable or portable
- Equipment will be “flexed” between processing rooms depending on batch needs
- OEB 5 equipment will be housed inside, movable, reconfigurable, rigid isolator

Unit Operation	OEB 3	OEB 4	OEB 5
Blending	✓	+	+
Milling	✓	+	+
Encapsulation	✓	+	+
Compression	✓	+	-
Roller Compaction	✓	+	-
Film Coating	✓	+	-

+	New capability	✓	Existing capability

Contained Charging and Discharging of Powders



ILC Dover EZ BioPac

- Entire diameter of the bag opens for dispensing powders
- Bag sealed and clamped on powder charging end
- Bag mated to 4 inch split butterfly valve for powder transfer

ILC Dover SF Bag

- Similar to EZ BioPac, but only 4 inch end of bag opens – will be mated to split butterfly valve
- Used for powder transfer between unit operations, not for dispensing into

Images courtesy of ILC Dover

Flexible Manufacturing in FLEx – OEB 4 Tablet Compression

Korsch XL100 WIPcon

- WIP capability
- 5 glove ports and 1 rapid transfer port
- Integrated HEPA vacuum
- Connection to contained OEB 4 de-duster (WIP capable)
- Charge and discharge with split butterfly valves
- Designed to be easily cleanable

Tablet Compression Cleaning Strategy

- WIP cycle is controlled via recipe and provide WIP capability for press, tablet deduster and dust collection system
- WIP procedure reduces airborne exposure risk during disassembly

Compression Unit

- Start by flooding dust extraction
- Spray down parts with water via fixed spray devices and hand spray gun
- Drain pipes
- Dry parts with compressed air via hand spray gun
- Compressed air purge of WIP piping at end of WIP cycle

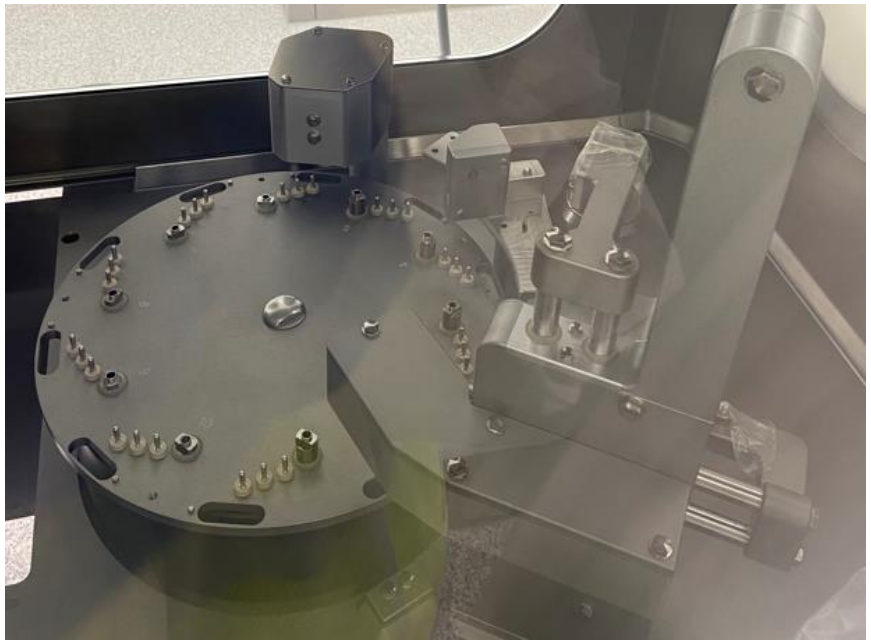
Deduster and Metal Check

- Start by flooding deduster and metal check (linked in series)
- Deduster vibrates at specified setting and duration
- Drain pipes
- Compressed air blown throughout column to dry
- Compressed air purge of WIP piping at end of WIP cycle

Flexible Manufacturing in FLEx – OEB 4 Encapsulation

Harro Hoffliger Encapsulator

- Fully contained enclosure for processing
- Charging/Discharging through SBVs
- Built in local exhaust ventilation to vacuum capsules as they are processed
- Built in WIP cycle and spray gun



Note: Tamper not installed in pic

Flexible Manufacturing in FLEx – OEB 4 Roller Compaction

Gerteis Roller Compactor

- Contained charging/discharging into polybags using split butterfly valves
- Fully contained processing verified by pressure decay test prior to processing
- Built in WIP cycle to wet all surfaces prior to disassembly

Flexible Manufacturing in FLEx – OEB 4 Film Coating

Film Coater

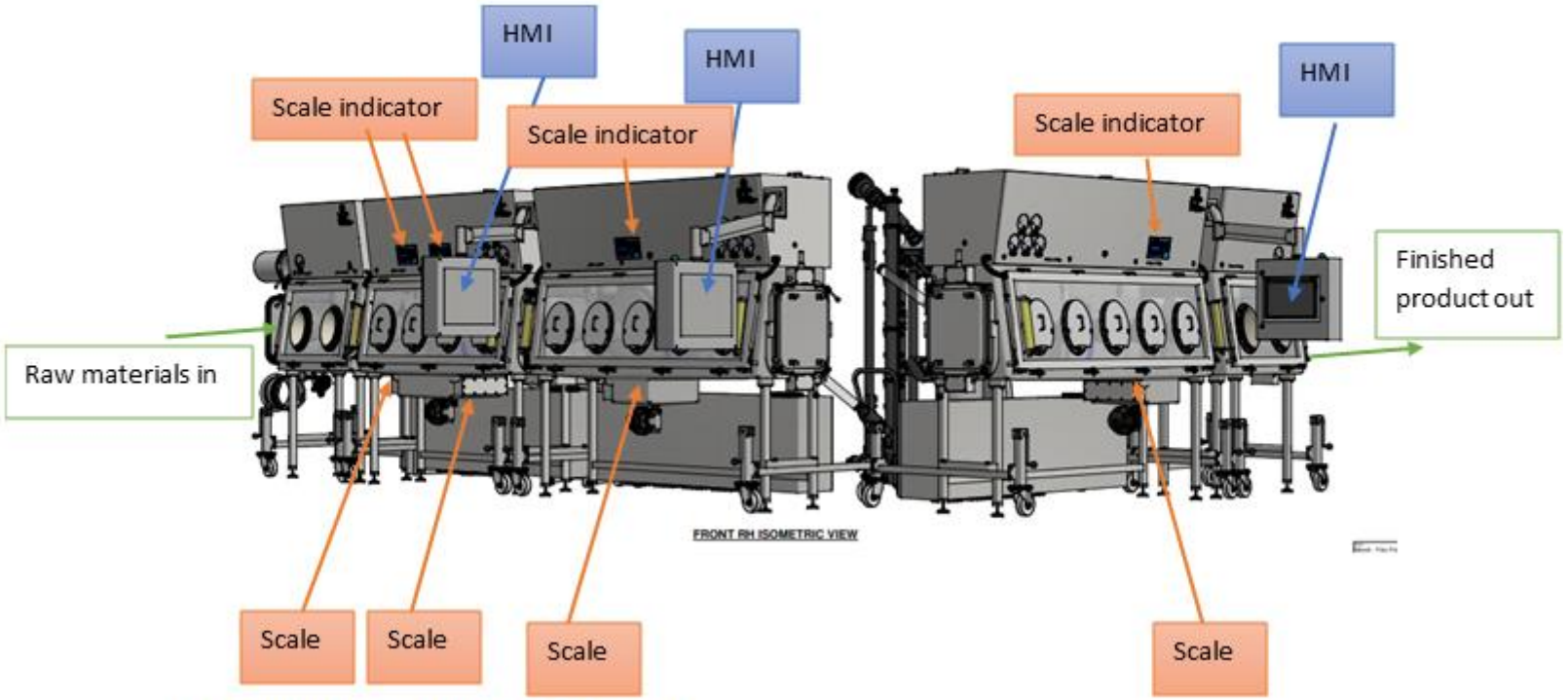
- Contained charging/discharging into polybags using split butterfly valves
- Fully contained processing verified by pressure decay test prior to processing
- Built in WIP cycle to wet all surfaces prior to disassembly
- Integrated dust extraction system
- Closed charging for solvents

Flexible Manufacturing in FLEx – OEB 4 Milling/Blending

Howorth Air Technologies OEB 4 Isolator

- Loading Chamber and Process chamber connected using Howorth DockSafe technology
- Either RTP or Donor Drum port for loading material
- Either RTP or automated split butterfly valve for discharging material
- Inflatable gaskets mate blender/mill to the isolator while keeping the drives outside of the isolator
- Isolator operated under negative pressure to contain API in event of breach – designed for leak rate of 0.5 volume% as per American Glovebox Standard
- WIP Sprayballs/guns for initial wetting of all surfaces

Flexible Manufacturing in FLEx – OEB 5 Blending/Milling/Encapsulation



Differences from OEB 4 Isolator

- RTP only method for material in/out (no SBV)
- Nitrogen inertion in all chambers
- Manual encapsulation/capsule polishing/weight sorting included

Containment Verification Strategy

- Successful containment to the target OEB/OEL level is verified via surrogate API testing (usually naproxen sodium) of the unit operation(s)
- Both personal (breathing zone) and area air samples collected to assess containment
- Wipe samples are also collected at key locations to assess containment
- Perform 6 iterations of unit operation(s) - charge, discharge, sample, minor clean, major cleaning and equipment disassembly
- Statistical analysis is performed by IH lab to ensure the Design Exposure Limit (DEL) and Containment Performance Target (CPT) are achieved and control both short-term (task-based) and full-shift exposures

Thanks!

Any Questions?