U.S. FOOD & DRUG ADMINISTRATION

Evaluating Therapeutic Performance of Complex Generic Drugs for Pulmonary Delivery: The FDA Generic Drug Approval Process

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May 19th, 2019
American Thoracic Society Annual Meeting

ATS 2019 Where today's science meets tomorrow's care™ dallas tx MAY 17-MAY 22, 2019

Disclaimer

- The opinions and conclusions expressed in this breakout session are the viewpoints of the speaker(s) and do not necessarily reflect the official position of the U.S. Food and Drug Administration.

Generic Drugs are “Copies” of Brand Name Drugs

- Each ANDA (Abbreviated New Drug Application) relies on a reference listed drug (RLD)
- Generic drugs mostly cost less to develop because applicants do not repeat the safety and efficacy studies required to approve the RLD
- Instead applicants provide evidence of “sameness” and equivalence

Drug Competition Action Plan (DCAP)- To Improve Drug Access

- Announced by FDA's Commissioner in June 2017
- Goal is to bring more competition to drug market as a way to improve drug access
- This plan has three main components:
  - **Reducing gaming by branded companies** that can delay generic drug entry;
  - **Resolving scientific and regulatory obstacles** that can make it difficult to win approval of generic versions of certain complex drugs;
  - **Improving efficiency and predictability of FDA's generic review process** to reduce the time it takes to get a new generic drug approved and lessen the number of review cycles undergone by generic applications before they can be approved

https://blogs.fda.gov/fdavoice/index.php/2017/06/fda-working-to-lift-barriers-to-generic-drug-competition/

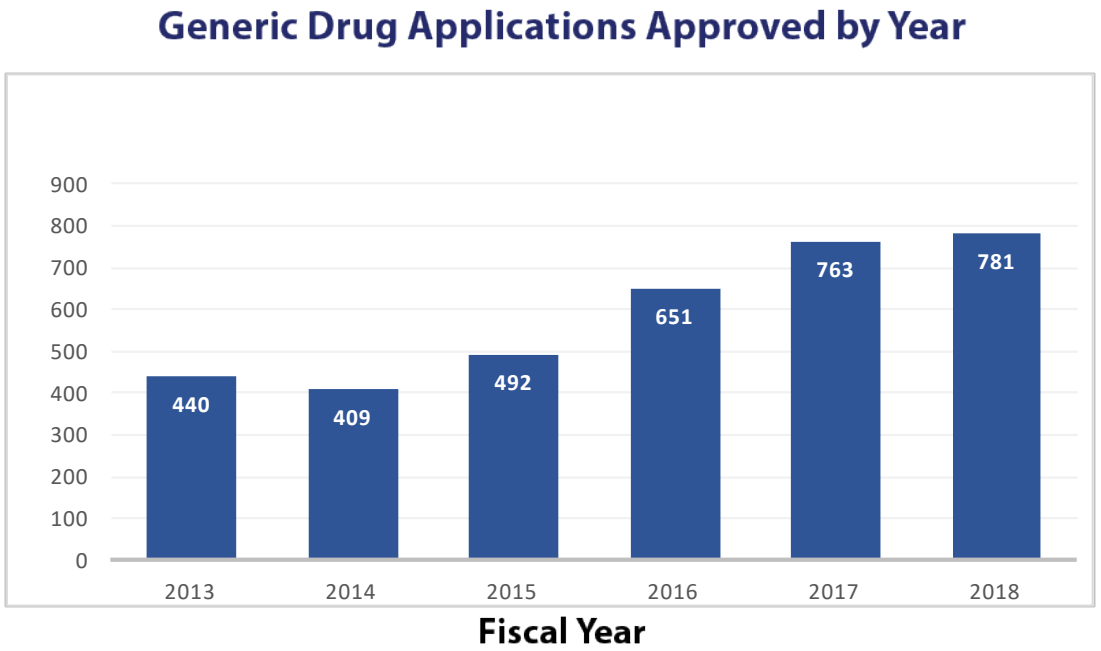
FDA Drug Competition Action Plan

- List of off-patent, off-exclusivity branded drugs without approved generics is published
- New policy to expedite review of generic drug applications where competition is limited
- Use of good review management practices
- Reduce application cycles – improved pre-ANDA interaction

GDUFA Regulatory Science

- GDUFA provides resources to allow FDA to perform and fund research to advance generic drug science
  - Goal: Access to generics in all product categories
  - 90+ on-going projects
  - Recent focus on complex drug products
- This provides new tools for FDA and industry to evaluate generic drug equivalence, to enable more efficient development of generic drugs and thus improve access

Generic Drug Science & Research Website:
https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm



Product-Specific Guidances (PSGs)

- Assist generic pharmaceutical industry by describing the Agency's current thinking and expectations:
    - how to develop generic drug products that are therapeutically equivalent to specific reference drugs
    - the most appropriate methods for generating evidence needed to support ANDA approval
  - Published in an incremental manner – 1,682 PSGs as of February, 2019
  - Under GDUFA 2 – PSGs are to be published at least 2 years prior to the earliest lawful ANDA filing date for non-complex drugs that are:
    - New chemical entities and
    - Approved on or after October 1, 2017,

Generic Drug Product Substitutability

In relation to the Reference Listed Drug, generic products are expected to be:

- **Pharmaceutically Equivalent (PE)**

  The same active ingredient, dosage form, strength, route of administration, and meet the same compendial standards (strength, quality, purity, and identity)

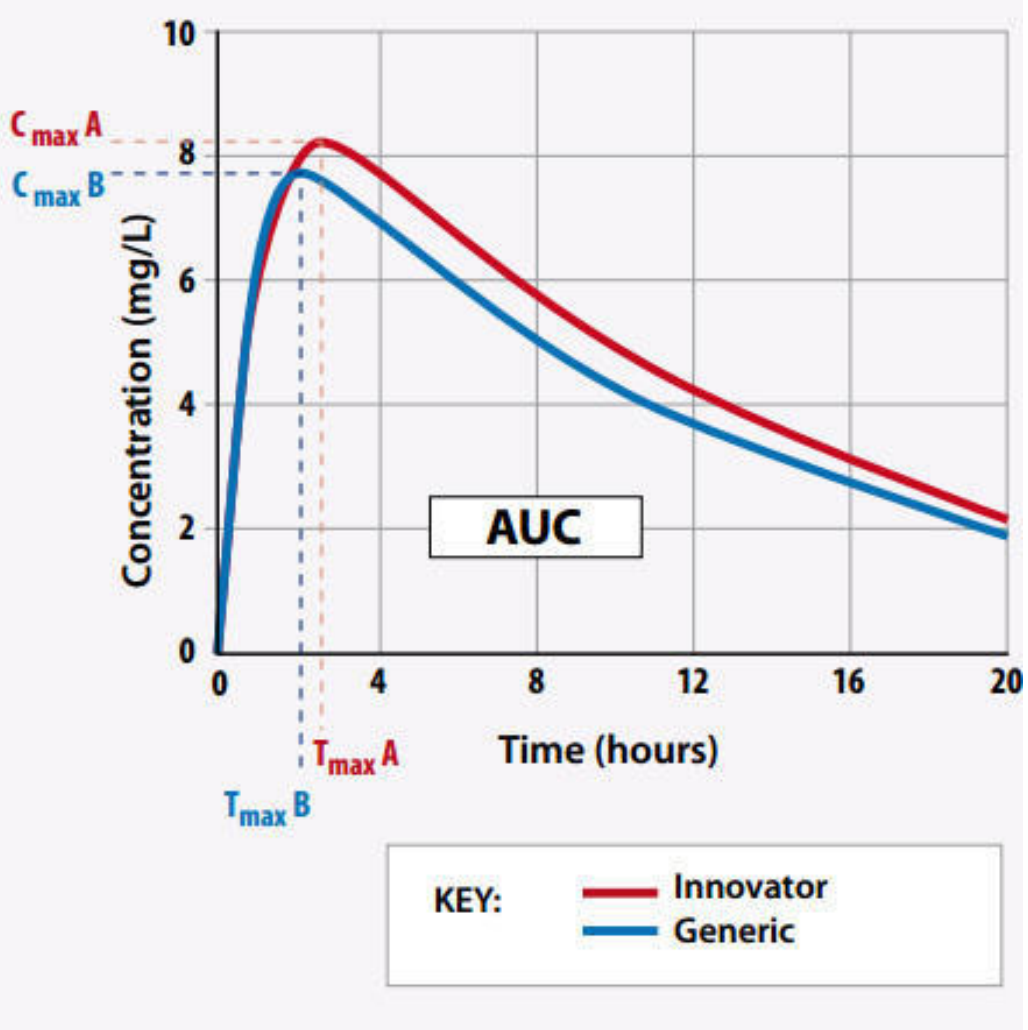
- **Bioequivalent (BE)**

  No significant difference in the rate and extent of absorption of the active ingredient at the site of action

- **Therapeutically Equivalent (TE)**

  Can be substituted with the full expectation that the generic product will produce the same clinical effect and safety profile as the RLD under the conditions specified in labeling

Bioequivalence Determinations



- For products with systemic site of action, BE via systemic PK endpoints (e.g., C_{max} and AUC) helps infer comparable safety and efficacy
- For products that are locally acting, it is more difficult to assess local exposure
- The site of action may not be directly correlated with systemic PK

OINDPs: Weight-of-Evidence Approach

- Includes the following:
  - Qualitative and quantitative sameness of formulation
  - In vitro comparative studies
  - In vivo PK studies
  - Pharmacodynamic (PD) or comparative clinical endpoint study
  - Device substitutability

Formulation Considerations

- Qualitative (Q1) sameness
  - Same inactive ingredient(s)
    - Critical to establishing equivalence between the test and reference DPI products
    - Limited choices of inactive ingredients for DPIs
- Quantitative (Q2) sameness
  - Same inactive ingredient(s) but may differ in concentration
    - Cannot exceed the levels used in other FDA approved products administered by the same route of administration
    - Effect of Q2 difference on bioequivalence assessed by in vitro and/or in vivo BE studies
    - Submit pharmaceutical development data to support the selected test formulation

In Vitro Considerations

- Single Actuation Content (SAC) and aerodynamic particle size distribution (APSD)
  - Critical attributes that are believed to affect the total and regional deposition of drugs in the lung
- SAC and APSD depend on, and sensitive to, product- and process-related factors
  - Physicochemical properties of API(s) and carrier
  - Device component properties
  - Process conditions

In Vivo Pharmacokinetic study Considerations

- This test is considered to be a reliable, sensitive, and objective method to determine differences in drug products
- Single dose studies are done in healthy subjects for all product strengths
- Dose is based on minimizing the number of inhalations balanced with assay sensitivity
- PK dose proportionality across doses and how product characteristics affect levels of target analyte in blood are ongoing research topics
- The blood level of drug drawn is after the site of deposition and action of the drug

In Vivo Pharmacodynamic study Considerations

- Pharmacodynamic (PD) testing is usually performed when there is an adequate dose response relationship (e.g., short-acting Beta-agonists)
- These PD BE studies are preferred over a comparative clinical endpoint BE study (next slide) when comparing test vs. reference drug products
- It is difficult to do PD BE studies for drugs with longer time of onset of effect (e.g., inhaled corticosteroids) or for products which do not demonstrate an adequate dose-response relationship

Comparative Clinical Endpoint Study Considerations

- Not necessarily the same endpoint as the NDA study
- Usual arms: Test (T), Reference (R), Placebo control
  - Lowest labeled dose
  - One indicated population for study reduces variability
  - BE is met if 90% confidence interval for T:R ratio falls within 80 to 125 percent.
- Comparative clinical endpoint bioequivalence studies are relatively blunt instruments (limited sensitivity)
- These studies can require large numbers of patients (usually hundreds), last for several weeks, and can be expensive to do

Acknowledgements

- **The Orally and Nasally Inhaled Generic Drug Product Team**
  - Kim Witzmann, MD – Lead for Orally and Nasally Inhaled Drug Products, Division of Therapeutic Performance, and Chair, Generic Drug Device Combination Product Working Group
  - Denise Conti, PhD, Bryan Newman, PhD, Sneha Dhapare, PhD, Han Liangfeng, MD, and ORISE Fellows: Elizabeth Bielski, PhD Susan Boc, PhD
- **Robert Lionberger, PhD**, Director, Office of Research and Standards

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