Office of Pharmaceutical Quality Science and Research: Abuse Deterrent Formulations

Cindy Buhse

Director, Office of Testing and Research

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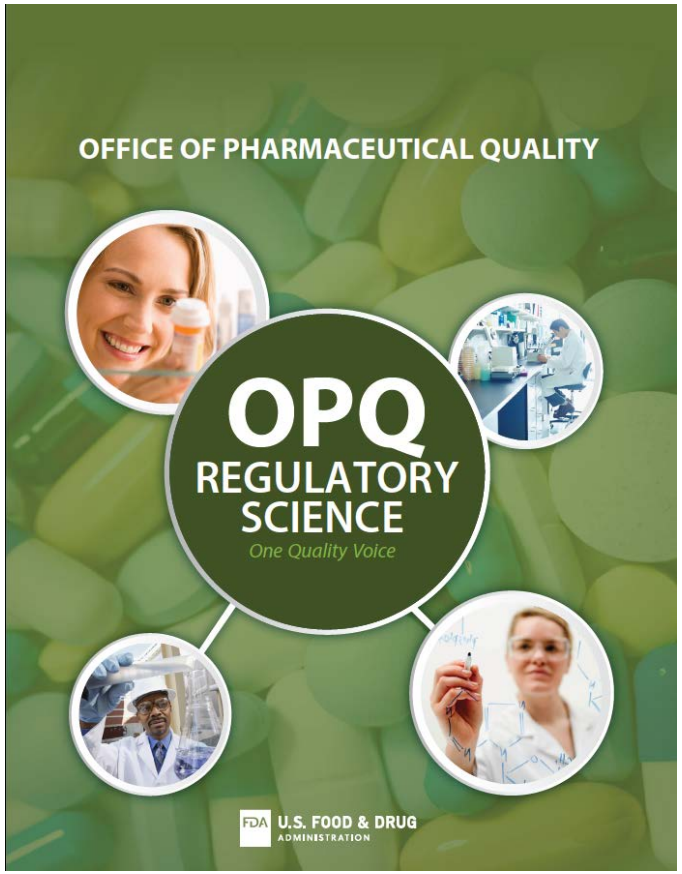
ADF Expectations:

- Technologies to impart abuse deterrence properties will continue to evolve
- New technologies should not be at risk for introducing a new vulnerability
- Product **strengths** and **vulnerabilities** will need to be communicated to the agency by the applicants
- FDA will need the knowledge and capability to assess the technologies and testing schemes submitted in applications

OPQ Science and Research



- Support the development of **scientific standards** and **policies** on the manufacturing and quality of human drugs
- Identify, evaluate, and develop **technologies to assess the safety and efficacy** of human drugs
- Address scientific needs in support of **review, facility evaluation,** and **surveillance** and prepare for **emerging science issues**
- Collaborate with external and internal stakeholders to leverage expertise, advance internal knowledge, and develop **novel technologies**

Outline

- **Encouraging new technologies: Emerging Technologies Team**
- Assessing testing: Method Verification Program
- Improving understanding: ADF Research

Emerging Technologies Address Quality Issues

- An emerging technology has **novelty** and **impact**:
  - Product technology (e.g., new dosage form)
  - Manufacturing process (e.g., novel manufacturing process)
  - Control strategy technology (e.g., innovative testing method)

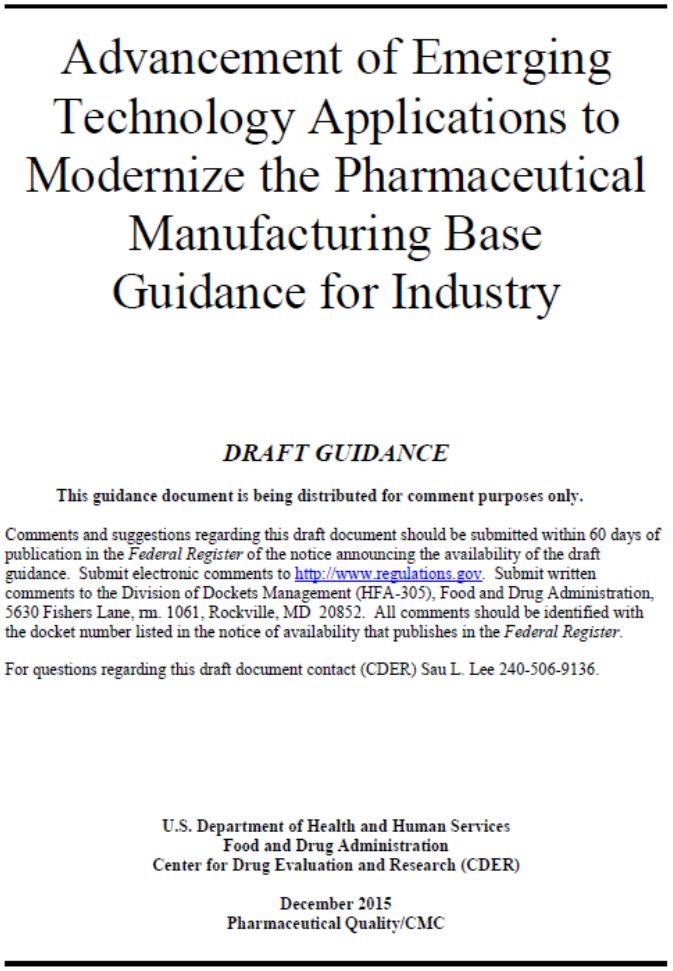
Any of these aspects could apply to an ADF product

Emerging Technology Program

OPQ Priority: A collaborative approach with manufacturers that encourages innovation and the adoption of new technologies

- The Emerging Technology Team (ETT) within OPQ:
  - A cross-functional team with representation from all relevant **CDER** (**OPQ and OC**) and **ORA** review and inspection programs
  - Ensures consistency, continuity, and predictability in review and inspection
  - ETT member(s) plays an active or leadership role in the OPQ quality assessment team for applications containing an emerging technology

Draft Emerging Technology Guidance



Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Sau L. Lee 240-506-9136.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Pharmaceutical Quality/CMC

- Provides recommendations to companies interested in participating in a program involving the submission of CMC information containing emerging manufacturing technology to FDA.
- Applicable to companies that intend the technology to be included as part of an: investigational new drug application (IND) or original or supplemental new drug application (NDA), abbreviated new drug application (ANDA), or biologic license application (BLA) reviewed by the Center for Drug Evaluation and Research (CDER), and where that technology meets other criteria described in this guidance.
- In the process of being finalized.

Integrated Quality Assessment under the Emerging Technology Program

- **Early Engagement (Pre-submission)**
  - Face-to-face meeting(s) with ETT involvement – provided upfront scientific input under the Emerging Technology Program
- **Pre-Operational Visit (POV) if needed**
  - Participation by OPQ (including the ETT member(s)) and/or ORA members
- **Integrated Quality Assessment (IQA)**
  - Interdisciplinary team with experts in Drug Substance, Drug product, Process/Facility, Biopharm, and/or Inspection
  - ETT member as a Co-Application Technical Lead
- **Pre-Approval Inspection (PAI)**
  - Conducted by team members from OPQ (including the ETT Member(s)) and ORA.

Outline

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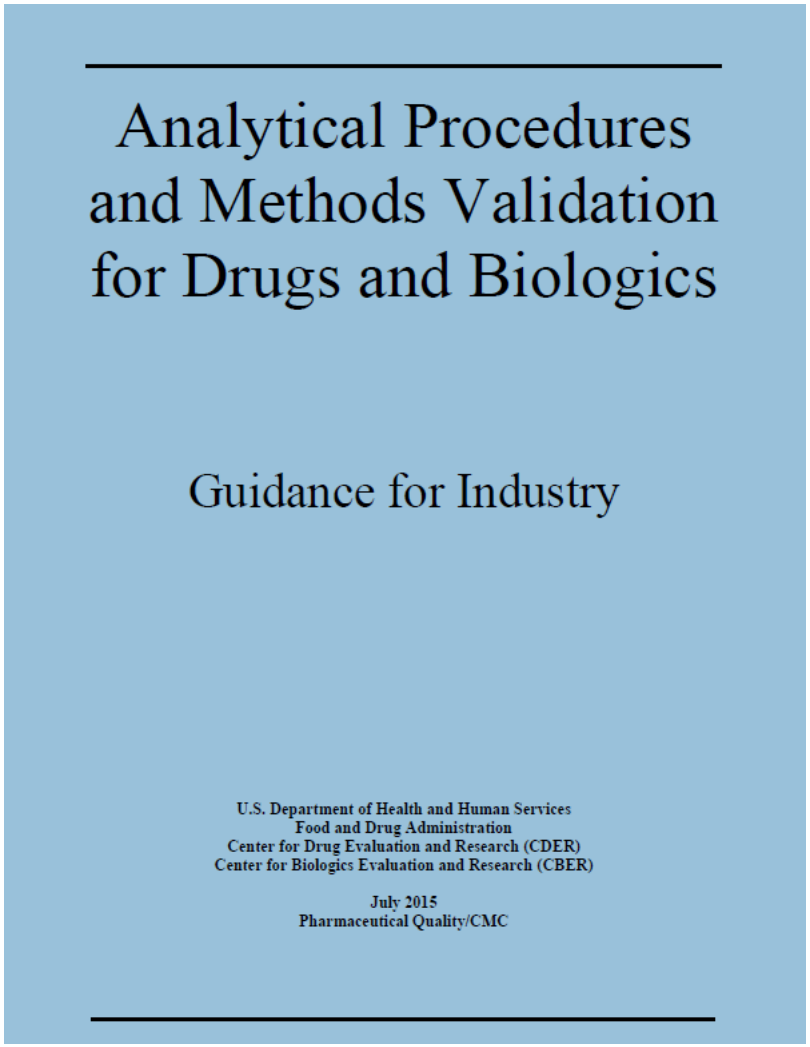
- **Assessing testing: Method Verification Program**
- Improving understanding: ADF Research

FDA Methods Verification



Part of the approval process for NDAs and ANDAs may include:

- FDA laboratory assessment to determine whether the analytical procedures are acceptable for **quality control** and suitable for **regulatory purposes**
- FDA laboratory will send a request detailing samples and supplies needed for verification
  - product samples, standards, critical reagents, material safety data sheets, and supplies
- Laboratory results and comments will be forwarded from the FDA laboratory to the product quality reviewer

➢ Similar wording available in 21 CFR 314.50(e)

Method Verification Program

- Addresses reviewer concerns of analytical method adequacy
- Verifications are performed for:
  - New Molecular Entities
  - Novel analytical methods or products
  - Critical methods for specific drug delivery systems
  - Methods for critical attributes (i.e. **abuse deterrent formulations**)
  - Methods that cause concern for adequacy
- Methods are assessed for their suitability for regulatory and quality control purposes

ADF Assessment as part of Method Verifications

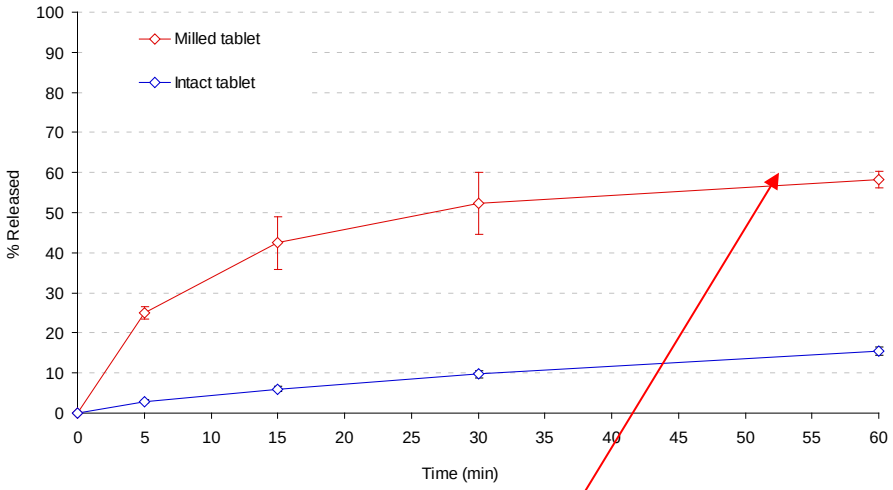
- Do the methods provided adequately evaluate the drug substance, drug product and possible impurities/degradants?
- Do the methods provide stability information for the drug substance and drug product?
- Do the methods clearly define the ability of the formulation to prevent abuse?
  - Laboratory Manipulation and Extraction Studies (Category 1)
    - Sample manipulation for inhalation or injection (crushing, splitting, grinding, heating, etc.)
    - Extraction and solubility studies (various solvents)
    - Effects of time, temperature, pH, and agitation on solvent extraction
    - Particle size distribution
    - Syringeability

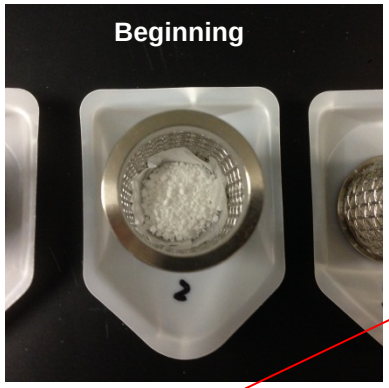
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf

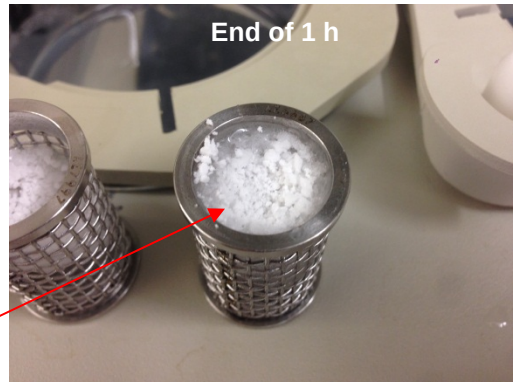
Physical Strength (against grinding)

Dissolution Challenges

- QC release methods may not be suitable to assess drug release after manipulation
  - Manipulated tablets (powders) float (USP 1&2) and prevent auto-sampling (USP 2)
  - Variations and incomplete release (USP 1&2)







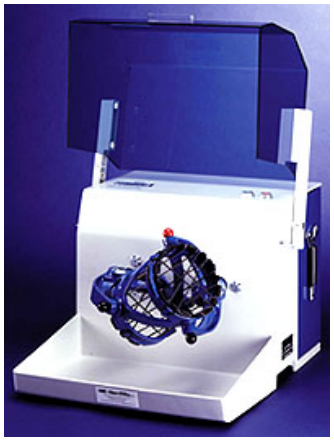
Rapid gelation of PEO prevents further water penetration and delay drug release/extraction

Outline

- Encouraging new technologies: Emerging Technologies Team
- Assessing testing: Method Verification Program
- **Improving understanding: ADF Research**
  - **Contract**
  - **FDA Laboratory work**

Ability to assess affect of formulation variables on ADF

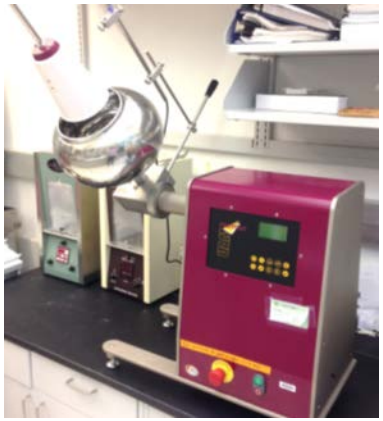
Turbula Blender



Mini Press

Twin-screw Hotmelt Extruder

UAM Coater/Mixer



High Shear Granulator

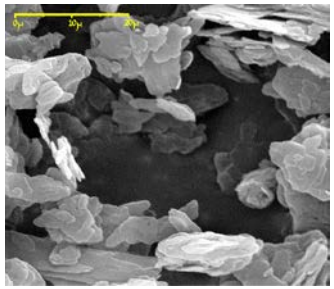
Fluid-bed

Ability for Advanced Material Characterization

Polymorphism

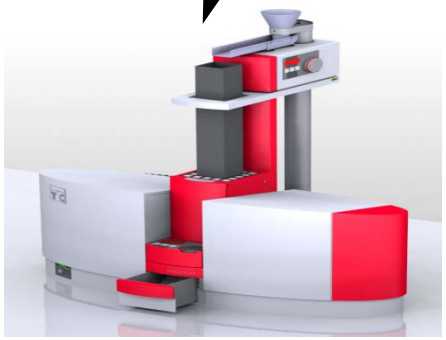
Moisture content

Surface Area



Bulk/Tapped Density

Moisture adsorption isotherm

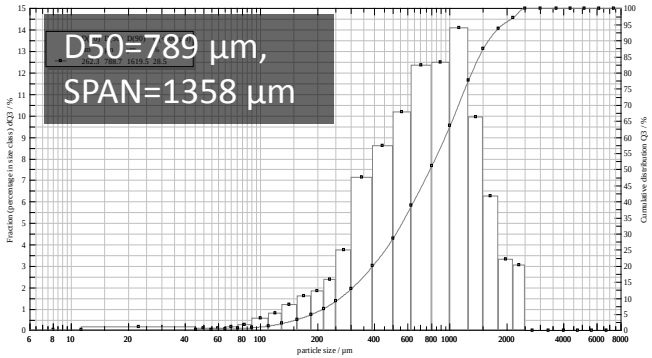


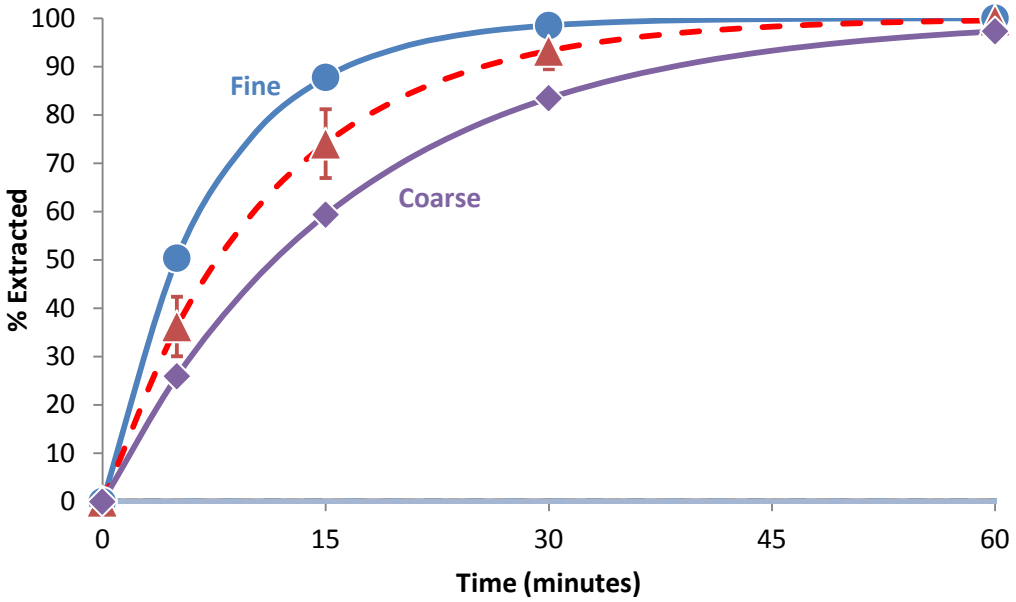
Particle Size

Rheology

Statistical Challenges

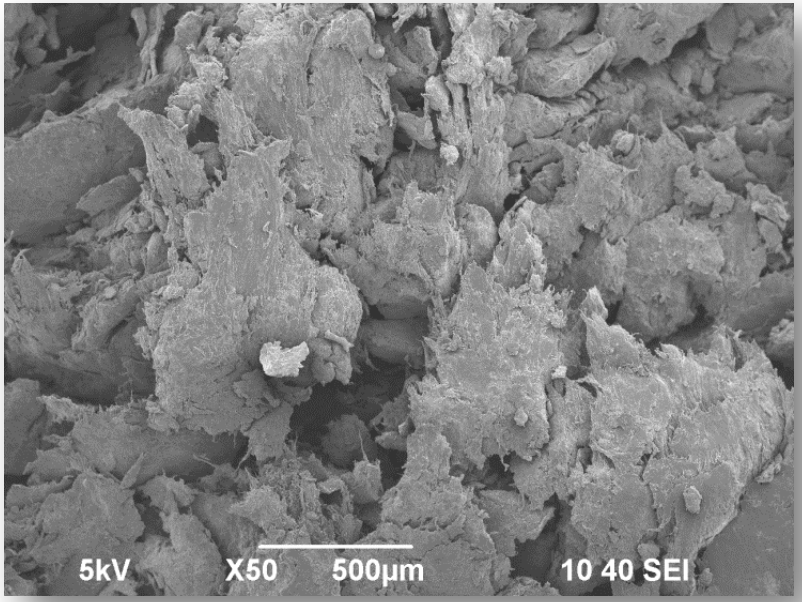
- Sources of variability
- Sampling procedures may impact statistical analysis



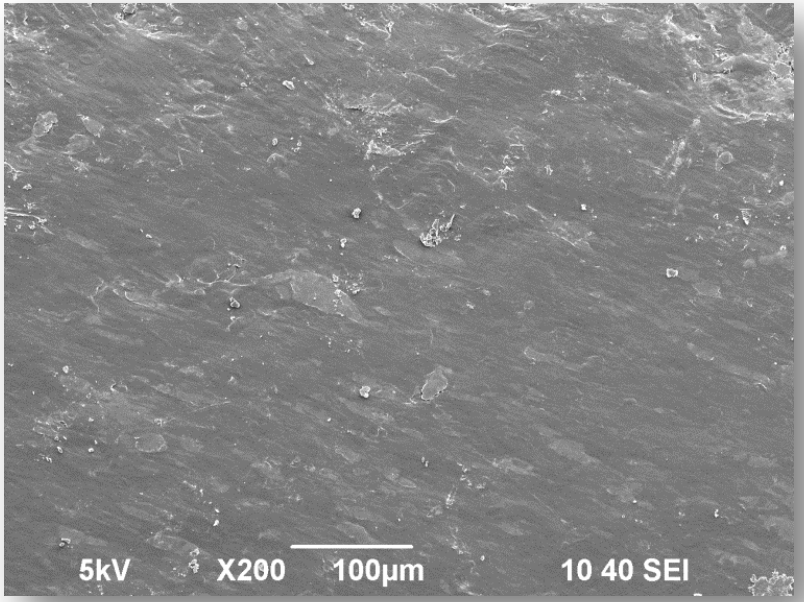


Understanding the Fundamentals…

Method 1
Tablet formed from Material A



Method 2
Tablet formed from Material B



Higher porosity observed in tablets formed from Material A leads to significant capillary action of the solvent. Additionally, due to the elastic nature of the Material A, tablets do not have sufficient physical strength as compared with the ones formed from Material B.

FDA generated data (not published), using sotalol as surrogate

Summary

- ADF features can be defeated with varying degrees of difficulty; and hence iterative improvements on the existing ADF technology and/or more innovative designs will continue to be needed
- To support the development of ADF products, FDA has committed resources for research on manufacturing science and in vitro standards in FDA and National Institute of Pharmaceutical Technology and Education (NIPTE) laboratories, and put the ETT in place to ensure predictability of review and inspection for new technologies
- Appropriate in-vitro assessment of ADF is critical: it should be based on knowledge of the formulation and the manufacturing process
- ADF features and testing should be applicable to the life cycle of the product, and FDA will continue to verify sponsor methods and challenge the ADF performance characteristics of products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