An Overview of Complex Drug Substances and Complex Formulations-A Quality Perspective

Katherine Tyner, PhD
Associate Director for Science (Acting)
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Disclaimer

This talk reflects the views of the author and should not be construed to represent FDA's views or policies. The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services.

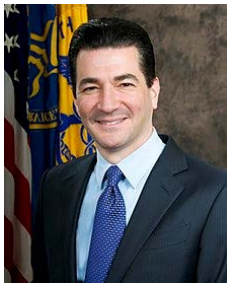
Outline

- Background to Complex Products and Quality
- Quality Considerations for Complex Drug Substances
- Quality Considerations for Complex Formulations
- Analytical and Emerging Technologies
- Helpful Tips

Complex Generics

As part of the FDA's efforts to promote drug competition and patient access, we've advanced many policies aimed at making it more efficient to bring generic competition to the market. We've been especially focused on a category of medicines known as complex drugs. These are drugs that, by nature of their formulation, delivery systems or the complexity of their active ingredients, for example, are harder to "genericize" under traditional approaches. As a result, these complex drugs often face less competition.

- Dr. Scott Gottlieb



Complex Products

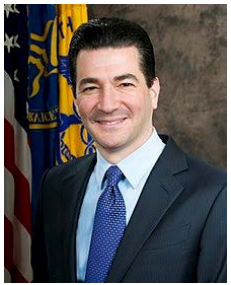
COMPLEX of:	Complex Product Type	Drug Products
Active Pharmaceutical Ingredients (APIs)	peptides, complex mixtures of APIs, naturally sourced ingredients	Glatiramer acetate injection, Sevelamer carbonate tablet/powder, Conjugated Estrogens tablet
Formulations/Dosage Forms	liposomes, colloids, transdermals, extended-release injectables, implantables	Doxorubicin HCl Liposome injection, Cyclosporin ophthalmic emulsion, Etonogestrel implant, Lidocaine patch
Routes of Delivery	locally acting drugs such as dermatological products, complex ophthalmological products	Acyclovir topical cream/ointment, Prednisolone acetate ophthalmic suspension
Drug-Device Combinations	dry powder inhalers, metered dose inhalers, nasal sprays, auto-injectors	Mometasone furoate nasal spray, Fluticasone propionate and Salmeterol inhalation powder, Epinephrine auto-injector
Other products	complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement	Abuse deterrent opioid formulations

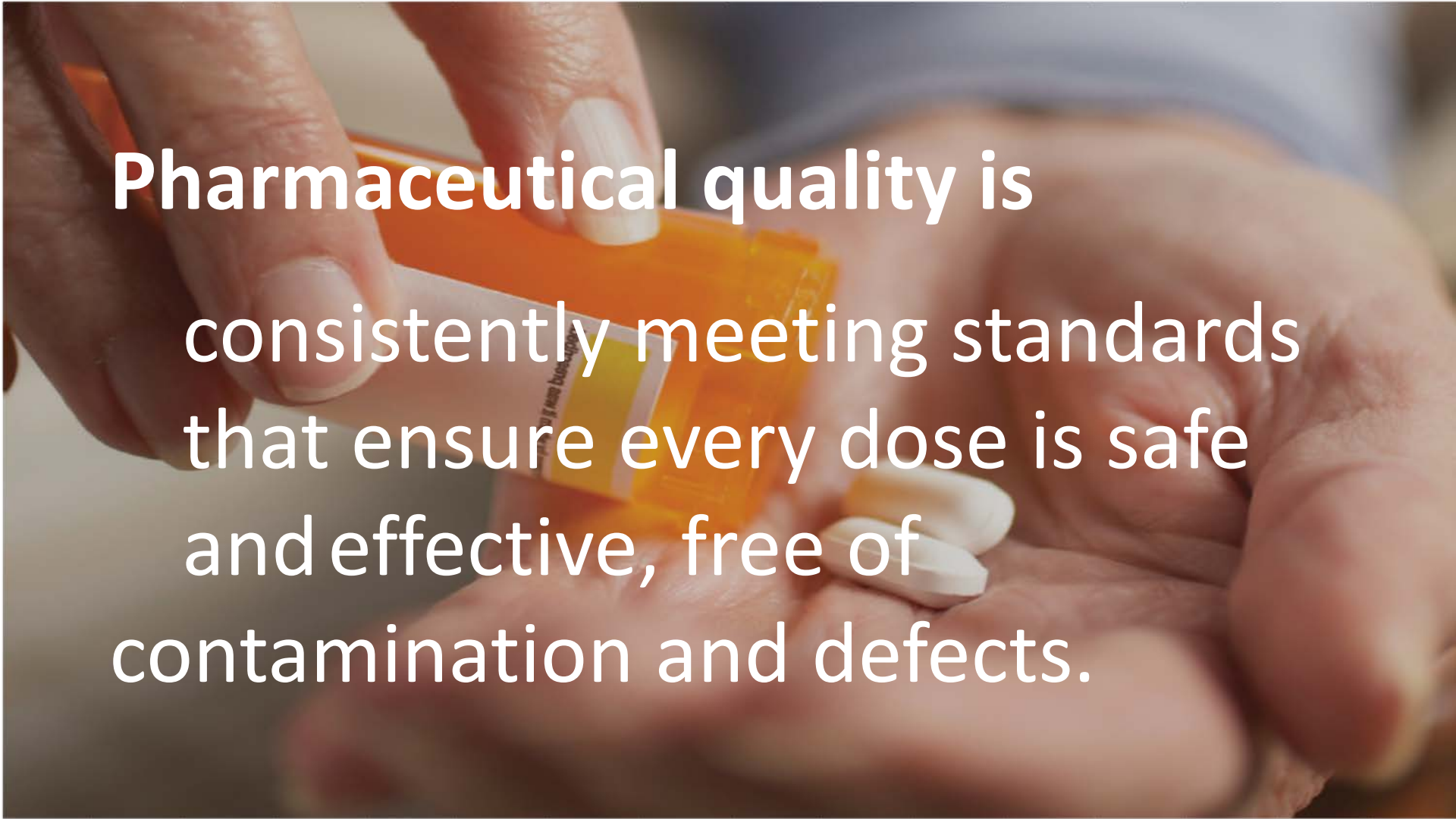
Generic Drug User Fee Amendments (GDUFA) II Commitment Letter:
https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

Complex Generics

Our aim is to enhance transparency, provide greater clarity and scientific guidance for generic drug developers, and support the availability of high-quality, safe and effective generic medicines.

- Dr. Scott Gottlieb




Pharmaceutical quality is
consistently meeting standards that ensure every dose is safe and effective, free of contamination and defects.

Quality Is a Shared Responsibility

- **FDA's Goal:** Ensure industry can manufacture products that consistently safely deliver their intended benefit to the patient.

- **Industry:** Understand and manage their manufacturing processes and expand the product/process body of knowledge to facilitate continual improvement (ICH Q10).

A Generic Drug Submitted to FDA for Approval Must Demonstrate:

- The generic drug is “pharmaceutically equivalent” to the brand
- The manufacturer is capable of making the drug correctly
- The manufacturer is capable of making the drug consistently
- The “active ingredient” is the same as that of the brand
- The right amount of the active ingredient gets to the place in the body where it has effect
- The "inactive" ingredients of the drug are safe
- The drug does not break down over time
- The container in which the drug will be shipped and sold is appropriate.
- The label is the same as the brand-name drug’s label
- Relevant patents or legal exclusivities are expired

https://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/UCM510852.pdf

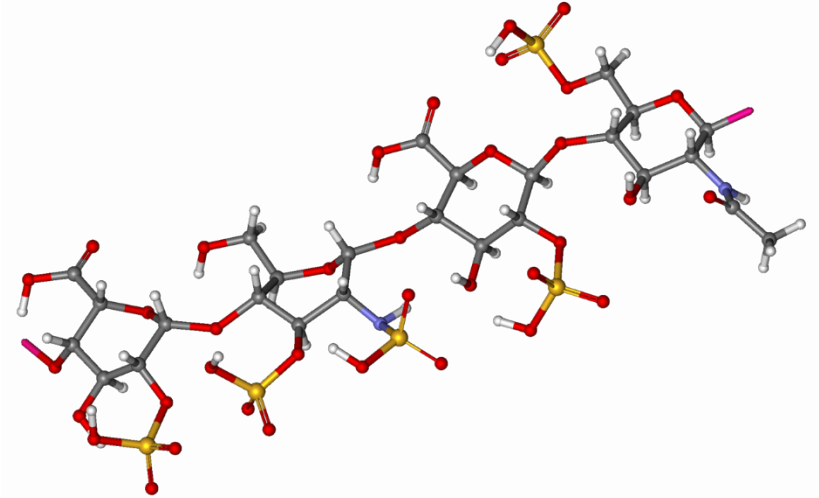
Complex Drug Products

- Present challenges for demonstrating product equivalence

- Present challenges for demonstrating product and process control

Quality Considerations for Complex Drug Substances

https://en.wikipedia.org/wiki/Crofelemer#/media/File:Sangre_de_Grado.jpg



https://en.wikipedia.org/wiki/Enoxaparin_sodium#/media/File:Enoxaparin_sodium_ball-and-stick.png

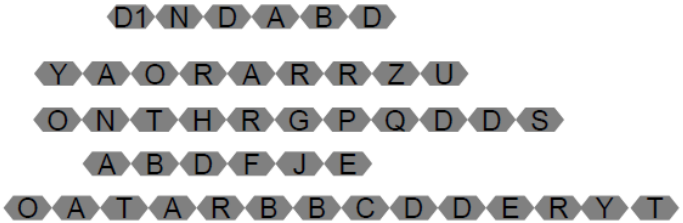
Complex Active Ingredients

- Sameness of the active ingredient typically determined via four elements:
  - Fundamental manufacturing scheme
  - Physicochemical properties
  - Structural signatures
  - Confirmatory assays

- Examples
  - Complex mixtures of APIs
  - Naturally sourced ingredients

Lovenox (Enoxaparin Sodium)

An anticoagulant drug used to prevent blood clots known as deep vein thrombosis

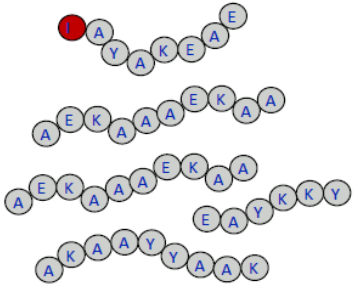


Highly heterogeneous mixture of disaccharides constitute the building bocks of the chain

Generics Approved as ANDAs
Sandoz (2010), Amphastar (2011), Teva (2014)

Copaxone (Glatiramer Acetate)

Reduce the frequency of relapses in patients with relapsing-remitting multiple sclerosis



Highly heterogeneous mixture of peptide copolymers containing four amino acids (Glu, Lys, Ala, Tyr) in a defined molar ratio

Generic Approved as ANDA
Sandoz (2015)

Slide Credit:
Andre Raw

Enoxaparin Sodium

Physicochemical Properties

Heparin Starting Material and Mode of Depolymerization

Disaccharide Mapping
Fragment Mapping
Oligosaccharide Sequencing

Biochemical/Biological Assays

In-Vivo Pharmacodynamic Profile

Nature Biotechnology, 31, 220-226 (2013)

FDA Letter to Covington & Burling (Docket FDA-2003-P-0273)

Glatiramer Acetate

Fundamental Reaction Scheme

Physicochemical Properties, Including AA Composition

Structural Signatures of Polymerization/Depolymerization

Biological Assays

FDA Letter to Teva Pharmaceuticals (Docket FDA-2015-P-1050)

Slide Credit:
Andre Raw

Analytical Methods

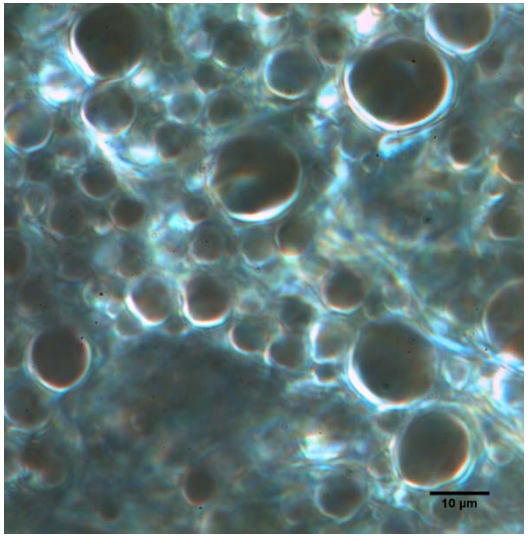
Summary of the analytical techniques applied to characterize crofelemer.

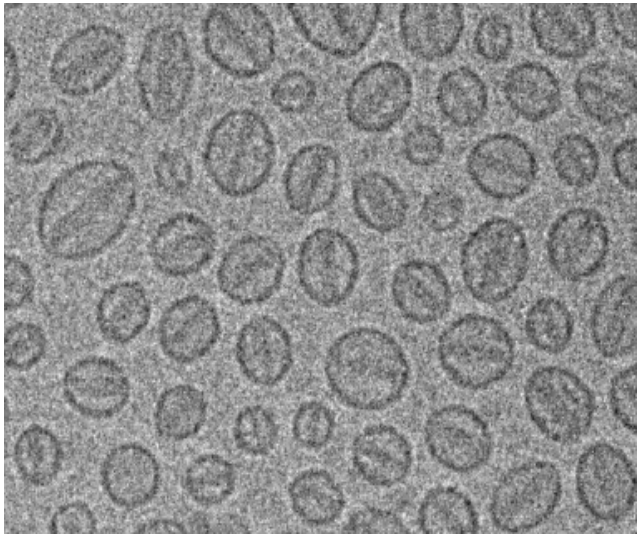
Type	Critical Quality Attributes	Assays
Physical and Composition	Mass Recovery	UV-Vis
	Compound ID and Purity	^{1}H NMR
		^{13}C NMR
	Average Degree of Polymerization	^{13}C NMR
		SEC-DAD
	MW Distribution	SEC-DAD
	Composition	HILIC HPLC-DAD
		FTIR
		Q-ToF
	Ratio of Procyanidins to Prodelphinidins	Thiolysis-LC-MS
	Higher-Order Structure	Circular Dichroism
Chemical Assays	Oxidation	C18 HPLC-UV
		QToF
Biological Activity	Cl^- Channel Inhibition	Fluorescent Assay in T84 Intestinal Cell Monolayer

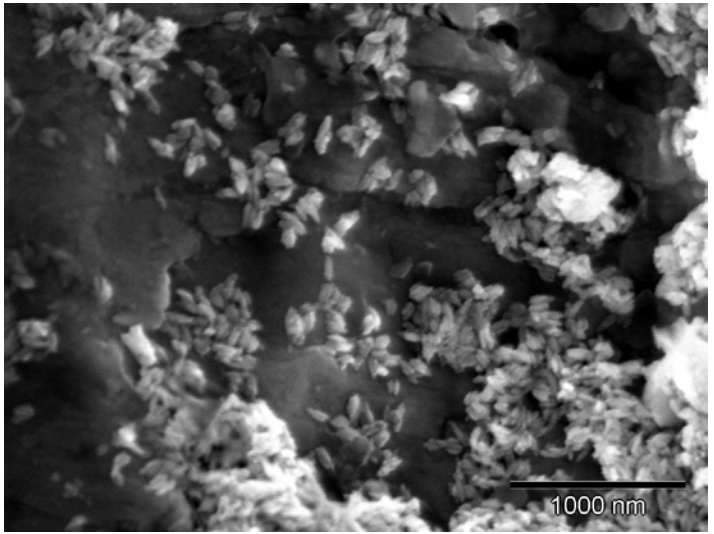
https://www.ncbi.nlm.nih.gov/pubmed/28743606

1U01FD005285-01

Quality Considerations for Complex Formulations







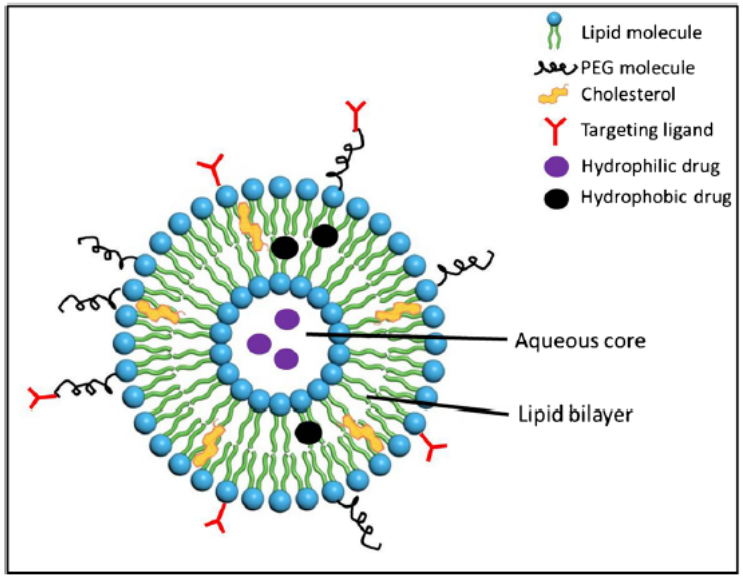
Complex Formulations

- Sameness of the formulation structure is typically determined via
  - Physicochemical measurements
  - In vitro assay (e.g. release or absorption)

- Examples
  - Liposomes
  - Ophthalmic emulsions

Case Study—Complex Formulation

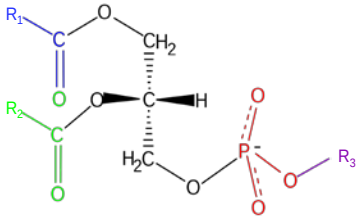
- Liposome: microvesicle composed of a bilayer and/or a concentric series of multiple bilayers separated by aqueous compartments formed by amphipathic molecules such as phospholipids that enclose a central aqueous compartment
- Liposome Drug Product: a drug product in which the active pharmaceutical ingredient (API) is contained in liposomes
- There are 12 FDA approved drug products containing liposomes
  - Commonly used to alter the biodistribution of an API

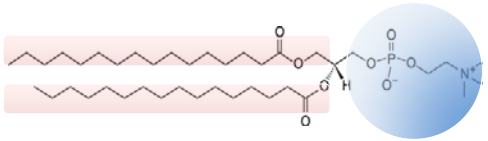


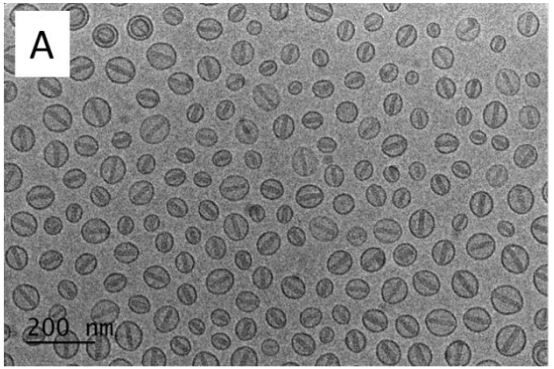
Draft Guidance for Industry. Liposome drug products, chemistry, manufacturing, and controls; human pharmacokinetics and bioavailability; and labeling documentation. U.S. Food and Drug Administration.
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070570.pdf (2015)

Liposome Drug Products are Complex Formulations

- Components of the liposome
  - Lipids
  - Other excipients
- Physical and chemical stability
  - Chemical degradation of lipids may form lysolipids
  - Liposome fusion
- In vitro release
  - Discriminate between acceptable and non-acceptable batches of the drug product
- Complex physicochemical testing

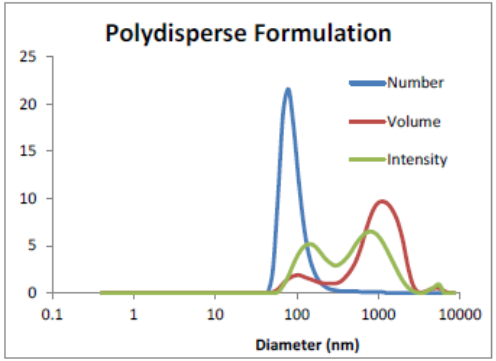


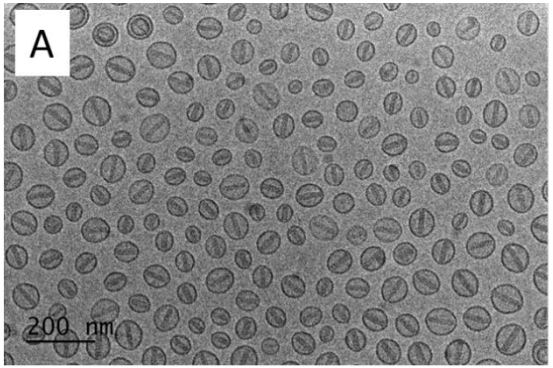




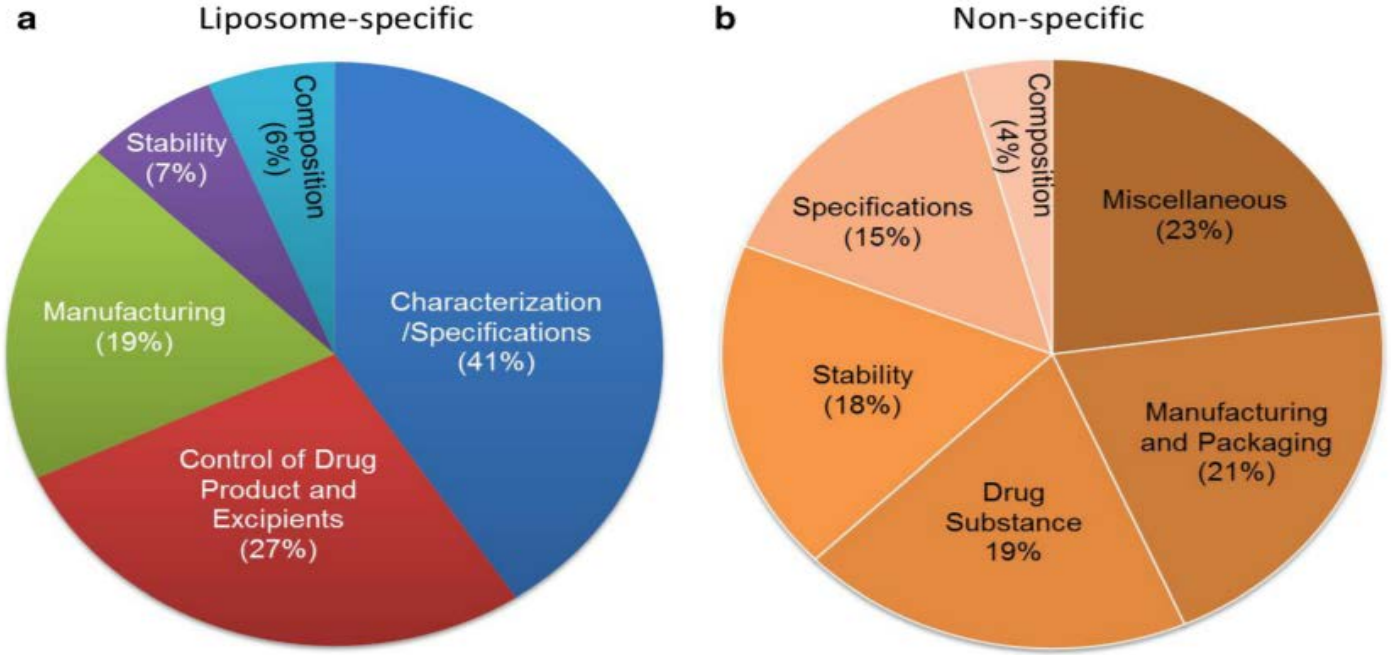
Liposome Drug Products Involve Complex Physicochemical Testing

- Suitable analytical methods need be employed to properly characterize liposome drug products, which can often be difficult given the complexity of liposome drug product formulations
- Use of inappropriate methods could produce false results, thereby calling into question data reliability and, hence, product quality
- Particle size is a critical quality attribute for liposome drug products
  - Impacts ADME, stability, drug release, etc.
  - Multiple techniques, such as dynamic light scattering (DLS) and electron microscopy (EM), are usually recommended to thoroughly characterize particle size and size distribution
- Size is not the only attribute that needs to be characterized
  - Morphology, drug loading, drug leakage etc.





Summary of Quality Issues for Liposome Drug Products



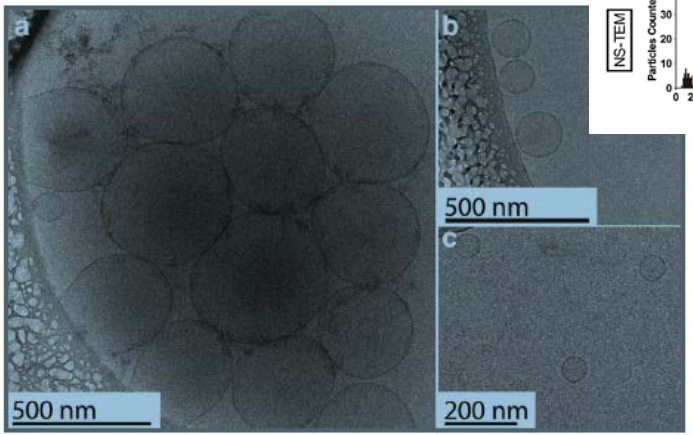
Challenges

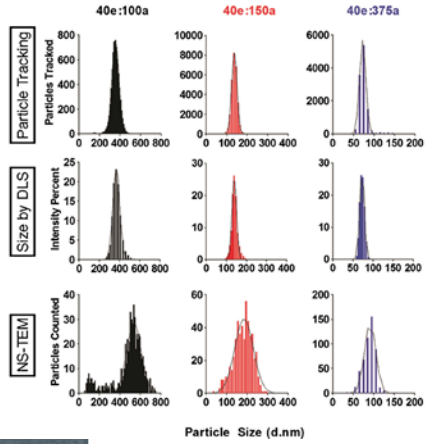
(1) Identification and appropriate characterization of critical quality attributes

(2) Suitable control strategies

Kapoor M. et al. AAPS J 19(3) 2017

Analytical Methods





Manufacturing method	Manufacturing step[a]	In-process controls
Passive loading	Hydration of thin lipid film	Visual inspection for complete lipid dissolution, residual solvents, lamellarity, pH
	Ethanol injection	Visual inspection for clarity, lamellarity, pH
	Homogenization/ extrusion	Particle size, PSD, extrusion membrane integrity, lamellarity, assay, individual lipid composition change
	Diafiltration	Solvent content, particle size, PSD, filter integrity, % drug encapsulation, % free drug, pH, individual lipid composition change
	Aseptic filtration	Bioburden, filter integrity, pH, lamellarity, individual lipid composition change
	Lyophilization	Fill weight and moisture content of final powder
	Capping and sealing	Visual inspection, fill weight test, leak test, release testing (including sterility)
Active loading	Concentration adjustment post drug loading	Particle size, PSD, % drug encapsulation, % free drug, assay, pH
Active loading before administration	After mixing empty liposomes with drug solution	Release testing (particle size, PSD, % drug encapsulation, % free drug, assay, pH, residual solvents, heavy metals, osmolality, lamellarity)
Double emulsion	First emulsification	Particle size, PSD, bioburden, conductivity
	Second emulsification	Free drug, particle size, PSD, pH

PSD particle size distribution
[a] Some steps in passive loading are also applicable to other manufacturing processes

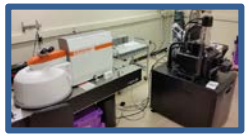
https://www.ncbi.nlm.nih.gov/pubmed/26428671

https://www.ncbi.nlm.nih.gov/pubmed/28160164

Analytical and Emerging Technology

Mass Spec

Continuous Manufacturing



SEM

Compression Machine

NMR

Gas Chromatography

XRPD

3D Printing

High Performance Liquid Chromatography

Particle Sizing

Dissolution

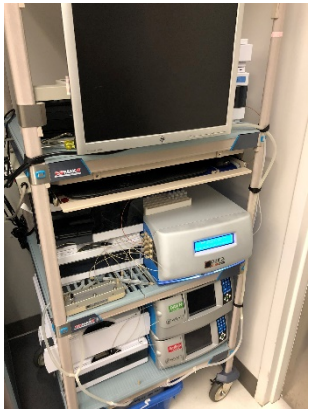
Slide Credit:
OTR

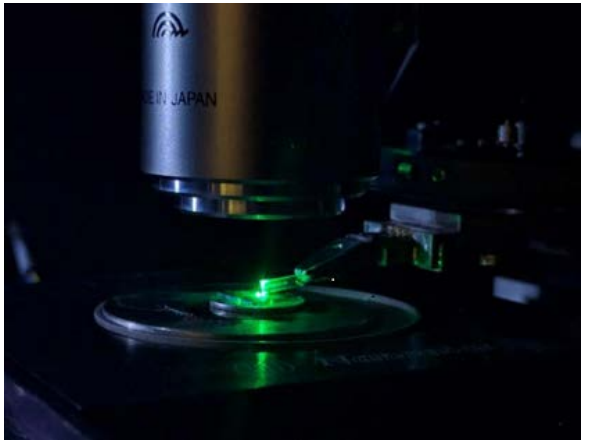
Analytical and Emerging Technology

- The properties, characterization, and methods of characterization may be different than what is typical for other drug products
- These challenges do not reduce the adequacy and standard requirements of the analytical methods
  - Guidance for Industry: Analytical Procedures and Methods Validation for Drugs and Biologics
- Instrumentation and methodology for characterization of complex drug products is an evolving area
  - Appropriate validation and justification of the method is critical
- It is often necessary to utilize multiple complementary or orthogonal techniques
  - Different methods can provide various key aspects of an attribute and thus provide a more complete characterization picture of the drug product

Analytical and Emerging Technology

- Challenging vs impossible
- Difficult vs infeasible
- Rapid advancements in analytical techniques foster the development of complex products





Picture Credit: Xiaoming Xu and Erin Wood

Helpful Tips

Consensus-Based Standards

- Development of technical voluntary consensus standards
  - Performance characteristics of dosage forms
  - Testing methodologies
  - Scientific protocols

- CDER participates in committees of several standards setting organizations
  - ASTM International
  - International Organization for Standardization

- CDER Standards Recognition Program
  - https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm631269.pdf

The Pre-ANDA Program

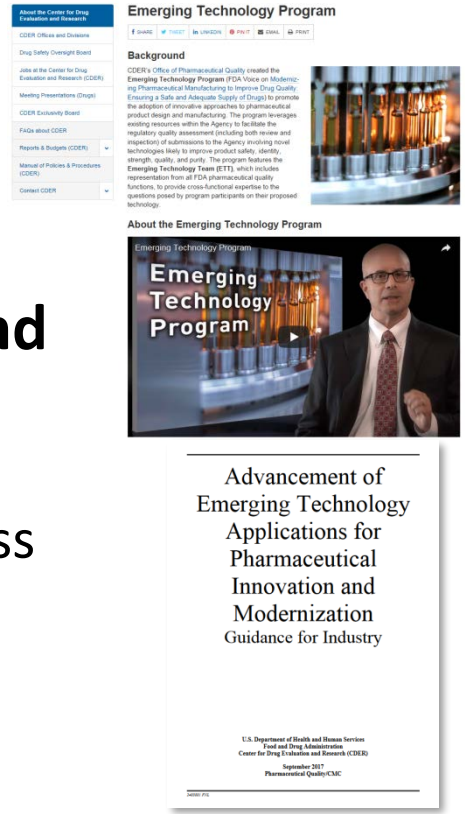
- To clarify regulatory expectations for prospective applicants early in product development

- Assist applicants to develop more complete submissions
  - Product development meeting
  - Pre-submission meeting
  - Mid-review cycle meeting

- Contact: PreANDAhelp@fda.hhs.gov

Emerging Technology Program

- Supports industry's development and implementation of innovative approaches in **pharmaceutical design and manufacturing**
- Identifies and **resolves potential scientific and policy issues** related to new approaches
  - Enabled the approval of the first switch from batch to continuous manufacturing (CM) process for an approved drug
- A website and Guidance for Industry are posted



Take-Aways

- There are many forms of complexity within drug products
- Complexity in drug products can translate to complexity in identifying, establishing, and maintaining quality
- A suite of analytical techniques is often needed in order to adequately demonstrate product quality
- There are multiple ways to interact with FDA during the development of complex products


FDA
U.S. FOOD & DRUG
ADMINISTRATION