Enabling Technologies for Manufacturing Thermostable & Cost-Effective Biopharmaceuticals: Value Creation Through Innovation

FDA Workshop on Innovations in Pharmaceutical Manufacturing,

National Academies of Sciences, Engineering and Medicine (NASEM)

Feb 26, 2020

Akhilesh Bhambhani. Ph.D.

New Technologies, Vaccine Drug Product Development

Understanding Innovation

- Definition: “The process of translating an idea or invention into a good or service that creates value ” (Source: Business dictionary)
- “Innovation is not an idea-problem. It is a recognition Problem” –David Burkus, Harvard Business Review, July 2013

Incremental Innovation

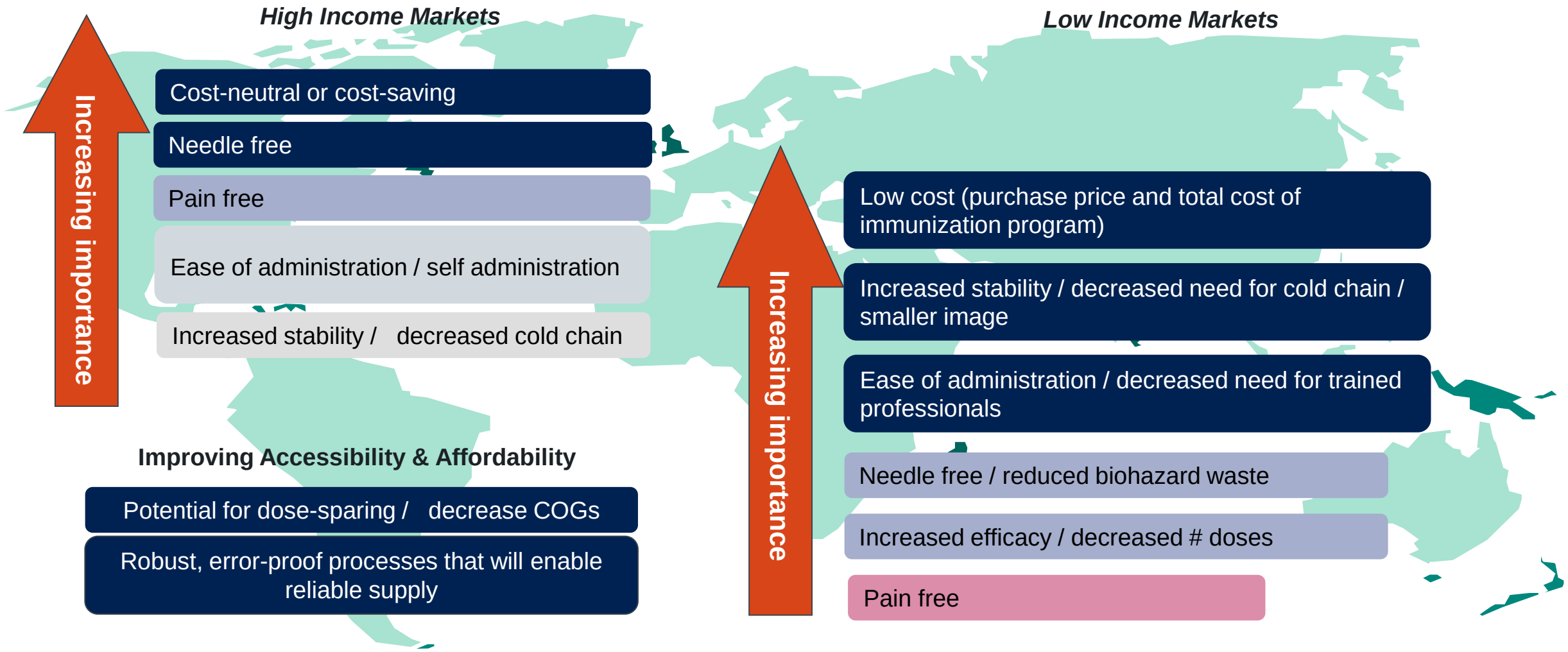
- Typically short-term (6 mo - 2 years)
- Improves existing product/process
- Improves existing market

Disruptive Innovation

- Typically long-term (≥ 10 years)
- Fundamental change/breakthroughs
- New-market or Low-end foothold

Type of Innovation is a f(Strategic Envelope)

Strategic Envelope: Scope for New Vaccine Technologies are based on Customer Input

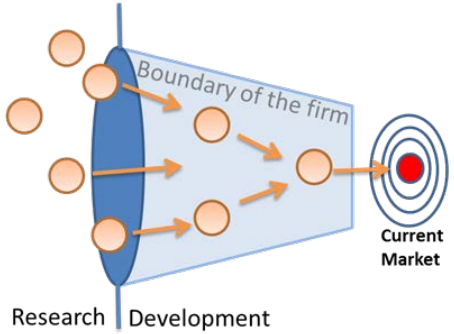


Improving Human Health Worldwide Requires an Integrated Drug Product Strategy w/ Pipeline, Supply & Customer Focus

MERCK
INVENTING FOR LIFE

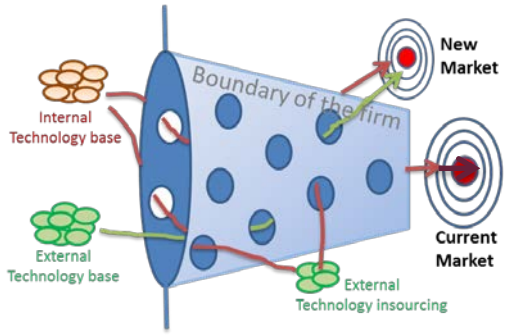
New Technologies-Vaccine Drug Product Development (VDPD, MRL)

Goal: Advance innovative opportunities that align around business drivers with an emphasis on improving affordability and accessibility of our products. Examples: Alternate delivery, Novel Adjuvants, Formulation & Manufacturing Technologies etc..



Closed Innovation

Process
Product
Customer



Open Innovation

Lyosphere Technology

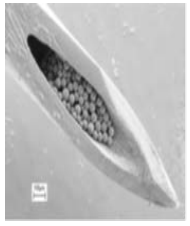
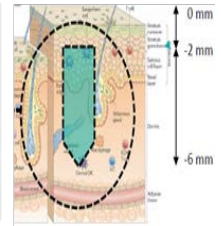



Key technologies reviewed

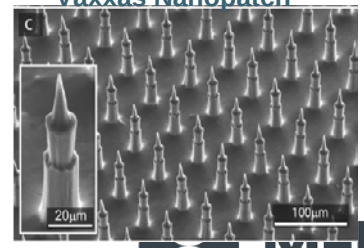
- **Thermostabilization**
- **Drying technologies**
- **Skin delivery**
- **Alternate delivery / devices**
-
-

Microwave Vacuum Drying

Particle Delivery / Implants*

Vaxxas Nanopatch™

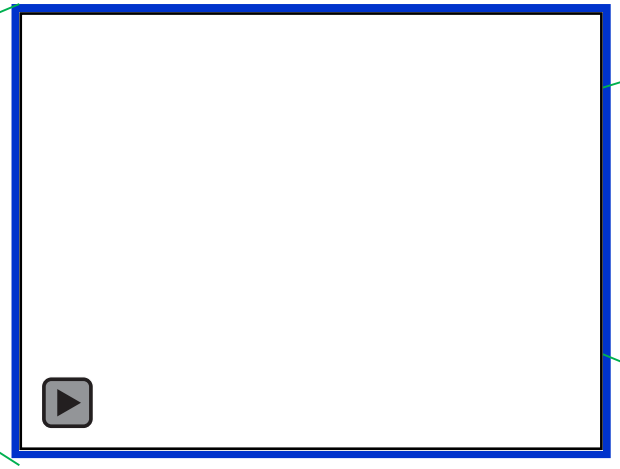


Nanopass MicronJet®

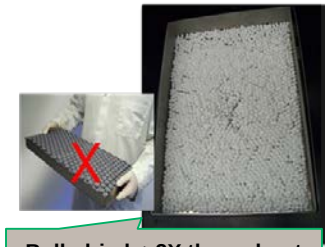
MERCK
INVENTING FOR LIFE

* Picture Courtesy Enesi Pharma

Lyosphere: A Merck-owned Formulation/Manufacturing Approach with Substantial IP



- **Dried Drug Product produced as consistent bead (10ul – 550 ul)**
- **Sphereon:** Proven benefits in Animal Health oral poultry vaccines
- **Lyospheres:** Human Health products includes ODT; Regulatory precedent with Puregon®



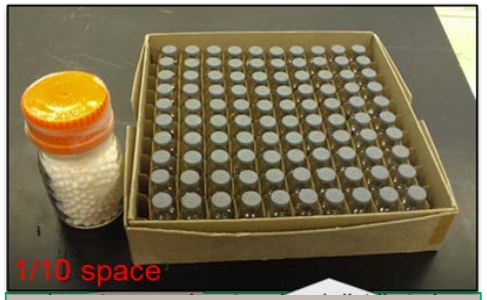
Bulk dried: >2X throughput

Bulk Drying

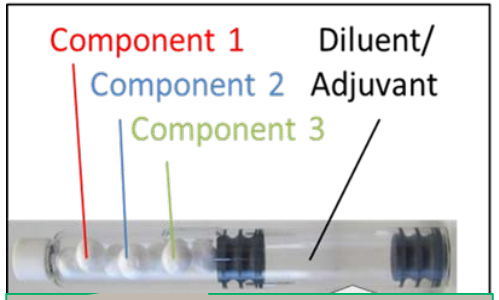
Potency Test/bead

Device filling

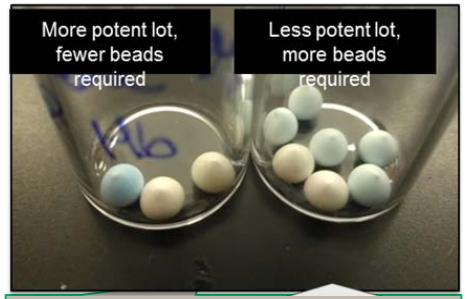
Final QC Check



Space saving bulk storage



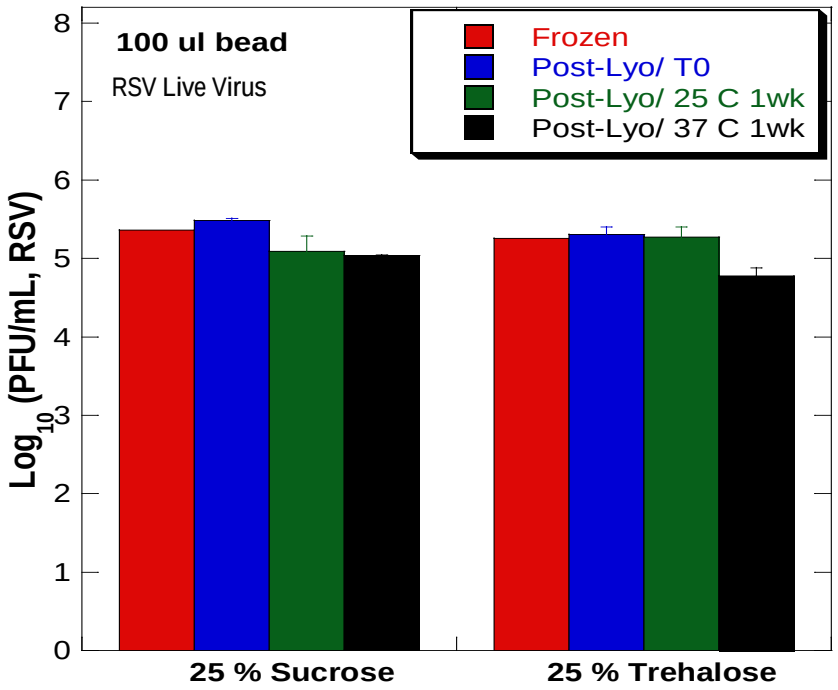
Superior Combination Products



Enables Titration of Doses

Flexible DP Packaging

LVV and Antibody Case Study: Product Improvement Through High Disaccharide Formulations



Respiratory Syncytial Virus

25% Sucrose:
1.1% moisture
25C/1wk: 0.4 log_{10}loss
37C/1wk: 0.5 log_{10}loss

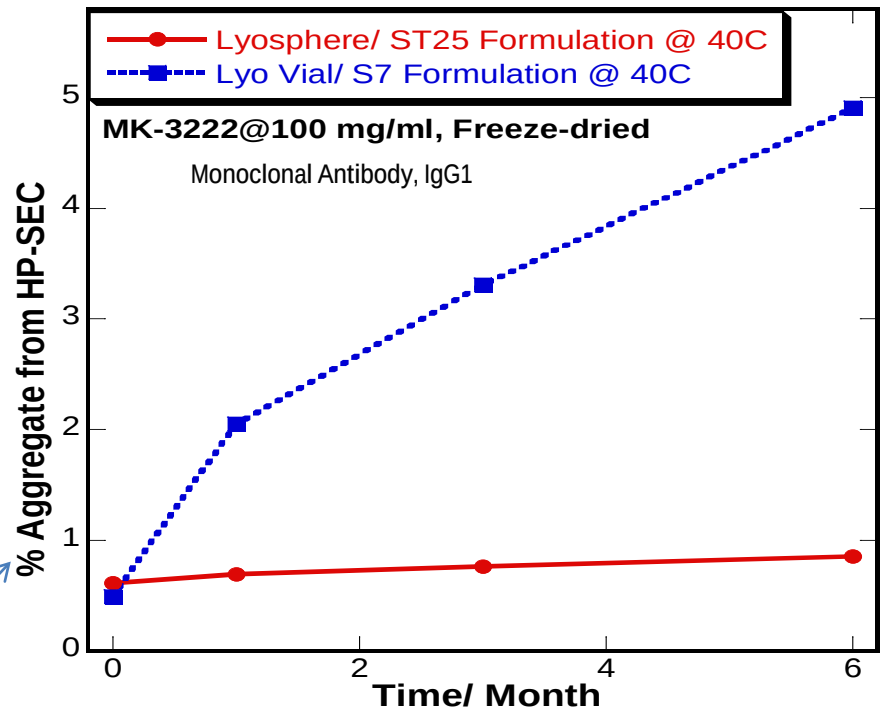
25% Trehalose:
~~1.6% moisture~~
25C/1wk: 0.1 log10loss
37C/1wk: 0.5 log10loss

***37C/ 1wk: 1.86 log10loss**

Anti-IL23 @ 100 mg/ml

7% Sucrose:
0.2% moisture
Recon Time: >15 min

25% Sucrose/Trehalose:
5.4% moisture
Recon Time: <5 min



Stability Improvement: RSV in HDF is superior to both published benchmark and internally developed lyo formulations (1.05 log_{10} loss @ 37C/ 1 week)

Why is it important?: Lyosphere may enable 2-8C formulation instead of a frozen image

Stability Improvement: MK-3222 mAb in HDF is superior to internally developed lyo formulations. Reconstitution time is also faster

Why is it important?: Lyosphere may enable room temperature stable product for the mAb

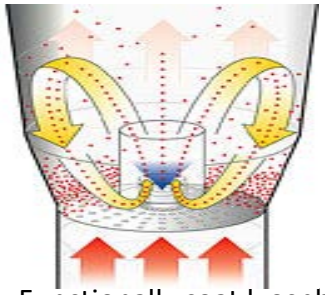
Leveraging Lyosphere Unit Size for Targeted Drug Delivery: Is it technically feasible?

MERCK
INVENTING FOR LIFE

Lyosphere for GI Targeted Oral Delivery: mAbs/Vaccines/Microbiome

Step 1: Formulate lyospheres containing active model DS

Step 2: Lyophilize lyospheres to remove water



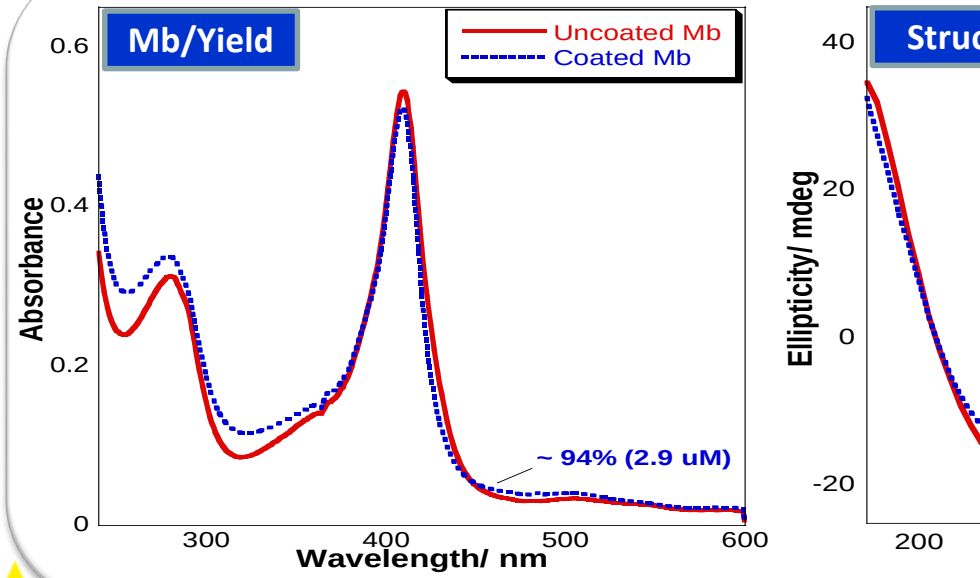
Step 3: Functionally coat lyosphere using a coating that target release in the colon

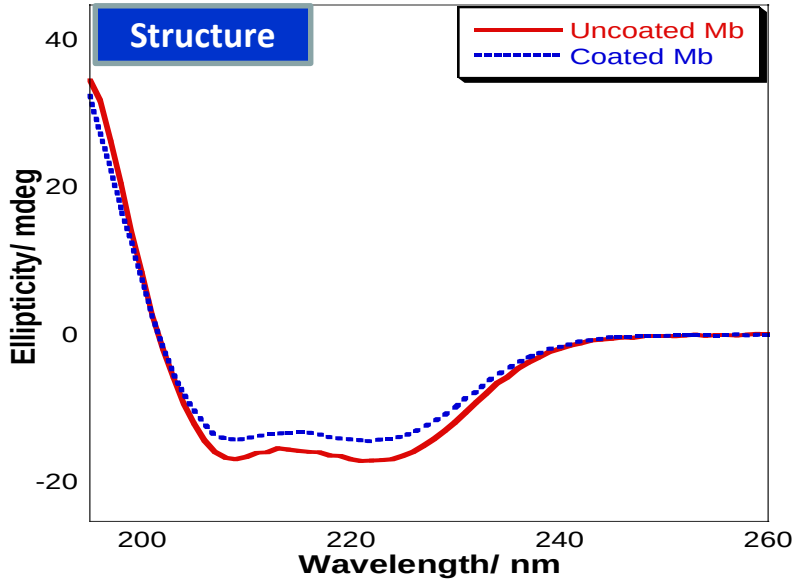
Step 4: Encapsulate coated lyospheres in a capsule/ sachet for oral administration

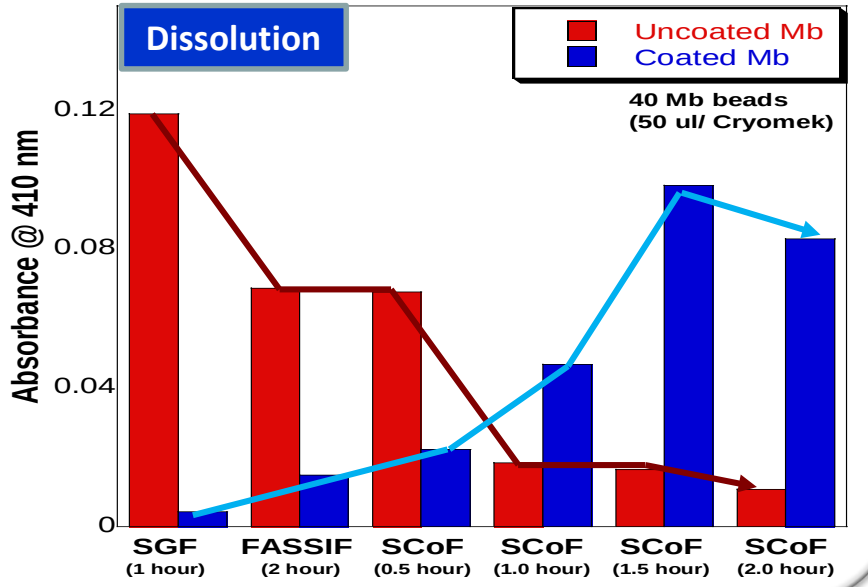
Identify a "robust" lyosphere formulation that can "resist" disintegration /attrition on aqueous spray coating

Identify coating process/ parameters that allows minimal bead attrition and stability impact

Establish initial PoC through dissolution build IP & create value through project integration







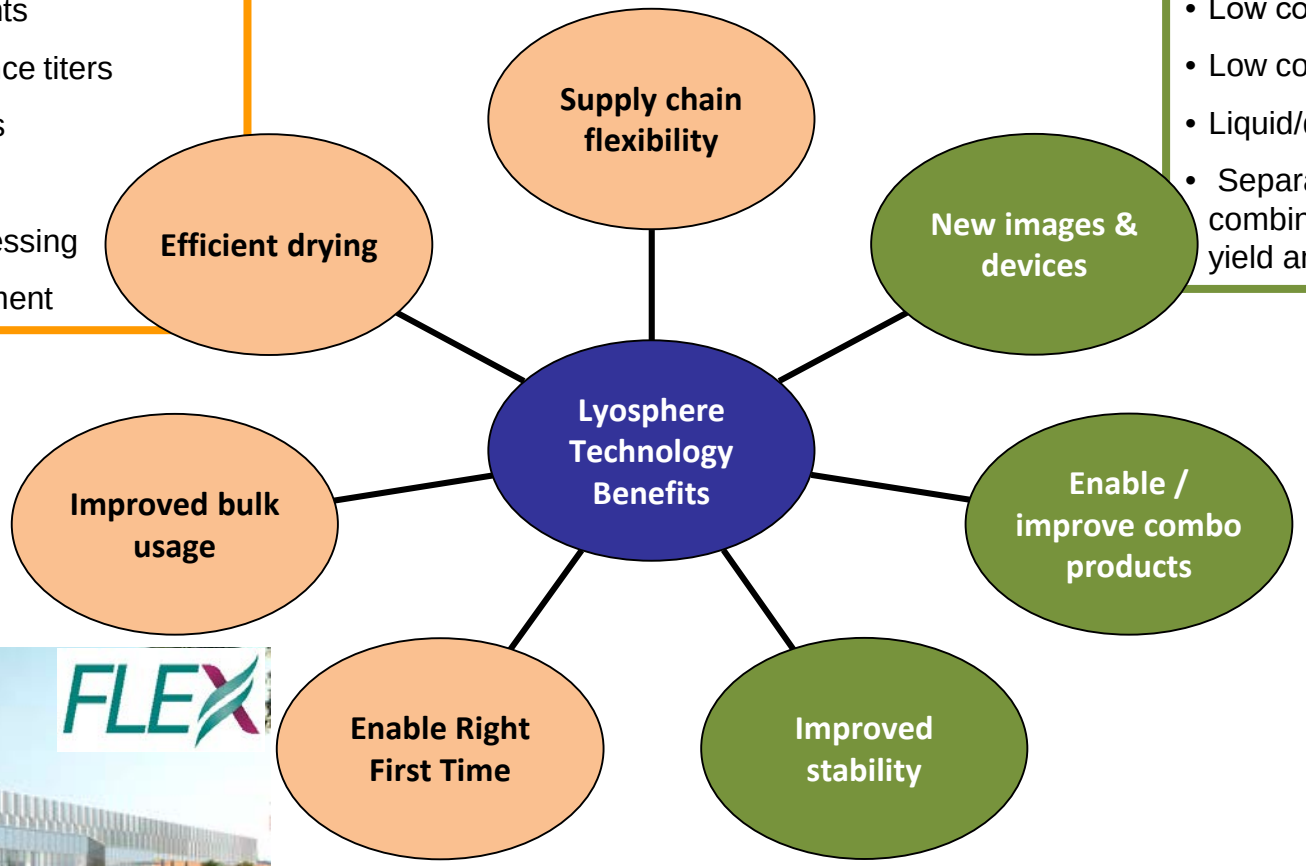
Summary: Lyosphere Enables Thermostable Vaccines/ Biologics with Convenient Delivery

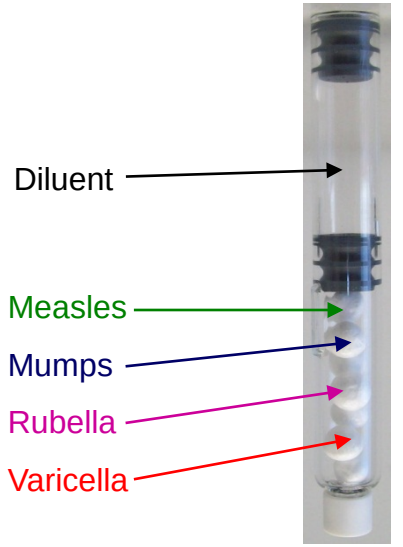
Supply Chain Gains

- Reduced overage requirements
- Lower threshold drug substance titers
- Elimination of potency failures
- Higher drying throughput
- Potential for end-to-end processing
- Simplified inventory management

Customer/Marketing Gains

- Low cost, ↓ cold chain footprint
- Low cost pre-filled syringes
- Liquid/dry combination products
- Separate “beads” enable new product combinations, with formulation optimized for yield and stability of each product component





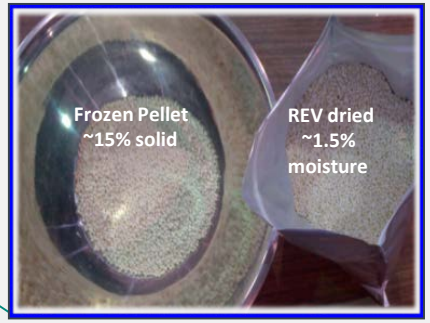
Lyosphere advancement ongoing as part of Merck RY FLEx (Formulation, Laboratory and Experimentation Center)

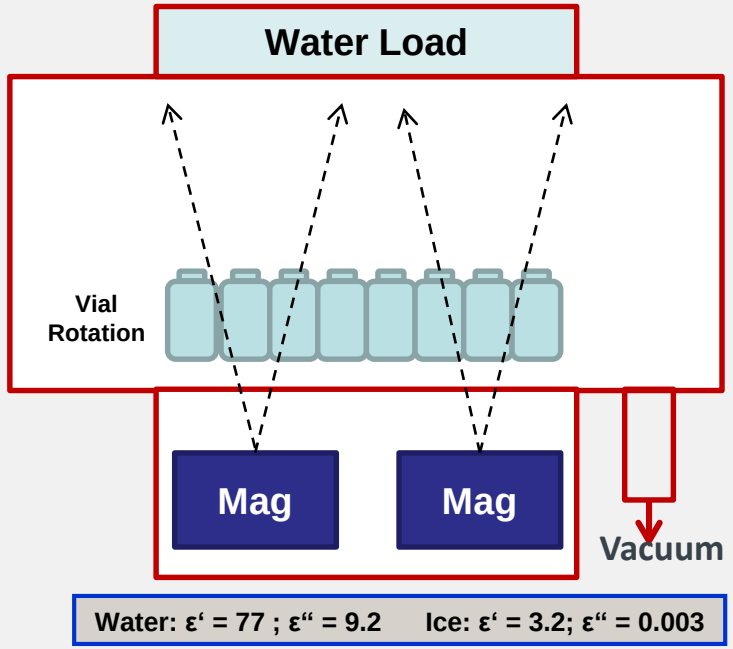
MERCK
INVENTING FOR LIFE

Microwave Vacuum Drying (MVD) or Radiant Energy Vacuum (REV) Technology

Introduction: Radiant Energy Vacuum (REV) (or Microwave Vacuum Drying (MVD)) is a proprietary form of applying microwave under vacuum to achieve dehydration at lower temperature (Adapted from food Industry)

- Drying is faster than lyophilization as heat transfer occurs by radiation (microwaves) instead of conduction
- Technology is **owned by EnWave Corporation;** Merck has a 10 year R&D non-exclusive agreement. Key technology enabling discoveries
  - Methods of distributing microwave field to avoid plasma discharge in vacuum, and
  - Means of achieving reliable, homogeneous dehydration across a large load





MVD Achieves Rapid Dehydration Enabling Semi-Continuous Manufacturing

Merck's rationale stems from the technology potential as a

- Faster drying technology that enables semi-continuous manufacturing:
  - Fit for World Class Supply (flexible on-demand manufacturing as well as high-volume products)
- Compatibility with multiple images/ delivery devices (e.g. vial, Dual Chamber Cartridges, pellets etc.)
- Enhanced thermostability through high disaccharide formulations (e.g. LVVs and mAbs)
- Reduced Grade A footprint and capital with lower operating cost vs. current lyophilization process

7 hrs. Vs. 5 day in traditional lyophilization

Demonstrated compatibility with multiple products tested to date with faster drying (~ 8-12 hrs Vs. days in lyophilization)

- Antibodies, Fusion Protein, Virus Like-particle, Live Virus Vaccines etc.

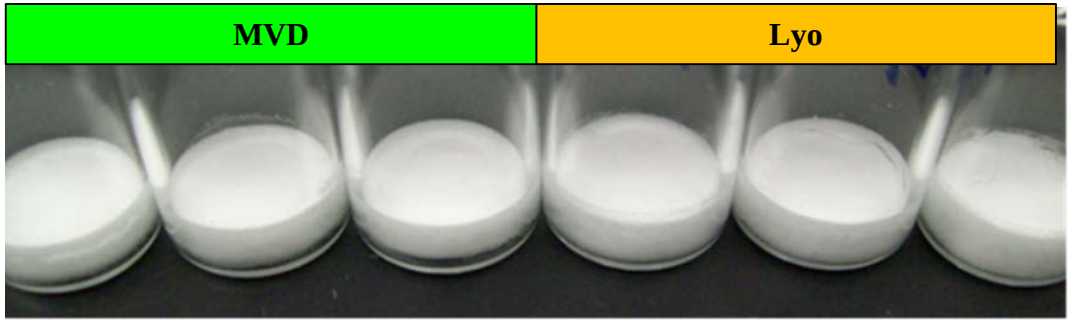
Non-Sterile Food Industry Benefit

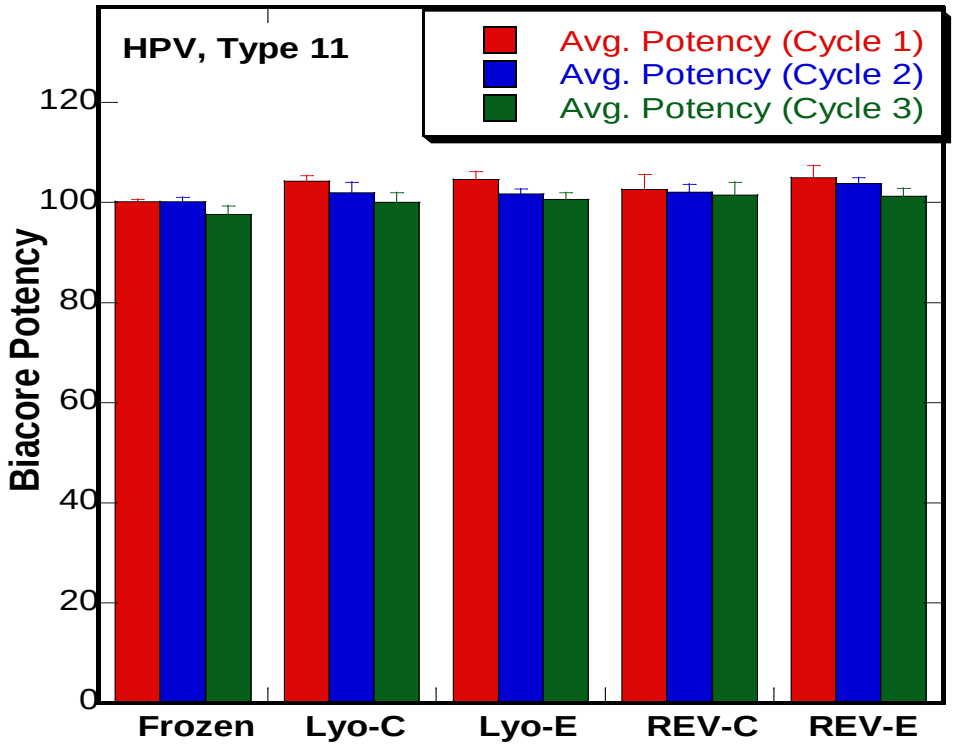
Scalability demonstrated in Food Industry

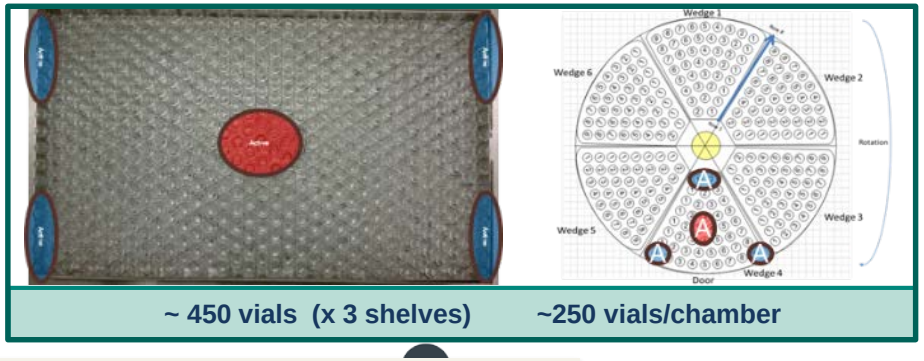
MERCK
INVENTING FOR LIFE

MVD Vs. Lyo Process: Similar Inter- & Intra-batch Variability

Statistical Analysis: HPV and VZV Potency*			
HPV Type 11/ modified formulation		Lyo	REV
	Biacore Potency	102.2%	102.7%
	Recon Time	5 sec	5 sec
	Variability (%RSD)	1.4%	1.8%
	Moisture	2.9%	3.2%
LVV 1 benchmark formulation	Cycle Time	45 hrs	7 hrs
	vEIA Potency	0.75-0.94	0.70-0.94
	Recon Time	< 2 min	< 2 min
	Variability (%RSD)	17%	18%
	2-8C/ 9 month	Comparable stability	

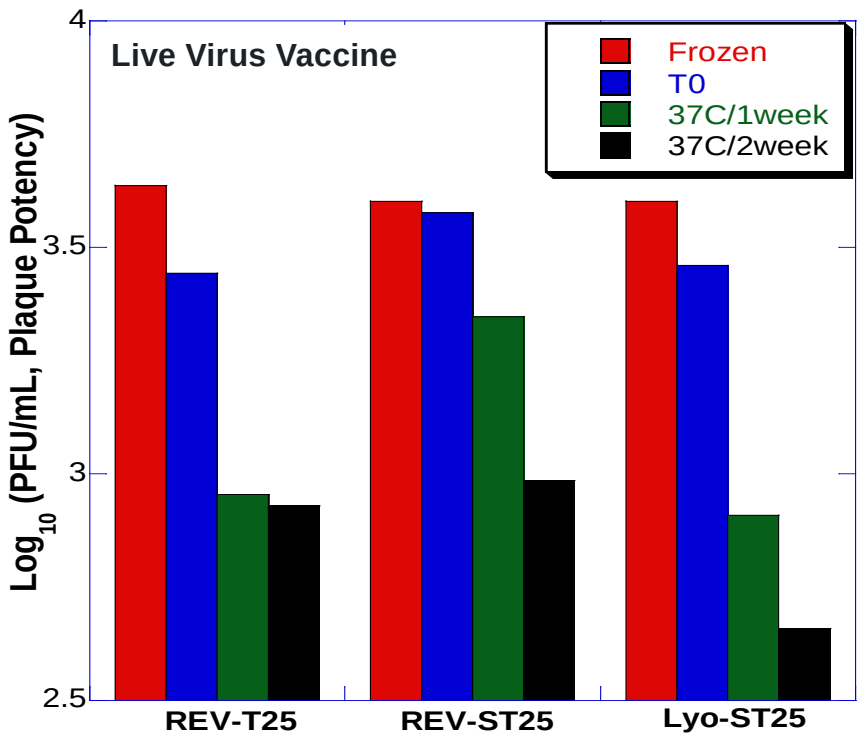


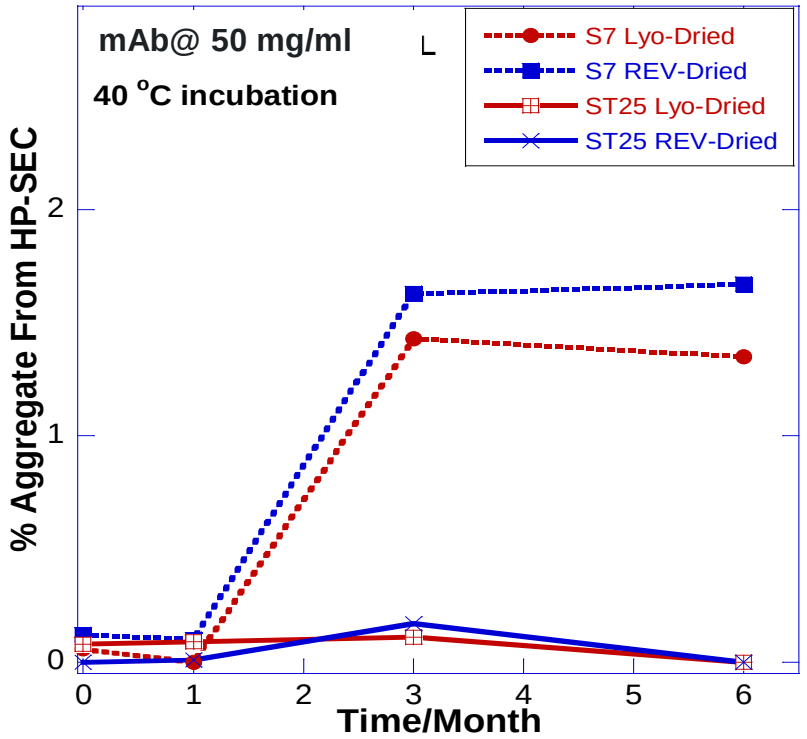




Compatibility of MVD Process with HDFs

LVV and Antibody Case Study: Product Improvement Through High Disaccharide Formulations





Thermostability of Measles in HDFs			
LVV in HDF (12.5% Sucrose, 12.5% Trehalose in MMR placebo)		**Lyo**	**REV**
	Cycle Time	**168 h***	**7 h**
	Recon Time	**< 2 min**	**< 2 min**
	Drying Loss (log_{10})	**0.14**	**0.02**
	37C/1 week loss	**0.55**	**0.23**

Thermostability of MK-3475 in HDF			
mAb in HDF (7% Sucrose, 18% Trehalose in placebo)		**Lyo**	**REV**
	Cycle Time	**168 h***	**7 h**
	Recon Time	**6 min**	**6 min**
	Moisture	**4.2%**	**3.7%**
	40 °C/6 months	**Comparable**	

* 7-day long lyo cycle attributed to SMART run

MERCK
INVENTING FOR LIFE

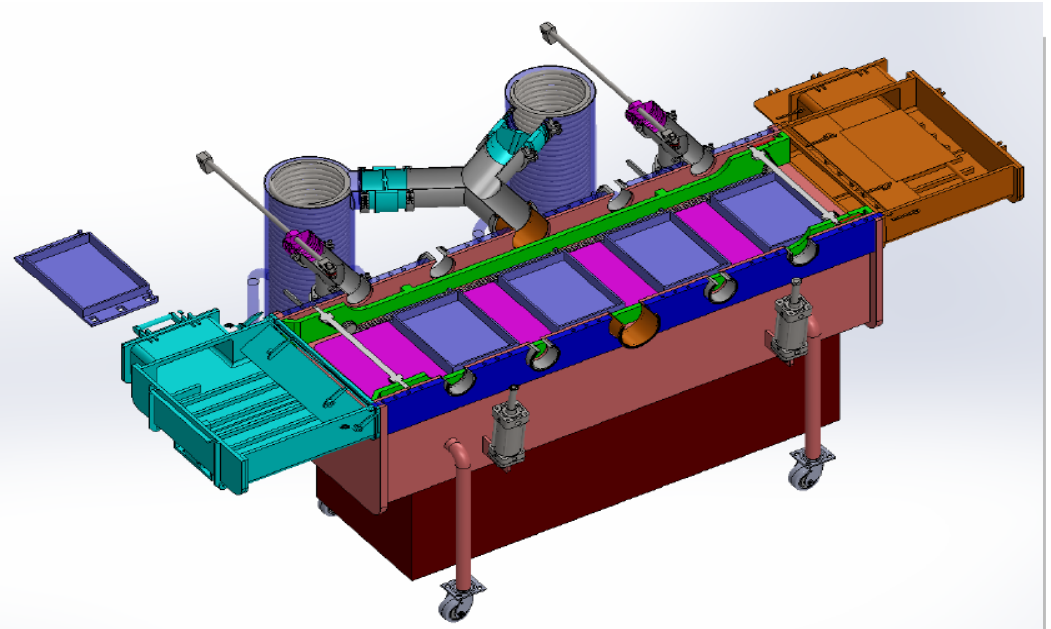
Microwave Vacuum Drying: Summary and Next Steps

Current State (2016/2017)

- Prototype Unit
- Batch Process

Owner	Process	Capability
EnWave	Batch Process	Non-GMP

First-of-its-kind GMP Microwave Vacuum Dryer



- Merck-owned GMP Microwave Vacuum Dryer
- Clinical Evaluation

Owner	Process	Capability
Merck	Semi-continuous & Batch Process	Non-GMP and GMP

MERCK
INVENTING FOR LIFE

Enabling Flexible Manufacturing Through Formulation, Laboratory and Experimentation Center

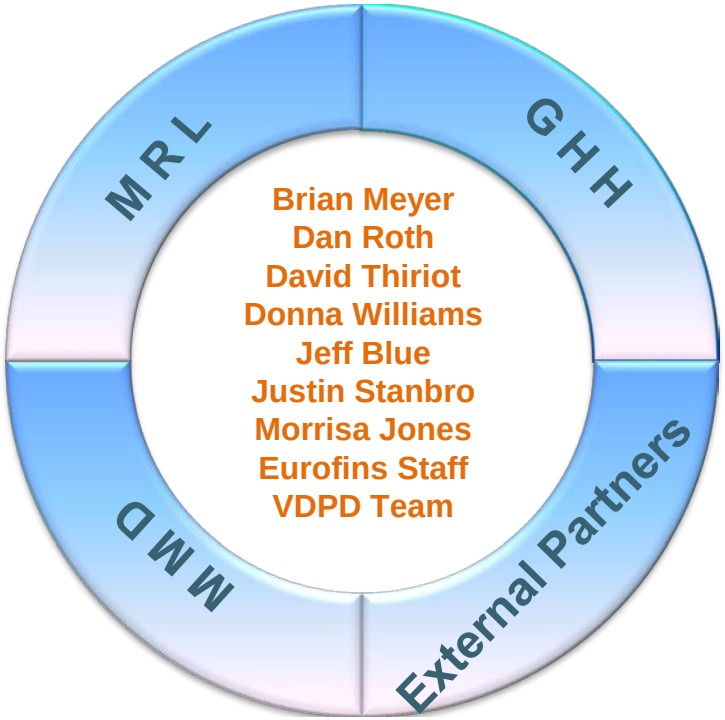
FLEX

Formulation, Laboratory and Experimentation Center

- Part of strategic investment from Merck in R&D and future state of formulation development. Design would enable 'flexible' manufacturing with new technology and ability to manufacture small GMP batches. Key features:
  - Rely on PODS to be nimble and flexible in manufacturing
  - Isolator/Robotics for improved compliance to Quality and Safety standards
  - Improved data analytics and IT integration
  - Includes continuous manufacturing, lyospheres, 3D printing, robotics etc.

Acknowledgments

- **Leadership/ CRC Sponsors:** Mike Kress, Tarit Mukhopadhyay and Jeff Blue
- **MRL:**
  - **Vaccine:** Justin Stanbro, Morrisa Jones, Corrine Wilson, David Thiriot, Julia McMahon, Kent Hamaker & Dengue Team, Kay Hunsberger & Team
  - **ID/Vax:** Andy Bett & team
  - **Biologics:** Greg Nyberg and SFS Team members
  - **Operations:** Don Boscoe, Dave Hamilton, Bill Egan, Kara Price & Team
- **MMD:**
  - **Quality:** Kimberleigh Ramsey-Testa, Terry Fennel & Team
  - **Analytical:** Aesha Jhaveri, Luca Benetti, Amy Brown, Theresa Coaxum & Team
  - **GES:** Dan Sawycky, Jeff Johnson, Mike Zivitz, & TEC Team
  - Luke Schenk, Phil Bennett, Sharon Ernst, Joni Valerio, Jessica Sinacola & Team
- **GHH:**
  - **Marketing & Finance:** John Markels & Team
- **Previous Team Members & Senior Leadership Teams**



NanoPass

ENWAVE ANNOUNCES SHIPMENT OF A PHARMACEUTICAL RADIANT ENERGY VACUUM FREEZE- DRYER FOR MERCK

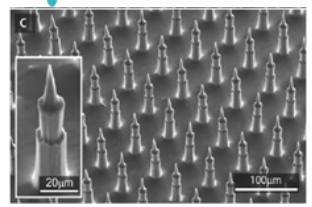
12/09/2018| PRESS RELEASE

SEP 12TH 2018, 06:00 AM

EnWave Corporation (TSX-V:ENW | FSE:E4U) ("EnWave", or the "Company") announced today that it has successfully completed Factory Acceptance Testing and has shipped its first 9 kW cGMP Radiant Energy Vacuum ("REV™") pharmaceutical freeze-dryer

EnWave Corporation

vaxxas



BARDA
Biomedical Advanced Research and Development Authority

INVENTING FOR LIFE

THANK YOU

Pharma Should Be More Like

THE TRANSFORMERS

- Quickly change from one function to another depending on situation
- Low cost to make transformation
- Able to shift workload to partners depending on demand
- Strong collaboration within team
- Without heavy regulatory oversight, work with authorities to make the world a better place

INVENTING FOR LIFE