COMPLEX GENERIC DRUG PRODUCT DEVELOPMENT WORKSHOP

Opening Remarks

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September 12, 2018

WELCOME

- What is a “Complex Generic Drug Product”?
- Why is this topic worthy of a 2-day workshop?
- Overview of FDA/OGD efforts targeting Complex Generic Drug Products

COMPLEX GENERIC DRUG PRODUCTS

Formally defined in GDUFA II Commitment Letter to include:

- Complex Mixtures
  - Peptides, polymeric compounds, complex mixtures of APIs, naturally sourced ingredients
- Complex formulations
  - Liposomes, colloids
- Complex Routes of Delivery
  - Locally acting such as dermatologic products and complex ophthalmologic and otic products that are formulated as suspensions, emulsions or gels
- Complex Dosage Forms
  - Transdermals, MDI, extended release injectables
- Complex drug-device combination products
  - Autoinjectors, MDI
- Other products where complexity or uncertainty would benefit from early scientific engagement

GDUFA II "Goals" or "Commitment" letter:
http://www.fda.gov/downloads/forindustry/userfees/genericdruguserfees/ucm525234.pdf

WHY?

- Complex drug products are critical to the care of many serious medical conditions such as multiple sclerosis, schizophrenia, metastatic breast cancer, osteoporosis, COPD, diabetes mellitus

- Some of these drugs are costly, thus limiting patient access

- Some markets for brand name drugs are BILLION dollar markets
  - Advair sales: $4.6 billion (2013); $69 billion (1992-2017[1])
  - Peptide products: ~100 global peptide products, $15-20 billion annual sales[2]
  - Restasis: $1.41 billion (2017[1])
  - Victoza: $1.8 billion (Q1&2 2017[3])
  - And More: Symbicort, Spiriva

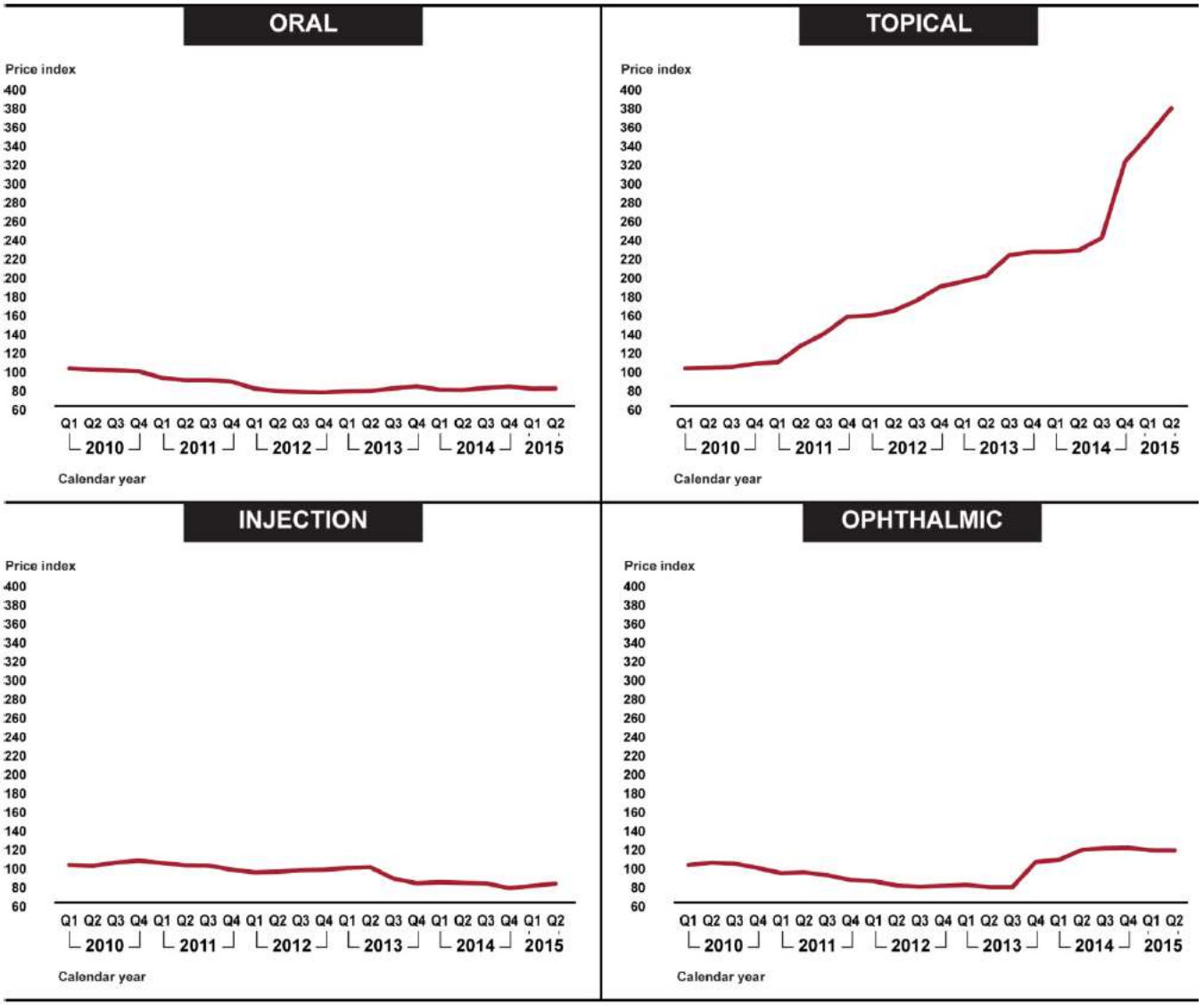
- Yet many complex drug products have relatively small market capitalization and are less enticing for generic drug developers
  - Lack of generic drug product development and ANDA submission
  - Results in little to no generic drug competition and limited patient access

- Challenging **scientific**, regulatory and legal considerations

1. www.fiercepharma.com
2. https://www.fda.gov/Drugs/ScienceResearch/ucm578111.htm
3. www.biopharmadive.com

GAO Report (GAO-16-706)

Price Increases for Brand and Generic Topical drugs



Source: GAO analysis of Medicare Part D prescription drug event data. | GAO-16-706

COMPLEX GENERIC DRUG PRODUCTS

- For some brand name drugs (or RLDs), FDA has not even received any generic drug applications (ANDAs)
  - FDA cannot approve generics if industry does not develop the drug and submit an ANDA
  - FDA publishes and updates List of Off-patent, off-exclusivity drugs without an approved generic (Part of Drug Competition Action Plan (DCAP))

    https://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/UCM564441.pdf

- Some uncertainly for industry on how to develop these generic drug products and gain approval

- Because of the complexity of developing complex generic drug products and demonstrating “sameness”/equivalence, closer FDA-industry communications are needed (Pre-ANDA program under GDUFA II)

CONTENTS OF GENERIC DRUG APPLICATION (ANDA)

- Identify Single Reference Listed Drug (RLD)
- Same Conditions of Use
- Same Active Ingredient
- Same Route of Administration
- Same Dosage Form
- Same Strength
- Same Labeling
- Bioequivalence (BE)
- Safety of Inactive Ingredients
- Patent Certifications, Exclusivity Information
- Chemistry, Manufacturing, and Controls (CMC) Information
- cGMPs (facilities)

GENERIC DRUG (ANDA) Requires Demonstration of *"SAMENESS" or EQUIVALENCE*

- Identify Single RLD
- Same Conditions of Use
- Same Active Ingredient
- Same Route of Administration
- Same Dosage Form
- Same Strength
- Same Labeling

Pharmaceutical Equivalence (PE)

- **Bioequivalence (BE)**

- Safety of Inactive Ingredients
- Patent Certifications, Exclusivity Information
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THERAPEUTIC EQUIVALENCE

Generic drug has the same clinical efficacy and safety profiles **(e.g., same therapeutic effect)** as brand name drug (RLD) when administered to patients under conditions specified in the labeling

- The generic drug product has no significant differences from the RLD
- Can be substituted for each other without any adjustment in dose or other additional monitoring or training
- Substitution occurs at the pharmacy level

CHALLENGES FOR COMPLEX GENERIC DRUG PRODUCTS

- Pharmaceutical Equivalence
  - How to demonstrate active ingredient “sameness”
- Bioequivalence
  - Straightforward BE (systemic PK) approach frequently not applicable
    - Comparative clinical endpoint bioequivalence (BE) studies not ideal
      - Insensitive indicator for equivalence
      - Large, expensive studies
      - Frequently poorly conducted
- Therapeutic Equivalence
  - What kinds of comparative analyses are needed to support substitution?
  - Are the inactive ingredients, if different from RLD, allowable?
- Historically (pre-GDUFA), lack of FDA guidance (Product Specific Guidances/PSGs) on how to demonstrate “sameness” or equivalence (PE, BE, TE)

RESEARCH STRATEGY FOR GENERICS

Scientific basis to demonstrate "sameness"/Equivalence

PRE-GDUFA I

GDUFA I (FY2012-2017)

- Robust GDUFA "Regulatory Science Program"
- Modest size ($100M)
- ~100 grants/contracts
- Published ~800 PSGs, 40% for complex generic drug products
- Created Foundational Elements for GDUFA II

GDUFA II (FY2018-FY2022)

- Continue GDUFA Regulatory Science program
- Creates timelines to publish PSGs for non-complex NMEs
- Establishes Pre-ANDA program for complex generic drug products

GDUFA REGULATORY SCIENCE PROGRAM

- Huge Success Story
- Spectacular return on investment for industry particularly related to the development, regulation and review of complex generic drugs
- Evidence-, research- and science-based standards setting program
- Develops and validates methodologies used to demonstrate “sameness”/Equivalence

OUTCOMES:

1. Provides information for industry on HOW to develop
2. Assists FDA assessors/reviewers and scientists when evaluating ANDA
3. Results in ANDA approvals

APPLY FOUNDATIONAL SCIENCE TO OVERCOME CHALLENGES

We can resolve these “sameness” or equivalence challenges by using foundational and state of the art science and scientific methodologies to:

- Characterize complex active ingredients
  - Complexity of API, e.g., peptides, oligonucleotides, mixtures
- To understand and measure the critical quality attributes of drug product formulations
  - Characterize microstructure and physicochemical properties
  - Minimize risk of drug product formulation failures
  - Enable in vitro approaches to BE
- To understand patient use
  - Complexity of drug-device combinations

SAMPLING OF ANDAS APPROVED

2017-2018

Complex API (all first approved generic)

- Sevelamer carbonate powder for suspension (6/2017)
- Sevelamer carbonate tablets (7/2017)
- Glatiramer acetate for injection, 20 & 40 mg/mL (10/2017)
- Colesevelam HCl tablets (5/2018)
- Colesevelam HCl powder for suspension (7/2018)

Complex Formulation

- Doxorubicin liposomal injection (05/2017)-2nd approved generic

Complex Route of Delivery

- 4 generics for Acyclovir Topical Ointment, 5% (8 Total ANDAs approved)
  - All ANDAs approved based upon a characterization-based BE method
- First generics approved (have PSGs)
  - Estradiol Vaginal Cream USP, 0.01% (12/2017)
  - Butenafine Hydrochloride Cream, 1% (11/2017)
  - Hydrocortisone Butyrate Lotion, 0.1% (11/2017)
  - Dapsone Gel, 5% (10/2017)

Complex Drug-Device Combination

- Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray, 137mcg/50mcg (4/2017)
- Epinephrine auto-injector (8/2018)

METHODS YOU WILL HEAR ABOUT….

- Q1, Q2, Q3 approaches
  - Qualitative, quantitative and physicochemical sameness
- In vitro testing (Q3) Methodologies
  - Release testing
  - Permeation
  - Raman spectroscopy
  - Computational fluid analysis
  - Microsampling strategies
  - Others
- Improved Study Design

  (directly the result of better understanding of drug product performance attributes)
- Modernized Statistical approaches
- Clinical Pharmacology tools
  - Modeling
  - Simulation

ALL WITH THE INTENT TO…..
compile and align orthogonal evidence to conclude “sameness”/Equivalence

MEETING FORMAT

OGD & OPQ scientists, reviewers and regulatory experts will:

- Explain what generic drug developers can learn from the GDUFA regulatory research studies and results
- Focus on key scientific review issues in order to improve the quality of ANDA submissions
  - Decrease Refuse to Receive (RTR) determination
  - Increase rate of first cycle approvals
  - Decrease number of review cycles to correct ANDA deficiencies and gain FDA approval
- Explain how to use the GDUFA II pre-ANDA program for complex generic drug products

Sessions organized by different complex drug product areas with presentations, Q&A and Panel Discussions


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