CDER's Emerging Technology Program

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Overview

- Emerging Technology Program (ETP) Overview
- ETP Trends
- Lifecycle of an Emerging Technology
- Interacting with the ETP

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 characterization, quality testing, process monitoring and/or control

Advanced Manufacturing Benefits

- **Produce better quality medicine**. Facilitates six-sigma operation, no more than 3.4 defects per 1M opportunities.
- **Re-shore drug manufacturing facilities.** Helps domestic drug manufacturers compete in a global market.
- **Develop drugs rapidly.** Speeds the development of novel or patient-focused therapeutics.
- **Prevent drug shortages.** Reduces today's quality-related manufacturing issues causing 62% of drug shortages.
- **Improve emergency preparedness.** Provides more agility and flexibility to help pivot in a public health emergency.

Advanced Manufacturing Programs

ADVANCED MANUFACTURING (AM)

ASSESSMENT AND INSPECTION

including Emerging Technology Program (ETP)

RESEARCH

POLICY

Including Framework for Regulatory Advanced Manufacturing Evaluation (FRAME)

ICH Q13 Guidance

What is The Emerging Technology Program?

WHAT	An OPQ program established in late 2014 that promotes and facilitates the **adoption of innovative approaches to pharmaceutical product design and manufacturing**
WHO	A **cross-functional team** (approximately 30 members with additional ad-hoc SME members) with representation from all relevant FDA quality review and inspection programs **Offices include: OPQ, OC, ORA (*One Quality Voice*)**
HOW	The program provides an **opportunity for industry to engage and collaborate early with the FDA** to discuss, identify, and resolve technical and regulatory issues during a novel technology's development and adoptions

Program Objectives

To serve as a **centralized location for external inquiries** on novel technologies

To provide a forum for firms to **engage in early dialogue with FDA** to support innovation

To **ensure consistency, continuity, and predictability** in review and inspection

To **engage international regulatory agencies** to share learnings and approaches

To **identify and evaluate potential roadblocks** relating to existing guidance, policy, or practice

To **facilitate knowledge transfer** to relevant CDER and ORA review and inspection programs

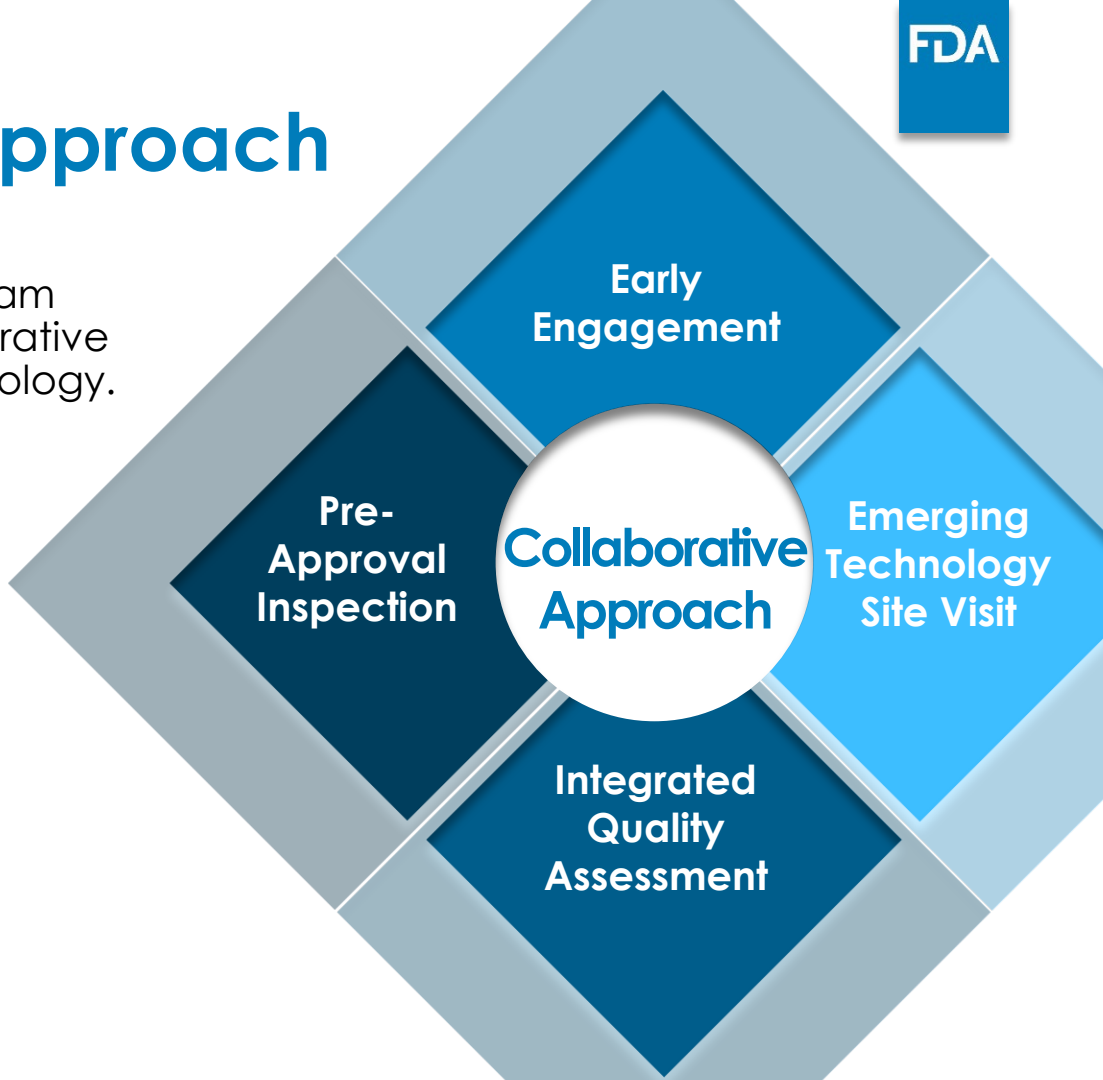
To help **establish scientific standards and policy**, as needed

ETP Collaborative Approach

Over the course of the ETP Technology Lifecycle, the Emerging Technology Team may employ a combination of collaborative approaches to engage with the technology.

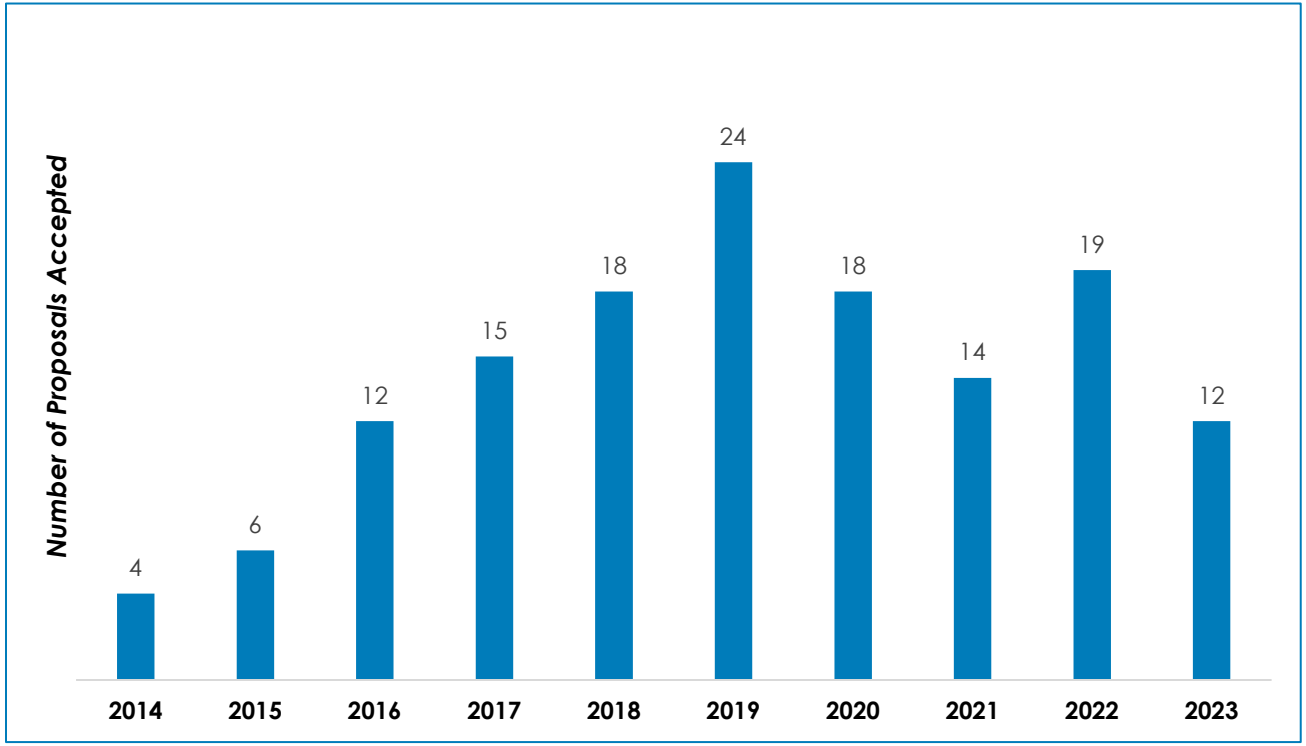
The same Emerging Technology Team representative(s) will be involved in the entire process.

The composition of a review team will likely remain the same throughout the entire process.



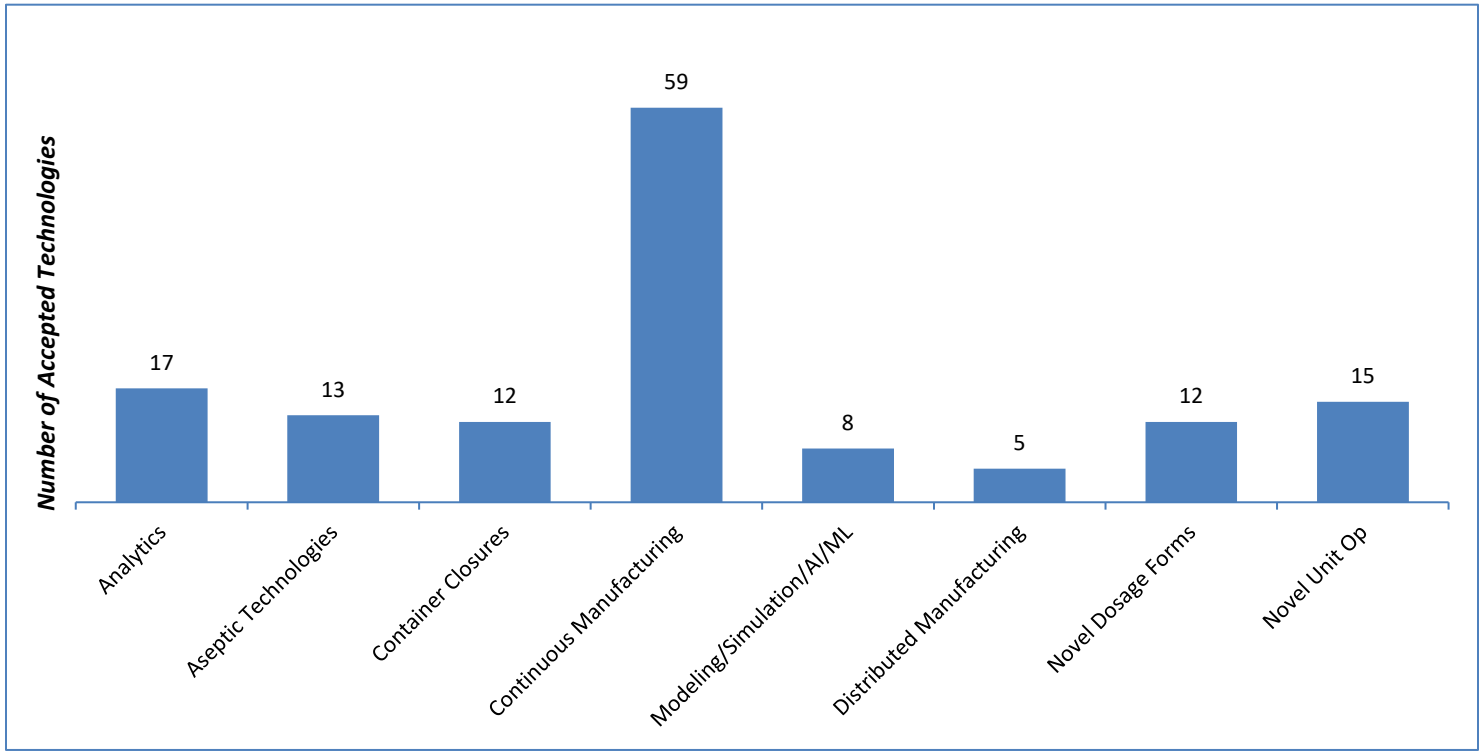
ETP Accepted Proposals

The Emerging Technology Program has accepted over 140 proposals since 2014



*As of September 2023

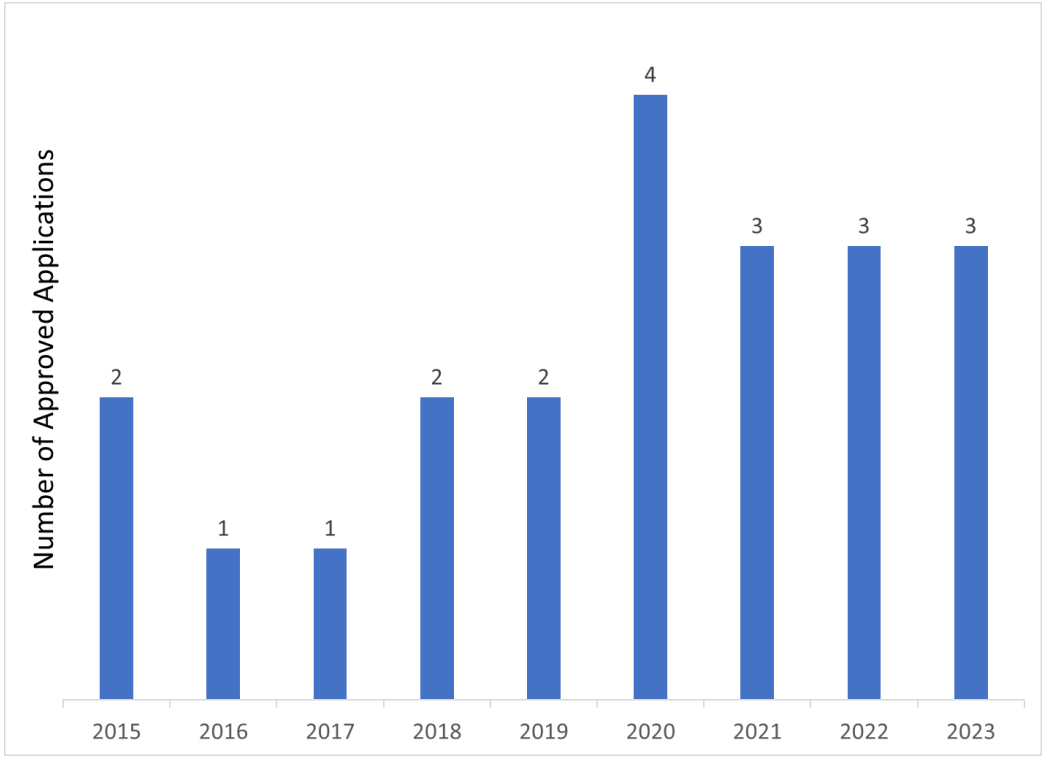
ETP Accepted Submissions by Technology



*As of September 2023

Total Approved Applications

There have been 21 approved applications since July 2015*



*As of September 2023

Recent Trends

- Continuous Manufacturing for complex products including biotechnology products

- Utilization of modeling and simulation in pharmaceutical development and manufacturing

- Novel technologies and modes of manufacturing for aseptic products

ETP in Food and Drug Omnibus Reform Act of 2022 (FDORA)

EMERGING TECHNOLOGY PROGRAM (ETP)

- **Establishes the ETP in statute**
- **A firm can seek a grant or contract** to "further research and development related to…innovative approaches to drug product design and manufacturing"
- **Requires FDA issue or update guidance**
  - To facilitate adoption and advance development of innovative approaches
  - To address regulatory requirements related to development or review including post-approval changes

ETP Program Enhancements

- Create and implement a communications plan to effectively share information about the program with industry
- Update existing ETP governance structure to support program operations
- Standardize technology intake process to manage participation requests from industry
- Identify new opportunities for engagement with ETP stakeholders and pharmaceutical industry

ETP Lifecycle at a Glance

Lifecycle of an ETP Technology

Industry requests input and feedback on an emerging technology while preparing a regulatory submission

ETP works with industry to discuss, identify, and resolve technical and regulatory issues related to the development and implementation of the novel technology

Technology is no longer considered "emerging" and passes through the standard quality assessment pathways

**A technology is eligible to graduate from ETP when at least three applications have been received from three unique companies. Meeting this threshold does not automatically initiate graduation.*

Graduation Benefits

Graduation indicates that FDA has gained sufficient experience with the graduating technology and is **confident in the ability of industry to submit successful future applications**

By transferring responsibility for the graduated technology to other FDA offices, ETP has the capacity to **accept future emerging technologies to keep pace with industry innovation**

With more assessors trained to review the graduated technology, **FDA can review more applications while continuing to meet the user fee goal dates.**

ETP core members remain available to FDA assessors as needed on regulatory submissions of graduated technologies.

ETP Graduates Continuous Direct Compression

- ETP determines technology's readiness to move forward with graduation
- ETP manages knowledge transfer related to the technology and trains FDA assessors to be prepared to review future application submissions
- FDA assessors review future applications from a graduated technology

Experience Bands

Continuous Direct Compression	
Drug Product	Immediate release only Either single API or fixed dose combination products Either high (>25%) and medium (5-25%) drug load BCS Class 1, 2, 3, 4
Formulation Changes (Legacy Products)	Only SUPAC Level 1 Quantitative differences in components if products are to be marketed congruently[2]
Manufacturing Process (Drug Product Only)	Integrated Process Steps Limited to loss-weight-feeding, continuous blending, compression, and continuous non-functional coating step (processes with fewer integrated steps such as batch coating are included in experience bands)
Advanced In-Process Controls	IPCs include ratio control for LIW feeders Quantitative spectroscopic based measurement for blend uniformity for routine commercial production (Process models such as RTD models for blend uniformity are currently excluded from experience bands)
Material Diversion	Includes RTD based diversion strategies
Real Time Release (RTRT is not required)	Assay and CU only: Spectroscopic measurement & tablet weight; Dissolution: Compendial test for batch release or RTR based on PLS models
Batch Definition / Batch Size	Must conform to definition in draft guidance

*Experience bands are the elements of an emerging technology that have graduated and can be submitted through the standard quality process

Impact on Assessment

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An audit of pharmaceutical continuous manufacturing regulatory submissions and outcomes in the US

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ABSTRACT

Continuous manufacturing (CM) sends materials directly and continuously to the next step of a process, eliminating hold times and reducing processing times. The potential benefits of CM include improved product quality, reduced waste, lower costs, and increased manufacturing flexibility and agility. Some pharmaceutical manufacturers have been hesitant to adopt CM owing to perceived regulatory risks such as increased time to regulatory approval and market entry, more difficulty submitting postapproval changes, and higher inspectional scrutiny. An FDA self-audit of regulatory submissions in the U.S. examined the outcomes, at approval and during the product lifecycle, of continuous manufacturing applications as compared to traditional batch applications. There were no substantial regulatory barriers identified for CM applications related to manufacturing process changes or pre-approval inspections. CM applicants had relatively shorter times to approval and market as compared to similar batch applications, based on the mean or median times to approval (8 or 3 months faster) and marketing (12 or 4 months faster) from submission, translating to an estimated $171-537 M in early revenue benefit.

1. Introduction

Continuous manufacturing (CM) is a technology that sends materials produced during each process step directly and continuously to the next step for further processing. In such a process, input materials are continuously fed into production and transformed, and processed output materials are continuously removed. CM has been adopted in many industries (e.g., petroleum, commodity chemicals), while the pharmaceutical industry has been slower to adopt CM (Lee et al., 2015; Rossi, 2022). The U.S. landscape of prescription drug products made using a CM process was roughly $3.09B in 2020 (Fig. 1), representing a small but growing portion of the $172B total market for branded, solid oral prescription drugs. The leading firm in the CM sector captures around 65% of total sales, with 20% of sales captured by the next largest firm. Many have pointed to the slow adoption of advanced manufacturing technologies, including CM, as one of the reasons that the pharmaceutical industry has not achieved the consistent six sigma manufacturing capability (i.e., <3.4 errors per million opportunities) common in other industries (Politis and Rekhas, 2011; Yu and Kopcha, 2017).

The United States Food and Drug Administration (FDA) has long championed the development and implementation of advanced manufacturing technologies like CM for drug substances and finished drug products because of the potential to improve product quality and reliability, lower manufacturing costs, reduce waste, decrease inventory, and increase manufacturing flexibility and agility in response to fluctuations in product demand. The cumulative effects of CM adoption could reduce or mitigate drug shortages (Lee et al., 2015). CM can be applied to all classes of products: new drugs submitted in New Drug Applications (NDAs) (Hernandez, 2015), generic drugs filed in Abbreviated New Drug applications (ANDAs) (Chaudhary et al., 2017), drug substances filed in Drug Master Files (DMFs) (Stauffer et al., 2019), biotechnology products filed in Biologics License Applications (BLAs) (Fisher et al., 2019), and nonprescription drugs (Griffin et al., 2016). There is now a rich source of scientific literature describing the benefits of CM in pharmaceutical manufacturing relating mostly to decreases in production/operating costs and improvements in product quality and reliability (Rossi, 2022; Badman et al., 2019). Perhaps most importantly for patients and consumers, CM has the potential to impact product availability; for example, by avoiding drug shortages due to manufacturing problems or expediting patient access through improved

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0378-5173/

- **CM applicants had <u>shorter</u> times to approval and marketing compared to batch applicants**
  - 3 months faster to approval
  - 4 months faster to marketing
  - Translates to <u>~$100-500M</u> in early revenue
- **No substantial regulatory barriers for CM related to:**
  - Manufacturing process changes
  - Pre-approval inspections

Engaging with the Emerging Technology Program

How to Apply to ETP

01

Start early in development (even potentially without a drug candidate identified)

02

Follow procedures described in the ETT guidance found on our website to request participation in the ETP

03

Develop proposal

- Describe the technology and explain why it is novel or unique
- Describe how it improves products
- Summarize development plan and implementation roadblocks
- Describe submission timeline

The sponsor must justify how the proposed emerging technology meet two criteria:

(1) Pharmaceutical Novelty
(2) Product Quality Advancement

* More detail can be found at: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/emerging-technology-program

Engaging with ETP: FAQs

Who can participate in the Emerging Technology Program?
ETP is open to companies that intend to include a novel technology as part of a regulatory submission reviewed by the Center for Drug Evaluation and Research (CDER).

Does the submitter of a proposal need to wait until a molecule is identified before joining ETP?
The group can join ETP before a molecule is identified as long as the technology used meets the criteria for acceptance.

Does the submitter of a proposal need to wait until a regulatory submission (e.g., an IND) is intended to join ETP?
The group can join ETP before a submission is intended.

Engaging with ETP: FAQs

What if the submitter of a proposal is still developing a particular technology and still determining what questions to ask. Should they wait to submit a proposal?

Waiting is not needed as the ETP engagement is not designed to be a single interaction. Rather, it's ideally a series of engagements throughout technology development.

How will the ETP be notified of an emerging technology within a regulatory submission?

If the technology in the application is part of a previous engagement, the ETT will be included in future interactions. It is helpful to reference the acceptance into the ETP in the cover letter of the submission and to notify the ETP mailbox upon submission.

Engaging with ETP: FAQs

Are new proposals appropriate for legacy products or only for new molecules in development?

Proposals are appropriate for new molecules in development as well as products that have been on the market for a long time. Proposals are appropriate for any type of molecule.

What is the criteria to be accepted into the ETP?

Acceptance is not guaranteed.

The ETT limits acceptance into the program to technologies that are likely to advance product design or modernize pharmaceutical manufacturing, and with which the Agency has limited prior experience and knowledge.

The proposed technology in the planned submission must have the potential to improve product safety, identity, strength, quality, or purity.

Conclusion

- The Emerging Technology Program serves as a centralized location for external inquiries on novel technologies, providing a forum for industry to engage in early dialogue with CDER/FDA.
- Through this early engagement, the ETP can identify and evaluate potential roadblocks relating to existing guidance, policy, or practice.
- Once FDA has enough confidence in industry's ability to successfully submit applications using the technology, it then "graduates" from the ETP.
- To request participation in the ETP, develop a proposal and be sure to:
  - Describe the technology, explain why it is novel, and how it improves products
  - Summarize development plan and implementation roadblocks
  - Describe submission timeline

Additional procedures are described in the ETT guidance found on our website:
https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/how-participate-etp