USP Complex Generics – Research Needs Based Upon Industry Feedback:

Prabhakar Reddy, Ph. D.
Director, Pharmaceutical Sciences
General Chapters and Complex Generics

FDA GDUFA Meeting – May 20-21, 2024

Agenda

- **USP Complex Generics (CGx) updates to include**
  - Current CGx documentary standards
  - USP CGx Initiatives
  - Stakeholder CGx Engagement Activities
  - Research needs for CGx product development
  - USP proposals for new chapters to support CGx

USP Current CGx Documentary Standards:

Monographs:

Category:	Number of Official Monographs:
Inhalation	24
Mucosal	22
Ophthalmic	101
Topical	201
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

Qualitative & Quantitative Surveys:

Qualitative survey (2021):

- 14 qualified stakeholders with complex generics experience (6 countries).
- In-depth telephone interviews.
- Challenges:
  - Technical
    - Complex equipment and methods, lack of in-vitro dissolution methods
  - Manufacturing
    - Scale-up, missing expertise, customized equipment
  - Regulatory
    - Limited guidance, complex bioequivalence
  - Others
    - Availability of API and RLD

Quantitative survey (2022):

- N=356 (global pharma, biotech, CDMO/CROs)
- Online survey
- CGx Product Support Needs:
  - Complex Injectables / parenterals (83%)
  - Topical / Transdermal (54%), Ophthalmic (48%), Inhalation (41%)
- CGx challenge areas:
  - Bioequivalence, Q3 characterization
  - E&Ls (lack of guidance and standards)
  - Nanomaterials / complex excipients
  - Biorelevant dissolution media / methods
- USP Focus areas:
  - CGx documentary standards
  - Physical reference standards, educational courses

USP Complex Injectable Open Forum:

Technical and regulatory challenges for the development of complex injectable products – April 25th and 26th, 2023:

- ~900 registrations (more than 30 countries):
- Invited presentations:
  - Product development and scale-up challenges
  - Characterization of drug products and excipients
  - Innovations in in vitro release testing
  - Functional excipients like complex polymers, lipids, etc.
  - Regulatory perspectives for complex injectable products
- Goals:
  - Understand the development challenges (technical and regulatory)
  - To know the gaps in the USP and other compendia

Feedback / Discussions:

- CQAs
  - Q3 physical characterization methods are not defined to match with RLD
  - Specifications and types of tests are not available
- Dissolution
  - Use of non-compendial methods (rotating bottle apparatus)
  - Lack of accelerated IVRT methods
  - No guidance for complex dosage forms
- Manufacturing challenges:
  - Product specific and project specific, lack of expertise
  - Terminal sterilization, Scale-up issues
- General challenges:
  - Lack of USP chapters for microspheres, liposomes, & MW
  - Lack of knowledge sharing (proprietary)
  - Lack of physical standards (MW, PLGA etc.,)
  - Lack of bioequivalence tools (in silico, simulation etc.,)

USP CGx Team India Visit:

Summary:

- Dates: Sep 5th to Sep 15th, 2023
- Locations:
  - Hyderabad (10 companies)
  - Vadodara (3 companies)
  - Ahmedabad (3 companies)
  - Mumbai (3 companies)
- Expertise
  - CGx manufacturers (16)
  - PLGA polymer manufacturer (1)
  - CRO (in-vitro methods for CGx) (1)
  - CRO for CGx Physical materials (1)

Feedback / Insights:

- Most of the companies are working on Iron colloidal formulations, as well as Microspheres.
- Other product categories include transdermal, ophthalmics, nasal and drug-device combination products.
- Lack of USP chapter or guidance on use of multiple orthogonal methods for Iron colloidal as well as microspheres, and no defined acceptable ranges.
- Lack of compendial dissolution methods for complex formulations.
- PSGs are helping but need to be aligned with additional information or guidance from USP. Acceptable ranges between RLD and the generic product must be defined.
- PLGA characterization methods and standards are not available.
- Need MW standards & methods for Iron Colloidal as well as Microsphere (PLGA based) products.
- Better alignment between USP/FDA/ICH on impurity limits and acceptance criteria.
- Published methods using advanced analytical technologies are not available commercially.
- Acceptance criteria for Q1 and Q2 sameness for complex products should be wider, i.e., more than 5%.

Research Needs to Support CGx Products:

- Development and validation of analytical methods for the characterization of PLGA polymers.
- Q1 and Q2 sameness – correlation to Q3 and bioequivalence: Design and conduct lab studies for various complex products.
- Evaluation of commercially available orthogonal analytical methods for the physical characterization of the complex products.
- Development of sensitive and specific particle size characterization methods (laser diffraction, optical microscopy, electron microscopy and others) for various complex drug products (emulsions, suspensions, liposomes, and microspheres).
- Identification, validation, and standardization of novel methods to replace the current BE requirements for complex generic orally inhaled nasal drug products (OINDPs).
- Development of biorelevant IVIVC correlation models / studies for complex products.
- Establishing equivalent alternate excipients to be used for the complex injectable products (Liposomes, Microspheres, Emulsions & Suspensions).
- Identification, development, and validation of universal analytical methods for the characterization of Iron colloidal formulations.
- Development and validation of analytical methods for the accurate determination of molecular weights to support the development of complex products (microspheres and Iron colloidal products).

New USP Potential 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 will be formed.
- <1156> Microspheres – Product Quality and Performance Tests.
  - General chapter Prospectus was posted on April 26th, 2024.
  - Expert panel will be formed.
- <1157> Drug-Device Combination Products – Product Quality Tests.
  - General Chapter Prospectus in preparation.
  - Classification of DDCP, define types of devices (PFS, DES, DCB, etc.,).
  - Joint Sub-Committee is currently working on.

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.
  - <1664.3> Leachable chapter for Topical and Transdermal drug products.

- **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.
  - <1664.1> Orally inhaled and nasal drug products (OINDPs).

Questions

The standard of trust