



# **Center for Drug Evaluation and Research: Pharmacology/Toxicology Perspective**

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# Outline

- CDER Pharmacology/Toxicology
  - Informs part of the risk:benefit equation
  - Perspectives: Office of New Drugs and Office of Generic Drugs (OGD)
- Generic Drugs
  - Growth and outreach for Pharm/Tox in OGD
  - GDUFA-funded research efforts

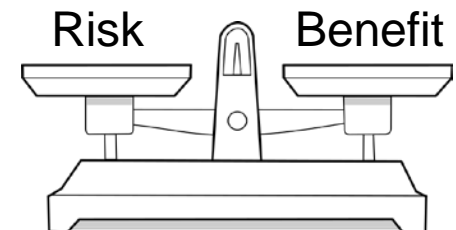
# CDER Pharm/Tox

- The Pharm/Tox discipline exists in:
  - Office of New Drugs (OND)
  - Office of Generic Drugs (OGD)
  - Office of Compliance (OC)
  - Office of Translational Science (OTS)
- Other Super-offices and Sub-Offices work with Pharm/Tox on a consult-basis



# CDER Pharmacology/Toxicology

- Pharmacology/Toxicology assesses the risk of several aspects of a drug formulation to a specific patient population
  - Active Pharmaceutical Ingredient (API)
  - Excipients
  - Drug product impurities
  - Residual solvents
  - Leachable and extractables
  - Elemental impurities
- Safety assessment considers several context-specific aspects
  - Context drives the decision about necessary toxicity assessments
  - Dose
  - Route of Administration
  - Duration of use
  - Patient population (disease and drug-related effects)
  - Risk/monitorability/public health



# Perspectives: New Drugs and Generics

Different information and challenges are presented across application-types

- A new-molecular entity (NME) undergoes testing to establish the safety and toxicity of the API and drug formulation- ICH M3(R2)
- In general, a 505(b)(2) application relies on referenced material
- A generic relies on the safety and efficacy established by the RLD/innovator product. The aim is bioequivalence

*An NME is assessed for its safety and efficacy for a patient population.*

*A generic must have the same safety profile as the RLD for the same patient population*



# What is a generic?

- Generic drug is a medication created to be the same as an already marketed brand-name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use.<sup>1</sup>
  - Generic drugs must establish bioequivalence with the reference listed drugs (RLD)
  - Generic drug applications are submitted as an Abbreviated New Drug Application (ANDA)
- A generic drug may differ from the RLD:
  - Excipients (21 CFR 314.94(a)(9))
  - Drug substance or drug product-related impurities
- Clinical safety studies are not submitted in an ANDA, but information should support that the generic has a similar safety profile

1) Generic Drugs: Questions and Answers:

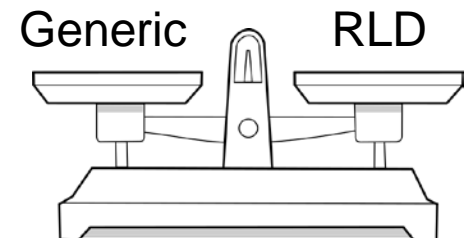
<https://www.fda.gov/drugs/resourcesforyou/consumers/questionsanswers/ucm100100.htm>

# OGD Pharmacology/Toxicology

- OGD Pharm/Tox assesses the risk of several aspects of a drug formulation to the same patient population as the RLD
  - Active Pharmaceutical Ingredient (API)
  - Excipients
  - Drug Substance or Drug Product Impurities
  - Residual Solvents
  - Leachable and Extractables
  - Elemental Impurities
- Safety assessment considers several context-specific aspects
  - Context drives the decision about necessary toxicity assessments
  - Dose
  - Route of Administration
  - Duration of use
  - Patient population (disease and drug-related effects)
  - Risk/public health



OGD Pharm/Tox



# Aiming for Consistency and Transparency

- OGD Pharm/Tox aims to document our experience and practice

## Review

- Comparative Risk Assessment of Formulation Changes in Generic Drug Products: A Pharmacology/Toxicology Perspective. *Toxicological Sciences* 146(1), 2015
  - Sree Rayavarapu, Elena Braithwaite, Robert Dorsam, James Osterhout, Lesley-Anne Furlong, Daiva Shetty, John R. Peters

## Posters

- Impurities in Generic Drug Applications: Trends in Regulatory Submission from a Pharm/Tox Perspective. *American College of Toxicology*, 2017
  - Common Deficiencies in Justifications of Potentially Genotoxic Impurities in Generic Drug Applications. OGD Science Day, FDA White Oak Campus
- Achieve consistency and transparency through knowledge management and collaboration
    - Achieved using databases, training and collaboration
    - NCTR's FDALabel, OND Pharm/Tox Smart Template



# GDUFA Research

- GDUFA supports research to develop new approaches to resolve complex generic drug development or review issues
- Over 100 external projects have been supported during GDUFA I
- Each year OGD hosts a public meeting to identify research priorities
  - FY 2018 list was posted recently

# GDUFA-related Science Priorities\*

- Complex active ingredients, formulations, or dosage forms
  - Improve advanced analytics for characterization of chemical compositions, molecular structures and distributions in complex active ingredients
  - **Establish predictive in silico, in vitro and animal studies to evaluate immunogenicity risk of formulation or impurity differences in generic products**
  - Develop predictive in vitro bioequivalence (BE) methods for long-acting injectables
- Routes of delivery
  - Improve Physiologically Based Pharmacokinetic (PBPK) models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)
  - Expand characterization-based bioequivalence (BE) methods across all topical dermatological and ophthalmic products
- Tools and methodologies for BE and substitutability evaluation
  - Improve quantitative pharmacology and bioequivalence trial simulation to optimize design of BE studies for complex generic drug products
  - Integrate predictive dissolution, PBPK and PK/Pharmacodynamic (PD) models for decision making about generic drug bioequivalence standards
  - **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**

\* Excerpted and abbreviated from:

<https://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/UCM582777.pdf>

# Research Example

- **Prediction and Testing of Excipient Molecular Targets**
  - PI: Brian Shoichet
- Ongoing Collaboration via FDA UCSF-Stanford Center of Excellence in Regulatory Science and Innovation (CERSI) since October 2015.
- The objective of this project is to examine potential interactions with pharmacologic targets of commonly used FDA-approved excipients
- The goal is to provide additional tools to help FDA and industry establish safe levels of excipients in generic drug formulations

# A public access excipients browser

<http://excipients.ucsf.bkslab.org/>

- Provides access to chemical structures of FDA approved excipients and links to public informatio

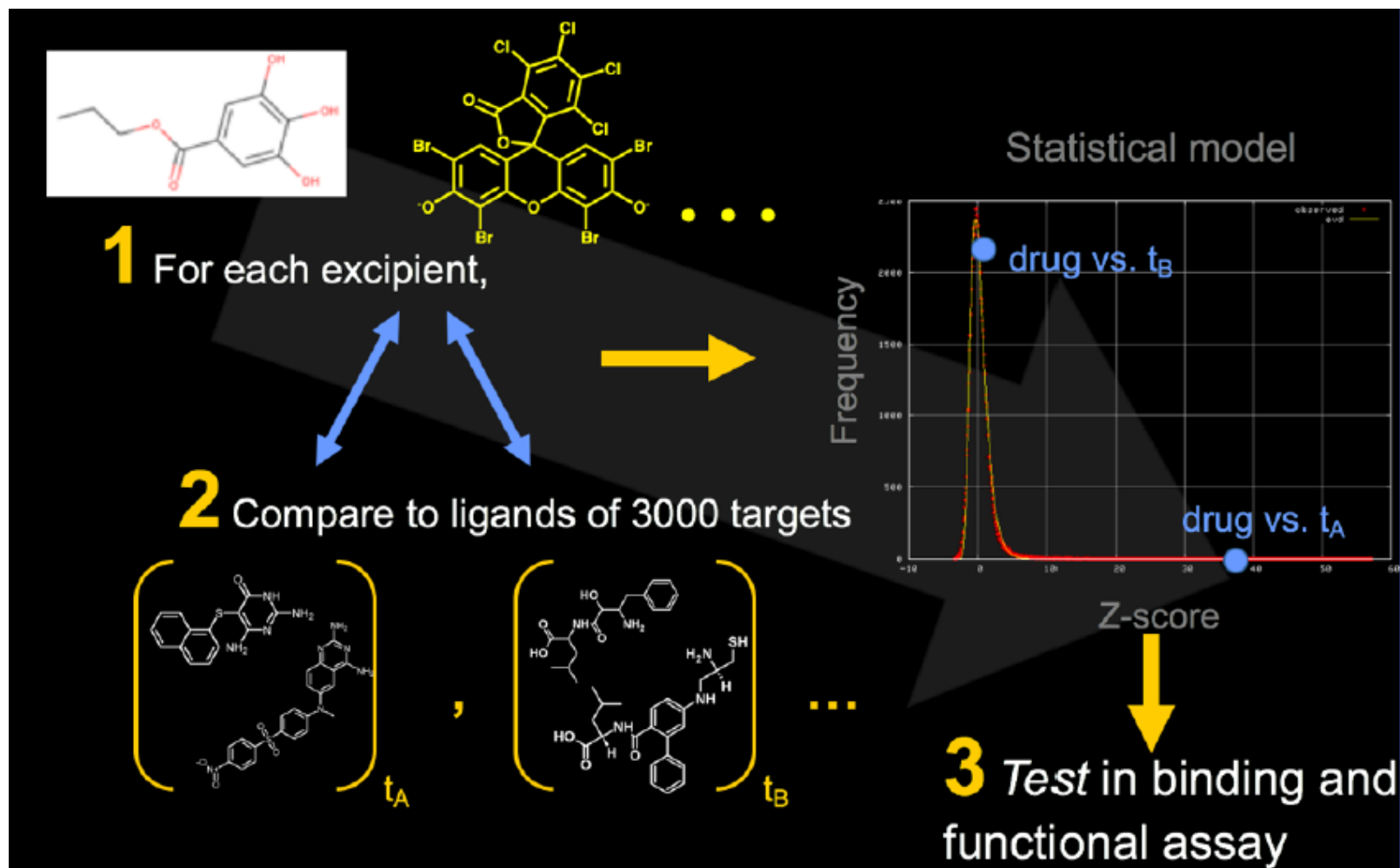
The screenshot shows the 'EXCIPIENTS BROWSER' website. At the top, there is a navigation bar with links for 'CERSI', 'Excipients', 'Home', 'Molecular', 'Oral', 'Unresolved', and 'Rarely Used'. The main header features the 'EXCIPIENTS BROWSER' title and logos for 'UCSF' and 'CERSI'. A disclaimer text states: 'The Excipients Browser was created with support from a CERSI grant from the FDA. Any errors of omission or commission in the database are the responsibility of the Irwin and Shoichet labs. Please report any error or provide feedback about the database. You must use the database at your own risk. The goal of the project is to curate and disseminate information about excipients, the assumed-inactive substances found in food and drugs. This includes: colors, flavors, stabilizers, bulking and delivery agents, fillers, packaging, and other purposes.'

Below the disclaimer, there are four categories of excipients:

- Molecular**: Explore small molecule excipients.
- Oral**: Explore excipients that are administered orally.
- Unresolved**: Explore non-molecular or ambiguous excipients.
- Rarely Used**: Explore excipients that are rarely used.

On the right side, there is a search bar labeled 'Excipient Name, SMILES or SMARTS' with a 'Search' button. Below the search bar is a 'JSME Molecular Editor' window with a toolbar and a vertical list of chemical elements (C, N, O, S, F, Cl, Br, I, X).

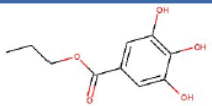
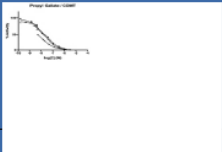
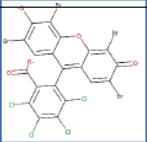
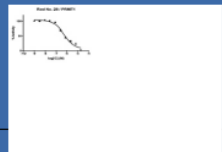
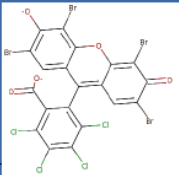

# Computationally screen excipients against known pharmacological targets



# Test computational predictions against assay results

Excipients	Predictions	Tested	Confirmed	False Positive - Aggregators
445	21565	73	31	4

Excipient	Structure	Target	SEA Score	IC50	D/R Curve
Propyl Gallate		COMT	$7.5 \times 10^{-22}$	20 nM	
D&C Red No. 28 (Phloxine B)		PRMT1 (Protein arginine methyltransferase)	$2.6 \times 10^{-19}$	700 nM	
D&C Red No. 28 (Phloxine B)		SLC22A6 (OAT1)	$7.8 \times 10^{-16}$	64 nM	

Josh Pottel, Ling Zou

# Summary

- Pharm/Tox in CDER evaluates the toxicity of drug products using context-specific elements
  - Risk:benefit is a key consideration
- The safety profile of the generic drug safety must be the same as the RLD
- OGD Pharm/Tox is growing and doing outreach
  - Open to collaboration that benefits generic drug safety review
  - Generic drugs present a host of challenging formulation issues that warrant further research
- Pharm/Tox plays a pivotal role in safety assessments for both new drugs and generic drugs in CDER

