FY2018 Generic Drug Regulatory Science Initiatives Public Workshop

FDA Research Update on the FY18 Initiatives

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FY2018 GDUFA Priority Areas

15 priority areas under 4 broad categories

1. Complex active ingredients, formulations, or dosage forms	**2. Complex routes of delivery**
3. Complex drug-device combinations	**4. Tools and methodologies for bioequivalence (BE) and substitutability evaluation**

https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm

Outline for Updates on Each Priority Area

- **FDA Internal Research**
- **FY2017 Grants/Contracts**
  - **Ongoing Grants and Contracts Funded in FY2017**
  - **New FY2017 Contracts Awarded**
    - No new grant was awarded in FY2017
- **Potential FY2018 Grants/Contracts**
- **Outcomes 2017-2018** (May 2017- April 2018)
  - Public Workshops
  - Publications
  - Guidances
    - General guidances
    - Product-specific guidances (PSGs)
  - Notable ANDA Approvals

1. Complex active ingredients, formulations, or dosage forms

(1) Improve advanced analytics for characterization of chemical compositions, molecular structures and distributions in complex active ingredients

(2) Improve particle size, shape and surface characterization to support demonstration of therapeutic equivalence of suspended and colloidal drug products

(3) Establish predictive in silico, in vitro and animal studies to evaluate immunogenicity risk of formulation or impurity differences in generic products

(4) Develop predictive in vitro bioequivalence (BE) methods for long-acting injectables

(5) Develop better methods for evaluating abuse deterrence of generic solid oral opioid products, including in vitro alternatives to in vivo nasal studies

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(1) Improve advanced analytics for characterization of chemical compositions, molecular structures and distributions in complex active ingredients

- **FDA Internal Research**
  - Characterization of complex active pharmaceutical ingredients (APIs)
    - Polymeric drugs, e.g., patiromer
    - Synthetic oligonucleotides
    - Peptides
      - Detecting and quantifying D-isomers in peptide drug products
  - Characterization of polymeric excipient critical quality attributes (CQAs): Polydimethylsiloxane (PDMS)

- **Ongoing Grants and Contracts Funded in FY2017**
  - Pentosan polysulfate in urine

(1) Improve advanced analytics for characterization of chemical compositions, molecular structures and distributions in complex active ingredients

- **Outcomes 2017-2018**
  - Public workshop: "Demonstrating Equivalence of Generic Complex Drug Substances and Formulations" (Oct 6, 2017)
  - Guidances:
    - General guidance (draft): "ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin" (10/2017)
    - PSG: Sucralfate oral suspension (10/2017)
  - Notable ANDA approvals:
    - Glatiramer acetate for injection, 40 mg/mL (10/2017)-first generics
    - Sevelamer carbonate tablets (7/2017)-first generics
    - Sevelamer carbonate powder for suspension (6/2017)-first generics

(2) Improve particle size, shape and surface characterization to support demonstration of therapeutic equivalence of suspended and colloidal drug products

- **FDA Internal Research**
  - Quantifying albumin structural changes due to manufacture process and corresponding changes in binding affinity to paclitaxel
  - Evaluating accuracy, precision and reproducibility of new particle analysis methods for measuring the size and concentration of liposomal and emulsion drug products
  - Examining if/how particle concentration measurement can be used to evaluate sameness of complex suspension and liposome formulations
  - Developing nanoparticle tracking in nanofluidic slits to simultaneously measure the CQAs (e.g., concentration, size, and composition) of liposomal formulations.
  - Cryo-electron microscopy (cryo-EM) for morphological characterization of complex nano-drug products to improve the review of in vitro bioequivalence studies
  - Particle size characterization methods for API in suspension-based aqueous nasal spray products using Morphologically-Directed Raman Spectroscopy (MDRS)
  - New methods on equivalence testing of complex particle size distribution profiles using Earth Mover's Distance (EMD)

- **Outcomes 2017-2018**
  - Public workshops:
    - "Demonstrating Equivalence of Generic Complex Drug Substances and Formulations" (Oct 6, 2017)
    - "New Insights for Product Development and Bioequivalence Assessments of Generic Orally Inhaled and Nasal Drug Products" (Jan 9, 2018)

(2) Improve particle size, shape and surface characterization to support demonstration of therapeutic equivalence of suspended and colloidal drug products

- **Outcomes 2017-2018 (Cont'd)**
  - Publications:
    - Barton Pai A, et al., Performance Of Redox Active And Chelatable Iron Assays To Determine Labile Iron Release For Intravenous Iron Formulations. *Clin Transl Sci.* 2017 May;10(3):194-200
    - Sun D, et al., Comparative Evaluation of U.S. Brand and Generic Intravenous Sodium Ferric Gluconate Complex in Sucrose Injection: Physicochemical Characterization. *Nanomaterials (Basel).* 2018 Jan 5;8(1)
    - Hu, M., et al. (2018). Equivalence Testing of Complex Particle Size Distribution Profiles Based on Earth Mover's Distance. *The AAPS journal*, 20(3), 62
  - Guidances (PSGs):
    - Barium sulfate oral suspension (02/2018)
    - Bupivacaine liposomal injection (02/2018)
    - Soybean oil injection (02/2018)
  - Notable ANDA approvals:
    - Doxorubicin liposomal injection (05/2017)-second approved generic

(3) Establish predictive in silico, in vitro and animal studies to evaluate immunogenicity risk of formulation or impurity differences in generic products

- **FDA Internal Research**
  - Immunogenicity assessment and impurity profiling
    - Peptides
    - Oligonucleotides

- **Potential FY2018 Grants/Contracts**
  - Evaluating immunogenicity risk of generic peptide drugs using non-clinical assays

(3) Establish predictive in silico, in vitro and animal studies to evaluate immunogenicity risk of formulation or impurity differences in generic products

- **Outcomes 2017-2018**
  - Public workshop: "Demonstrating Equivalence of Generic Complex Drug Substances and Formulations" (Oct 6, 2017)
  - Guidance:
    - General guidance (draft): "ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin" (10/2017)

(4) Develop predictive in vitro bioequivalence (BE) methods for long-acting injectables

- **FDA Internal Research**
  - In vitro BE for suspension injectables
- **Ongoing Grants and Contracts Funded in FY2017**
  - Four grants and two contracts on long-acting injectable (LAI) modeling, poly(lactic-co-glycolic acid) (PLGA)-peptide interactions, and PLGA characterization
- **New FY2017 Contract**
  - "In vitro in vivo correlation of the long-acting injectable suspensions to improve scientific approaches to evaluate generic drugs"
    - Awarded to the University of Connecticut (#HHSF223201710135C)
  - "Development of analysis technique for structural characterization of star-shaped polyesters used for drug delivery"
    - Awarded to Akina Inc (#HHSF223201710123C)
- **Potential FY2018 Grants/Contracts**
  - Influence of raw materials, manufacturing variables, and storage conditions on bioequivalence of large peptides and potential peptide PLGA interactions
  - Impact of polymer source variations on parenteral microsphere drug product performance

(4) Develop predictive in vitro bioequivalence (BE) methods for long-acting injectables

- **Outcomes 2017-2018**
  - Public workshop: "Demonstrating Equivalence of Generic Complex Drug Substances and Formulations" (Oct 6, 2017)
  - Publications:
    - Andhariya JV, et al., Development of in vitro-in vivo correlation of parenteral naltrexone loaded polymeric microspheres. *J Control Release*. 2017 Jun;255:27-35
    - Doty AC, et al., Mechanisms of in vivo release of triamcinolone acetonide from PLGA microspheres. *J Control Release*. 2017 Jun 28;256:19-25
    - Garner J, et al., Beyond Q1/Q2: the impact of manufacturing conditions and test methods on drug release from PLGA-based microparticle depot formulations. *J Pharm Sci.* 2018 Jan;107(1):353-361
  - Guidance:
    - PSG: Leuprolide acetate intramuscular injectable depot (02/2018)

(5) Develop better methods for evaluating abuse deterrence of generic solid oral opioid products, including in vitro alternatives to in vivo nasal studies

- **FDA Internal Research**
  - Lab-based, 16 active projects covering 9 key areas
    - Technical profiles of reference listed drugs (RLDs)
    - Determination of syringeability and injectability
    - In vitro manipulation and extraction studies
    - Nasal powder characterization
    - Nasal regional deposition model
    - Chewing IVIVC model
  - Quantitative analysis
    - IVIVC development of opioid products using in vitro chewing method and PBPK modeling
    - Advanced PK modeling of opioid following nasal insufflation of physically manipulated products (3-D computation fluid dynamics (CFD) model, regional deposition, dissolution/diffusion studies)
    - Pharmacokinetic/pharmacodynamic (PK/PD) relationship of abuse deterrent (AD) opioid products

- **Ongoing Grants and Contracts Funded in FY2017**
  - Contract on nasal PK study of opioids following insufflation of physically manipulated products (OXYCONTIN)
    - Study was completed. Preliminary PK results were obtained

(5) Develop better methods for evaluating abuse deterrence of generic solid oral opioid products, including in vitro alternatives to in vivo nasal studies

- **Potential FY2018 Grants/Contracts**
  - Nasal PK/PD studies with oral agonist/antagonist combination products
  - Oral chewing PK/PD studies with oral opioid products

- **Outcomes 2017-2018**
  - Publications:
    - Boyce H, et al. In Vitro Assessment of Nasal Insufflation of Comminuted Drug Products Designed as Abuse Deterrent Using the Vertical Diffusion Cell. *AAPS PharmSciTech* (2018): 1-14.
  - Guidances:
    - General guidance (final): "General principles for evaluating the abuse deterrence of generic solid oral opioid drug products" (Nov 2017)

2. Complex routes of delivery

(6) Improve Physiologically Based Pharmacokinetic (PBPK) models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)

(7) Expand characterization-based bioequivalence (BE) methods across all topical dermatological products

(8) Expand characterization-based BE methods across all ophthalmic products

(9) Develop more efficient alternatives to the use of forced expiratory volume in one second (FEV1) comparative clinical endpoint BE studies for inhaled corticosteroids

(10) Develop alternatives to comparative clinical endpoint BE studies for locally-acting nasal products

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(6) Improve Physiologically Based Pharmacokinetic (PBPK) models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)

- **FDA Internal Research**
  - Topical: Physics-based modeling predictions of evaporation, spreading, and penetrability for non-Q1/Q2 solution product
  - Ophthalmic: PBPK-based assessment of impact of Q3 differences on local bioavailability/bioequivalence for 3 different suspension products; tear film break-up time and local bioavailability modeling of an emulsion product
  - Inhalation: Upper and lower human airway deposition predictions of solution pMDIs and "soft mist inhalers"
  - Nasal: Local and systemic delivery predictions of nasally insufflated abuse deterrent formulation
  - Locally-acting drug products physiochemical and pharmacokinetic knowledgebase

- **Ongoing Grants and Contracts Funded in FY2017**
  - 3 Grants for CFD-based modeling of lung deposition
  - 1 Grant for CFD and PBPK model for nasal products
  - 2 Grants to advance ophthalmic PBPK modeling
  - 2 Grants to advance topical/transdermal PBPK modeling

(6) Improve Physiologically Based Pharmacokinetic (PBPK) models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)

- **Potential FY2018 Grants/Contracts**
  - Formulation drug product quality attributes in dermal physiologically-based pharmacokinetic models for topical dermatological drug products and transdermal delivery systems
  - Characterize skin physiology parameters utilized in dermal physiologically-based pharmacokinetic model development across different skin disease states
  - CFD and discrete element modeling (DEM) approach for predictions of dry powder inhaler (DPI) drug delivery
  - Three-dimensional approach for modeling nasal mucociliary clearance via CFD
  - Potential contract/BAAs to support continued development of CFD and/or PBPK models for products with complex routes of delivery
  - Contract to order in vitro and animal studies to support internal research efforts

(6) Improve Physiologically Based Pharmacokinetic (PBPK) models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)

- **Outcomes 2017-2018**
  - Publications:
    - Pak J, et al., Computational modeling of drug transport across the in vitro cornea. *Computers in biology and medicine*. 2018 Jan 1;92:139-146
    - Kannan RR, et al., A Compartment-Quasi3D multiscale approach for drug absorption, transport, and retention in the human lungs. *International journal for numerical methods in biomedical engineering*. 2017 Dec 22
    - Kannan R, et al., A Quasi-3D compartmental multi-scale approach to detect and quantify diseased regional lung constriction using spirometry data. *International journal for numerical methods in biomedical engineer*ing. 2018 Feb 27:e2973
    - Yousef S, et al., Mechanistic evaluation of hydration effects on the human epidermal permeation of salicylate esters. *The AAPS journal*. 2017 Jan 1;19(1):180-190
    - Wittum R, et al., Mathematical modelling of the viable epidermis: impact of cell shape and vertical arrangement. *Mathematics and Mechanics of Solids*. 2017 Dec 7:1081286517743297
  - Upcoming public workshop:
    - PBPK modeling for locally-acting products (March 13, 2019, ASCPT Pre-Conference, Washington DC)

(7) Expand characterization-based bioequivalence (BE) methods across all topical dermatological products

- **FDA Internal Research**
  - Development of novel bio-relevant in vitro skin permeation tests (IVPT) using in-line flow through diffusion cells
  - Manufacture of AT-rated topical ointment formulations for in vitro release test (IVRT) method validation

- **Ongoing Grants and Contracts Funded in FY2017**
  - 1 Contract to expand characterization-based BE methods across petrolatum-based topical ointments, including AT-coded ointments
  - 3 Grants to advance in vitro cutaneous pharmacokinetic BE methods (IVPT studies) and expand characterization-based BE methods across all topical dermatological products
  - 2 Grants to develop in vivo cutaneous pharmacokinetic BE methods (dermal microdialysis/microperfusion clinical studies) to expand the availability of novel, efficient BE methods across all topical dermatological products, including non-Q1/Q2 generics

(7) Expand characterization-based bioequivalence (BE) methods across all topical dermatological products

- **Potential FY2018 Grants/Contracts**
  - Bioequivalence of Topical Products: Evaluating the Cutaneous Pharmacokinetics of Topical Drug Products Using Non-Invasive Techniques
  - Bioequivalence of Topical Products: Elucidating the Thermodynamic and Functional Characteristics of Compositionally Different Topical Formulations
  - Establish a correlation between local and systemic drug concentrations leveraging dermal open-flow microperfusion (dOFM) data

- **Outcomes 2017-2018**
  - Public workshop: "Topical Dermatological Generic Drug Products: Overcoming Barriers to Development and Improving Patient Access" (Oct 20, 2017)
  - Publications:
    - Tiffner KI, et al., A comprehensive approach to qualify and validate the essential parameters of an in vitro release test (IVRT) method for acyclovir cream, 5%. *Int J Pharm.* 2018 Jan 15;535(1-2):217-227

(7) Expand characterization-based bioequivalence (BE) methods across all topical dermatological products

- **Outcomes 2017-2018 (Cont'd)**

Notable Guidances (PSGs):

Each includes a novel BE approach developed based on GDUFA Research

- Bimatoprost Topical Solution, 0.03% (02/2018)
- Crisaborole Topical Ointment, 2% (02/2018)
- Dapsone Topical Gel, 5% (rev 10/2017)
- Dapsone Topical Gel, 7.5% (10/2017)
- Docosanol Topical Cream, 10% (10/2017)
- Ivermectin Topical Cream, 1% (10/2017)
- Silver Sulfadiazine Topical Cream, 1% (07/2017)

Notable ANDA Approvals:

4 more generics approved for Acyclovir Topical Ointment, 5% (*8 Total*)

- All ANDAs approved based upon a characterization-based BE method

4 more first generics approved (all with 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)

(8) Expand characterization-based BE methods across all ophthalmic products

- **FDA Internal Research**
  - Asymmetric flow field flow fractionation measurement of cyclosporine ophthalmic emulsion
  - Unit dose content testing and particle size/size distribution testing of
    - ciprofloxacin ophthalmic ointment
    - dexamethasone ophthalmic suspension
  - Evaluating physicochemical testing of non-Q2 ophthalmic solution products
  - Evaluating rheological properties of in-situ forming ophthalmic gels: impact of excipient grade and diluent media composition
  - Animal model ocular bio-distribution studies: impact of formulation viscosity and particle size
  - Assessment of in vitro release testing methods for ophthalmic emulsion products

- **Ongoing Grants and Contracts Funded in FY2017**
  - Contract on pulsatile microdialysis for in vitro release of ophthalmic emulsions

(8) Expand characterization-based BE methods across all ophthalmic products

- **Potential FY2018 Grants/Contracts**
  - In vitro studies (tissue-based assays) for topical products (ophthalmic)

- **Outcomes 2017-2018**
  - Public workshop: "Demonstrating Equivalence of Generic Complex Drug Substances and Formulations" (Oct 6, 2017)
  - Publications:
    - Bao Q, et al., Physicochemical attributes and dissolution testing of ophthalmic ointments. *International Journal of Pharmaceutics*. 2017;523(1):310-319
    - Bao Q, et al., In vitro release testing method development for ophthalmic ointments. *International Journal of Pharmaceutics*. 2017;526(1-2):145-156
    - Bao Q. et al., In vitro and ex vivo correlation of drug release from ophthalmic ointments. *J Control Release* 2018 Apr 28;276:93-101
    - Qu H, et al., Asymmetric flow field flow fractionation for the characterization of globule size distribution in complex formulations: a cyclosporine ophthalmic emulsion case. *Int J Pharm* 2018 Mar 1;538(1-2):215-22
  - Guidances (PSGs that incorporated in vitro BE approaches supported by research):
    - Fluorometholone Ophthalmic Suspension (10/2017)
    - Loteprednol Etabonate Ophthalmic Suspension (02/2018)

(9) Develop more efficient alternatives to the use of forced expiratory volume in one second (FEV1) comparative clinical endpoint BE studies for inhaled corticosteroids

- **FDA Internal Research**
  - Biorelevant methods for assessing quality and performance of inhalation products
    - Realistic mouth-throat for deposition

- **Ongoing Grants and Contracts Funded in FY2017**
  - 1 Contract for PK study on dry powder inhaler (DPI)
    - The PK study on DPI was completed
  - 1 Grant for PK study on metered dose inhaler (MDI)

- **New FY2017 Contracts**
  - "Investigating the microstructure of dry powder inhalers using orthogonal analytical approaches"
    - Awarded to the University of Bath (#HHSF223201710116C)

- **Potential FY2018 Grants/Contracts**
  - CFD and discrete element modeling (DEM) approach for predictions of dry powder inhaler (DPI) drug delivery
  - Impact of differences in aerodynamic particle size distribution (APSD) and device resistance on CFD predictions of dry powder inhaler drug delivery
  - Development of empirical models and in vitro methods for prediction of batch to batch variability of dry powder inhaler formulations
  - Characteristic tracheobronchial models of adult female and male chronic obstructive pulmonary (COPD) patients for CFD analysis

(9) Develop more efficient alternatives to the use of forced expiratory volume in one second (FEV1) comparative clinical endpoint BE studies for inhaled corticosteroids

- **Outcomes 2017-2018**
  - Public workshop: "New Insights for Product Development and Bioequivalence Assessments of Generic Orally Inhaled and Nasal Drug Products" (Jan 9, 2018)
  - Publications:
    - Bhagwat S, et al., Predicting pulmonary pharmacokinetics from in vitro properties of dry powder inhalers. *Pharm Res*. 2017 Dec;34(12):2541-2556
    - Sheth P, et al., Influence of formulation factors on the aerosol performance of suspension and solution metered dose inhalers: a systematic approach. *The AAPS Journal*. 2017;19(5):1396-1410
    - Wei X, et al., In Vitro Tests For Aerosol Deposition. V: Using Realistic Testing To Estimate Variations In Aerosol Properties At The Trachea. *J Aerosol Med Pulm Drug Deliv*. 2017 Oct;30(5):339-348
  - Guidances: 6 new PSGs
    - Glycopyrrolate Powder (07/2017)
    - Tiotropium Bromide Powder for Inhalation (10/2017)
    - Fluticasone Propionate Powder for Inhalation (10/2017)
    - Fluticasone Propionate Inhalation Aerosol (10/2017)
    - Mometasone Furoate Powder for Inhalation (10/2017)
    - Salmeterol Xinafoate Powder for Inhalation (10/2017)

(10) Develop alternatives to comparative clinical endpoint BE studies for locally-acting nasal products

- **FDA Internal Research**
  - Particle size characterization methods for API in suspension-based aqueous nasal spray products using MDRS (also under (2))
  - Meta-analysis of in vitro BE data submitted in the ANDA applications for nasal products

- **Ongoing Grants and Contracts Funded in FY2017**
  - Contract for nasal PK study

- **New FY2017 Contracts**
  - "Investigating orthogonal analytical approaches to demonstrate bioequivalence of nasal suspension formulations"
    - Awarded to the University of Bath (#HHSF223201710163C)

(10) Develop alternatives to comparative clinical endpoint BE studies for locally-acting nasal products

- **Potential FY2018 Grants/Contracts**
  - Improving in vitro tests for clinical relevance (nasal models)
  - Three dimensional approach for modeling of mucociliary clearance via CFD

- **Outcomes 2017-2018**
  - Public workshop: "New Insights for Product Development and Bioequivalence Assessments of Generic Orally Inhaled and Nasal Drug Products"(Jan 9, 2018)
  - Guidances: 2 new PSGs
    - Azelastine Hydrochloride Spray, metered (05/2017, RLD: NDA 20114)
    - Azelastine Hydrochloride Spray, metered (10/2017, RLD: NDA 22203)
  - Notable ANDA Approvals
    - Azelastine Hydrochloride and Fluticasone Propionate Nasal Spray, 137mcg/50mcg (4/2017)

3. Complex drug-device combinations

(11) Evaluate the impact of identified differences in the user-interface on the substitutability of generic drug-device combination products

https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm

(11) Evaluate the impact of identified differences in the user-interface on the substitutability of generic drug-device combination products

- **New FY2017 Contracts**
  - "Patient's perception of dry powder inhaler airflow resistance"
    - Awarded to Imperial College of Science and Technology (#HHSF223201710072C)

- **Potential FY2018 Grants/Contracts**
  - Patients' perceptions to device substitution

- **Outcomes 2017-2018**
  - Publications:
    - SH Choi et al. Generic drug device combination products: Regulatory and scientific considerations;., *International journal of pharmaceutics* (Available on line; Nov 2017) https://doi.org/10.1016/j.ijpharm.2017.11.038
  - Upcoming public workshop:
    - DIA-FDA Complex Generic Drug-Device Combination Product workshop (Oct 9-10, 2018, Silver Spring, MD)

4. Tools and methodologies for BE and substitutability evaluation

(12) Improve quantitative pharmacology and bioequivalence trial simulation to optimize design of BE studies for complex generic drug products

(13) Integrate predictive dissolution, PBPK and PK/Pharmacodynamic (PD) models for decision making about generic drug bioequivalence standards

(14) Expand the scientific understanding of the role of excipients in generic drug products to support the expansion of the Biopharmaceutics Classification System of Class 3 bio-waivers to non-Q2 (quantitatively inequivalent) formulations

(15) Develop methods that will allow FDA to leverage large data sets (such as bioequivalence study submissions, electronic health records, substitution and utilization patterns and drug safety and quality data) for decisions related to generic drug approval and post-market surveillance of generic drug substitution

https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm

(12) Improve quantitative pharmacology and bioequivalence trial simulation to optimize design of BE studies for complex generic drug products

- **FDA Internal Research**
  - Quantitative analysis of PK/PD relationship of abuse-deterrent opioid products
  - Clinical trial simulation on comparative clinical endpoint BE studies for locally acting drug products
  - Use of PK/PD modelling and simulation for assessment of post-market risk

- **Ongoing Grants and Contracts Funded in FY2017**
  - Contract for BE methods for PK using sparse sampling
  - Pharmacometric modeling and simulation for a generic drug substitutability evaluation and post-marketing risk assessment
  - Pharmacometric modeling and simulation and statistical analysis for LAI microsphere products

- **New FY2017 Contracts**
  - "Evaluation and development of model-based bioequivalence analysis strategies"
    - Awarded to Uppsala University (#HHSF223201710015C)

- **Potential FY2018 Grants/Contracts**
  - Bioequivalence evaluation of nanoparticulate and molecular medicines
  - Developing PBPK/PD models for IUDs to evaluation alternative BE approaches
  - Alternate BE study design for long acting products

(12) Improve quantitative pharmacology and bioequivalence trial simulation to optimize design of BE studies for complex generic drug products

- **Outcomes 2017-2018**
  - Public workshop: "Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review" (Oct 2-3, 2017)
  - Publications: 7 manuscripts

    Examples:
    - Fang, et al., Model Informed Drug Development and Review for Complex Generic Products: Summary of FDA Public Workshop. *Clinical Pharmacology and Therapeutics*. 2018
    - Li et al., Risk-Based Bioequivalence Recommendations for Antiepileptic Drugs, *Current Neurology Neuroscience Reports.* 2017; 17: 82
  - Guidances: 46 PSGs

    Examples:
    - Ivermectin topical cream (10/2017)
    - Naloxone nasal spray (4/2017)
  - Notable ANDA Approvals: 29 related ANDA approvals
    - Brimonidine topical gel (tentative approval in 07/2017)

(13) Integrate predictive dissolution, PBPK and PK/Pharmacodynamic (PD) models for decision making about generic drug bioequivalence standards

- **FDA Internal Research**
  - PBPK modeling and simulations to (1) assess impact of dissolution profiles on PK and BE, (2) assess a chewing device for abuse deterrence assessment, (3) identify the drug interaction mechanism of nifedipine ER and a proton pump inhibitor, omeprazole, and (4) identify the rate-limiting step for Omega-3 ethyl ester intestinal absorption
  - Multivariate similarity testing for multi-batch dissolution profiles

- **Ongoing Grants and Contracts Funded in FY2017**
  - Grants on supersaturation models, in vivo predictive dissolution methodology, wireless analysis device to measure in vivo drug dissolution, PK study on IVIVC for amorphous dispersions, PK study on PPI interactions, contract for MRI measurements of GI water content, grants for PK/PD studies on metoprolol and methylphenidate

- **New FY2017 Contracts**
  - "Phase behavior and transformation kinetics of a poorly water soluble weakly basic drug upon transit from low to high pH conditions"
    - Awarded to Purdue University (#HHSF223201710137C)

- **Potential FY2018 Grants/Contracts**
  - Development of a virtual bioequivalence trial simulation platform that integrates population pharmacokinetic modeling algorithms into physiologically-based pharmacokinetic models
  - Evaluation of relative bioavailability of pediatric products
  - Establishment of alternative bioequivalence evaluation methodology by integrating sequential design and Bayesian methodology

(13) Integrate predictive dissolution, PBPK and PK/Pharmacodynamic (PD) models for decision making about generic drug bioequivalence standards

- **Outcomes 2017-2018**
  - Public workshop: "Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review" (Oct 2-3, 2017)
  - Publications: 9 manuscripts

    Examples:
    - Zhang X, et al. Mechanistic Oral Absorption Modeling and Simulation for Formulation Development and Bioequivalence Evaluation: Report of an FDA Public Workshop. *CPT Pharmacometrics Syst Pharmacol*. 2017 Aug;6(8):492-495
    - Hens B, et al. Measuring the Impact of Gastrointestinal Variables on the Systemic Outcome of Two Suspensions of Posaconazole by a PBPK Model. *The AAPS Journal*. 2018 Mar 29;20(3):57
    - Fan J, et al., Utility of Physiologically Based Pharmacokinetic Absorption Modeling to Predict the Impact of Salt-to-Base Conversion on Prasugrel HCl Product Bioequivalence in the Presence of Proton Pump Inhibitors. *The AAPS Journal*. 2017; 19 (5), 1479-1486
    - Ni Z, et al. Physiologically Based Pharmacokinetic and Absorption Modeling for Osmotic Pump Products. *The AAPS Journal*. 2017; 19 (4), 1045-1053
    - Hens B, et al. Low Buffer Capacity and Alternating Motility along the Human Gastrointestinal Tract: Implications for in Vivo Dissolution and Absorption of Ionizable Drugs. *Molecular Pharmaceutics*. 2017; 14 (12) 4281-4294
  - Notable ANDA Approvals:
    - Prasugrel hydrochloride tablets (7/2017)

(14) Expand the scientific understanding of the role of excipients in generic drug products to support the expansion of the Biopharmaceutics Classification System of Class 3 bio-waivers to non-Q2 (quantitatively inequivalent) formulations

- **FDA Internal Research**
  - Bi-phasic dissolution systems
  - Impact of excipients on drug solubility, passive permeability, and intestinal metabolism and transport
  - A database on commonly observed excipients in IR products for BCS Class III drug substances

- **Ongoing Grants and Contracts Funded in FY2017**
  - Effect of excipients on intestinal drug transporters

(14) Expand the scientific understanding of the role of excipients in generic drug products to support the expansion of the Biopharmaceutics Classification System of Class 3 bio-waivers to non-Q2 (quantitatively inequivalent) formulations

- **Outcomes 2017-2018**
  - Publications:
    - JJ Irwin, et al, A Molecular Basis for Innovation in Drug Excipients, *Clin Pharmacol Ther*. 2017 Mar;101(3):320-323
    - (poster): Z. Gao, et al, Development of a bi-phasic dissolution method with in vivo PK prediction potential for a BCS Class III compound metformin HCl, AAPS Annual Meeting, 2017
  - Guidances:
    - General guidance (final): "Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. Guidance for Industry" (Dec 2017)
    - ICH harmonization discussion on-going

(15) Develop methods that will allow FDA to leverage large data sets (such as bioequivalence study submissions, electronic health records, substitution and utilization patterns and drug safety and quality data) for decisions related to generic drug approval and post-market surveillance of generic drug substitution

- **FDA Internal Research**
  - Machine learning/neural network analysis to predict the association between kinase targets and adverse reactions
  - Big data analytics for post-marketing signal detection

- **Ongoing Grants and Contracts Funded in FY2017**
  - Grant on use of pharmacometrics for post-market surveillance

- **Potential FY2018 Grants/Contracts**
  - Generic utilization and substitution of thyroid agents
  - Machine learning for IVIVC PK and PD analysis

(15) Develop methods that will allow FDA to leverage large data sets (such as bioequivalence study submissions, electronic health records, substitution and utilization patterns and drug safety and quality data) for decisions related to generic drug approval and post-market surveillance of generic drug substitution

- **Outcomes 2017-2018**
  - Public workshop: "Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review" (Oct 2-3, 2017)
  - Publications:
    - Gong X, et al., Big Data Toolsets to Pharmacometrics: Application of Machine Learning for Time-to-Event Analysis. *Clin Transl Sci.* 2018; 00, 1–7
    - Hansen RA, et al., Comparison of outcomes following a switch from a brand to an authorized vs. independent generic drug. *Clin Pharmacol Ther.* 2018 Feb;103(2):310-317
    - Liu Q, et al., The adoption of generic immunosuppressant medications in kidney, liver, and heart transplantation among recipients in Colorado or nationally with Medicare part D. *Am J Transplant.* 2018 Mar 31 [Epub ahead of print]
    - Dasai RJ, et al., Differences in rates of switchbacks after switching from branded to authorized generic and branded to generic drug products: cohort study. *BMJ.* 2018 Apr 3;361:k1180. doi: 10.1136/bmj.k1180

Research Outcomes Summary (May 2017-April 2018)

Public Workshops

5

Publications

29 in FY2017
19 in 2018

Guidances

General: 3
PSGs: 229
(60 for complex, 26%
48 new, 11 rev, 1 final)

First Generics Approvals (4/2017-3/2018)

80
(18 complex, 23%)
15 of 18 (83%) had PSGs

Future Workshops in 2018 and 2019

- CDER Small Business and Industry Assistance (SBIA) Regulatory Education for Industry (REdI): Complex Generic Product Development Workshop (September 12-13, 2018)
- Drug Information Association (DIA)/FDA Generic Drug-Device Combination Products Workshop (October 9-10, 2018)
- PBPK Modeling for Locally-Acting Products (March 13, 2019)

https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm

GDUFA Science and Research Website

New Look!

https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm

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Public Workshops
May 2017-April 2018

- May 19, 2017: Oral Absorption Modeling and Simulation for Formulation Development and Bioequivalence Evaluation Workshop
- October 2-3, 2017: Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review
- October 6th, 2017: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations
- October 20th, 2017: Topical Dermatological Generic Drug Products: Overcoming Barriers to Development and Improving Patient Access
- January 9th, 2018: New Insights for Product Development and Bioequivalence Assessments of Generic Orally Inhaled and Nasal Drug Products

https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm