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

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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

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

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

Complex Drug Products

• Present challenges for demonstrating product equivalence

• Present challenges for demonstrating product and process control
Quality Considerations for Complex Drug Substances


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

Copaxone
(Glatiramer Acetate)

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

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

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

Generics Approved as ANDAs

Generic Approved as ANDA
Sandoz (2015)
**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)*
Analytical Methods

Summary of the analytical techniques applied to characterize croflemer.

<table>
<thead>
<tr>
<th>Type</th>
<th>Critical Quality Attributes</th>
<th>Assays</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical and Composition</td>
<td>Mass Recovery</td>
<td>UV-Vis</td>
</tr>
<tr>
<td></td>
<td>Compound ID and Purity</td>
<td>$^1$H NMR</td>
</tr>
<tr>
<td></td>
<td>Average Degree of Polymerization</td>
<td>$^{13}$C NMR</td>
</tr>
<tr>
<td></td>
<td>MW Distribution</td>
<td>SEC-DAD</td>
</tr>
<tr>
<td></td>
<td>Composition</td>
<td>FTIR</td>
</tr>
<tr>
<td></td>
<td>Ratio of Procyanidins to Prodelphinidins</td>
<td>Q-ToF</td>
</tr>
<tr>
<td></td>
<td>Higher-Order Structure</td>
<td>Thiolyis-LC-MS</td>
</tr>
<tr>
<td>Chemical Assays</td>
<td>Oxidation</td>
<td>C18 HPLC-UV</td>
</tr>
<tr>
<td>Biological Activity</td>
<td>$Cl^-$ Channel Inhibition</td>
<td>Fluorescent Assay in T84 Intestinal Cell Monolayer</td>
</tr>
</tbody>
</table>
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.

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

HHSF223201310117C

Manufacturing step

- 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/extraction
  - Particle size, PSD, extrusion membrane integrity, lamellarity, assay, individual lipid composition change
- Dialfiltration
  - Solvent content, particle size, PSD, filter integrity, % drug encapsulation, % free drug, pH, individual lipid composition change
- Aseptic filtration
  - Bio-burden, filter integrity, pH, lamellarity, individual lipid composition change
- Lyophilization
  - Fill weight and moisture content of final powders
- 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
  - 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, bio-burden, conductivity
  - Free drug, particle size, PSD, pH

PSD particle size distribution

Some steps in passive loading are also applicable to other manufacturing processes

Analytical and Emerging Technology

- Mass Spec
- SEM
- Continuous Manufacturing
- Compression Machine
- NMR
- XRPD
- Gas Chromatography
- High Performance Liquid Chromatography
- Particle Sizing
- Dissolution
- 3D Printing

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
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