USP Initiatives for Complex Generics – Documentary and Physical Standards:

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USP - General Chapters and Complex Generics

11th September 2024

200 usp
The standard of trust

Complex Products (FDA definition):

Complex product category:	Definition:	Examples:
Complex API	Peptides less than 40 amino acid units, complex mixtures, natural source products, oligonucleotides, metal complex products	Glatiramer acetate, Ferumoxytol, Colesevelam HCl
Complex Formulations / Dosage Forms	Any non-oral complex formulation / dosage form product where there are often two or more discrete states of matter within the formulation. Parenteral drug products containing nanomaterials, long-acting injectables, liposomes, microspheres, emulsions, nano suspensions	Doxorubicin, Leuprolide Depot, Lanreotide, Patisiran, Paclitaxel, etc.,
Complex Routes of Delivery	Locally acting drugs such as dermatological products and complex ophthalmic products	Acyclovir cream, Cyclosporine emulsion
Drug-Device Combination Products	A device is used for the drug delivery, such as dry powder inhalers, nasal sprays, transdermal systems, etc.,	Mometasone nasal spray, Epinephrine injection, pre-filled syringes, etc.,
Other Products	Complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement	Abuse deterrent opioid formulations

USP Current CGx Documentary Standards:

Monographs:

Category:	Number of Official Monographs:
Inhalation	24
Mucosal	22
Ophthalmic	47
Topical	199
Transdermal	4
Injectable	24
Device	10

General Chapters:

Category:	Chapter names / numbers:
Complex API:	Iron Dextran & Iron Sucrose
Complex route of delivery:	<3>, <4>, <104>, <1004>, <603>, <724>, <771>,<789>, <1771>, <1724>
Complex dosage forms:	<1>, <110>, <787>, <788>, <790>, <1788>, <1790>, <1001>
Complex drug-device combination products:	<5>, <601>, <602>, <604>, <771>, <1601>, <1602>, <1603>, <1604>, <861>, <871>, <881>
Other products:	None

Complex Generics - USP Initiatives:

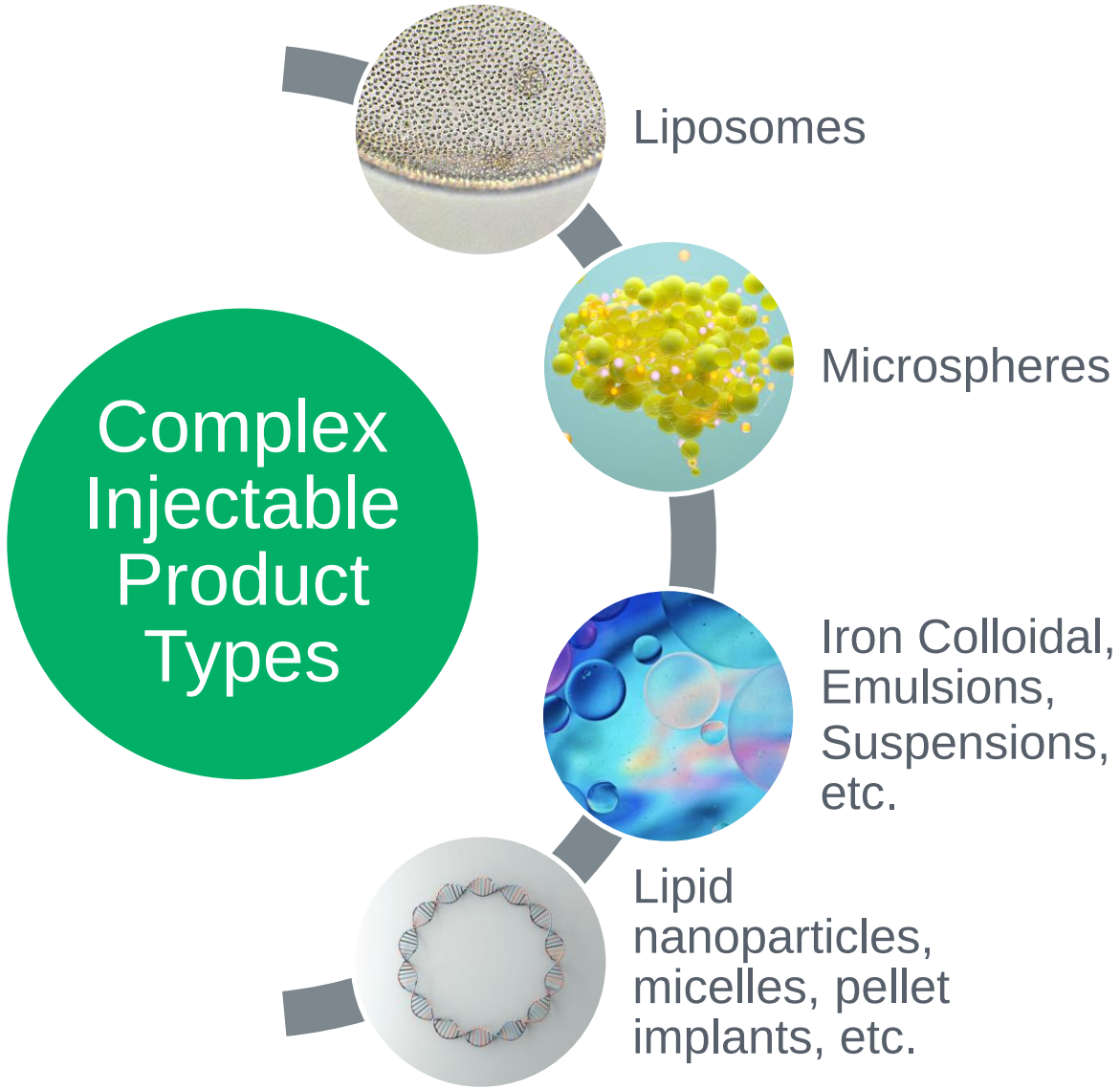
- Complex Generics Program Unit (PUT) – newly created
- Stakeholder Engagements:
  - CGx Qualitative Survey (2021)
  - CGx Quantitative Survey (2022)
  - Complex Injectable Open Forum (2023)
  - CGx Industry Visit (2023)
- Comprehensive Gap Analysis
  - USP Expert Panel created (New advancements in product performance testing - NAPPT)
  - Gap analysis for all complex product performance tests
  - Published several (7) stimuli articles to obtain feedback
  - Partnered with AAPS to present (webinars) for additional industry feedback
- USP committed to continuing to provide solutions for the complex generics industry

Complex Generics – Stakeholder Feedback:

- Complex Injectables:
  - Lack of guidance (for bioequivalence and approvals)
  - Lack of physical characterization methods (microspheres, iron colloidals, etc.,)
  - Lack of compendial dissolution methods (lack of monographs)
  - Need of physical reference standards (complex excipients, MW & calibration standards, etc.,)
- Extractables & Leachables for CGx products:
  - System suitability standards (single or mixes)
  - E&L reference standards
  - E&L guidance on testing – when, what and how
  - Searchable / digital library for quick identification of unknowns
  - Training & educational courses related to E&L

Complex Injectables:

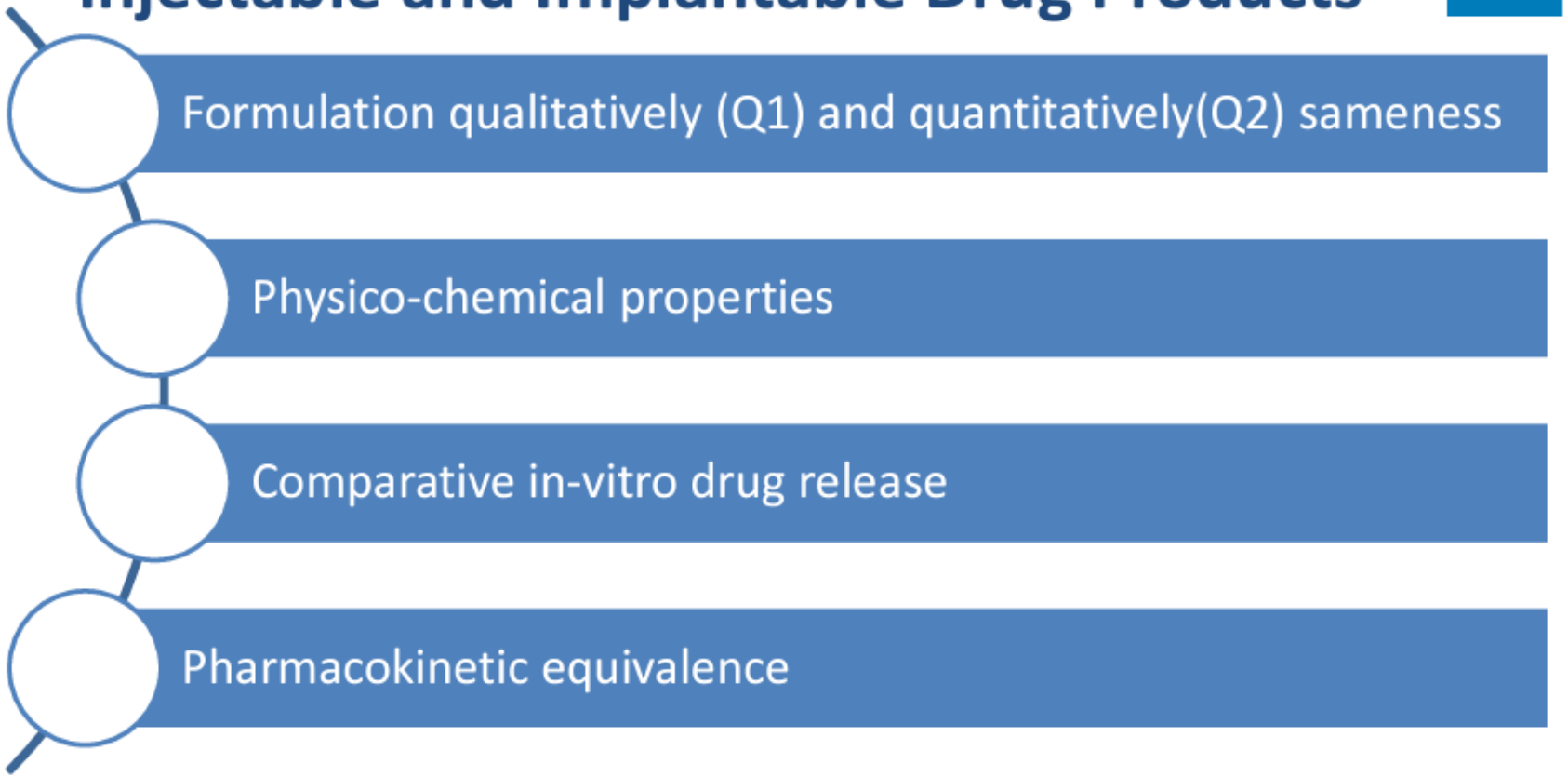
Complex Injectables



- **Advantages:**
  - Small molecules – both hydrophobic and hydrophilic
  - Biologics – Proteins, plasmids, nucleic acids, and gene therapy drugs
  - Long acting (up to several months) – patient compliance
  - Controlled release - reduced toxicity
  - Targeted delivery – improved efficacy

Complex Generic Product Development:

Equivalence Demonstration of Complex Injectable and Implantable Drug Products



Challenges in Developing a Complex Injectable Generics:

- Limited reverse characterization data available
- Lack of in vivo / in vitro correlation tools (IVIVC)
- Lack of standard compendial methods for in vitro release (dissolution)
- Complex characterization methods, ex use of SEC-MALS-4D for MW determination
- Use of complex excipients (PLGA, PLA, Phospholipids, etc.,) and their characterization methods
- Proprietary technologies & methods
- Challenges with manufacturing, scale-up and storage
- Expensive clinical trials
- Limited expertise
- Dedicated sterile facilities
- RLD variability and non-available in some cases

New USP CGx General Chapters (Complex Injectables & Drug-Device Combination Products):

- <1155> Iron Colloidal Formulations – Characterization Methods.
  - General Chapter Prospectus was posted on April 26th, 2024.
  - Expert panel formed – August 2024.
  - Chapter development in progress.
- <1156> Microspheres – Product Quality and Performance Tests.
  - General chapter Prospectus was posted on April 26th, 2024.
  - Expert panel formed – August 2024.
  - Chapter development in progress.
- <1157> Drug-Device Combination Products – Product Quality Tests.
  - General Chapter Prospectus was posted on May 18th, 2024.
  - Classification of DDCP, define types of devices (PFS, DES, DCB, etc.,), and their quality tests.
  - Joint Sub-Committee is currently working on.

New Physical Standards to Support CGx Products:

- Complex Excipients:
  - PLGA Polymers (for microsphere products)
    - 14 new standards being introduced
    - Technical Guide is in development
  - Phospholipids (for liposomes and LNPs)
    - Evaluating several phospholipids and their impurities
    - New analytical methods will be developed (TLC vs HPLC)
    - Technical Guide will be developed
- Molecular weight standards:
  - Microsphere products
  - Iron colloidal products

Extractables & Leachables:

CGx products have a higher risk for E&Ls:

	Likelihood of interaction between packaging component and dosage form		
Degree of concern associated with Route of Administration	High	Medium	Low
Highest	Inhalation aerosols and solution Injections and injectable suspensions	Sterile powders Injection powders Inhalation powders	
High	Ophthalmic solutions and suspensions Transdermal ointments and patches Nasal aerosols and sprays		
Low	Topical solutions and suspensions Topical and lingual aerosols Oral solutions and suspensions	Topical powders Oral powders	Oral tablets Oral hard capsules Oral soft gelatin capsules

USP E&L System Suitability Standards Proposal:

- GC-MS
- Headspace GC-MS
- LC-MS, ESI with positive and negative ionization
- LC-MS, APCI with positive and negative ionization

  - Based on the stakeholder survey, discussion with E&L experts, decided to develop system suitability standards for the above 4 methods.
  - These 4 methods are required for a complete organic E&L studies for product approvals.

Why System Suitability Standards?

- The need:
  - Overwhelming (80%) feedback from the stakeholders
  - Currently USP chapters or other standards do not provide
  - Data accurate - How do you assess the quality? and acceptance criteria?
  - Multiple instruments, columns and locations – inconsistent results / data
- The Purpose:
  - Consistent data generated across multiple locations and labs
  - Confidence in results generated –may be less scrutiny by the regulators
  - Methods are sensitive to detect low level compounds – adding sensitivity compound to the mix
  - Address the column degradation, instrument fluctuations, analyst errors, and other issues
  - Mix of several chemical diversity compounds to address the column selectivity

USP E&L System Suitability Standards Development:

- **2021:**
  - Qualitative survey (N=14)
  - Initial feedback on the need for system suitability standards
- **2022:**
  - Quantitative survey (N=365)
  - Overwhelming support for USP to develop system suitability standards
  - Designed, planned and conducted lab work (with help from Nelson Labs)
- **2023:**
  - Stimuli article was published in USP PF 49(4), July 2023 issue
  - Received extensive comments from more than 80 individuals / entities
- **2024:**
  - Addressed all comments and revised the set of system suitability standards
  - Presented at E&L conference and requested participants to be part of a round robin study
  - 12 labs have accepted and in the process of completing the round robin study, including USP lab
  - USP will finalize the revised set of system suitability standards (end of Sep / Oct)
  - Publish second stimuli article, maybe in 2025

USP E&L: Other Ongoing Projects:

- **Develop individual standards for difficult to obtain compounds.**
  - 7 rubber oligomer standards were developed and released with a ‘Technical Guide”
- **Develop set of standards for material types- in progress** (tubing, filters, rubber stoppers, gaskets, IV bags, SUS, etc.,)
  - container closure systems
  - manufacturing components
- **Compound Library / Searchable Tools for quick unknown Identification**
  - Identified a GC-MS and LC-MS software system to create libraries of known compounds
  - Prototype development is complete
  - Final product launch (TBD)

Rubber Oligomer Technical Guide (Aug 2024)

Technical Guide

Extractable and Leachable Studies

Importance of evaluating rubber oligomers in drug products – the why, how and what

Background

In the pharmaceutical and biologics industries, the function of a packaging material is to adequately preserve the integrity of a drug product. However, sometimes the packaging of pharmaceutical dosages forms can compromise the most stable formulation. Hence, the potential adulteration of drug products by extractable and leachable (E&L) compounds that enter a drug product from a container, closure system, or disposable device is an area of increasing concern. The primary U.S.FDA regulation addressing drug product containers and closures, U.S. FDA 21 CFR 211.94(a), describes the basic requirements for drug product containers and closures.

Mechanism and chemistry of oligomers formation

Oligomers (i.e., short chains of butyl and halo butyl) are inherent to the raw rubber before and after manufacture of the elastomeric closures. Once the raw rubber is manufactured into the final component, the chemistry becomes more complex because of additives, fillers, vulcanization agents, processing aids, by-products of the curing reaction and other residuals.

It is proposed that these oligomers are formed during the polymerisation process by an intramolecular cyclization

New E&L General Chapters to support CGx Products:

- **New Chapter Proposals:**
  - <1664.2> Leachable chapter for Parenteral drug products.
  - <1664.3> Leachable chapter for Ophthalmic drug products.
  - <1664.4> Leachable chapter for Topical and Transdermal drug products.
  - <1664.5> Leachable chapter for Oral Dosage Forms

- **Existing chapters to support E&Ls:**
  - <1663> Assessment of extractables associated with pharmaceutical packaging / delivery systems.
  - <1664> Assessment of drug product leachables associated with pharmaceutical packaging / delivery systems.
  - <1665> Characterization and qualification of plastic components and systems used to manufacture pharmaceutical drug products and biopharmaceutical drug substances and products
  - <1664.1> Orally inhaled and nasal drug products (OINDPs).
  - <381> Elastomeric components in injectable pharmaceutical product packaging / delivery systems
  - Others (<87>, <88>, <665>, <661.1>, <661.2>, etc.,)

Thank You