

Future of Continuous Manufacturing in Drug Products Containing Nanomaterials

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Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.

Outline

- Continuous manufacturing
- Opportunities for nanomaterials
- A research example
- Regulatory considerations

Innovation in Manufacturing

THEN

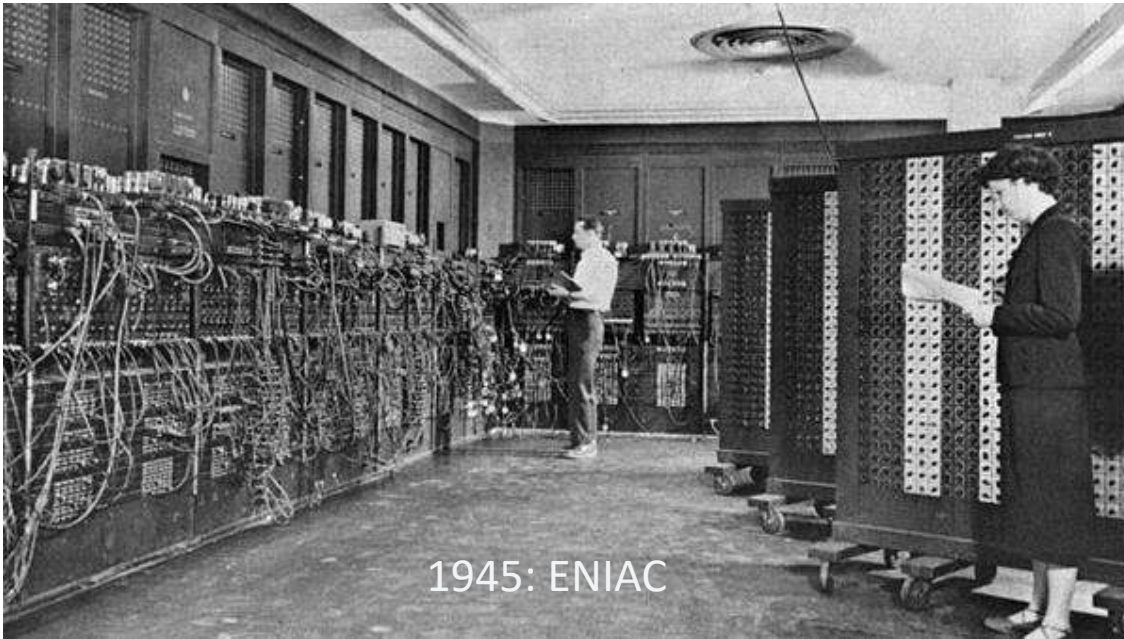


NOW



Another Example...

THEN



NOW





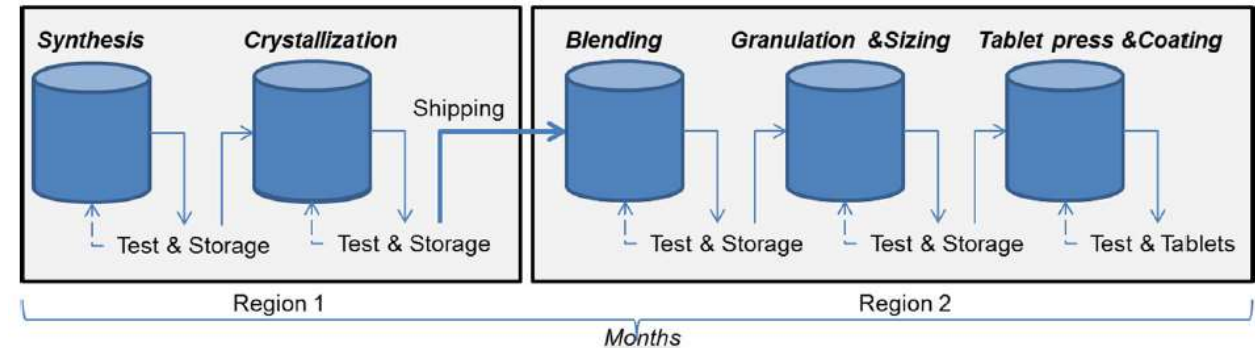
Pharmaceutical industry is also
evolving...

What is Continuous Manufacturing (CM)?

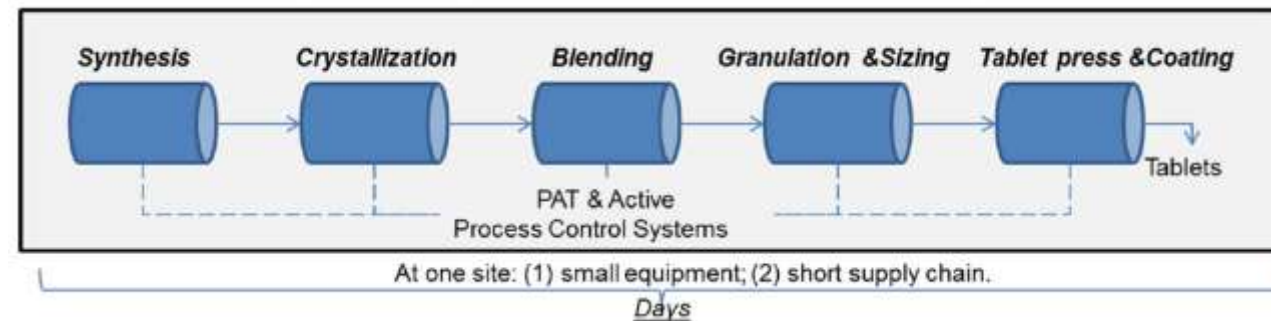


- CM is an integrated process
- Consists of two or more steps
- Continuous flow of material
- Intensified process

A typical batch manufacturing process

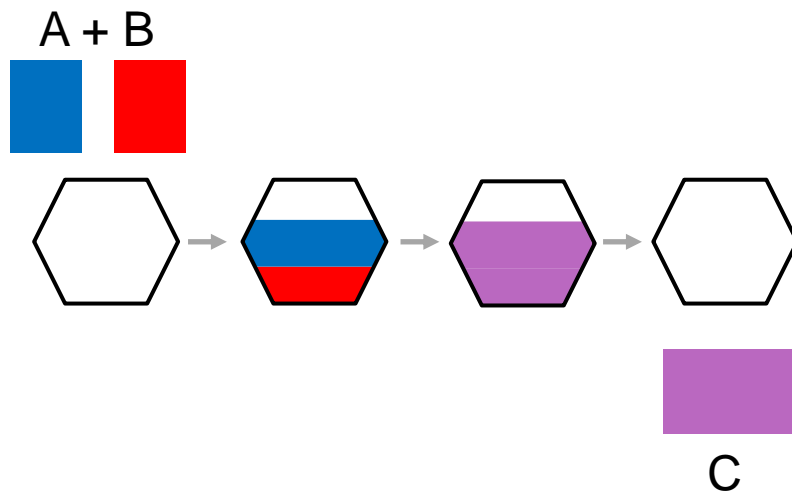


A conceptual integrated continuous manufacturing process



Continuous Manufacturing: A Blending Example

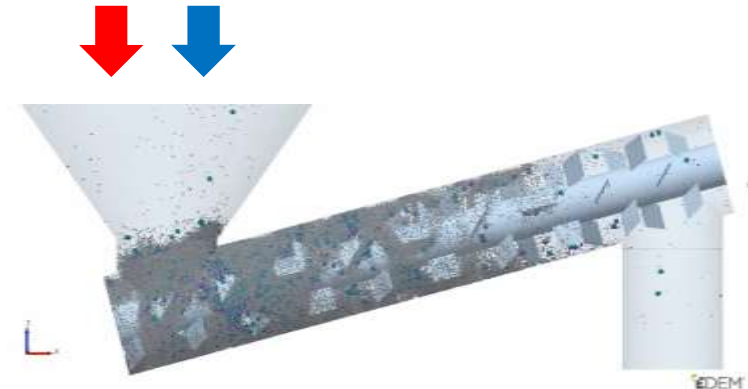
Batch Process



Input: Fixed amount of **A + B**
Output: Fixed amount of **C**
Variables: Speed, time, fill level
Keywords: **Endpoint, Scale**

Continuous Process

Continuous feeding of materials at $A + B = C$ rate



Input: Feeding **A** and **B** at a defined rate
Output: C rate
Variable: Feed rate and speed
Keywords: **Time, line rate**

Why CM?



- FDA has identified CM as an emerging technology
- FDA recognizes that CM has the potential to increase the efficiency, flexibility, agility, and robustness of pharmaceutical manufacturing
 - Integrated processing with fewer discrete steps
 - No manual handling, increased safety
 - Shorter processing times
 - Smaller equipment and facilities
 - More flexible operation
 - Lower capital costs, less work-in-progress materials
 - Reduced environmental footprint
 - Feasible to manufacture small batch sizes
 - On-line monitoring and control for increased product quality assurance in real-time
 - Amenable to Real Time Release Testing approaches
- Benefits to both patients and industry



CDER Progress with CM



6

Approved
CM solid
oral dosage
forms

1

Approved
semi-CM
small
molecule API

2

Approved
semi-CM
sterile
products

1

Approved
semi-CM
biotechnology
product

CDER collaborated on research to support CM application assessment and policy development

For details regarding activities related to emerging technology including CM, please visit the Emerging Technology Program (ETP) Website

<https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm523228.htm>



FDA's Regulatory Approach for CM



Science & Research



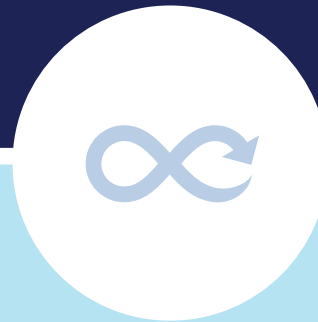
- Foster innovation and development of CM (e.g., intramural and extramural research)
- Understand key CM concepts and identify CM specific risks to product quality
- Develop a framework for control strategy considerations

Regulations & Guidance



- Existing regulations and ICH guidances are generally applicable to CM (e.g., Q7 through Q12)
- New ICH Q13 focuses on CM
- Emerging Technology Guidance and MAPP (establishment of Emerging Technology Team, ETT)

Feedback & Assessment



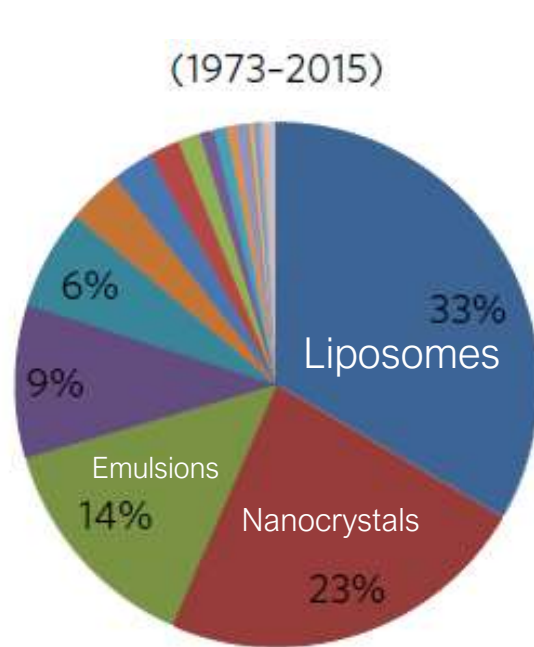
- Early engagement with ETT to address scientific and regulatory gaps
- Site visits
- Integrated review and facility assessments including pre-approval inspection

Reg. Basis Maturation

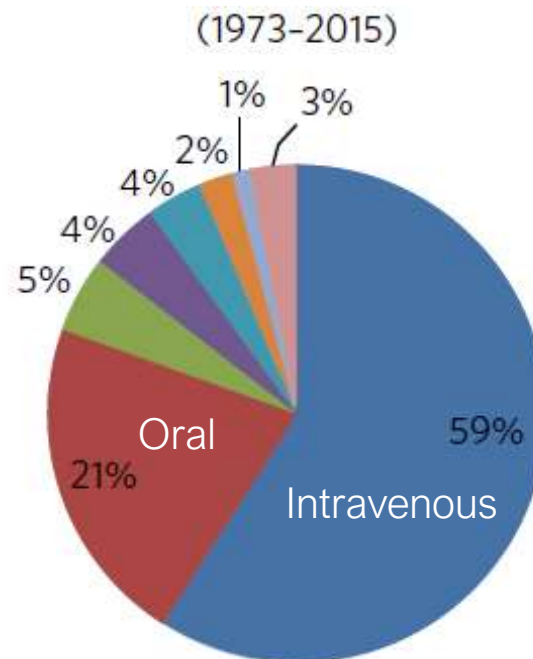


- Evolution of regulatory basis as experience gained with CM applications
- Knowledge management
- Regulatory guidance (e.g., FDA, ICH)

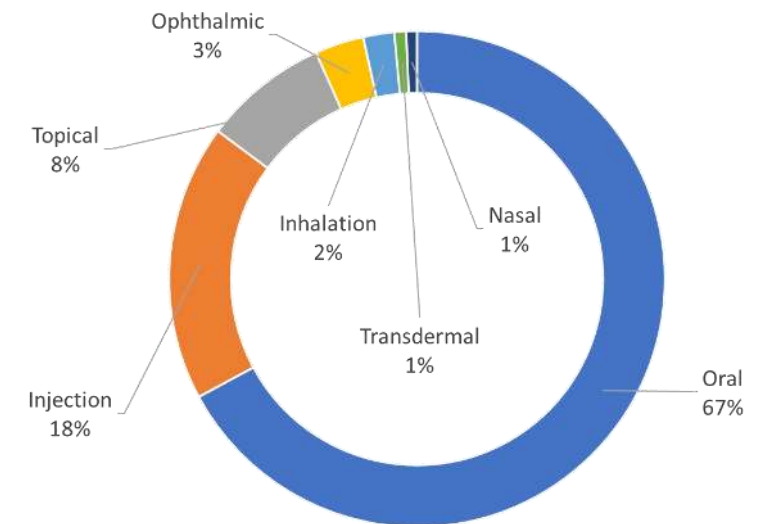
Why CM for Nanomaterials?



Type of Formulation



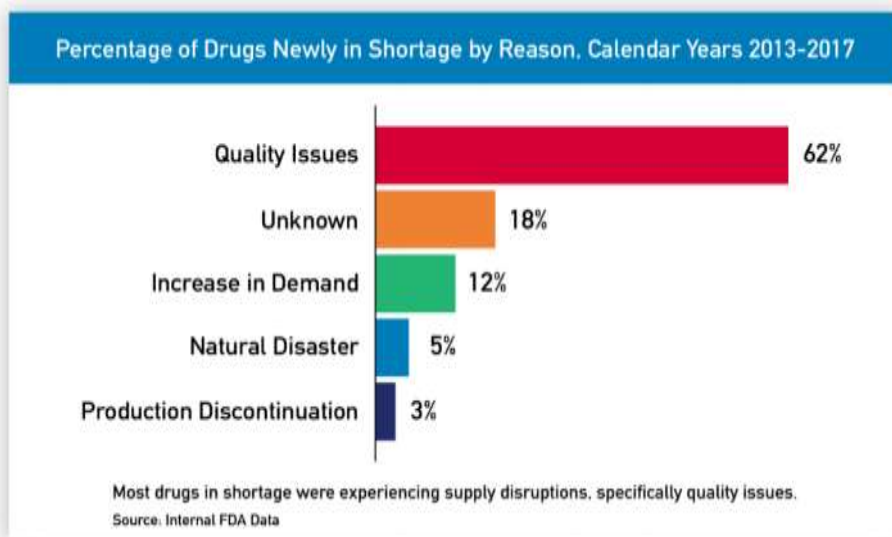
Route of Administration
for Nanomaterials



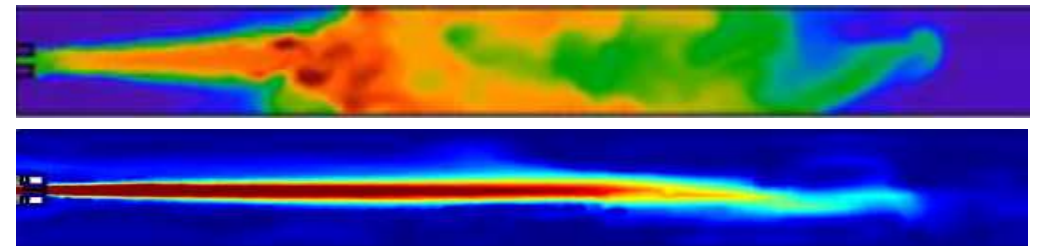
Route of Administration for
All Approved Products
(data from Drugs@FDA)

CM for Nanomaterials: Two Sides of the Coin

Quality issues were the most common reason for disruptions that became shortages



63% were Injectables





RESEARCH EXAMPLE

Extramural Research

UConn
SCHOOL OF PHARMACY

A Continuous Manufacturing Platform for Complex Dosage Forms

HHSF223201310117C, HHSF223201610105C, 1U01FD005773,
75F40120C00201, 1U01FD006975

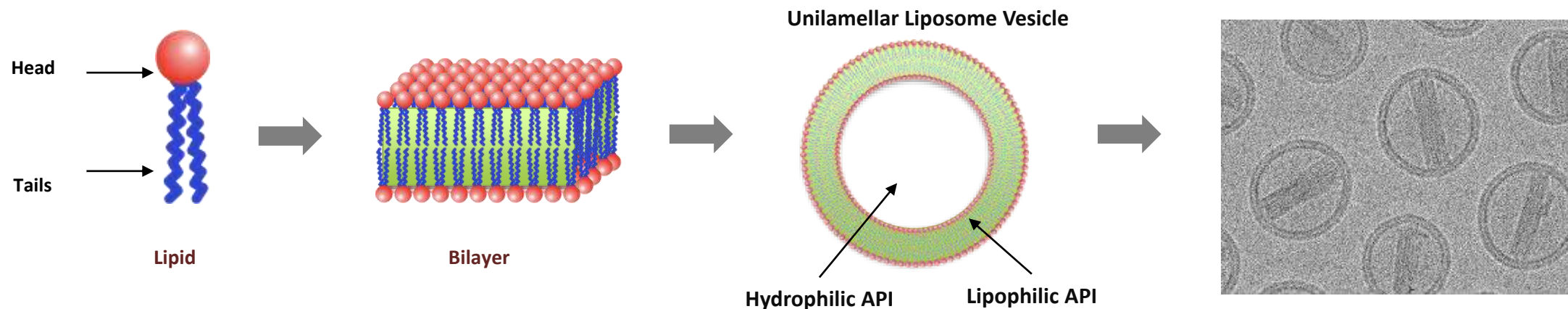
Dr. Diane Burgess (PI)

Dr. Antonio Costa

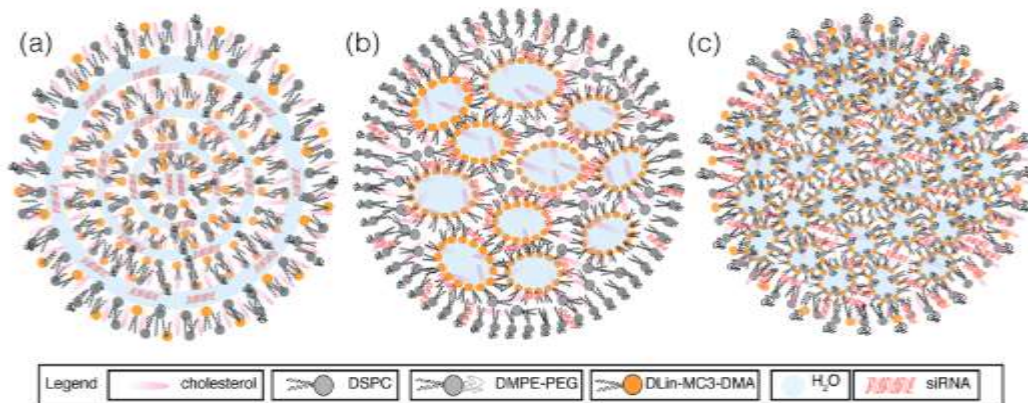
Dr. Chaudhuri Bodhisattwa

Dr. Raman Bahal

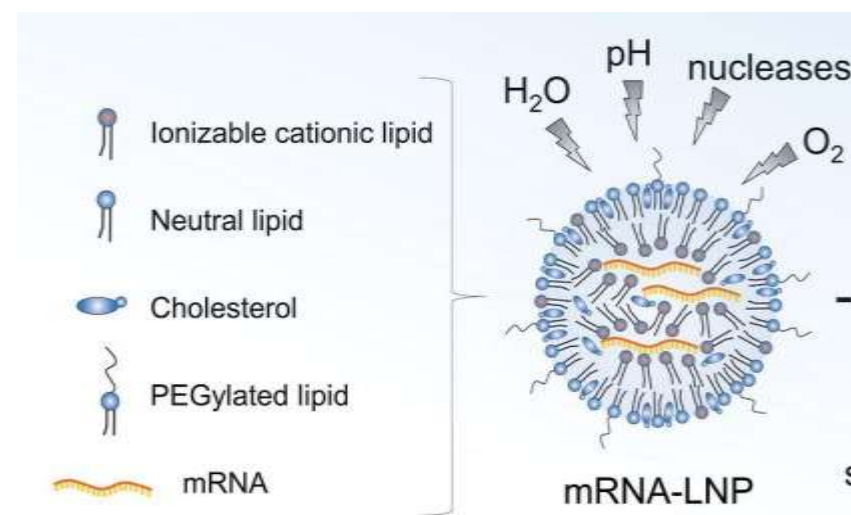
Liposomes and Lipid Nanoparticles



Scheme 1. Cartoon Diagrams of Three Models for LNP Structures⁴⁷



⁴⁷(a) Multilamellar vesicles (onion), (b) nanostructure core, and (c) homogeneous core shell.

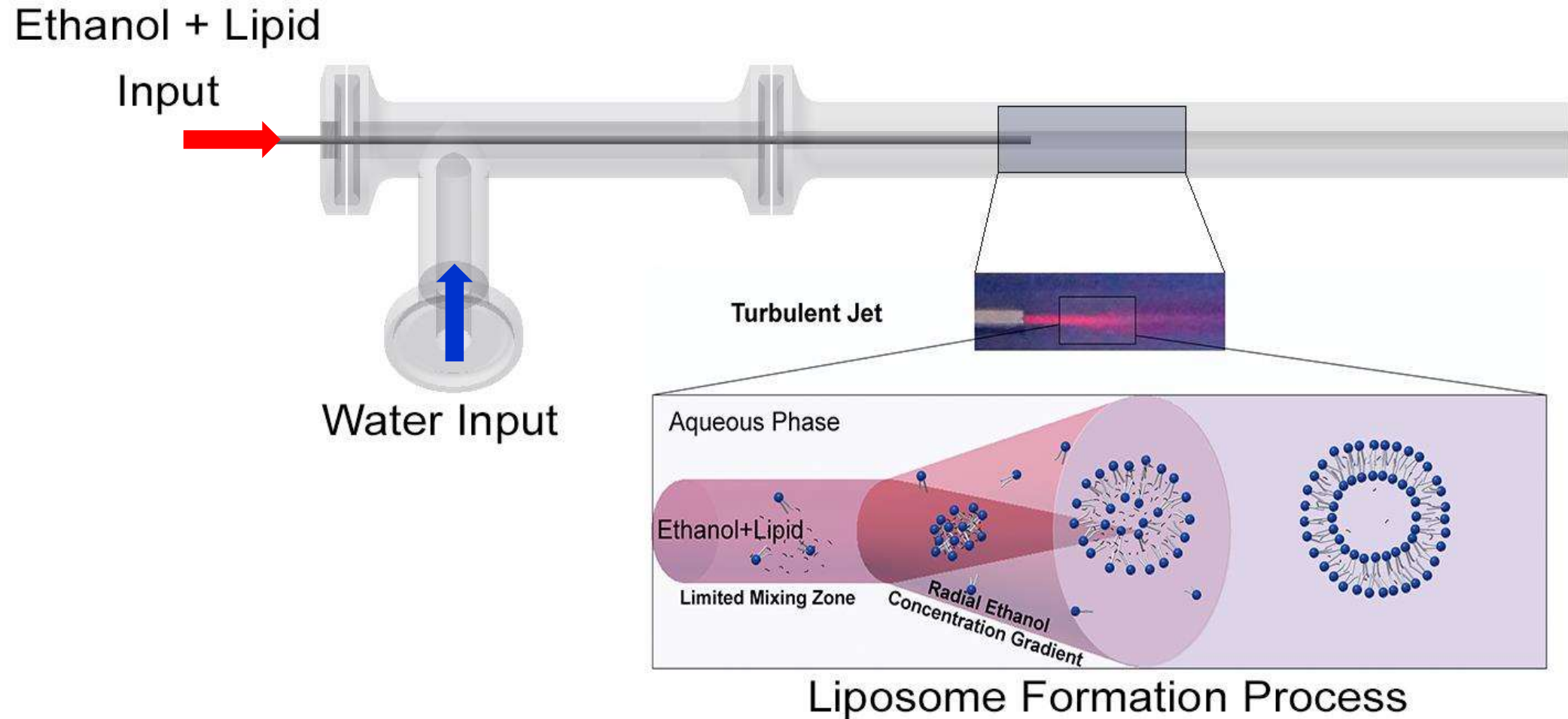


Typical Batch Process of Liposome Manufacturing



1. Liposome (empty) formation (e.g., film hydration, **ethanol injection**, reverse phase evaporation)
2. **Down-sizing** (e.g., sonication, extrusion, microfluidization)
3. Drug encapsulation (e.g., passive-, active- loading)
4. Purification (diafiltration, dialysis)
5. Fill-finish

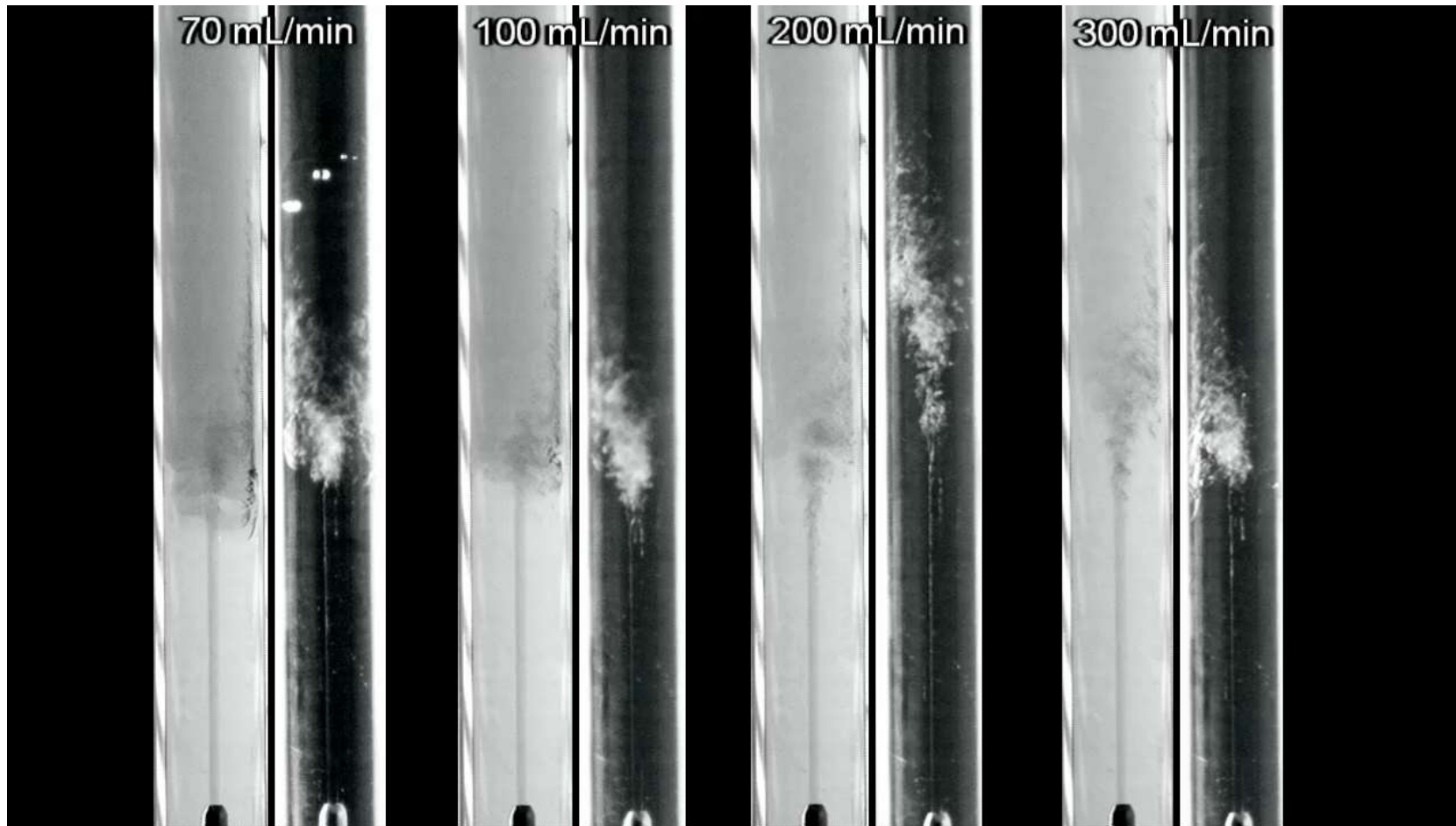
CM Enables One-step Unilamellar Liposome Formation



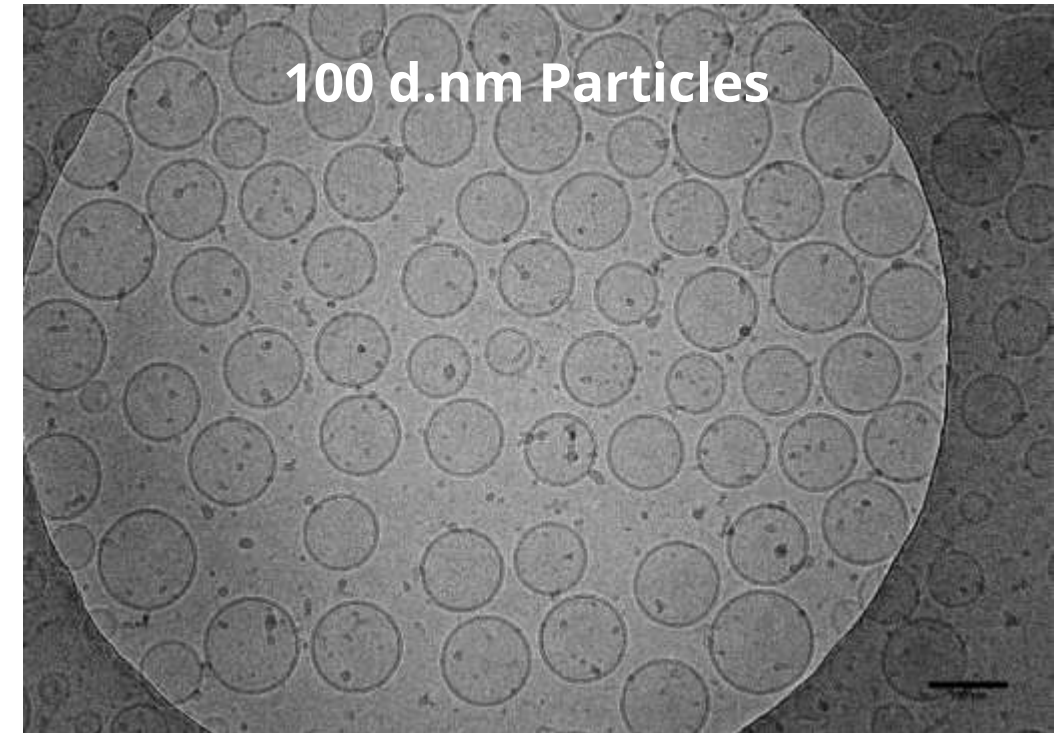
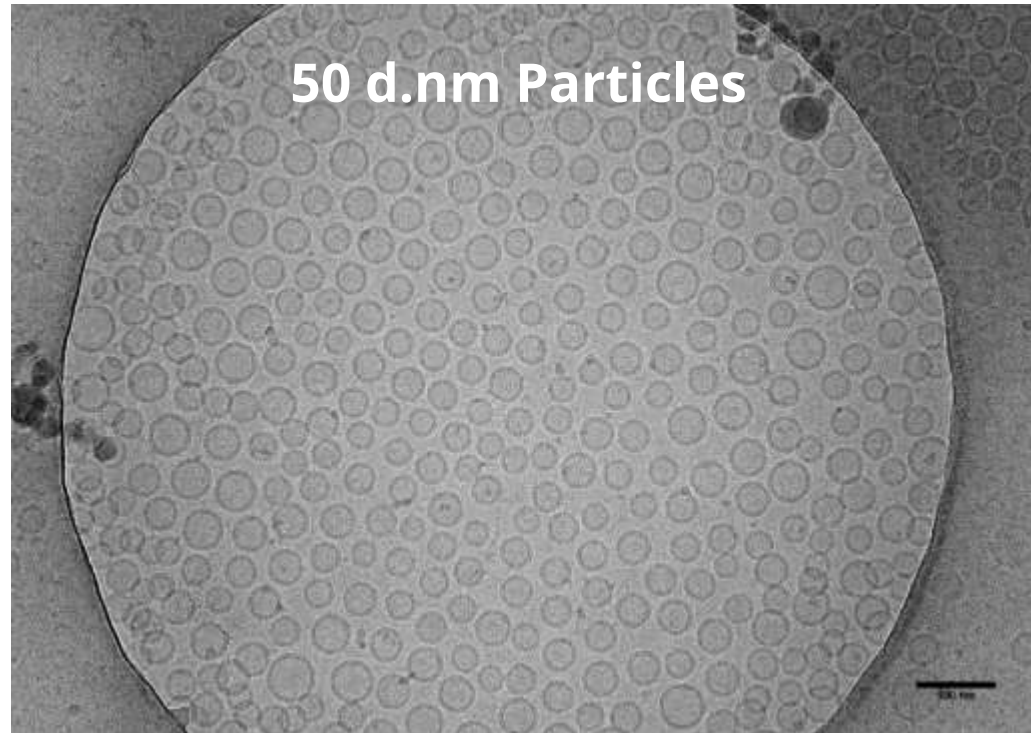
High-Speed Camera: Jet Formation



Entire 30 second video takes place in less than 1 second...



Improved Precision and Robustness

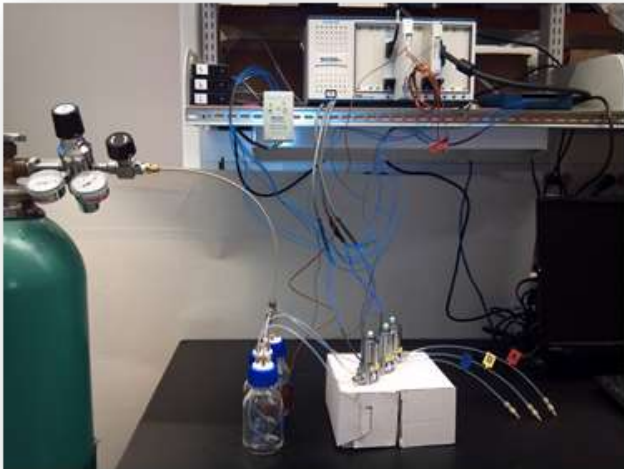


| Sample ID | Z-Average (d.nm) | ± | PDI | ± |
|-----------|------------------|------|-------|-------|
| 50 nm | 50.08 | 0.27 | 0.029 | 0.015 |
| 100 nm | 97.63 | 0.73 | 0.047 | 0.019 |

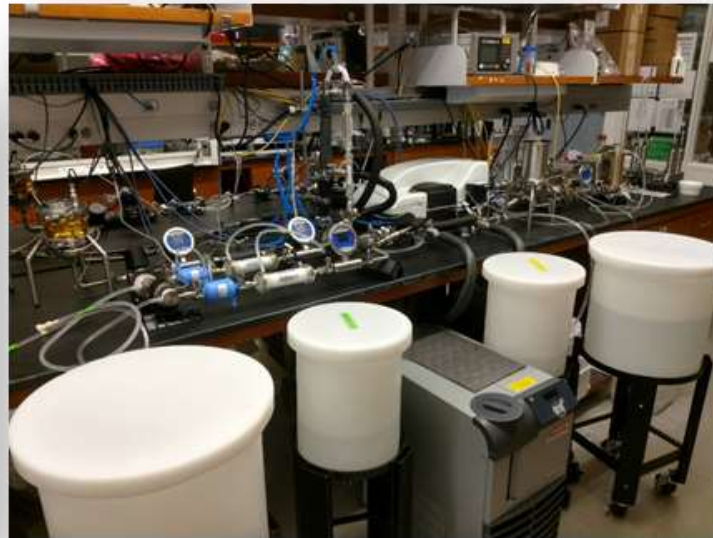
* Measured by Dynamic Light Scattering

Concept to Production: CM Development Journey

2014



2018



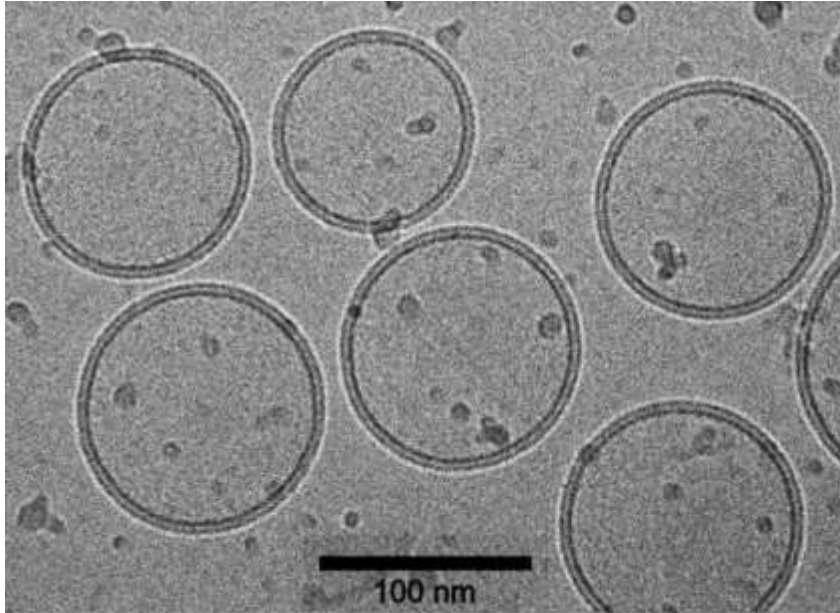
2022



One CM System, Multiple Nanoparticles

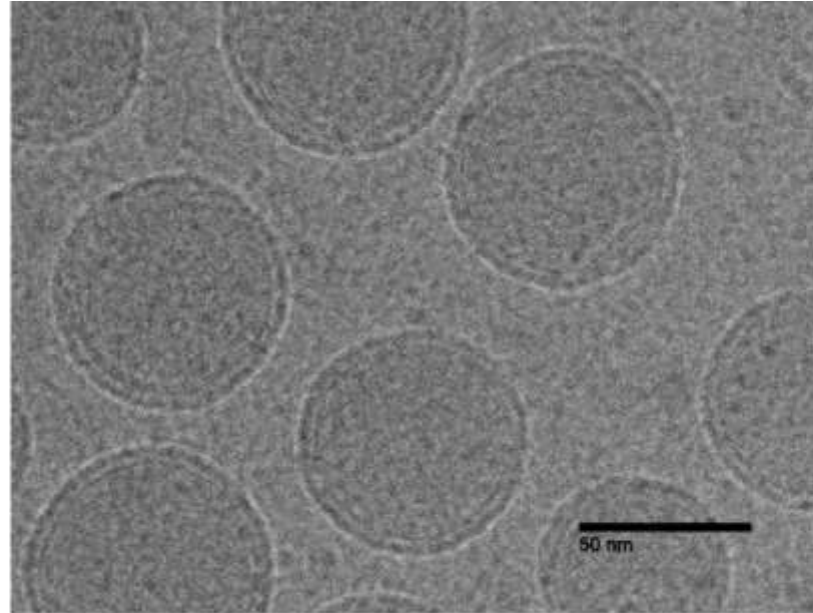


Liposomes



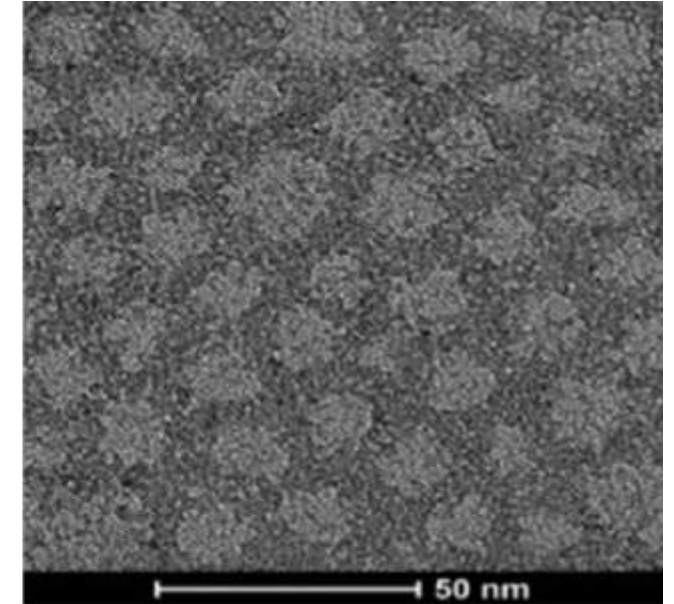
Bilayer Structure
Aqueous Core

Lipid Nanoparticles



Outer Lipid Layer
Aqueous/Lipid/Nucleic Acid Core

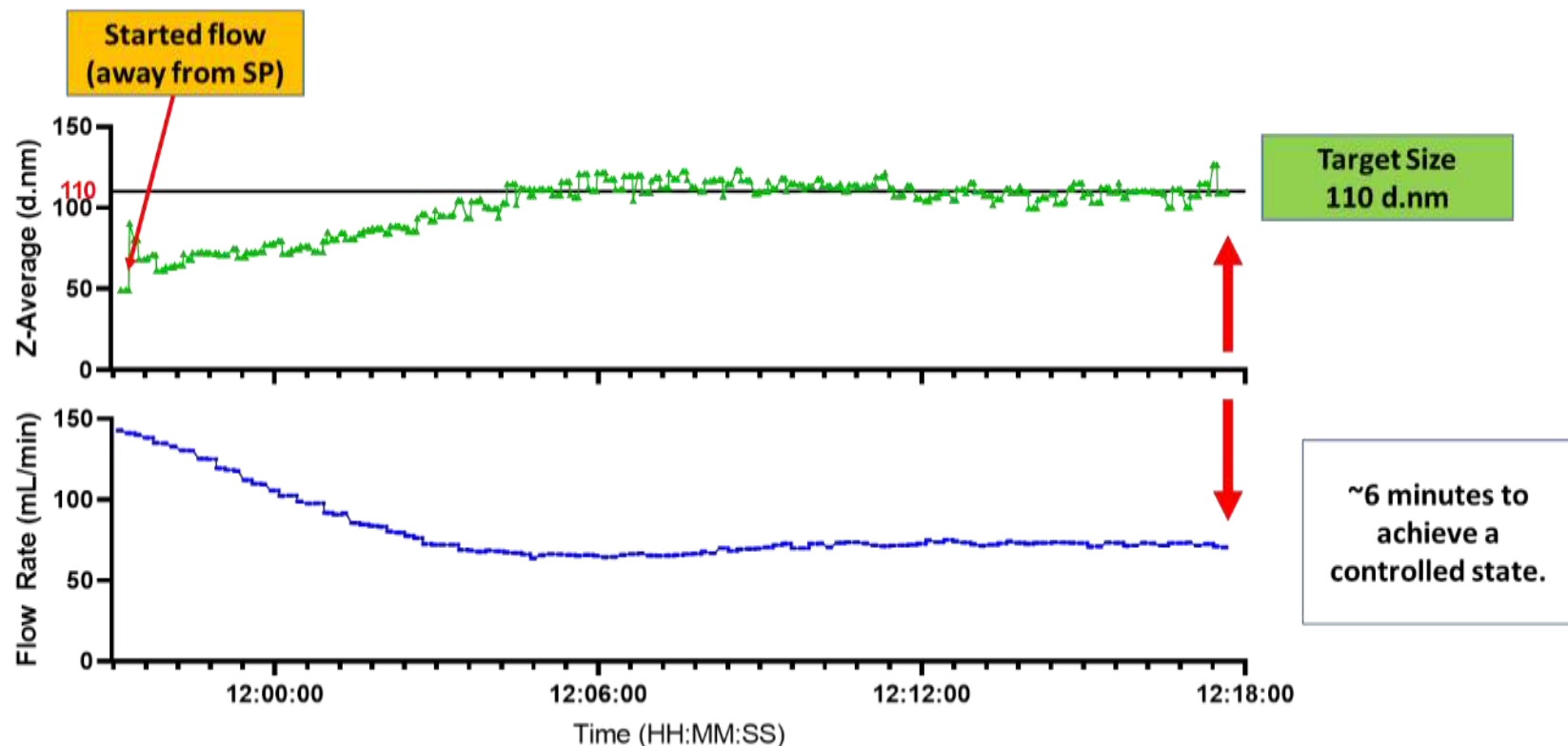
Polymeric Micelles



Block copolymer
Hydrophobic Core

- Yenduri, G., et al. "Impact of critical process parameters and critical material attributes on the critical quality attributes of liposomal formulations prepared using continuous processing." *International Journal of Pharmaceutics*, 619 (2022): 121700.
- Gupta, A., et al. "Continuous processing of paclitaxel polymeric micelles" *International Journal of Pharmaceutics*, 607 (2021): 120946.

Enables Automated Process Control



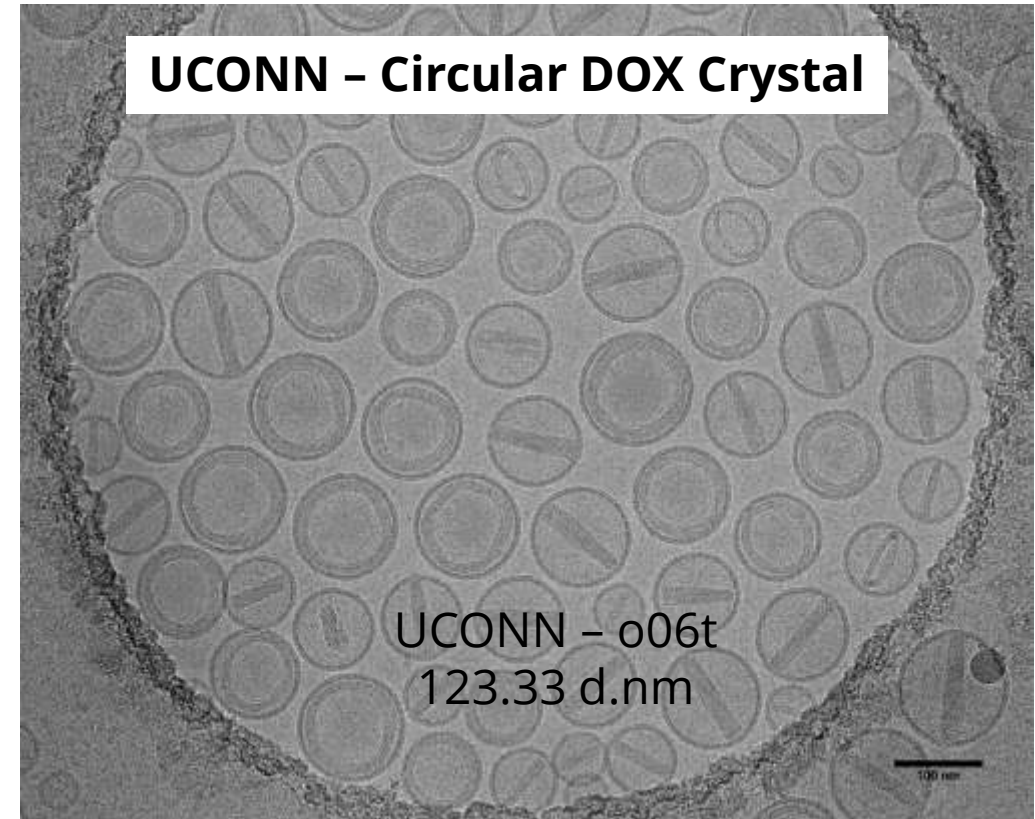
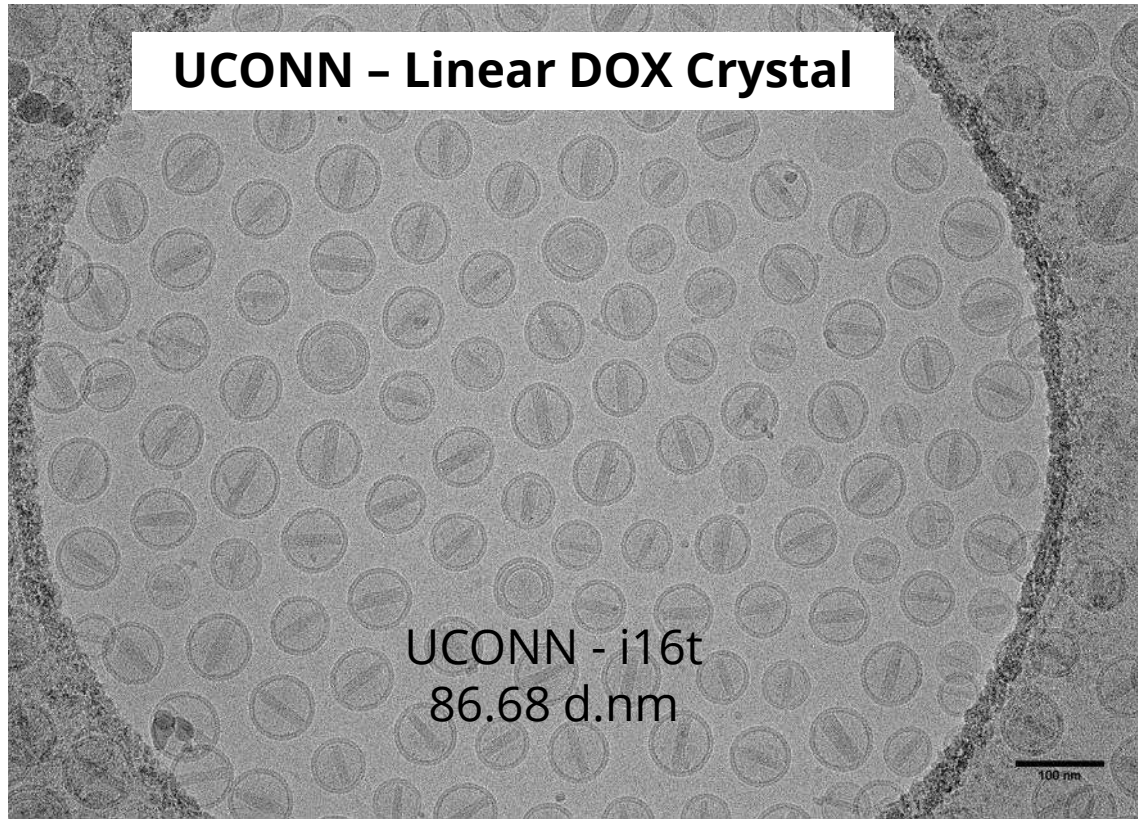
NanoFlowSizer
Spatially-Resolved DLS



“Product output change” is time dependent. Consistent quality can be maintained via appropriate PAT tools

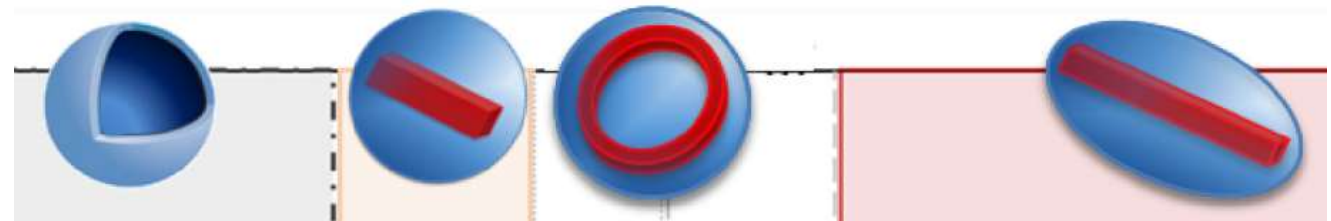
Example 20 Liters of Liposomes at 20 mM lipid conc. (about 3 hrs run)

Does Shape Matter?



Two types:

- Liposome (spherical vs. elongated)
- Crystal (linear vs. circular)



Modeling and Simulation to Enhance Process Understanding



Coarse-Grained Molecular Dynamics Simulation

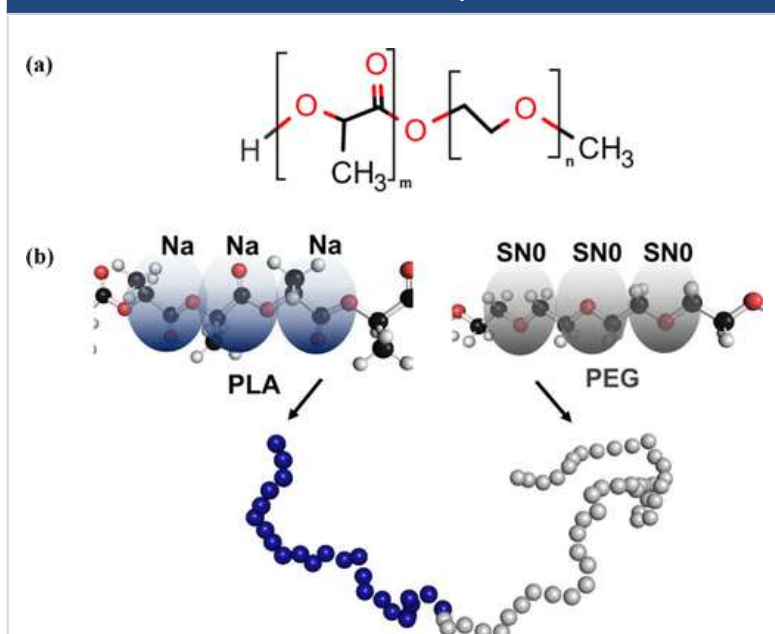
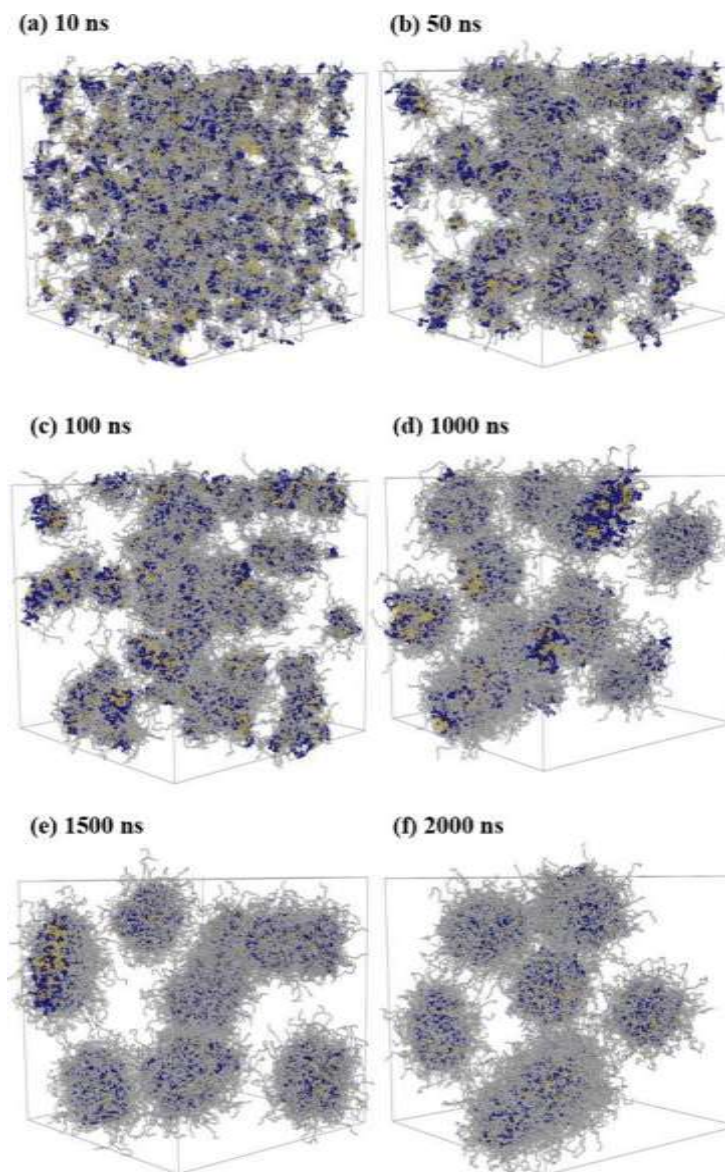


Figure 1. (a) Chemical structure of PEG-PLA and (b) correspondence between the AA and CG (MARTINI) models of PEG-PLA.

Figure 2. CG-MD simulation results of loading of the drug (paclitaxel) into PEG-PLA polymeric micelles over the course of 2000 nanoseconds



Modeling and simulation tools like discrete element method (DEM), computational fluid dynamics (CFD), molecular dynamics (MD), artificial intelligence and machine learning (AI/ML), and digital twins can enhance the product and process understanding, enabling the design of advanced process controls

Lesson learned

REGULATORY CONSIDERATIONS

CM Elements Discussed Between CDER and Industry

- System dynamics, RTD and transient disturbances
- Raw material control
- Sampling strategy
- Material traceability
- Start up and shut down
- PATs, models and RTRT
- Product collection and material diversion
- Process monitoring and control

Control
Strategy

- Model maintenance and update
- System integration, data processing and management
- Equipment qualification, maintenance and cleaning
- Process performance qualification
- Continued process verification

Facility and
Process
Validation

- Minor formulation changes
- Comparability and bioequivalence
- Stability data package

Bridging
Batch to
Continuous

- Batch size – flow rate and run time
- Scale up – run time increase
- Primary stability batch size
- Mass balance or yield

Batch and
Lot
definition

Quality Assessment Focus

- Characterization of process dynamics for critical steps and integrated system
 - Residence time distribution for a proposed mass flow rate
 - Understanding of the system response to transient disturbances
- Evaluation of the proposed attributes and specifications of raw materials
 - Impact of variations in material properties on the performance of CM and product quality
- Process monitoring and control strategy
 - Monitor and detect transient disturbances and process deviation
 - Frequency of PAT measurements
 - Active process controls
- Material collection and diversion
 - Start up and shutdown
 - Strategy to identify, isolate and divert non-conforming materials
- Real-time release testing
 - PAT tools for assay and content uniformity
 - Dissolution models



Characterization of Residence Time Distribution (RTD) during Continuous Manufacturing (CM)



Problem statement:

- Understanding CM process dynamics as a function of material properties, process conditions and equipment design through characterization of RTD

Approaches:

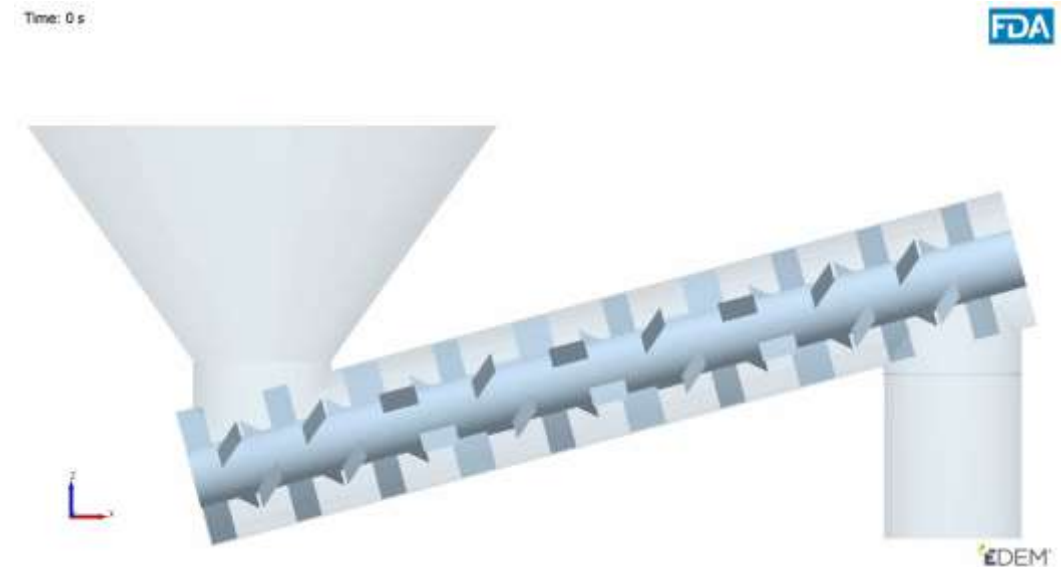
- Experimental RTD studies and *in silico* RTD modeling

Outcomes:

- Comprehensive Design of Experiment (DoE) for investigating the effects of material properties, process parameters, and equipment configuration on RTD in a continuous powder blending process at the commercial scale
- A modeling framework for assessment of RTD-based control strategy using Discrete Element Method (DEM)

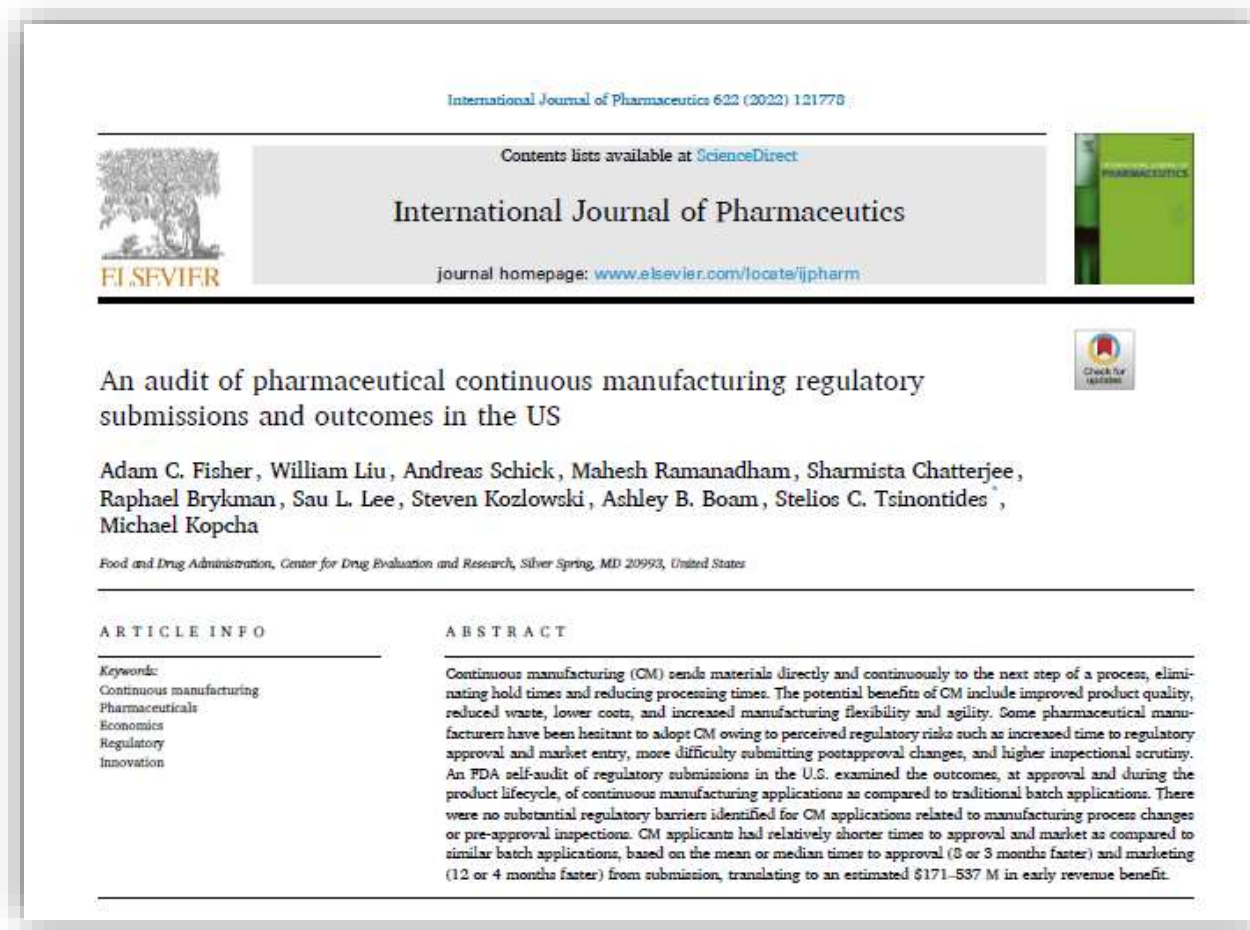
- W. Yang., et al. "Assessing Residence Time Distributions and Hold-up Mass in Continuous Powder Blending using Discrete Element Method", Under Peer-review.

In Silico RTD Modeling via DEM



Impact: RTD model provides insight into CM process and supports quality assessment, policy development and reviewer training

Impact of Continuous Manufacturing



- **CM applicants had shorter times to approval and marketing compared to batch applicants**
 - 3 months faster to approval (median)
 - 4 months faster to marketing
 - ~\$171-537M in early revenue benefit
- **No substantial regulatory barriers for CM related to:**
 - Manufacturing process changes
 - Pre-approval inspections

Closing thoughts



- FDA and CDER continue to foster innovation and the responsible development of drug products containing nanomaterials.
- Research to better understand product quality is crucial.
- Innovation in manufacturing and characterization is needed.
- Further development and utilization of continuous manufacturing in nanomaterials can be valuable to enhance the agility and quality of the products, benefiting the patient and society.

Acknowledgement



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- Anand Gupta
- Gowtham Yenduri
- Tibo Duran



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ADMINISTRATION