Critical Roles of Excipients in the Development of Generic Drug Products

Robert Lionberger
Director, Office of Research and Standards
Office of Generic Drugs, Food and Drug Administration
October 17, 2021

Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies. ~~*The opinions expressed in this presentation are those of the speaker and may not reflect the position of the U. S. Food and Drug Administration*~~

Importance of Excipients

- FDA approves drug **products**
- Excipients have activity, ~~and~~ function, and side-effects that affect safety, efficacy, and equivalence
- Over the past 10 years, GDUFA (the generic drug user fee program) has supported science and research related to the use of excipients in generic drugs

GDUFA Science and Research Report

- The FY2020 GDUFA Science and Research Report ~~will be~~ is available at: https://www.fda.gov/drugs/generic-drugs/generic-drug-research-related-guidances-reports
- It highlights the scope and impact of **all** GDUFA-supported research across FDA
- High transparency to the generic industry on what we use GDUFA resources for

Active vs. Inactive Ingredients

- An Active Ingredient (per 21 CFR 210.3(b)(7))
  - Any component of a drug product intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body.

- An Inactive Ingredient (per 21 CFR 210.3(b)(8))
  - Any component of a drug product other than the active ingredient

Goals of GDUFA Research

- Generic drug development is first and foremost product development
- Advance the science of excipient selection and regulatory evaluation
  - Regulatory science is decision science
  - Make better and faster decision about excipients
- Encourage innovation in product development
  - Value of excipient function to drug product performance and equivalence
  - Expand access to complex generics

Intersections of Generic Drug Development with Excipients

- Excipients effect on oral bioavailability
- Safety of excipients
- Excipients in locally acting products
- Excipients in complex products

Excipients are a Constraint!

Both safety and regulations limit the excipients that can be used in generic development

ORAL DOSAGE FORMS

Excipients and Oral Products

- Difference in excipients between brand and generic product are allowed by regulations
- Excipients in generic products generally must be used at levels below those of approved products for that route of administration
  - See FDA's Inactive Ingredient Database
- Excipients impact the in vivo performance of generic products

Food Effects and Fed Bioequivalence (BE)

- Generally accepted that co-administration with food can change bioavailability
  - Routinely evaluated in new drug development and used to inform product label
  - Food effects can arise from both the active ingredient and the formulation
  - Routinely evaluated in generic drug development as part of evaluation of bioequivalence (fed BE study)
    - Some difference between EMA and FDA on when fed BE is needed

Biopharmaceutics Classification System (BCS) based Biowaivers

- BCS class I (high solubility, high permeability)
  - Waivers when the drug product (test and reference) is rapidly dissolving
- BCS class III (high solubility, low permeability)
  - Waivers when the drug product (test and reference) is **very** rapidly dissolving
  - **the product formulations are qualitatively the same and quantitatively very similar**
    - Based on a concern that excipient might affect bioequivalence

Biopharmaceutics Classification System 2015 Draft Guidance
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070246.pdf

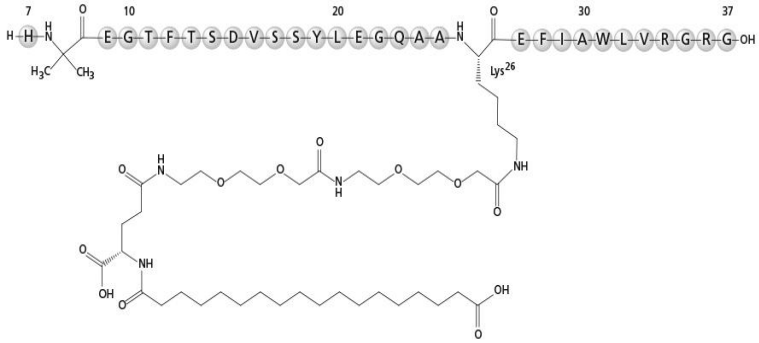
Excipients and Drug-Drug Interactions (DDIs)

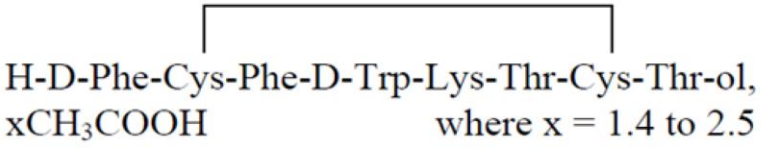
- DDIs are generally expected to be the same for brand and generic products
- If DDIs occur in the GI tract, then differences in excipients could change the DDIs
  - Uptake and efflux transporters
  - Gut wall metabolism
  - Interactions with proton pump inhibitors (PPI)

Absorption Enhancers

- FDA recently approved new drug products for the oral delivery of peptides

	RYBELSUS®	MYCAPSSA®
Active ingredient	Semaglutide	Octreotide acetate
Dosage form, route of administration	Tablet, Oral	Capsule, Oral
Strength	3, 7, 14 mg (RS)	20 mg (RS)
Application number	NDA 213051	NDA 208232
Approval date	Sep 20, 2019	Jun 26, 2020
Applicant holder	Novo Nordisk	Chiasma
Indication	Glycemic control in T2D	Somatostatin analog for acromegaly patients





Comparison of Delivery Strategy

	Semaglutide oral tablet	Octreotide DR capsule
Objective	Prevent enzyme degradation, enhance absorption	
Formulation	Uncoated immediate release tablet	Capsule, oily suspension of solid hydrophilic particles in lipophilic medium
Absorption site	Erosion in stomach	Disintegration in small intestine
Absorption enhancer	SNAC	Sodium caprylate
Mechanism	• Buffering effect • Monomerization • Permeation enhancer	• Delayed-release (enteric coating agent) • Permeation enhancer

Generic Drug Path

- Their products rely on excipients to function
  - Do generic products have to have the same excipients?
- First FDA product specific guidance posted in August 2021
  - https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_213051.pdf
- More in vivo data need when there are excipient differences

Future Directions

- PBPK models of absorption should be able to predict all of these effects on a mechanistic basis
- Clinical and Quantitative Pharmacology input into size of acceptable differences
  - What size food effect or DDI effect impacts labeling or BE?
- GDUFA research support because of the impact on key generic drug decisions by both industry and FDA

EXCIPIENT SAFETY EVALUATION IN ANDAS

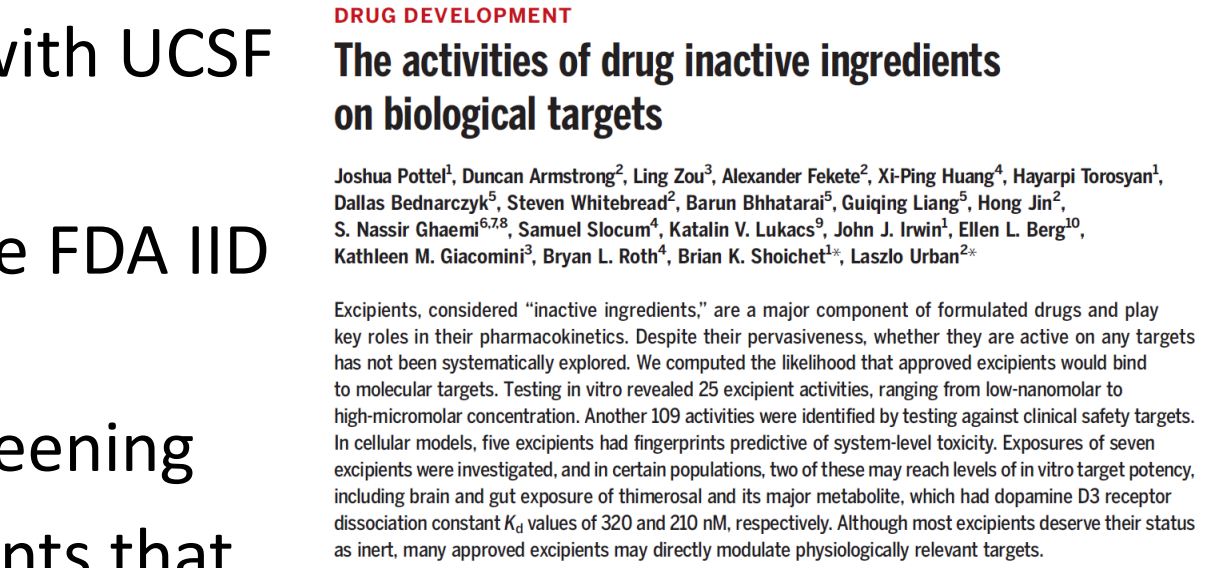
Excipient Safety Assessments

- For new drug products, clinical studies are conducted using the drug product (including its excipients)
  - Novel excipients submit pre-clinical data
- For generic drug products, safety evaluation of excipients is generally based on prior knowledge (no new pre-clinical or clinical safety studies)
  - FDA's prior knowledge on excipients (Inactive Ingredient Database) is organized based on route of administration
  - The review is focused on safety of the proposed excipient for the patient population
    - Route, dose, duration of use, existing safety info
    - Patient population: drug toxicity, disease

FDA Guidance for Industry: **Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients**
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf

GDUFA Research

- Collaboration with UCSF
- Computational screening of the FDA IID
- Follow up high throughput screening
- Identify excipients that have potential pharmacological activity



DRUG DEVELOPMENT

The activities of drug inactive ingredients on biological targets

Joshua Pottel[1], Duncan Armstrong[2], Ling Zou[3], Alexander Fekete[2], Xi-Ping Huang[4], Hayarpi Torosyan[1], Dallas Bednarczyk[5], Steven Whitebread[2], Barun Bhhatarai[5], Guiqing Liang[5], Hong Jin[2], S. Nassir Ghaemi[6,7,8], Samuel Slocum[4], Katalin V. Lukacs[9], John J. Irwin[1], Ellen L. Berg[10], Kathleen M. Giacomini[3], Bryan L. Roth[4], Brian K. Shoichet[1]*, Laszlo Urban[2]*

Excipients, considered "inactive ingredients," are a major component of formulated drugs and play key roles in their pharmacokinetics. Despite their pervasiveness, whether they are active on any targets has not been systematically explored. We computed the likelihood that approved excipients would bind to molecular targets. Testing in vitro revealed 25 excipient activities, ranging from low-nanomolar to high-micromolar concentration. Another 109 activities were identified by testing against clinical safety targets. In cellular models, five excipients had fingerprints predictive of system-level toxicity. Exposures of seven excipients were investigated, and in certain populations, two of these may reach levels of in vitro target potency, including brain and gut exposure of thimerosal and its major metabolite, which had dopamine D3 receptor dissociation constant K_d values of 320 and 210 nM, respectively. Although most excipients deserve their status as inert, many approved excipients may directly modulate physiologically relevant targets.

- Pottel et al., Science 369, 403–413 (2020)

Future Direction

- A better understanding of the pharmacological activity of excipients will support better decisions on safety evaluations that involve exposure of a particular patient population to an excipient in a generic drug application
- Evaluation of grades of polymeric excipients needs to consider sensitivity of activity and exposure to molecular weight

LOCALLY ACTING DRUG PRODUCTS

Locally Acting Drug Products

- Products directly deliver drug and excipients to the site of action
- Systemic drug exposure (PK) is often a side effect and may not be measurable
- Clinical pharmacology and bioequivalence assessments are harder

Excipients and Locally Acting Products

- For inhalation, nasal and topical products FDA regulations allow differences in excipients
- FDA bioequivalence recommendations sometimes are different based on formulation sameness (no excipient differences)

Topical Dermatological

- GDUFA research has established the Q1 Q2 Q3 pathway for in vitro BE for topical products
  - Q1: Components in a product
    - Q1 characterization of a reference product provides a profile of the qualitative components (ingredients) in that reference product
  - Q2: Composition of a product
    - Q2 characterization of a reference product provides a profile of the quantitative formulation composition of that reference product
  - Q3: Arrangement of matter in a product
    - Q3 characterization of a reference product provides a profile of physicochemical and structural attributes that is quintessentially characteristic of that reference product

Topical Dermatological

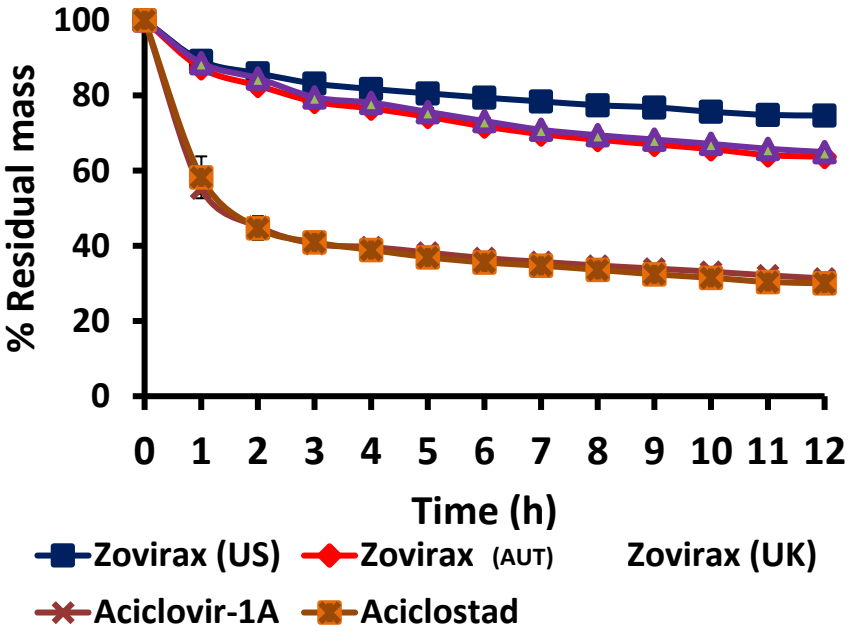
- Current efforts are building the science for non-Q1 Q2 topicals (differences in excipients)
- The formulation of a topical semisolid dosage form can influence its performance
- Excipients may exert their influence, by modulating the physicochemical and microstructural arrangement of matter in the dosage form
- The resulting physical and structural characteristics of topical dosage forms, and their metamorphic properties on the skin, can directly influence topical bioavailability

Topical Dermatological Drug Products

- Do topical excipients act on the disease state?
  - Inactive ingredients in a placebo vehicle may account for some of the therapeutic effect.
  - Inactive ingredients may modulate the delivery/bioavailability of the active ingredient, which then acts on the disease state. This is the most widely characterized.
  - Do changes in the quality of topical excipients impact therapeutic effect, either way?

Dosage Form Metamorphosis

- Solvent Activity and Drying Rate

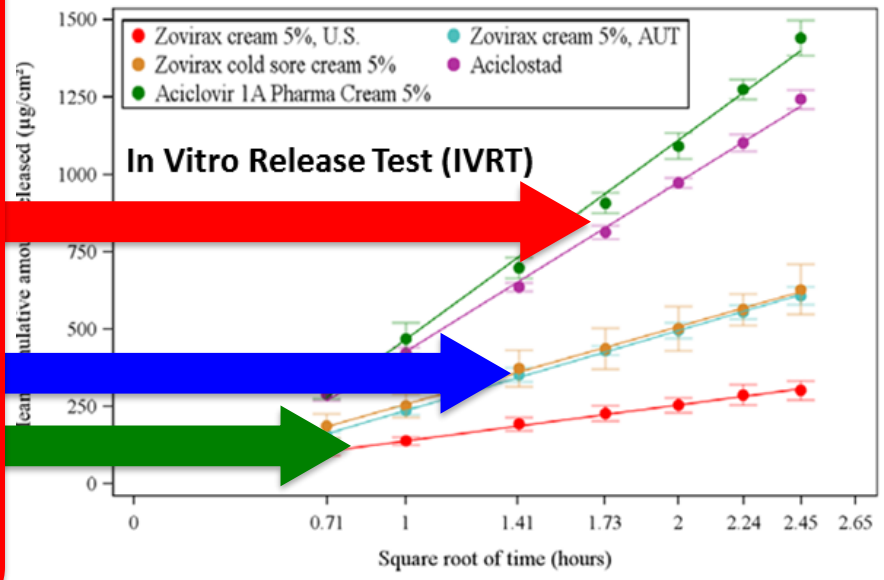


Product	Solvent Activity (a_w)
Zovirax (US)	0.753 ± 0.002
Zovirax (AUT)	0.735 ± 0.000
Zovirax (UK)	0.732± 0.002
Aciclovir 1A	0.948 ± 0.001
Aciclostad	0.948 ± 0.003

Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223***

In Vitro Characterization (Acyclovir)

	Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir-1A (Austria)
	Water	Water	Purified water	Water	Water
	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol
	Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
	White petrolatum	White soft paraffin	White Vaseline	White Vaseline	White Vaseline
	Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcohol	Cetyl alcohol	Cetyl alcohol
	SLS	SLS	SLS		
	Poloxamer 407	Poloxamer 407	Poloxamer 407		
		Dimethicone 20	Dimethicone 20	Dimethicone	Dimethicone
		Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate
		Polyoxyethylene stearate	Polyoxyethylene stearate	Macrogol stearate	Polyoxyethylene stearate
Density (g/cc)	1.02	1.02	1.02	1.02	1.01
Content Uniformity (%)	97.9 ± 0.7	99.6 ± 1.4	100 ± 2.2		
Polymorphic Form	2,3 hydrate	2,3 hydrate	2,3 hydrate		
Crystilline Habit	Rectangular	Rectangular	Rectangular	Ovoid	Ovoid
Particle size (d50) (µm)	3.8				
pH	7.74	7.96	7.54	4.58	6.05
Work of Adhesion	59	81	60	17	18
Drug in Aq (mg/g)	0.49	0.64	0.49	0.37	0.26
Drying Rate (T-30%)	>12h	~8h	~7h	<1h	<1h
Water Activity	0.75	0.73	0.74	0.95	0.95

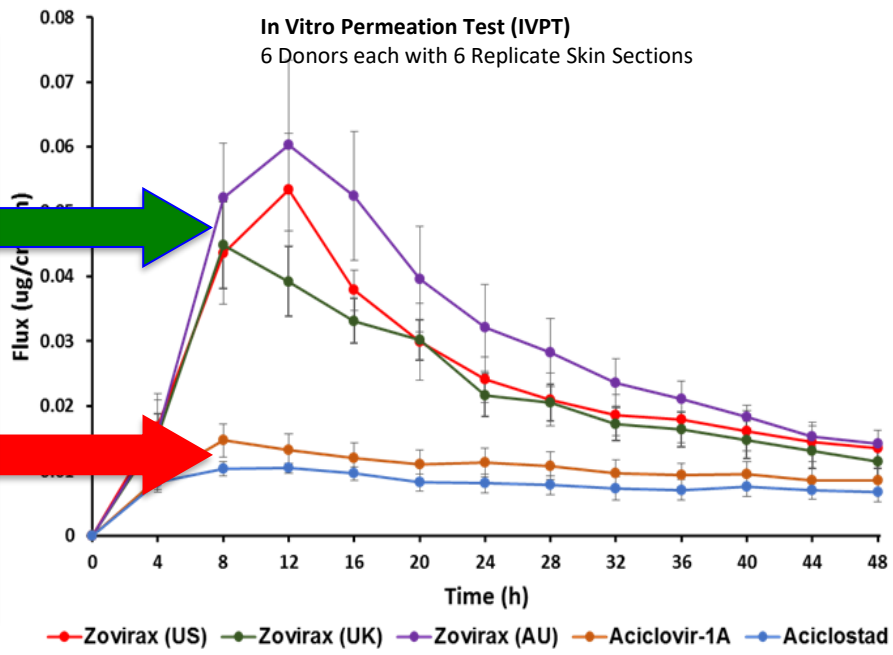


Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223***

In Vitro Characterization (Acyclovir)

In Vivo Cutaneous PK Study

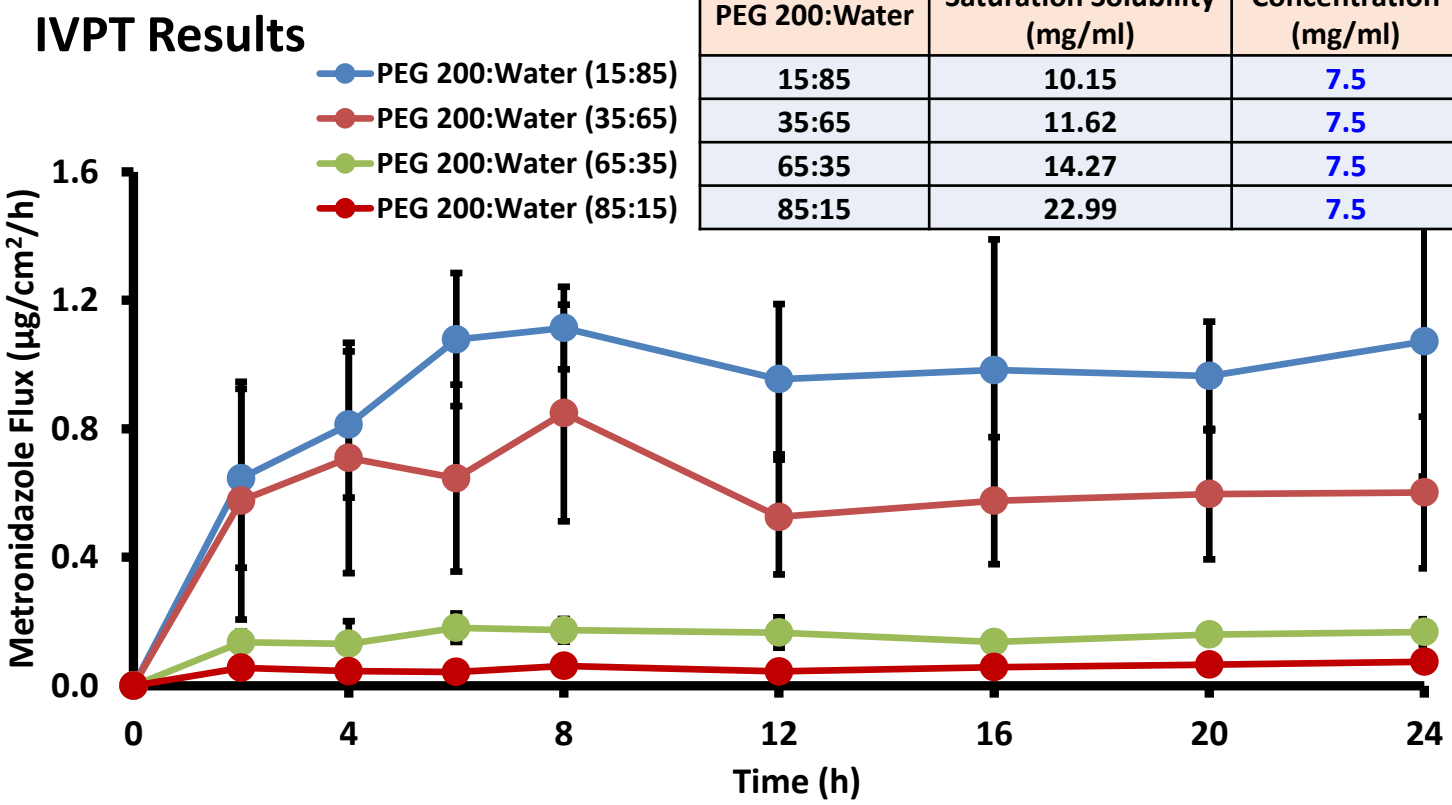
	Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir-1A (Austria)
	Water	Water	Purified water	Water	Water
	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol
	Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
	White petrolatum	White soft paraffin	White Vaseline	White Vaseline	White Vaseline
	Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcoh	Cetyl alcohol	Cetyl alcohol
	SLS	SLS	SLS		
	Poloxamer 407	Poloxamer 407	Poloxamer 407		
		Dimethicone 20	Dimethicone 20	Dimethicone	Dimethicone
		Arlacel 165	Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate
		Arlacel 165	Polyoxyethylene stearate	Macrogol stearate	Polyoxyethylene stearate
Density (g/cc)	1.02	1.02	1.02	1.02	1.01
Content Uniformity (%)	97.9 ± 0.7	99.6 ± 1.4	100 ± 2.2	99.7 ± 1.7	98.3 ± 2.6
Polymorphic Form	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate
Crystilline Habit	Rectangular	Rectangular	Rectangular	Ovoid	Ovoid
Particle size (d50) (µm)	3.8	2.5	3.4	6.8	6
pH	7.74	7.96	7.54	4.58	6.05
Work of Adhesion	59	81	60	17	18
Drug in Aq (mg/g)	0.49	0.64	0.49	0.37	0.26
Drying Rate (T-30%)	>12h	~8h	~7h	<1h	<1h
Water Activity	0.75	0.73	0.74	0.95	0.95



Data provided courtesy of Prof. Narasimha Murthy (University of Mississippi) ***FDA Award U01-FD005223***

Thermodynamics (Metronidazole)

PEG 200:Water	Saturation Solubility (mg/ml)	Concentration (mg/ml)	α
15:85	10.15	7.5	0.74
35:65	11.62	7.5	0.65
65:35	14.27	7.5	0.53
85:15	22.99	7.5	0.33



Data provided courtesy of Dr. Narasimha Murthy associated with FDA funding for award U01FD0006507

Summary

- Generic topical product may use different excipients than the brand product
- FDA has efficient BE methods for topical products that are Q1 Q2
- Current research is focused on bioequivalence for products that may not be Q1 Q2

PARENTERAL DRUG PRODUCTS

Excipients and Parenteral Products

- Generally, a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the [RLD].
  - However, an applicant may seek approval of a drug product that ***differs from the [RLD] in preservative, buffer, or antioxidant*** provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product
- Sameness of excipients in complex parenterals has been a key GDUFA research focus

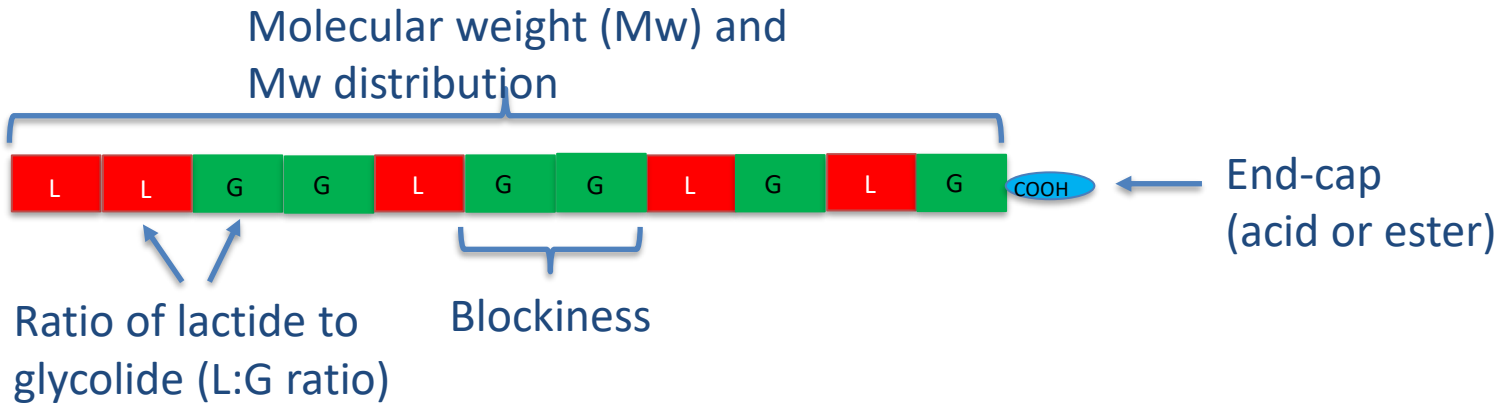
Complex Parenterals

- Emulsions
- Liposomes
- Nanosuspensions
- In situ forming gels
- Implants
- Microspheres

- All have structures formed by excipients
  - Complexity in structure and composition
  - May be difficult to purify or analyze
  - Excipient in finished drug product may not be the same as starting raw material
- Generic products must use the same excipients to build the same structures

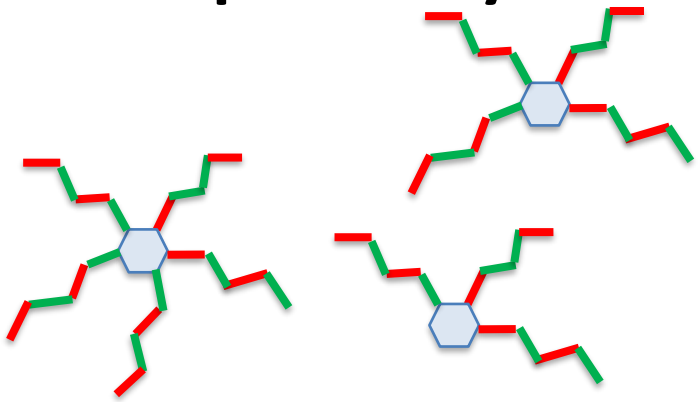
PLGA Polymers

- PLGAs are biodegradable random copolymers
  - Poly(D,L-lactic and glycolic acid) (PLGA) copolymers
- PLGA polymers have been used in ~20 long-acting injectable products as the rate controlling excipient



More Polymer Complexity

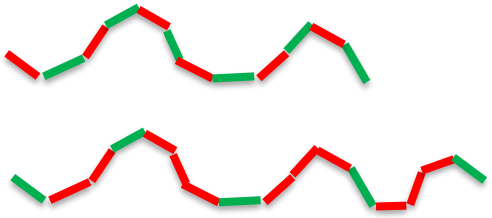
vs.



Linear polymer

glucose star polymer

vs.



Single polymer

mixed polymers

FDA Regulatory Advice

- How to do this?

The proposed parenteral drug product should be qualitatively (Q1) and quantitatively (Q2) the same as the reference product for all strengths (12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial). Please provide characterization data on poly(lactide-co-glycolide) (PLGA) for both the test and reference product including polymer composition (ratio between glycolic acid and lactic acid), molecular weight and weight distribution, and PLGA architecture (e.g., linear or star-branched PLGA). Additional data on PLGA characterization may be requested during the review of the ANDA.

GDUFA Research Program

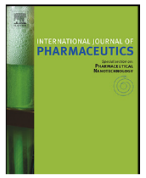
- Improved understanding on characteristics of PLGA polymers
- Development of analytical tools for structural characterization for star-shaped polyesters used for drug delivery
- Advanced analytical techniques for separating PLGA polymers when used in the same formulation

Example Publications

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm



A protocol for assay of poly(lactide-*co*-glycolide) in clinical products

John Garner[a], Sarah Skidmore[a], Haesun Park[a], Kinam Park[a,*], Stephanie Choi[b], Yan Wang[b]

[a] Akina, Inc., 3495 Kent Avenue, Suite O-100, West Lafayette, IN 47906, USA
[b] Food and Drug Administration, Center for Drug Evaluation and Research, Office of Generic Drugs, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA

Journal of Controlled Release 304 (2019) 75–89

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Characterization of branched poly(lactide-*co*-glycolide) polymers used in injectable, long-acting formulations

Justin Hadar[a], Sarah Skidmore[a], John Garner[a], Haesun Park[a], Kinam Park[a,b,*], Yan Wang[c], Bin Qin[c], Xiaohui Jiang[c]

[a] Akina, Inc., 3495 Kent Avenue, Suite A200, West Lafayette, IN 47906, USA
[b] Biomedical Engineering and Pharmaceutics, Purdue University, 206 S. Martin Jischke Drive, West Lafayette, IN 47907, USA
[c] Food and Drug Administration, Center for Drug Evaluation and Research, Office of Generic Drugs, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA

Summary

- Excipients can be a key constraint on generic product development both from their function and from the regulations around them
- The GDUFA research program has invested in the science of characterizing excipients and understanding their impact on product performance in order to accelerate the development of generic products

Thanks!

- To the hundreds of staff across CDER in OGD/ORS, OPQ/OTR and OTS/DARS, and other offices that contributed to the research described in the research report
- To our many expert non-FDA research collaborators
- For more details
  - https://www.fda.gov/drugs/generic-drugs/science-research


FDA
U.S. FOOD & DRUG
ADMINISTRATION