# Technological Innovation in Manufacturing

Thomas O'Connor, Ph.D.

Office of Pharmaceutical Quality
US FDA Center for Drug Evaluation and Research

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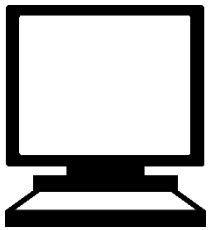
# Disclaimer

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

# Pharmaceutical Quality

**A quality product of any kind consistently meets the expectations of the user.**



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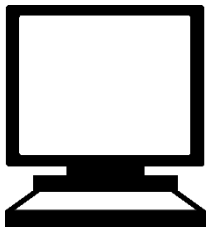



**Drugs are no different.**


FDA
Patients expect safe and effective medicine with every dose they take.

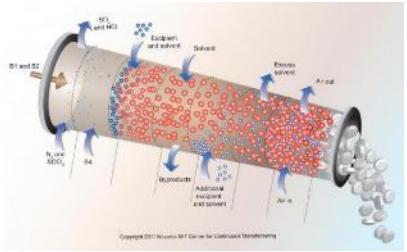
**Pharmaceutical quality is**

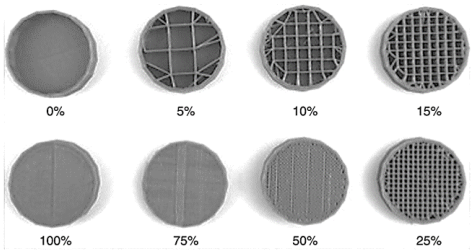
assuring *every* dose is safe and effective, free of contamination and defects.


It is what gives patients confidence in their *next* dose of medicine.

# What is Advanced Manufacturing?

- Novel **manufacturing methods** to improve process robustness and efficiency
- Novel **dosage forms** or delivery systems to improve drug delivery and targeting
- Novel **analytical tools** to improve product quality testing, process monitoring and/or control





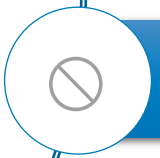

# Advanced Manufacturing

Our vision is to achieve “a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight.” *Janet Woodcock MD, Director, CDER FDA*

**Advanced manufacturing** can improve drug manufacturing and help ensure that quality medicine is available.

**Produce better quality medicine.** A transition to advanced manufacturing technology can facilitate operation above a six-sigma level, meaning manufacturers would see no more than 3.4 defects per million opportunities**.**

**Develop drugs rapidly.** Advanced manufacturing technology speed the development novel or patient-focused therapeutics (e.g., orphan drugs, oncology drugs, breakthrough therapies).



**Prevent drug shortages.** FDA found 62% of drug shortages were associated with manufacturing or quality problems. Advanced manufacturing can proactively reduce today’s quality-related manufacturing issues.

**Improve emergency preparedness.** More agile and flexible manufacturing technology can help manufacturers pivot quickly to address unanticipated demands in a public health emergency.

# CDER Efforts in Advanced Manufacturing

## Emerging Technology Program

**US FDA Center for Drug Evaluation and Research**

# Mission

Encourage and support the adoption of **innovative technology**

to modernize pharmaceutical **development and manufacturing**

through **close collaboration** with industry and other relevant stakeholders

## Team

A small **cross-functional** Emerging Technology Team (ETT)

with representation from all relevant FDA **quality assessment and inspection** programs

(CDER/OPQ, CDER/OC & ORA)

# Program Objectives

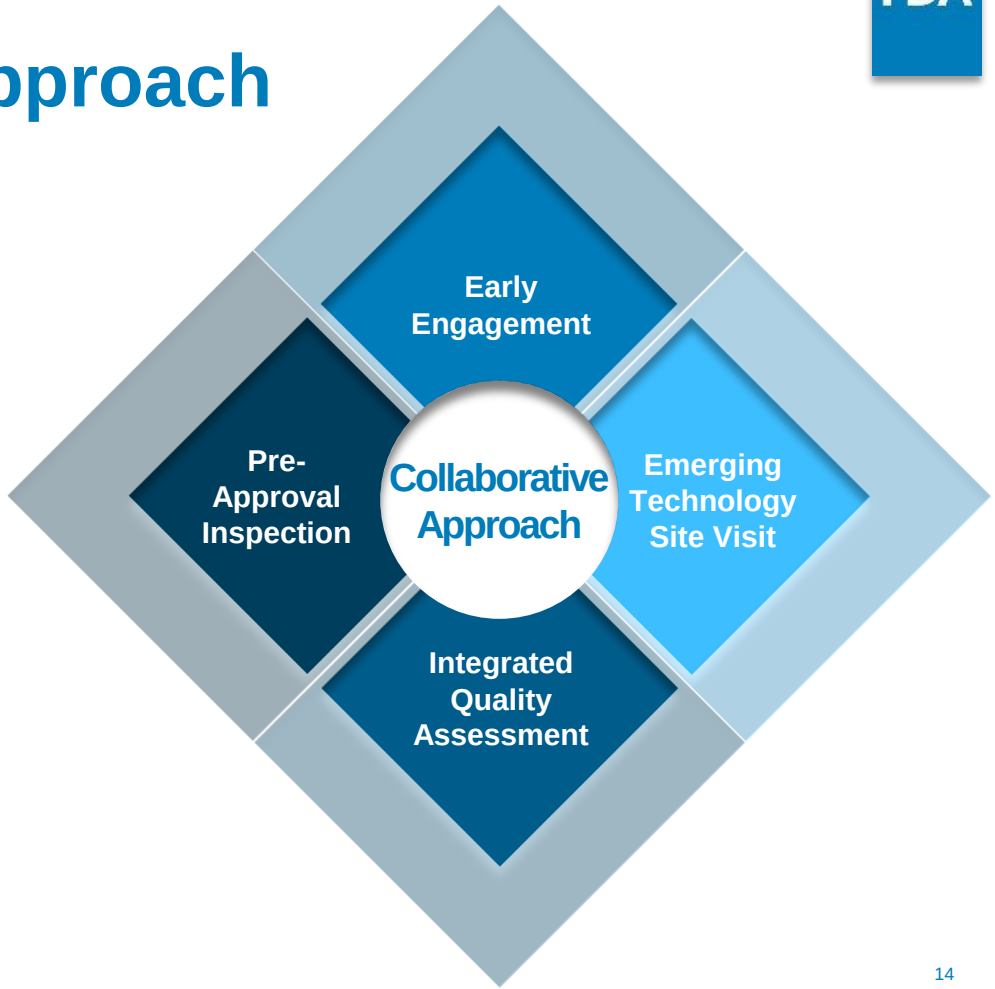

Contact us: CDER-ETT@fda.hhs.gov

# ETT Collaborative Approach

Over the course of an ETP project, ETT may employ a combination of early engagement, ET site visits, integrated quality assessments or Pre-Approval Inspections

The same ETT representative(s) will be involved in the entire process

The composition of an assessment team will likely remain the same throughout the entire process



# Progress in Emerging Technology

Approval of a first regulatory application utilizing 3D printing technologies

Approvals of applications utilizing continuous manufacturing (CM)

- Small molecule drug product and drug substance
- Automated semi-continuous sterile manufacturing


Requests accepted to the ET program since launching in late 2014

- Received over 100 ETT proposals and accepted ~50% of these proposals to the program

## Right Mindset and Culture

# Getting Ready for ETT Meetings

### Regulatory Agencies

- Willing to learn / understand and recognize potential of new technologies with an open mind
- Make science- and risk-based assessments and decisions
- Be transparent to industry and not afraid to ask questions
- Multi-disciplinary approach (collaborative)

### Industry

- Be transparent and willing to share with the agency early
- Not afraid to receive and answer many questions from the agency
- View regulators as part of your team

**We are getting there!**

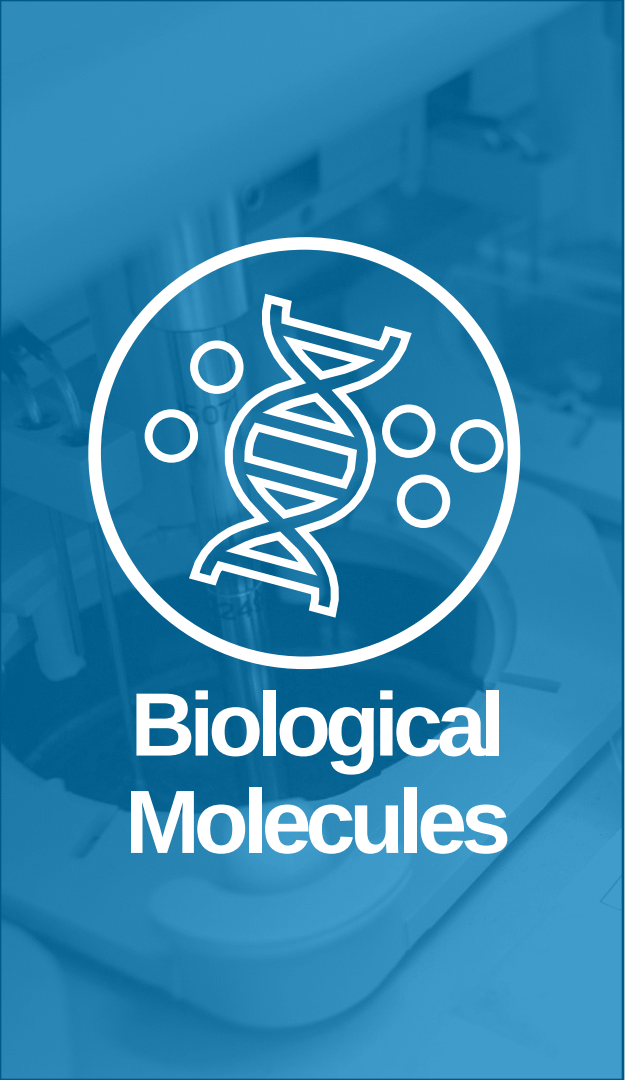
# For ETT Activities visit the ETP website:

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

Small Molecules

# FDA Experience: Emerging Technologies

- CM of drug substance
- CM of drug product
- End-to-end CM
- Pharmacy-on-demand
- Model-based control strategy for continuous manufacturing
- Continuous aseptic spray drying
- 3D printing manufacturing
- Ultra long-acting oral formulation




# FDA Experience: Emerging Technologies

- Controlled ice nucleation for lyophilization processes
- Comprehensive product testing using a single multi-attribute assay (multi-attribute method)
- Continuous manufacturing for a downstream process
- End-to-end integrated bioprocess
- Pharmacy on demand (small manufacturing platform for continuous bioprocesses)

Multiple Technologies

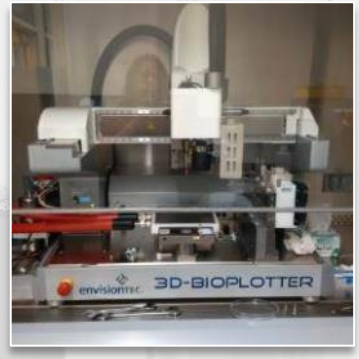
# FDA Experience: Emerging Technologies

- Distributed Manufacturing
- Closed aseptic filling system
- Isolator and robotic arm for aseptic filling
- Novel container and closure system for injectable products

# FDA Science and Research Activities: Emerging Technology

## OPQ Science and Research

- Process modeling and simulation
- Multi-attribute methods
- Controlled ice nucleation
- Characterization of novel glass designs
- In-house laboratory capability for advanced manufacturing technologies
- High throughput analytical approaches
- Emerging Therapies (oligonucleotides)

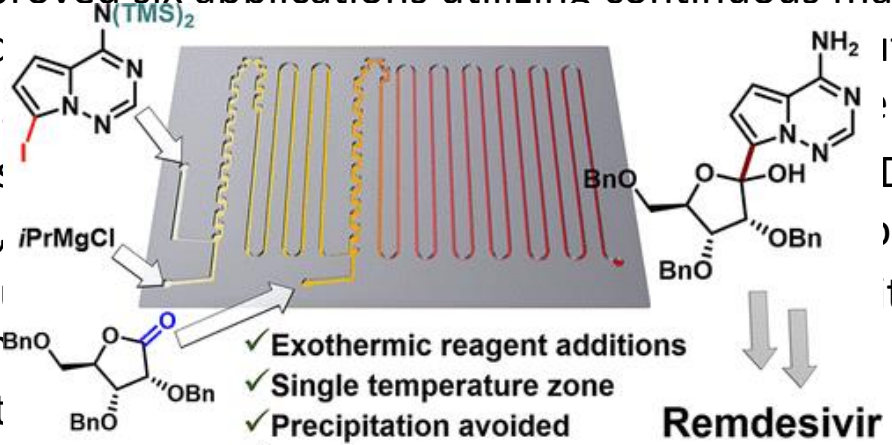



Emerging Technology Program:

1) Continuous Manufacturing
2) Industry 4.0: Advanced Process Control and Modeling
3) Distributed Manufacturing

# Continuous Manufacturing

- CDER approved six applications utilizing continuous manufacturing for finished d… …ilizing it for a top-sellin… … injectable
- Standards… …DA draft guidance, … …rmulated
- Continuo… …ty in unit operation…
- Manufact…
  - Isolated… …s flow reactors)



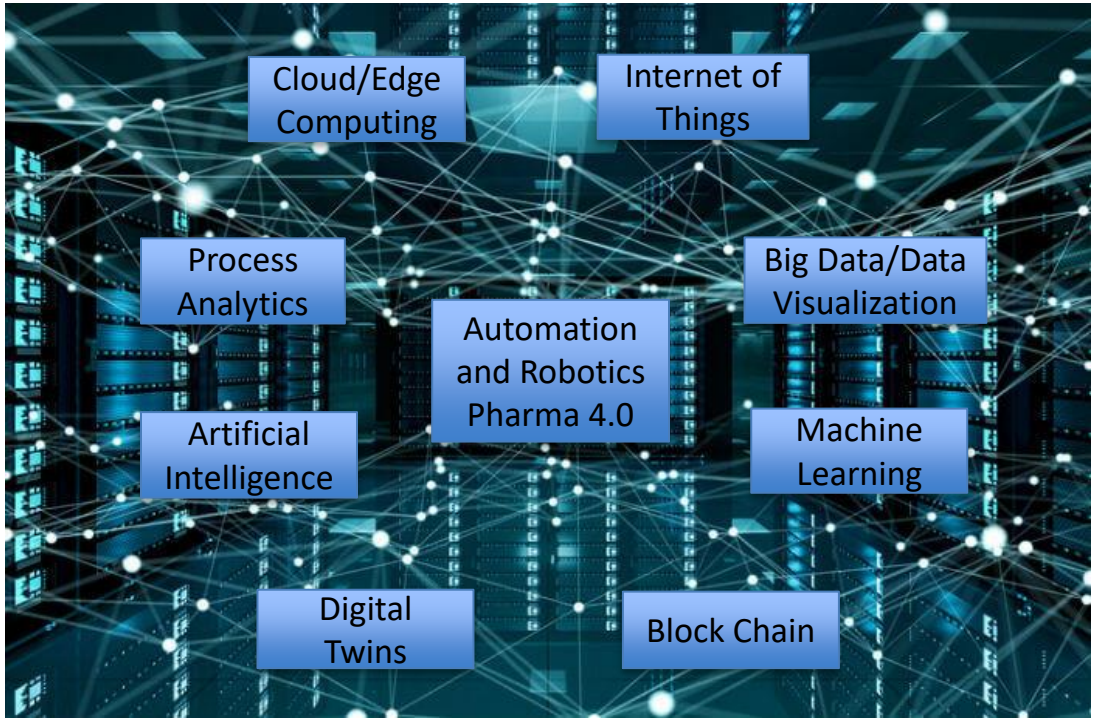

- Continuous Flow C-Glycosylation via Metal−Halogen Exchange: Process Understanding and Improvements toward Efficient Manufacturing of Remdesivir
  Org. Process Res. Dev. 2020, 24, 2362−2368
  - Better synthetic routes, and new capabilities
  - Improved Health, Safety, and Environmental performance

# Continuous Synthetic API Manufacturing

- Telescoped reactions
  - Can lead to complex reactions with many different species in the mixture
- Integrated process lines often contain surge capacity that decouple segment of the process train
- Process monitoring approach is a common ETT-Industry discussion area
  - In process controls may combine process parameter limits with a specified duration (e.g. outside of +/- 10% for 20s)
  - Specify context of use of PAT in the control strategy
- Process robustness: solids may be present in the reaction as reagents, intermediates, byproducts, or as the product causing process disruptions

Vapourtec Flow Chemistry System

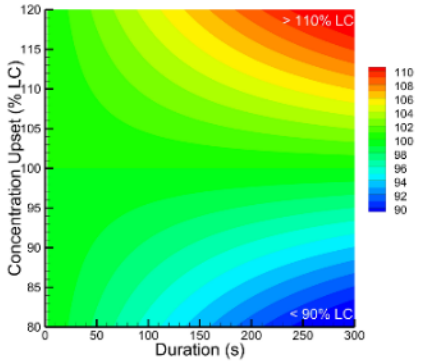
# Emerging Digital Tools and Technologies in Pharmaceutical Drug Manufacturing



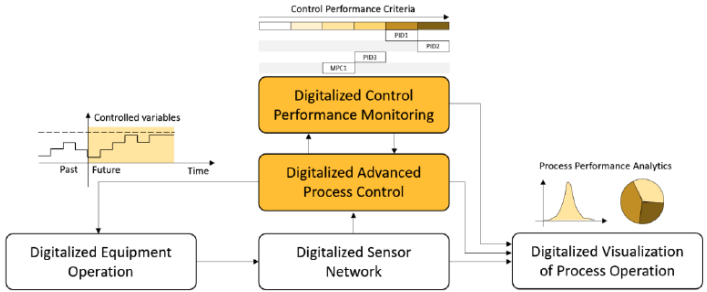

What is the Scope for Product Quality?

# Digital Twins: Modeling and Simulation

- Advanced manufacturing a potential driving force for utilization of process modeling
- Modeling approaches evolving in the pharmaceutical industry (e.g. digital twins)
- Models can facilitate risk assessment, improve process design, and improve process performance through online monitoring and control
  - Predictive models have appeared in regulatory submissions
  - FDA has developed internal process modeling and simulation capability
- Technology Specific Considerations
  - Model categorization considering purpose, impact and risk
  - Exploring utility of risk-based model validation assessment frameworks
  - Model maintenance plans over product lifecycle




Models for In-Process Control

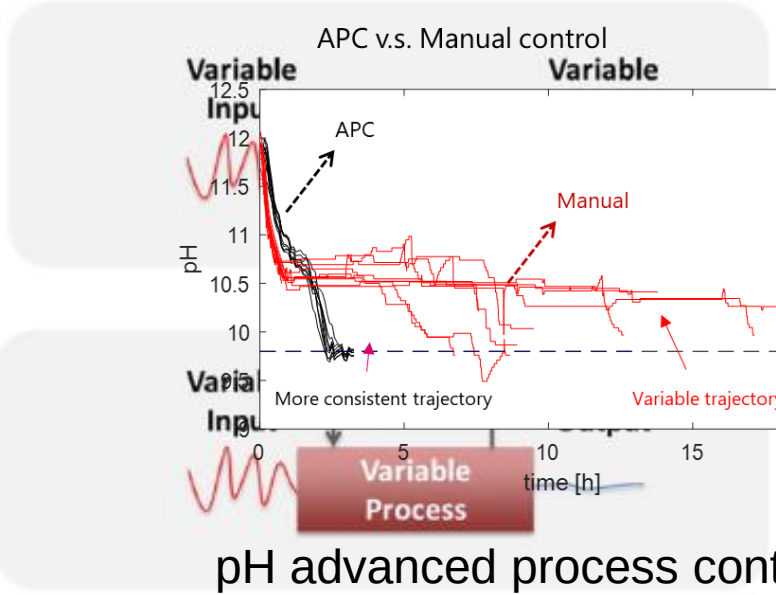



Digital Twins

https://doi.org/10.1016/j.compchemeng.2019.06.033

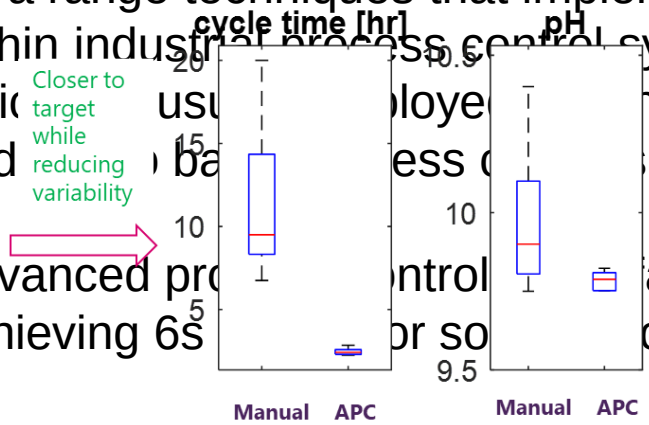
Courtesy of Prof. Ierapetritou, University Delaware

# Advanced Process Control (APC)




Advanced process control is umbrella term for a range techniques that implemented within industrial process control systems, which usually employed automatically and in addition to basic process controls.

Advanced process control facilitate achieving 6s or so processes




Two enablers for APC:

- Measurement of process outputs
- Product and process understanding that could be used to adjust process to maintain a uniform output

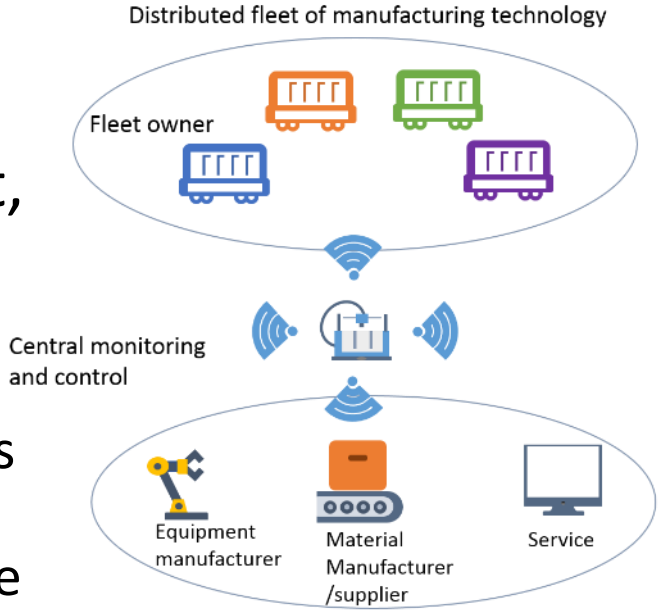
pH advanced process control for improving robustness and reducing cycle time

L.X. Yu, M. Koncha International J. Pharm. 528 (2107) 354-359

Accepted Journal of Advanced Manufacturing and Processing

# Distributed Manufacturing (DM)

- *Distributed Manufacturing (DM)*: is a decentralized manufacturing platform that is coordinated by one management, is mobile, and can be deployed to multiple locations.
  - DM typically comprises of pre-fabricated, mobile, modular manufacturing/testing units
  - Oversight is established by centralized QA, execution of manufacturing occurs where the unit is deployed



# Use Cases for DM Discussed with ETT

**Expanding capacity at a given facility**

- Implementing POD within existing facility

**Mobile**

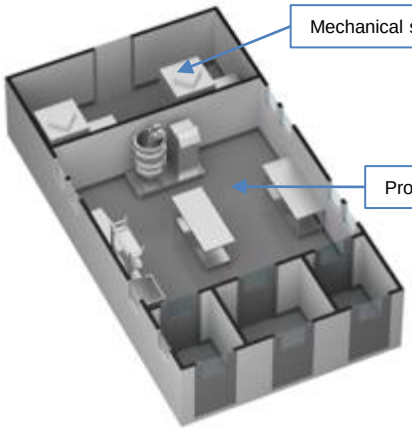
- Relocating PODs between existing facilities

**Cloning**

- Replicating PODs to increase capacity

**Response to Public Health**

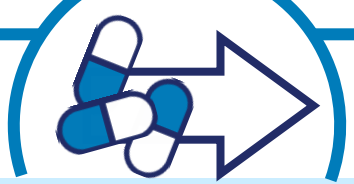
- Moving POD to point of care/ emergency response




Courtesy D. Powers G-CON

# Acknowledgements

Emerging Technology Team



OPQ Leadership

Industry Partners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ADMINISTRATION
Thank You!