IMPACT OF EXCIPIENT GRADE (Q1/Q2) ON THE BIOEQUIVALENCE OF GENERIC DRUG PRODUCTS

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

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

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.

Need for Q1 and Q2 equivalence

- Regulations require Q1 and Q2 equivalence:
  - Parenteral
  - Ophthalmic
- Q1 and Q2 equivalence may support use of in vitro option:
  - Inhalation
  - Dermal
  - GI acting

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

In vitro equivalence approaches

- **Characterization based**
  - Strong Q1/Q2/Q3 characterization
  - Excipients need to be characterized and equivalent
- **Performance based**
  - Q3 differences may be observed
  - Excipients may have allowable differences that need data to show they do not impact equivalence

Excipient grade on bioequivalence assessment

- Different grades of an excipient are generally permitted for use in a test product submitted under an ANDA (Abbreviated New Drug Application)
- For products that qualify for solely in vitro studies to demonstrate bioequivalence, change in grade may need further justification

Effect of excipient grade on bioequivalence

- Could a difference in grade (i.e., viscosity, particle size, molecular weight) impact the rate and extent to which the active ingredient becomes available at the site of action?
- Bioequivalence is usually assessed through in vivo studies
- For products that are not evaluated by in vivo studies, proper in vitro tests must be conducted

Considerations when using a different excipient grade

- Is the product a systemically acting or a locally acting product?
- Is the product an immediate release (IR) or extended release (ER) formulation? Is the excipient a release controlling excipient?
- Is there a difference in specifications?
- Will the excipient be acquired from a different source?
- Is the product a complex drug product?
- Will in vivo studies be conducted to demonstrate bioequivalence?

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

Draft Guidance on Dexamethasone; Tobramycin

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: Dexamethasone; Tobramycin

Dosage Form; Route: Suspension; ophthalmic

Recommended Study: Two options

I. Option One: In vitro studies

To qualify for the in vitro option for this drug product (dexamethasone; tobramycin 0.05%; 0.3%), all of the following criteria should be met:

i. The test and reference listed drug (RLD) formulations are qualitatively[1] and quantitatively[2] the same (Q1/Q2).

ii. Acceptable comparative physicochemical characterizations of the test and RLD formulations. The characterization study should be performed on at least three exhibit batches of both the test and RLD products[3] and should include:

- Comparative crystalline habit of dexamethasone
- Comparative appearance, pH, specific gravity, osmolality, surface tension, buffer capacity, and viscosity as a function of applied shear (Viscosity measurement should be conducted in the presence and absence of tear fluid.)
- Comparative re-dispersibility (time required to re-disperse the formulation, and sedimentation time)
- Comparative soluble fraction of dexamethasone in the final drug product
- Comparative unit dose content (one drop per unit dose, for both APIs) (Provide data for the amount of unit dose (one drop) with assay for both APIs from a minimum of ten units from three batches each of the test and reference products. The unit dose content should be compared using population BE (95% upper confidence bound).)

Draft Guidance on Cyclosporine

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Active Ingredient: Cyclosporine

Dosage Form; Route: Emulsion; ophthalmic

Strength: 0.05%

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

I. In vitro option:

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

i. The test and reference listed drug (RLD) formulations are qualitatively (Q1)[1] and quantitatively (Q2)[2] the same[3].

ii. Acceptable comparative physicochem formulations. The comparative study batches of both test and RLD product

Parameters to measure: Globule si applied shear, pH, zeta potential, osm dynamic light scattering method (or PCS, QELS) to measure the globule size of the test and RLD formulations, and provide comparable size distribution profiles (intensity-weighted histograms) upon serial dilutions. Information on the instrument, analysis mode (if applicable), dilution medium, and level of dilution used for globule size measurement should be provided.

No changes (source, grade, etc.) should be made to the structure forming excipient or solubilizing excipient in the product for commercial batches unless adequate supporting data and risk assessment are provided to demonstrate that the changes will not affect the product performance and quality

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

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

Goal of GDUFA Research

- Enhance access to generic versions of complex products
  - Expand the use of in vitro BE approaches
- Excipient 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

Research projects on excipients

Title	Award Institution	Start Year
ORAL		
Chemoinformatic tools to predict the effects of excipients in generic drugs	University of California, San Francisco	2015
Effects of excipients in generic drug products on intestinal drug transporters	University of California, San Francisco	2015
INHALATION		
Comprehensive evaluation of formulation effects on metered dose inhaler performance	Cirrus Pharmaceuticals (Recipharm); University of Florida	2013
OPHTHALMIC		
Evaluation and development of dissolution testing methods for semisolid ocular drug products	University of Connecticut	2014
Dissolution methods for predicting bioequivalence of ocular semi-solid formulations	University of Connecticut	2014

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Title	Award Institution	Start Year
COMPLEX DRUGS		
Dissolution methods for parenteral sustained release implant drug products	University of Connecticut	2014
Influence of raw materials, manufacturing variables, and storage conditions on release performance of long acting release microsphere products	University of Michigan	2015
TOPICAL		
Topical products and critical quality attributes	University of Mississippi	2014
Characterization of critical quality attributes for semisolid topical drug products	University of South Australia	2014

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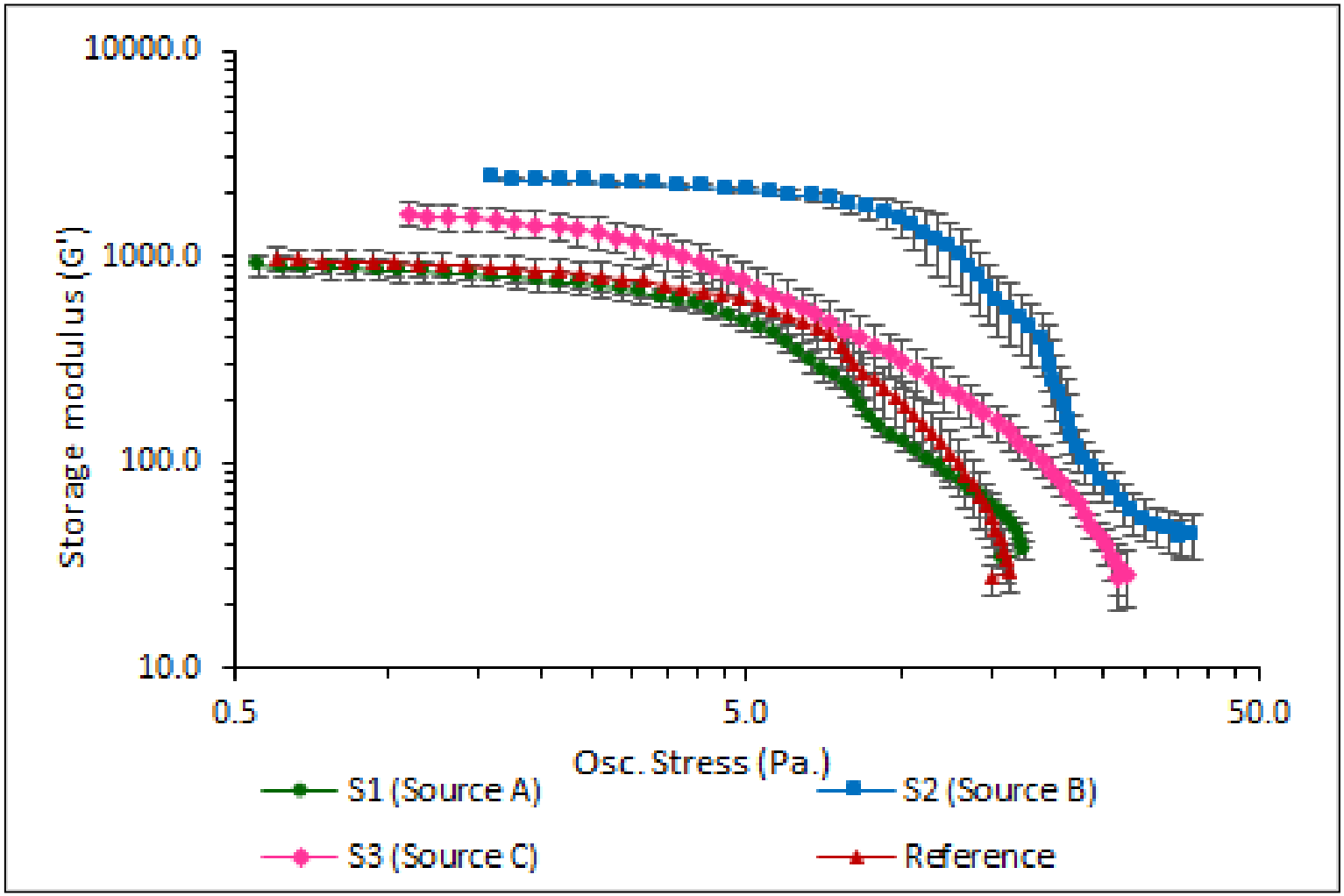
Ophthalmic Ointments

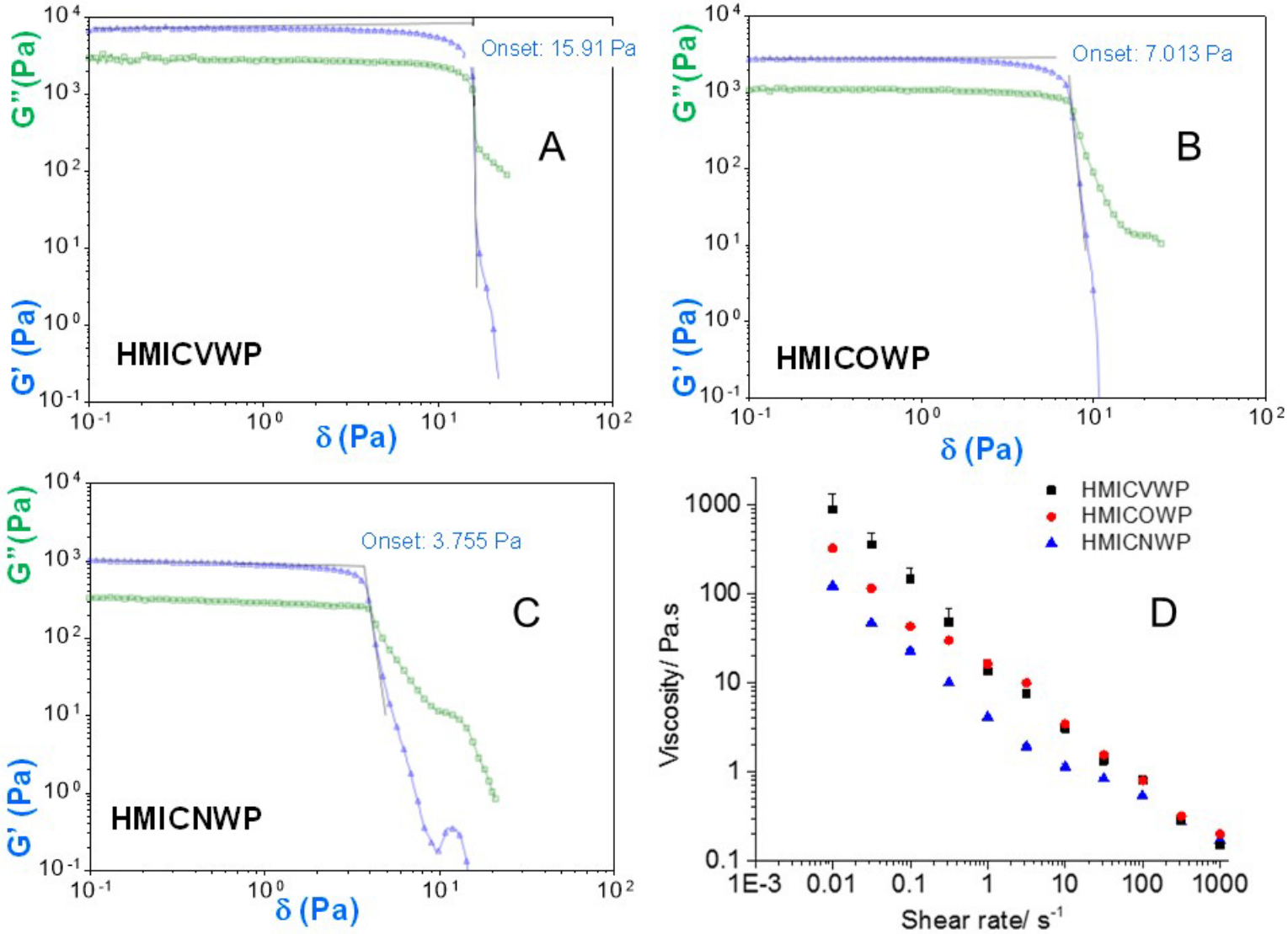
- 39 ophthalmic ointment Reference standards approved
- Generics only available for 6 ophthalmic ointment products
- Need for in vitro approaches to demonstrate bioequivalence
  - What physicochemical tests should be recommended to evaluate bioequivalence?

Petrolatum source on physicochemical characteristics of ocular ointments



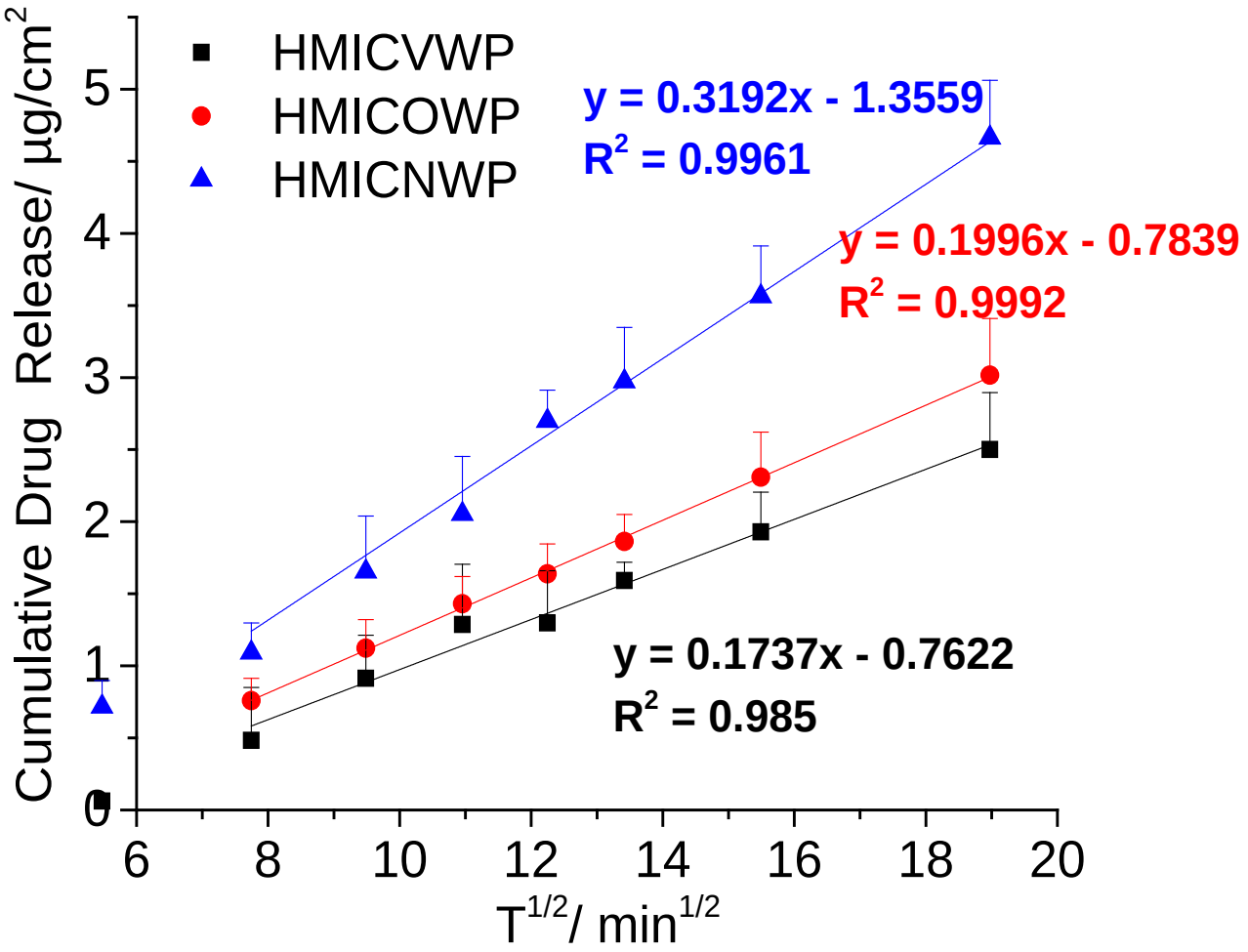
S Patere, et al. Influence of Excipients on Physicochemical Characteristics of Ocular Semisolid Formulations and Their In Vitro Drug Release. AAPS. Orlando, FL. 2015. W5057

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



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PLGA-based drug products

- PLGA (poly(lactic-co-glycolic acid)) is used in FDA approved drug products for a variety of formulations (microspheres, implants, in situ gelling depot)
- 15 PLGA-based Reference standards approved
- No generic products available

Drug Product (Active Ingredient)	Dosage Form	Route of Administration	Indication(s)
Ozurdex (Dexamethasone)	Implant	Intravitreal	macular edema, non-infectious uveitis, and diabetic macular edema
Zoladex (Goserelin acetate)	Implant	Subcutaneous	Prostate cancer
Atridox (Doxycycline hyclate)	In situ forming gel	Periodontal	periodontitis
Eligard (Leuprolide acetate)	In situ forming gel	Subcutaneous	advanced prostate cancer
Lupron (Leuprolide acetate)	Microsphere	Intramuscular	endometriosis
Lupron Depot (Leuprolide acetate)	Microsphere	Intramuscular	advanced prostatic cancer
Lupron Depot-PED (Leuprolide acetate)	Microsphere	Intramuscular	central precocious puberty
Trelstar (Triptorelin pamoate)	Microsphere	Intramuscular	advanced prostate cancer
Risperdal Consta (Risperidone)	Microsphere	Intramuscular	schizophrenia and bipolar I disorder
Signifor LAR (Pasireotide pamoate)	Microsphere	Intramuscular	acromegaly
Vivitrol (Naltrexone)	Microsphere	Intramuscular	alcohol dependence
Arestin (Minocycline HCl)	Microsphere	Periodontal	periodontitis
Bydureon (Exenatide)	Microsphere	Subcutaneous	type 2 diabetes
Sandostatin LAR (Octreotide)	Microsphere	Subcutaneous	acromegaly
Somatuline Depot (Lanreotide acetate)	Microsphere	Subcutaneous	gastroenteropancreatic neuroendocrine tumors

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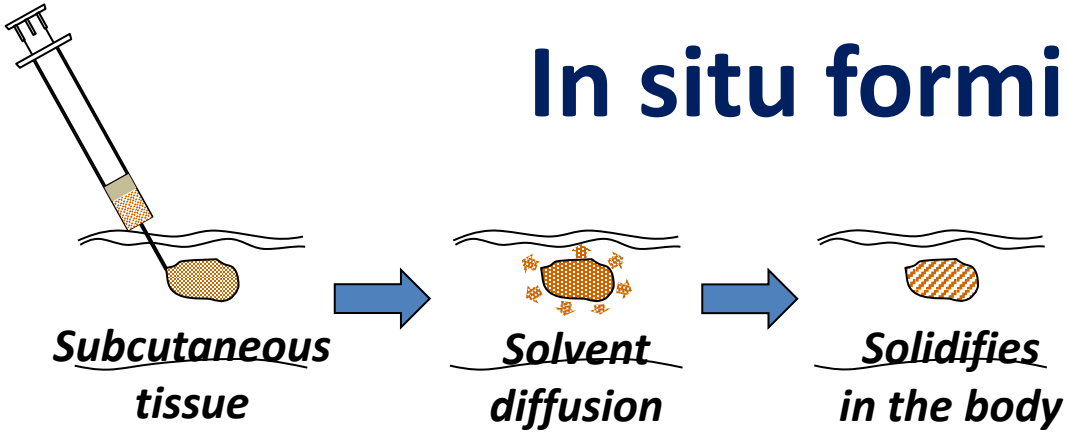
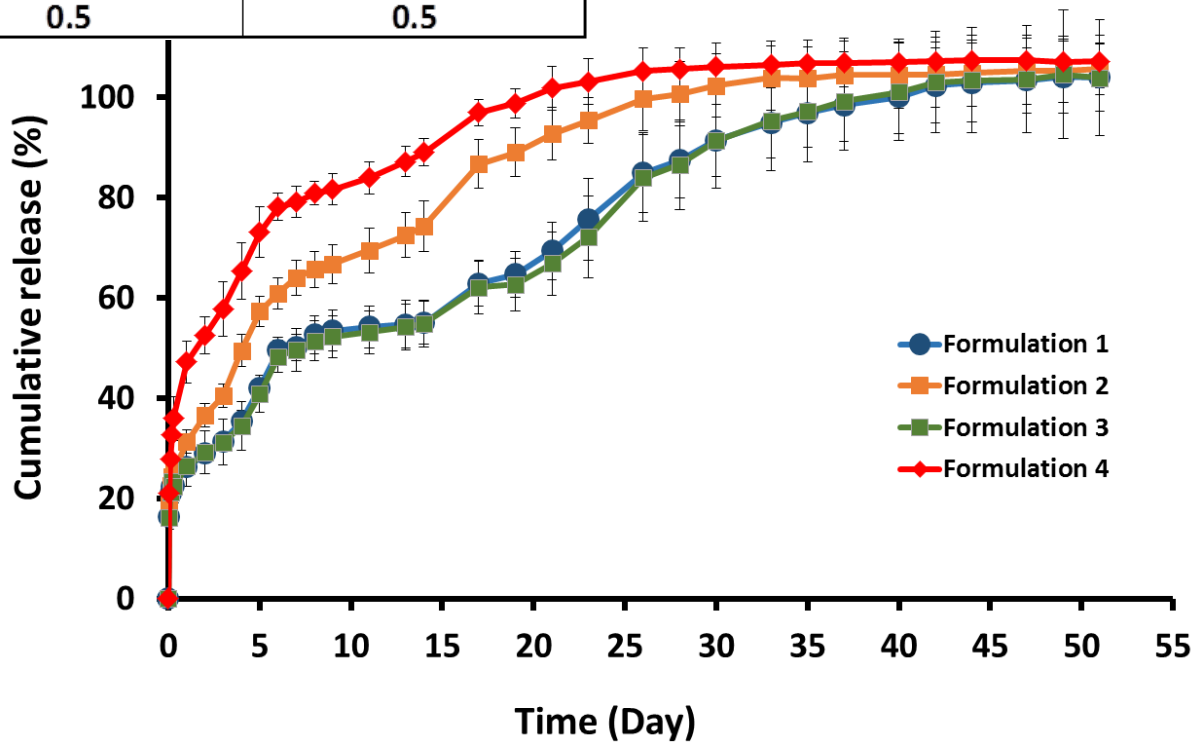
In situ forming gels



Suh M, et al. Effect of solvent diffusion from in situ-forming implants on drug release. AAPS. Denver, CO. 2016. 22T0230

Formulation	Polymer vendor	Water content in NMP (%)	Freeze-dried volume (ml)
1	A	0.05	0.5
2	B	0.05	0.25
3	A	0.5	0.25
4	B	0.5	0.5



Conclusions

- Change in excipient grade may or may not have an impact on bioequivalence and bioavailability depending on the formulation, route of administration, and function of the excipient
- To address questions regarding changes in excipient grade, FDA has established a research program for generic drugs in various product categories
- Outcomes from research studies will help in development of guidances and recommendations to industry on excipient selection for generic products

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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