GENERIC DRUG REGULATORY RESEARCH: IN VITRO EQUIVALENCE TESTING

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Stephanie H. Choi, Ph.D.
Acting Associate Director for Science
Office of Research and Standards
Office of Generic Drugs/FDA

Generic Drug User Fee Amendments (GDUFA)

- Passed in July 2012 to speed access to safe and effective generic drugs to the public
- Requires user fees to supplement costs of reviewing generic drug applications and provide additional resources, including support for regulatory science research
- Agreement that user fees can directly support regulatory science research activities

GDUFA Regulatory Science Program

- Supports access to generic drugs in all product categories
  - inhalation, nasal, topical dermatological, ophthalmic, liposomal, sustained release parenteral
- Development of new tools to evaluate drug equivalence and support drug development
  - Simulation tools to predict drug absorption
  - Advanced analytical methods for product characterization
  - In vitro methods to predict in vivo performance

Goals of GDUFA Research

- Enhance access to generic versions of complex products
  - Expand the use of in vitro BE approaches
- Research identifying issues that need to be addressed in pharmaceutical development
- Provides characterization methods and performance tests that are needed for in vitro BE approaches

GDUFA Regulatory Science Program

- Over 100 extramural grants/contracts awarded since 2013 by the **Office of Research and Standards** in the Office of Generic Drugs
  - External collaborations: academia, industry
  - Internal collaborations: FDA labs, other government agencies

Regulatory Science Priorities

- Topic 1: Post-market evaluation of generic drugs (16 extramural projects awarded)
- Topic 2: Equivalence of complex drug products (30)
- Topic 3: Equivalence of locally acting products (20)
- Topic 4: Therapeutic equivalence evaluation and standards (19)
- Topic 5: Computational and analytical tools (18)

Bioequivalence

- Refers to the absence of a significant difference in the rate and extent to which the active ingredient in a pharmaceutically equivalent drug product becomes available at the site of action, when administered to subjects at the same molar dose under similar conditions

Approaches to demonstrate bioequivalence

- In vivo:
  - Pharmacokinetic study
  - Pharmacodynamic study
  - Clinical endpoint study
- In vitro:
  - Characterization:
    - "Q1/Q2/Q3 equivalence"
  - Performance:
    - In vitro test that correlates with and is predictive of human in vivo bioavailability data
    - Dissolution rate test
    - In vitro permeation test

Definition of Q1/Q2

- **Q1 (qualitative sameness)** means that the test product uses the same inactive ingredient(s) as the reference product.
- **Q2 (quantitative sameness)** means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product.

Concept of Q3

- Even if a product is formulated Q1/Q2, there could be differences in the arrangement of matter within the dosage form which may impact product performance
- These differences in arrangement of matter (**structural similarity – "Q3"**) arise from differences in manufacturing
- Differences in Q3 can be evaluated by comparative physicochemical data
- Sameness in physicochemical characteristics will ensure equivalence in in vivo performance

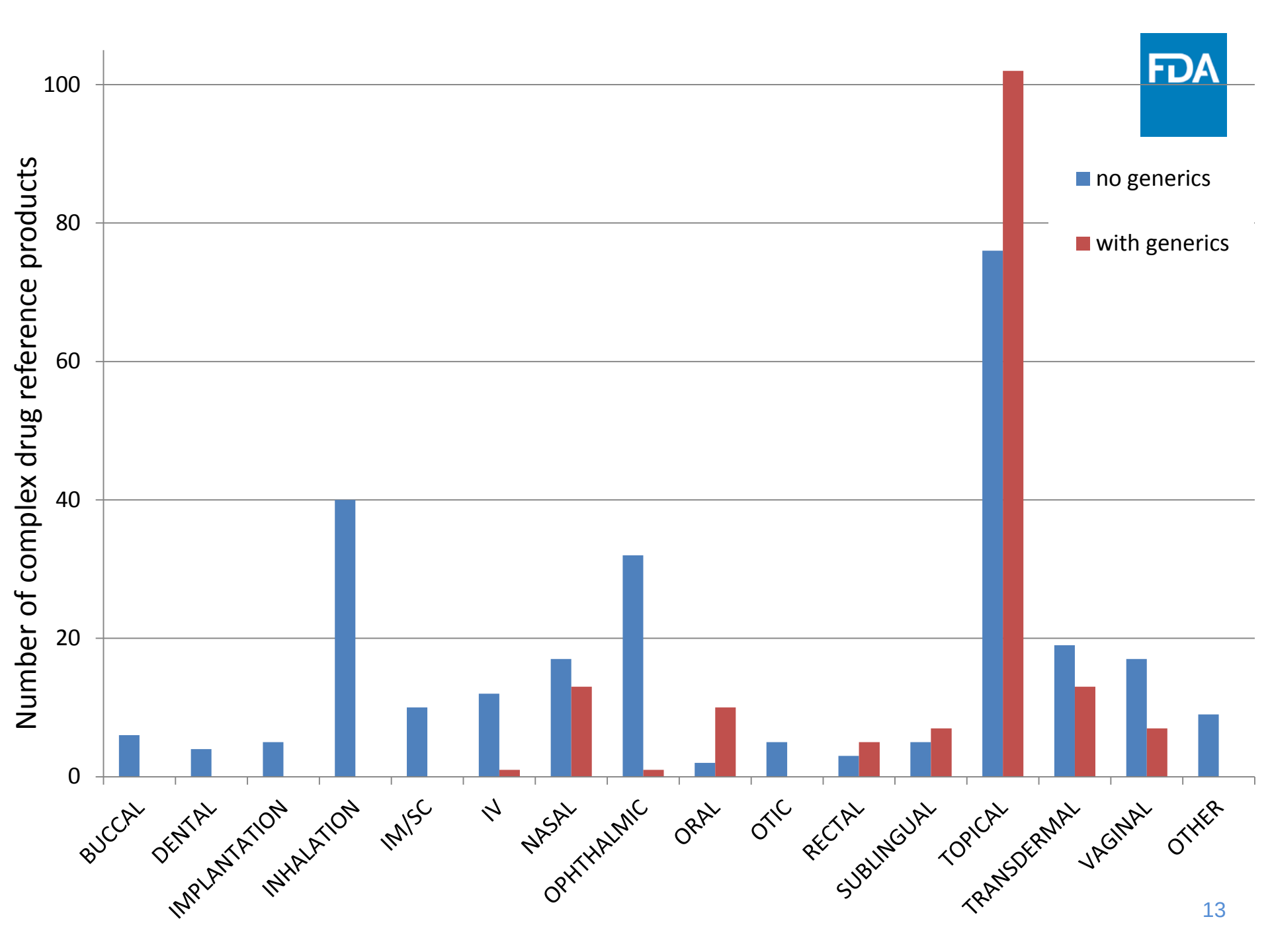
Need for In Vitro Testing Methods

- Clinical studies require large numbers of subjects due to high intersubject variability
- For products with modest clinical efficacy, clinical studies may not be sensitive enough to detect differences when comparing a potential generic product to the branded product
- Alternative approaches to demonstrate equivalence (other than clinical studies) are warranted to provide a pathway for generic product approval, such as in vitro studies

Complex Drug Products

- Complex active ingredients
- complex formulations
- complex active routes of delivery
- complex dosage forms

- 262 complex drug products (reference standards) without generics
- 210 complex drug products with generics:
  - 51 products had in vivo bioequivalence waived


Number of complex drug reference products
100
80
60
40
20
0
no generics
with generics
BUCCAL
DENTAL
IMPLANTATION
INHALATION
IM/SC
IV
NASAL
OPHTHALMIC
ORAL
OTIC
RECTAL
SUBLINGUAL
TOPICAL
TRANSDERMAL
VAGINAL
OTHER

Examples of products with an In vitro option (Q1/Q2/Q3) to demonstrate bioequivalence

- Inhalation products:
  - Budesonide inhalation suspension
  - Ciclesonide nasal aerosol metered
  - Olopatadine HCl nasal spray metered

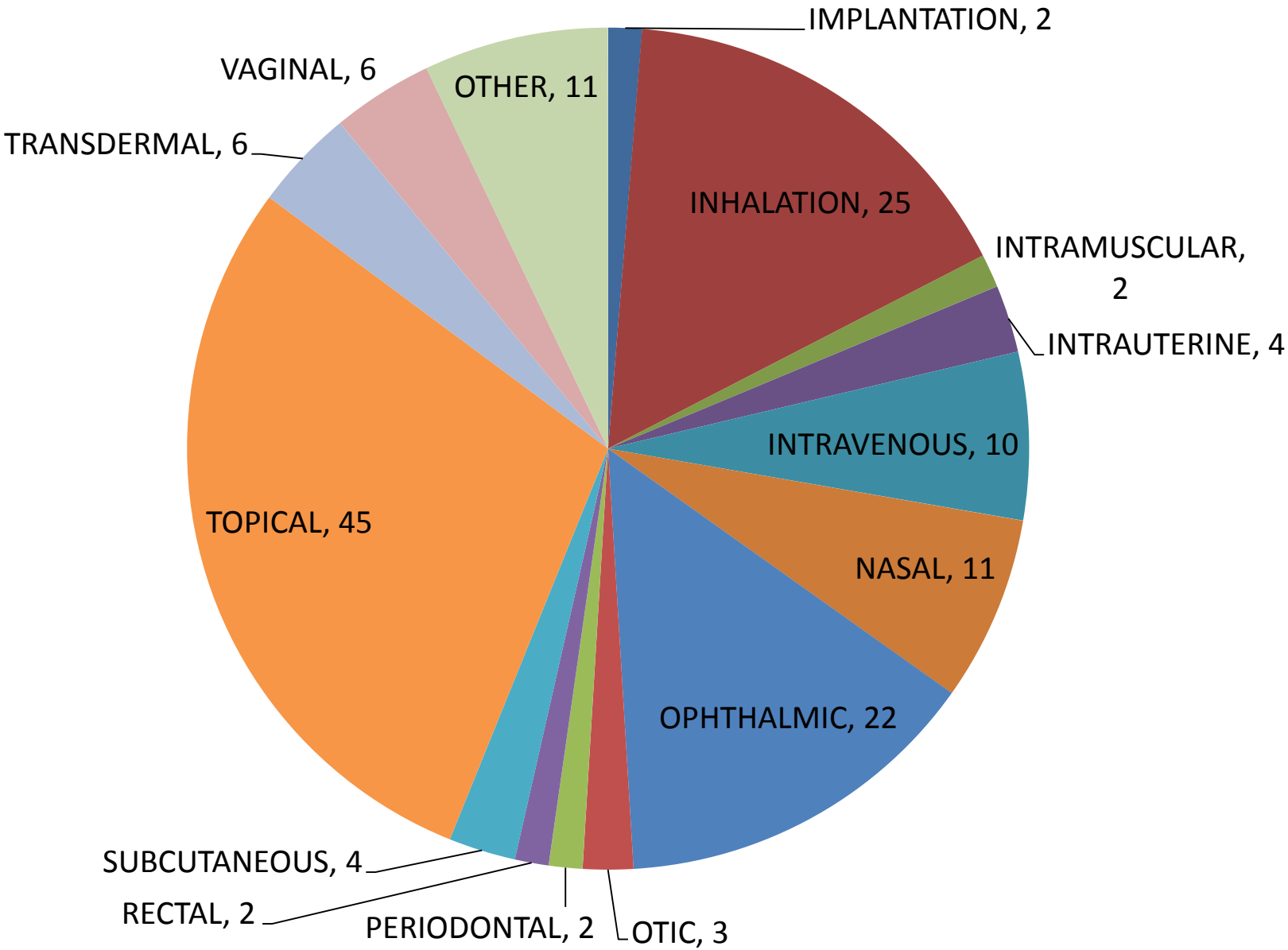
- Ophthalmic products:
  - Cyclosporine emulsion
  - Difluprednate emulsion
  - Dexamethasone; tobramycin suspension
  - Nepafenac suspension

- Otic products:
  - Ciprofloxacin; dexamethasone suspension
  - Ciprofloxacin HCl; hydrocortisone suspension

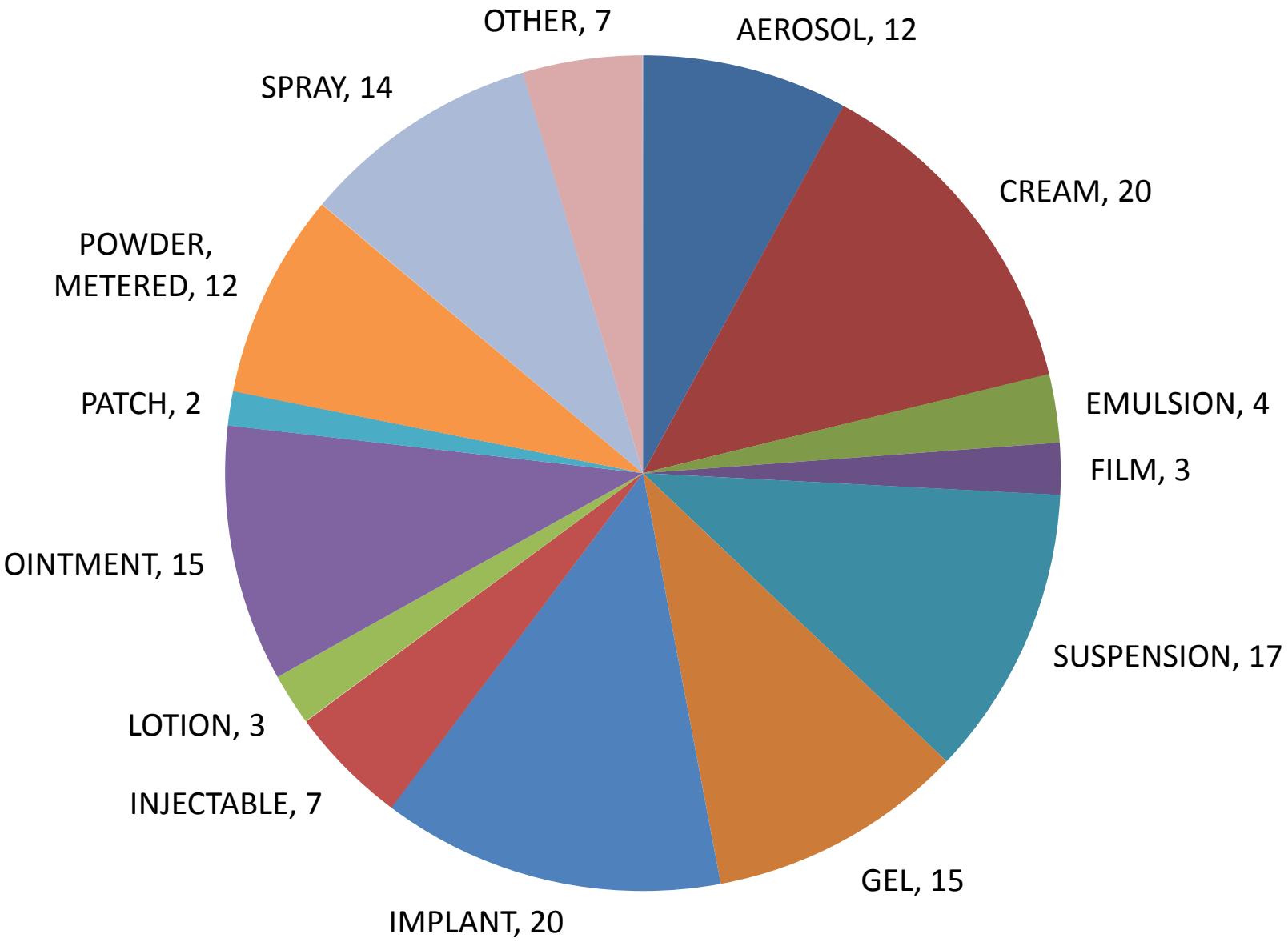
- Topical products:
  - Acyclovir cream
  - Acyclovir ointment
  - Benzyl alcohol lotion
  - Betamethasone valerate topical foam aerosol
  - Ciclopirox topical solution
  - Clindamycin phosphate topical form aerosol
  - Clobetasol propionate topical foam aerosol
  - Ketoconazole topical foam aerosol
  - Minoxidil topical foam aerosol
  - Spinosad topical suspension

- Complex drug products:
  - Verteporfin injection

Approved Complex Drug Products Without Product-Specific Guidance or Generics (Dosage Route)



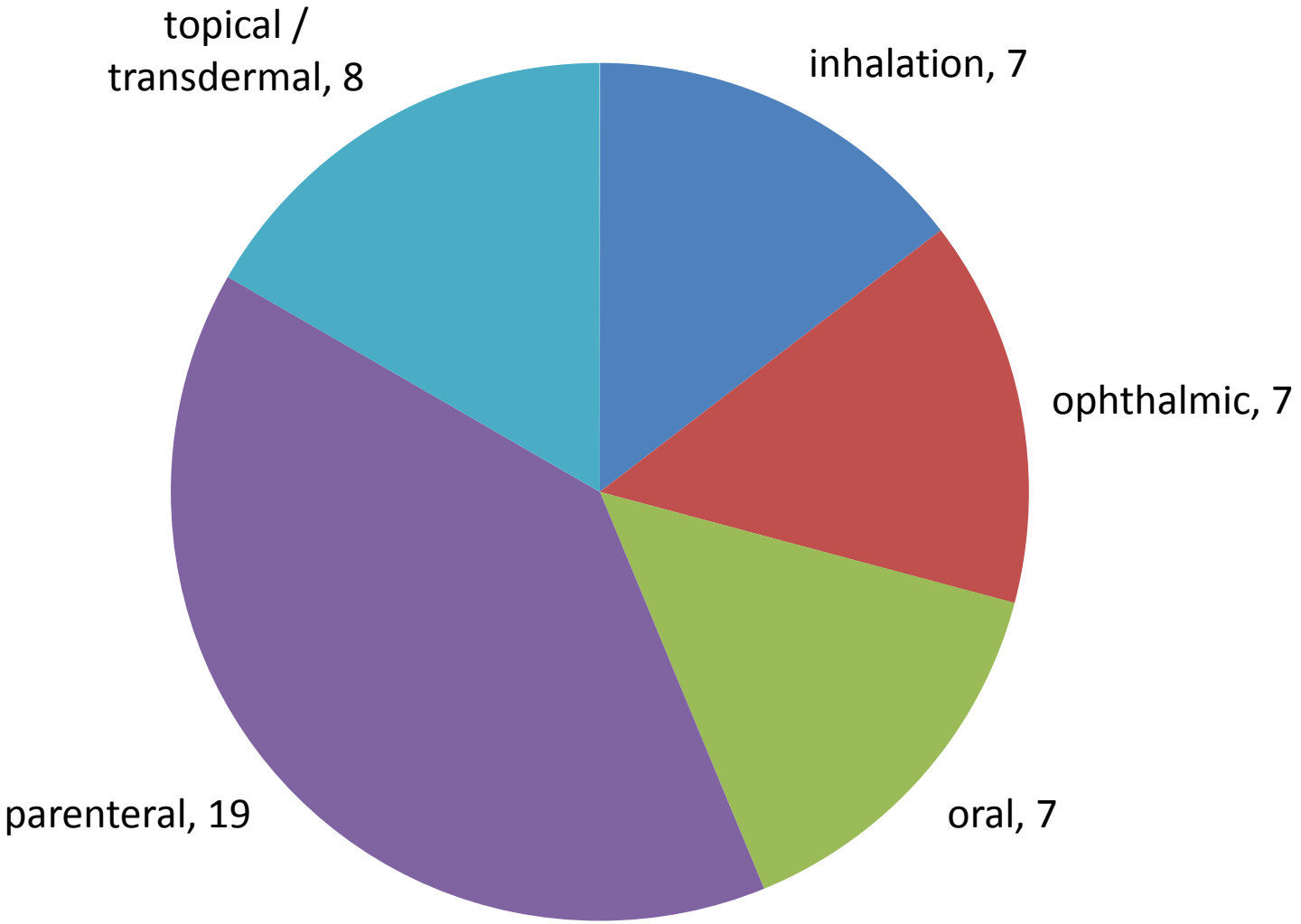
Approved Complex Drug Products Without Product-Specific Guidance or Generics (Dosage Form)



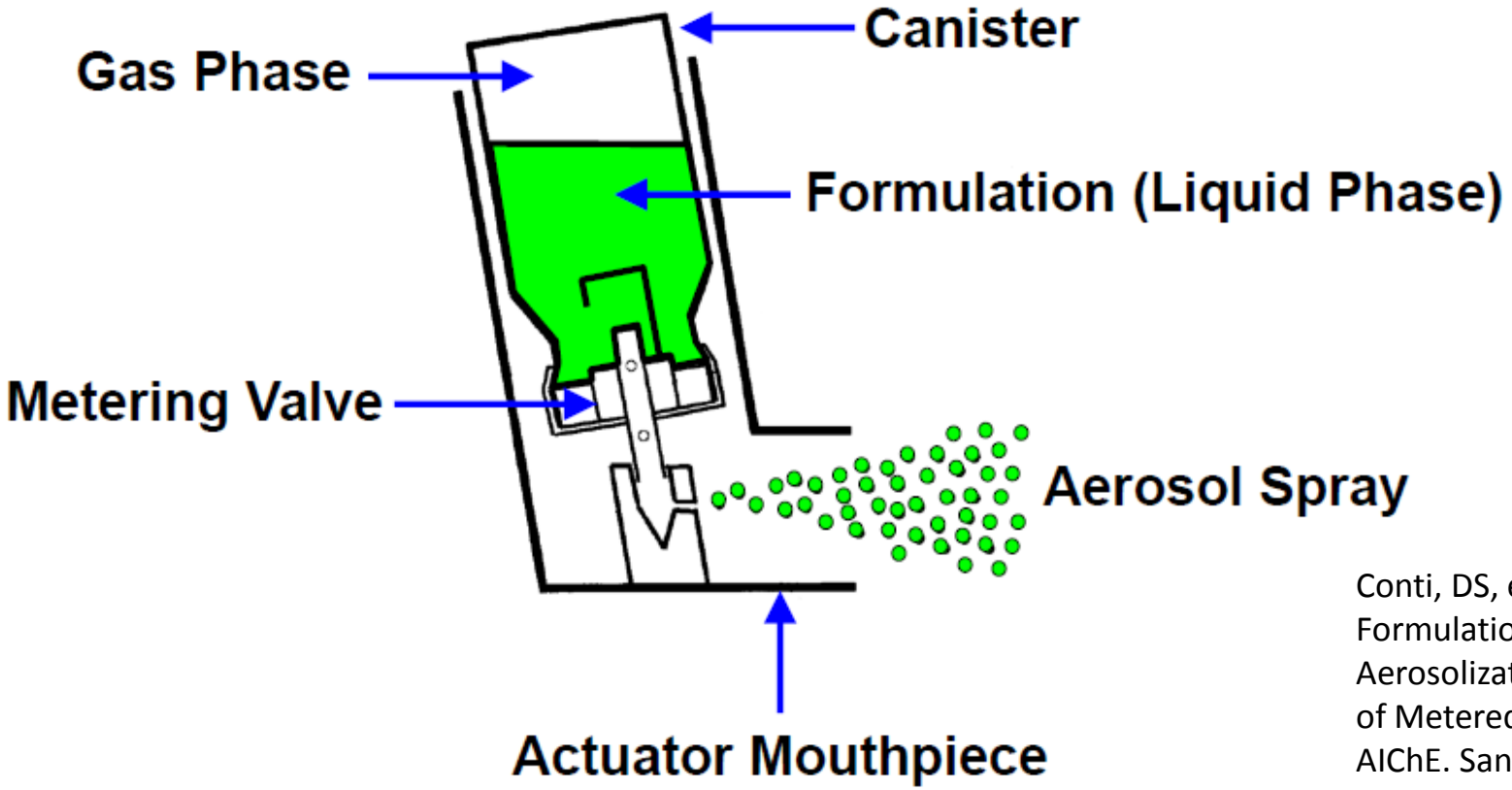
In Vitro Testing Research Areas

- Investigation of key physicochemical properties that affect drug release and bioavailability (12 funded extramural projects)
- Development of in vitro release testing (IVRT) methods which are predictive of in vivo release (15)
- In vitro-In vivo correlations (IVIVCs) (6)
- Predictive models correlating in vitro and in vivo performance (3)
- Physicochemical characterization methods (4)
- Impact of excipients on bioequivalence (9)

In Vitro Testing Research Areas



Formulation factors on Aerosolization Performance of MDIs



Conti, DS, et al. The Effects of Formulation Factors on the Aerosolization Performance of Metered Dose Inhalers. AIChE. San Francisco, CA. 2016.

Figure 1. Schematic of a typical MDI.[3]

MDI Formulation	***PSD D_{50} (μm)***	***EtOH (% w/w)***	***OA (% w/w)***
Albuterol Sulfate (AS) Suspension	*1.4 - 2.5*	*7 - 20*	*0.005 - 0.1*
Mometasone Furoate (MF) Suspension	*1.1 - 2.0*	*0.45 - 3.6*	*0.001 - 0.025*
Beclomethasone Dipropionate (BDP) Solution	*N/A*	*7- 9*	*0 - 2*

Formulation factors on Aerosolization Performance of MDIs

Delivered Dose

DoE MDIs	Factors	DD
AS Suspension	Drug PSD D_{50}	0.4717
	Ethanol	0.0193
	Oleic Acid	0.2645
MF Suspension	Drug PSD D_{50}	0.2433
	Ethanol	0.0122
	Oleic Acid	0.2433
BDP Solution	Ethanol	0.8691
	Oleic Acid	0.0006

Table 1: ANOVA for DD of DoE MDIs ($p < 0.05$ yellowed).

The effects of ethanol and oleic acid were statistically significant.

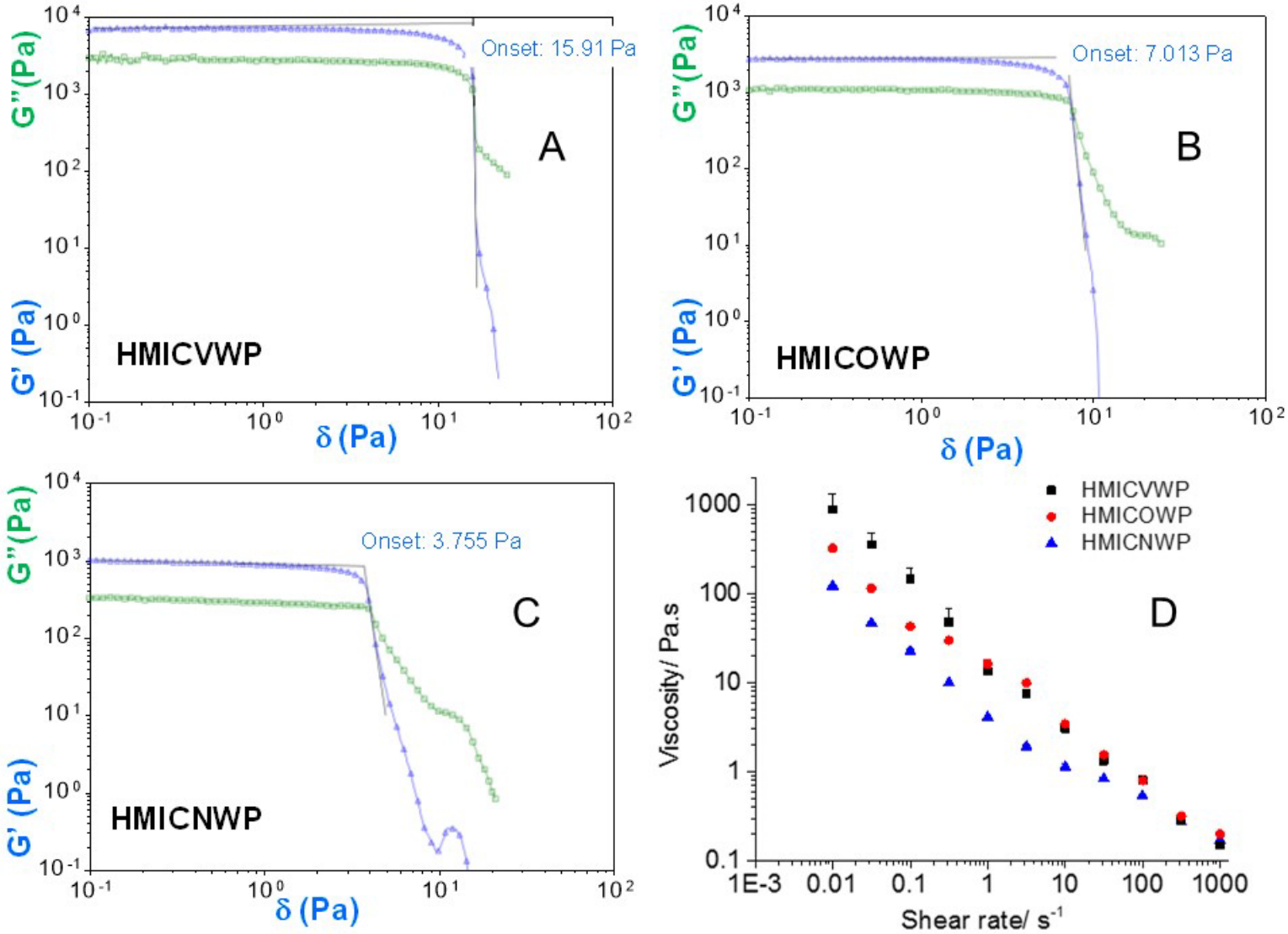
Fine Particle Dose < 5 μm

DoE MDIs	Factors	FPD<5
AS Suspension	Drug PSD D_{50}	0.0006
	Ethanol	0.0000
	Oleic Acid	0.5790
MF Suspension	Drug PSD D_{50}	0.0001
	Ethanol	0.0014
	Oleic Acid	0.0445
BDP Solution	Ethanol	0.5973
	Oleic Acid	0.0121

Table 2: ANOVA for FPD<5 of DoE MDIs ($p < 0.05$ yellowed).

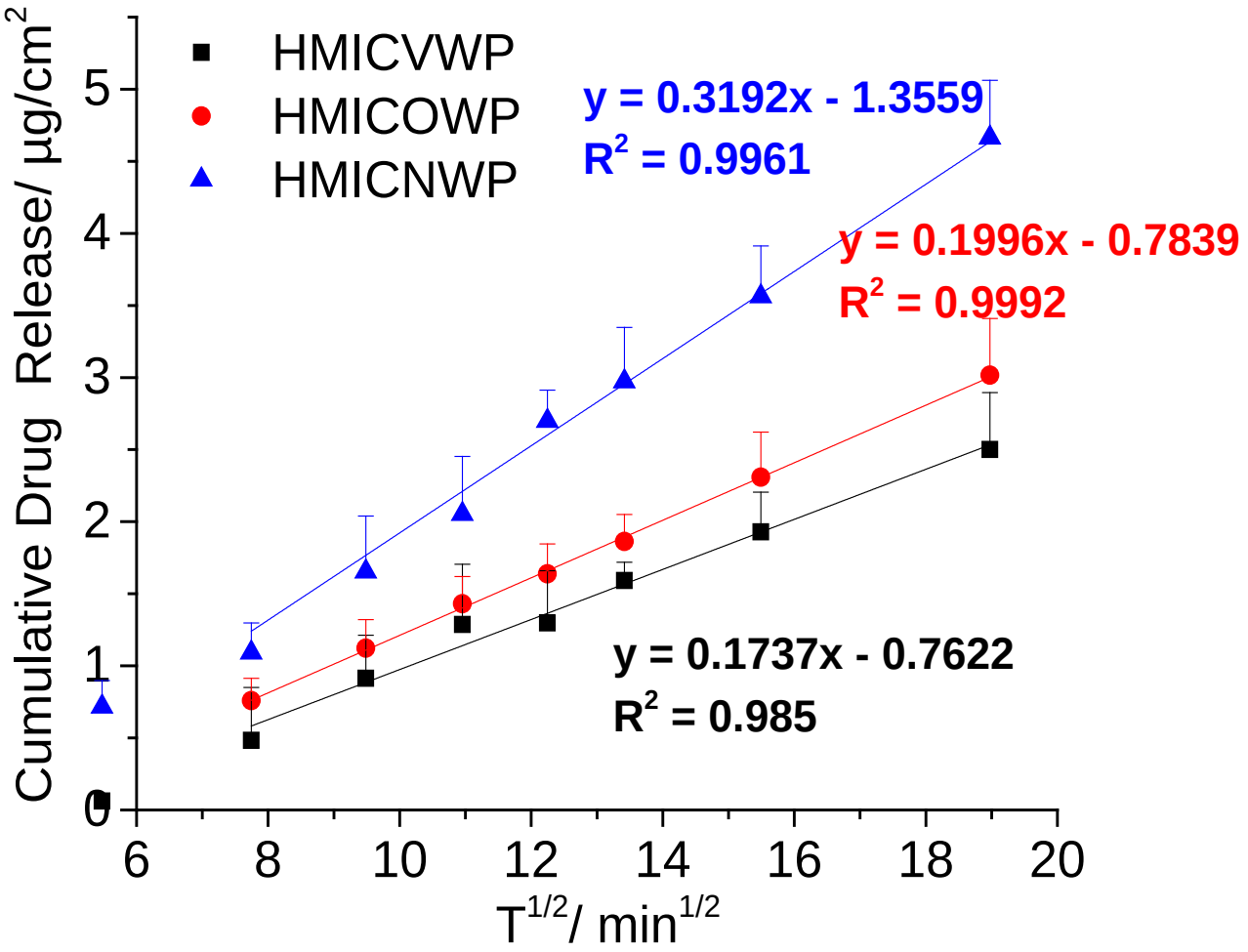
The effects of ethanol, oleic acid and drug PSD D_{50} were statistically significant.

Rheological profiles of ointments with different petrolatum sources



Bao Q, et al. Impact of Excipient Sources on *In Vitro* Drug Release Characteristics of Semisolid Ophthalmic Ointments. AAPS. Denver, CO. 2016. 34T0900

In vitro drug release profiles of ointments with different petrolatum sources



Bao Q, et al. Impact of Excipient Sources on *In Vitro* Drug Release Characteristics of Semisolid Ophthalmic Ointments. AAPS. Denver, CO. 2016. 34T0900

Draft Guidance on Acyclovir

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Acyclovir

Dosage Form; Route: Cream; topical

Recommended Studies: Two options: in vitro or in vivo study

I. In vitro option:

To qualify for the in vitro option for this drug product the following criteria should be met:

A. The test and Reference Listed Drug (RLD) products are qualitatively (Q1) and quantitatively (Q2) the same as defined in the Guidance for Industry *ANDA Submissions – Refuse-to-Receive Standards,* Revision 1 (May 2015).[1]

B. The test and RLD products are physically and structurally similar based upon an acceptable comparative physicochemical characterization of a minimum of three lots of the test and three lots (as available) of the RLD product.

C. The test and RLD products have an equivalent rate of acyclovir release based upon an acceptable in vitro release test (IVRT) comparing a minimum of one lot each of the test and RLD products using an appropriately validated IVRT method.

D. The test and RLD products are bioequivalent based upon an acceptable in vitro permeation test (IVPT) comparing the rate and extent of acyclovir permeation through excised human skin from a minimum of one lot each of the test and RLD products using an appropriately validated IVPT method.

Additional comments: Specific recommendations are provided below.

3. Comparison of physical and structural similarity for the test and RLD products should include the following physicochemical characterizations for each lot of test and RLD products:

   a. Assessment of appearance

   b. Analysis of the acyclovir polymorphic form in the drug product

   c. Analysis of particle size distribution and crystal habit with representative microscopic images at multiple magnifications.

   d. Analysis of the rheological behavior which may be characterized using a rheometer that is appropriate for monitoring the non-Newtonian flow behavior of semi-solid dosage forms. The following evaluations are recommended:

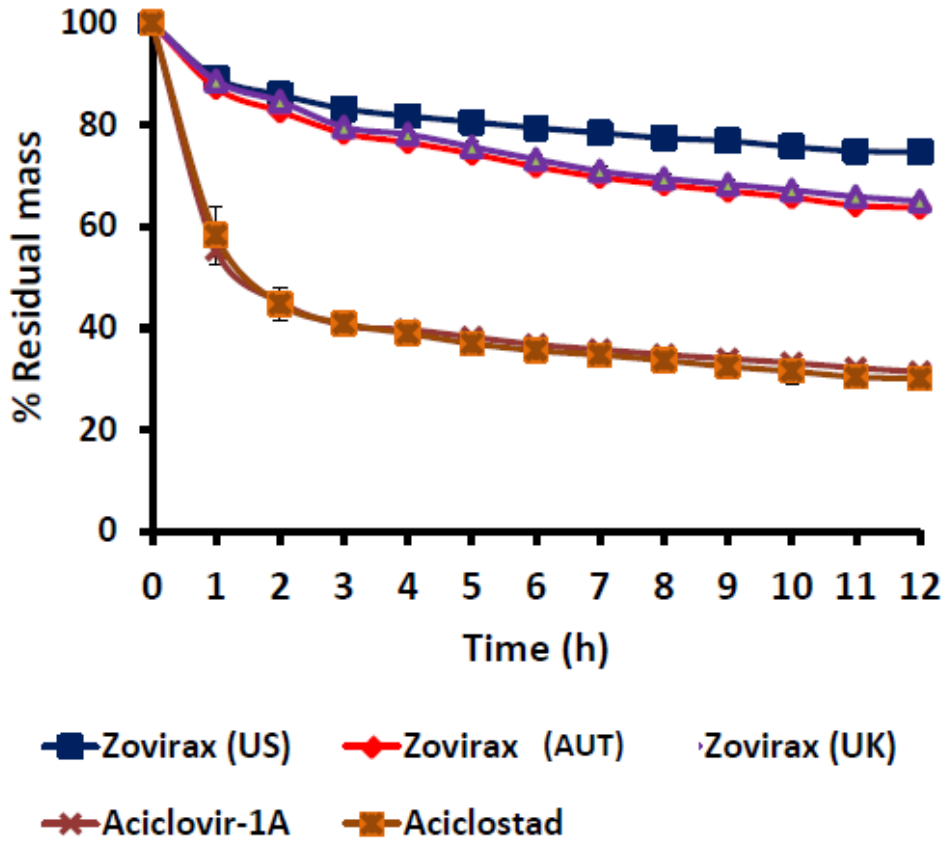
      - A complete flow curve of shear stress (or viscosity) vs. shear rate should consist of multiple data points across the range of attainable shear rates, until low or high shear plateaus are identified.
      - Yield stress values should be reported if the material tested exhibits plastic flow behavior.
      - The linear viscoelastic response (storage and loss modulus vs. frequency) should be measured and reported.

   e. Analysis of specific gravity, water activity, pH and any other potentially relevant physical and structural similarity characterizations.

Q3 and Dosage Form Metamorphosis

- Solvent Activity and Drying Rate

Prof. Narasimha Murthy FDA Award U01-FD005223



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Product	Solvent Activity (a_w)
Zovirax (US)	0.753 ± 0.002
Zovirax (AUT)	0.735 ± 0.000
Zovirax (UK)	0.732± 0.002
Aciclovir 1A	0.948 ± 0.001
Aciclostad	0.948 ± 0.003

Courtesy of Sam Raney, FDA

Assay of PLGA

- Mw, L:G ratio, polymer end-cap
- GPC, 1H NMR, 13C NMR

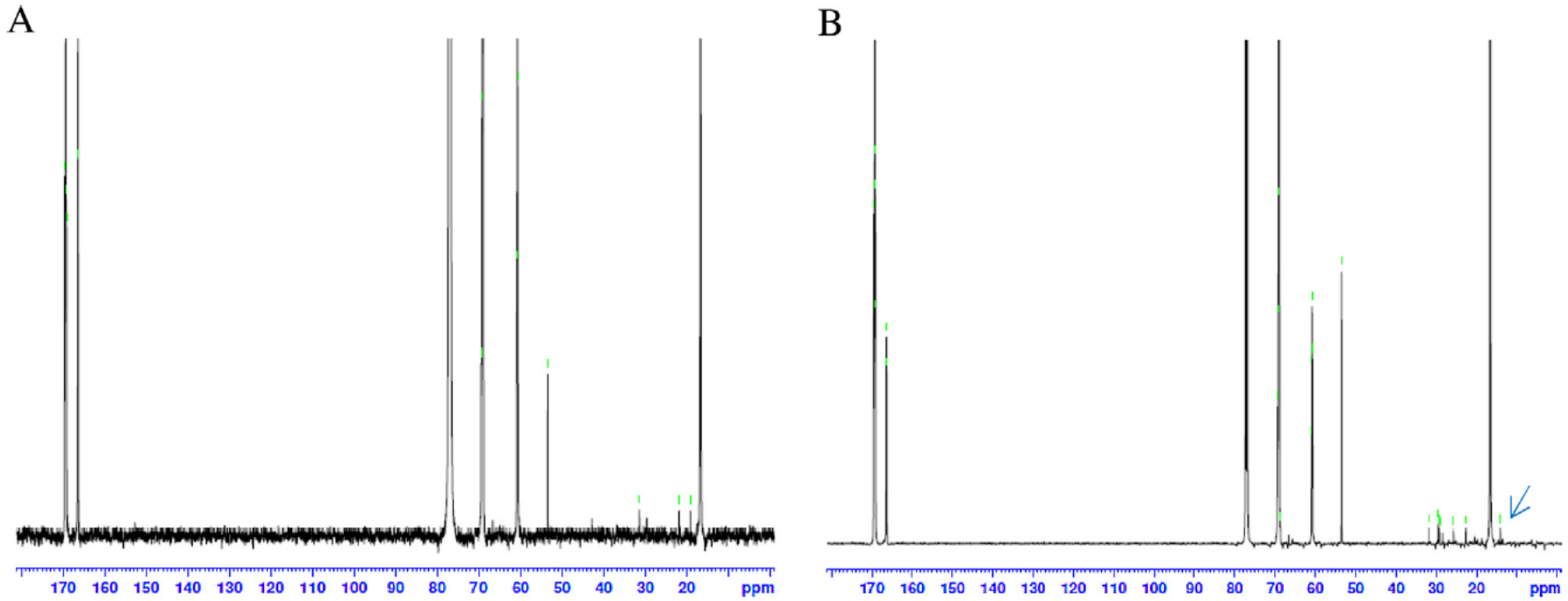

Fig. 2. ^{13}C NMR of purified PLGA from microparticles made of acid end-capped PLGA (A) and ester end-capped PLGA (B).

Garner J, et al. A protocol for assay of poly(lactide-co-glycolide) in clinical products. Int J Pharm. 2015 Nov 10;495(1):87-92.

FY17 Generic Drug Research Public Workshop

- Wednesday, May 3, 2017 at the FDA White Oak Campus (Bldg 31, Great Room A) in Silver Spring, MD
- To obtain input from industry and other interested stakeholders on the identification of regulatory science priorities for FY 2018.
- Please monitor the Federal Register and the GDUFA Regulatory Science webpage (www.fda.gov/GDUFARegScience) for registration information and instructions on providing comments.

Conclusions

- Bioequivalence of some products may be assessed through in vitro methods
- In vitro methods can provide additional options for bioequivalence assessment and supports generic development and approval for products without generic counterparts
- FDA has an extensive generic drug research program established under GDUFA covering a wide range of dosage forms and therapeutic areas to develop and evaluate in vitro testing methods for equivalence
- Outcomes from research studies will help in development of guidances and recommendations to industry on development of in vitro bioequivalence methods

Questions?

Stephanie Choi, Ph.D.

Acting Associate Director for Science

Office of Research and Standards

Office of Generic Drugs

Stephanie.Choi@fda.hhs.gov

GDUFA Regulatory Science Website:

www.fda.gov/GDUFARegScience