



# Perspectives in Percutaneous Penetration Fifteenth International Conference La Grande Motte, France

30th March – 1st April 2016

## TOPICAL SEMISOLID DRUG PRODUCT CRITICAL QUALITY ATTRIBUTES (Q3 CHARACTERIZATION) WITH RELEVANCE TO TOPICAL BIOEQUIVALENCE



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SAARLAND  
UNIVERSITY

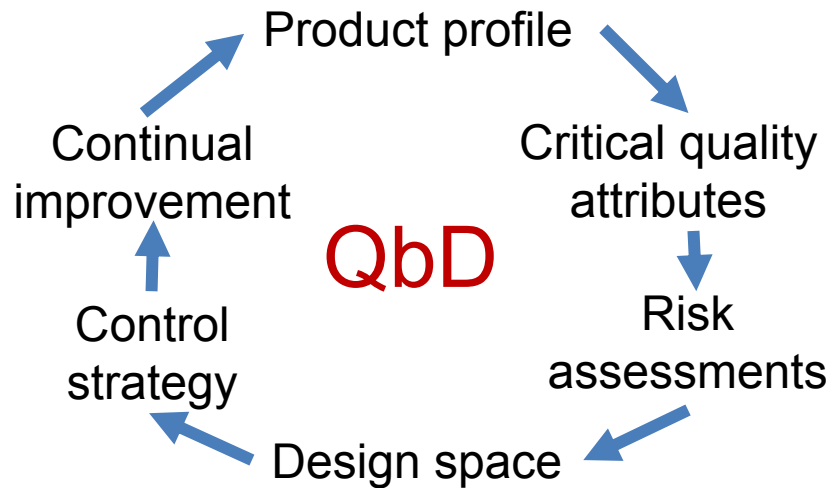
TRIO



THE UNIVERSITY  
OF QUEENSLAND  
AUSTRALIA

# Overview of presentation

There has been an emphasis on assessing product quality by design (QbD)



Here, we add Quality by Design and Testing (QbDT)

- **Focus:** Testing Acyclovir products for quality and performance
- Relating *In Vitro* Permeation Tests (IVPT) to formulation attributes

Where product equivalence defined by:

- **Q1**; same components as reference listed drug (RLD);
- **Q2**; same components in same concentration as the RLD;
- **Q3**; same components in same concentration, with the same arrangement of matter (microstructure) as the RLD

# FDA Product quality – what is needed?

## Objective

To support development of regulatory standards and guidances for industry:

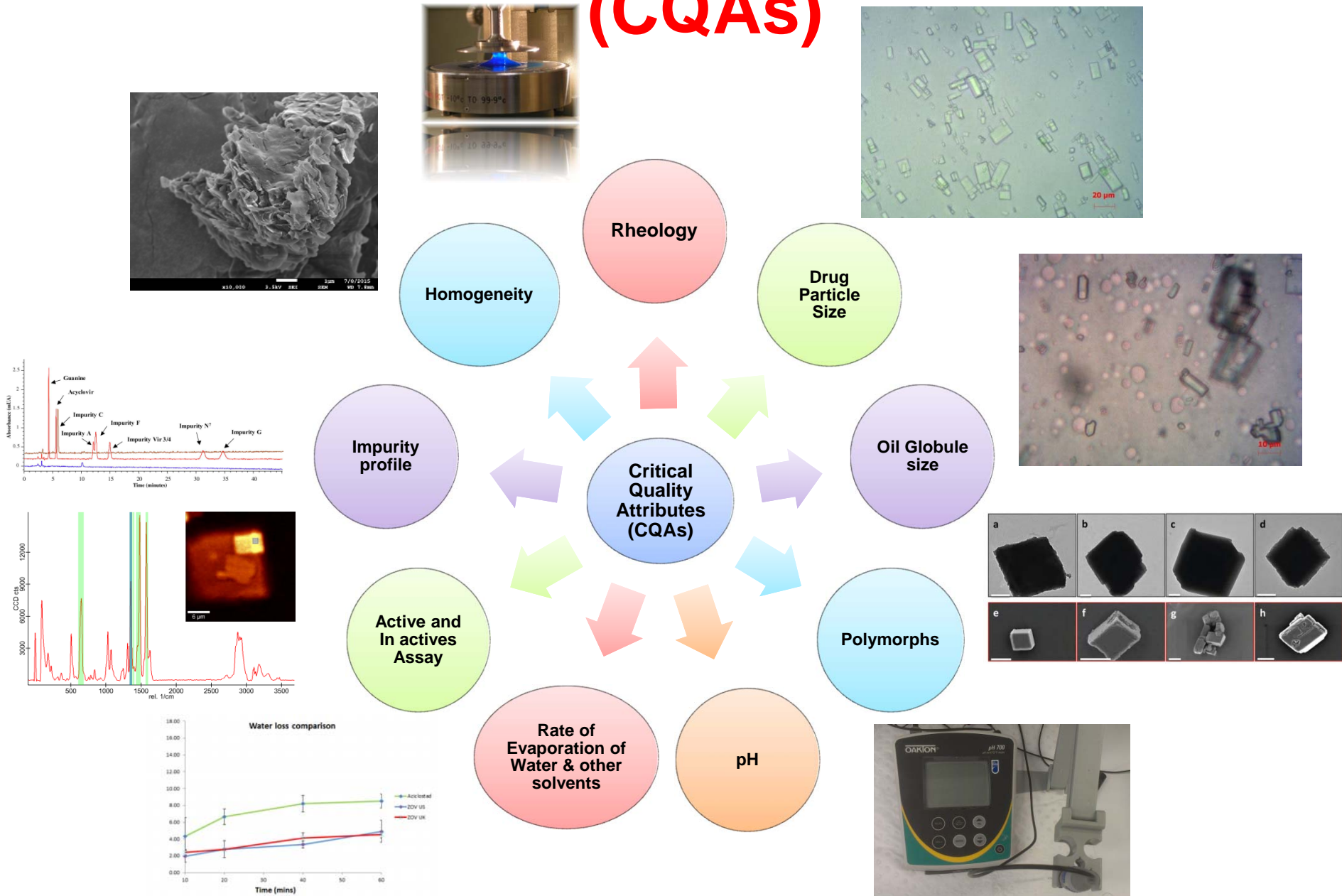
- for semisolid topical drug products,
- based upon well-defined critical quality & performance attributes
- that best characterize these products.

## Scope

- Characterize all measurable physical/chemical qualities of different dosage forms of semisolid topical drug products
- Identify appropriate methodologies for measuring each of these quality attributes
- Characterize formulation and manufacturing parameters that alter the arrangement of matter in the dosage form as measured by specific quality attributes
- Utilize *in vitro* and/or *in vivo* measures of product performance to correlate variations in critical quality attributes with a failure mode for a drug product



# Defining the critical quality attributes (CQAs)



# Product variables, critical quality attributes (CQAs) & potential failure modes

Ingredient & Formulation Variables

Formulation variables

CQAs

- Particle size
- pH
- Rheological properties
- Globule size
- Polymorphs
- Phase ratio
- Type of emulsion
- Solubility

Manufacturing variables

- Globule size-coalescence
- Phase separation
- pH
- Rheology
- Product uniformity
- Stability of actives
- Precipitation
- Recrystallization

Packaging

- Package integrity
- Compatibility
- Viscosity
- Loss of water and volatiles
- Leaching from plastic
- Desorption

Failure Modes

Developing **tests** for CQA's will mitigate the risk of performance failure which encompasses

- Physical stability (size of continuous phase, homogeneity, rheology, crystallization and sensorial properties)
- Chemical stability (polymorphic forms present, pH and active stability)
- Performance and compliance (Skin feel, appeal and rate and extent of penetration)

***Microstructure is a critical quality of the product & microstructural differences between an RLD and generics could lead to potential failure of the product***

# Q3 – Key CQA questions in testing acyclovir (*acyclovir*) products

- ❑ Are all Acyclovir products from around the world microstructurally similar ?
- ❑ What tests can be used to assess Q3 differences and similarities ?
  - Zovirax US
  - Zovirax UK
  - Zovirax Germany
  - Zovirax Austria
  - Aciclostad Austria
  - Aciclovir 1A Pharma Austria



# Important precursor study to this work



Available online at [www.sciencedirect.com](http://www.sciencedirect.com)



International Journal of Pharmaceutics 304 (2005) 63–71

international  
journal of  
pharmaceutics

[www.elsevier.com/locate/ijpharm](http://www.elsevier.com/locate/ijpharm)

## Are all aciclovir cream formulations bioequivalent?

L. Trottet<sup>a,\*</sup>, H. Owen<sup>b</sup>, P. Holme<sup>b</sup>, J. Heylings<sup>b</sup>, I.P. Collin<sup>c</sup>, A.P. Breen<sup>c</sup>,  
M.N. Siyad<sup>a</sup>, R.S. Nandra<sup>a</sup>, A.F. Davis<sup>a</sup>

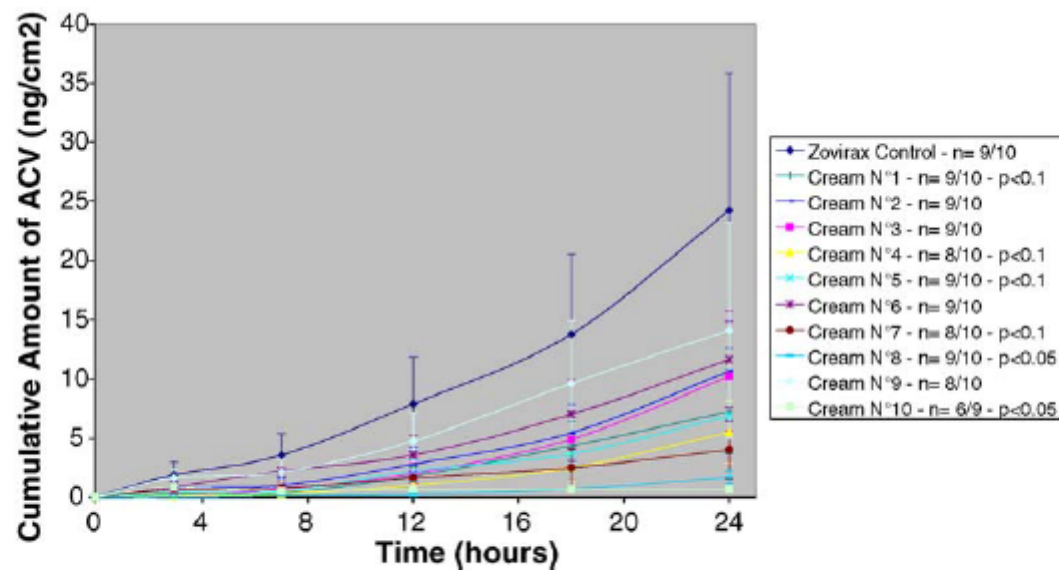


Fig. 2. Percutaneous permeation of aciclovir from 11 different creams. External study results. 3/3 exclusion criteria met (standard error).

# Propylene glycol (PG) key role in acyclovir skin permeation

- Especially when all other parameters, e.g. excipients, their concentrations, characteristics of acyclovir powder or manufacturing processes are not kept constant

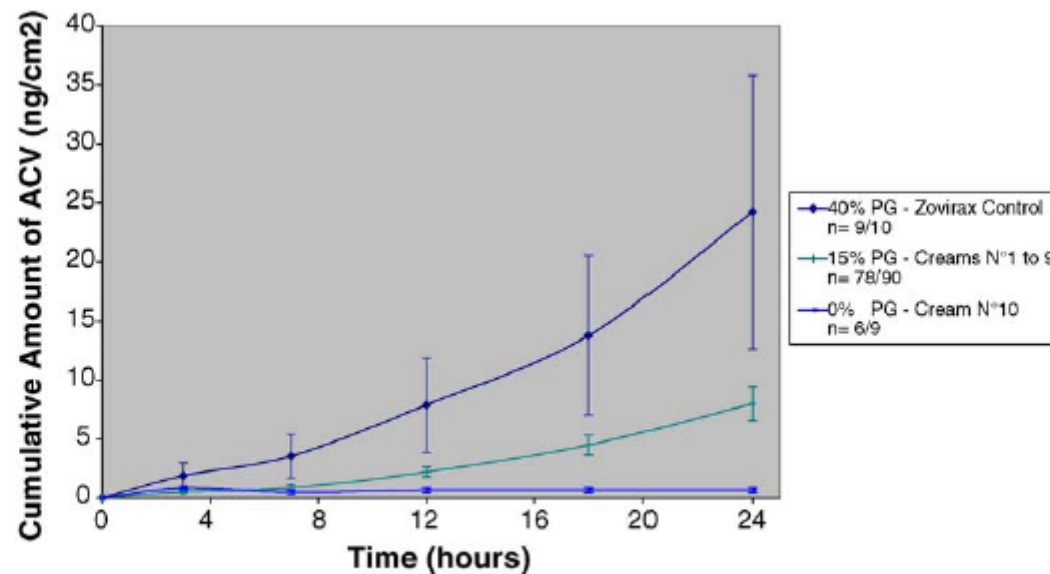
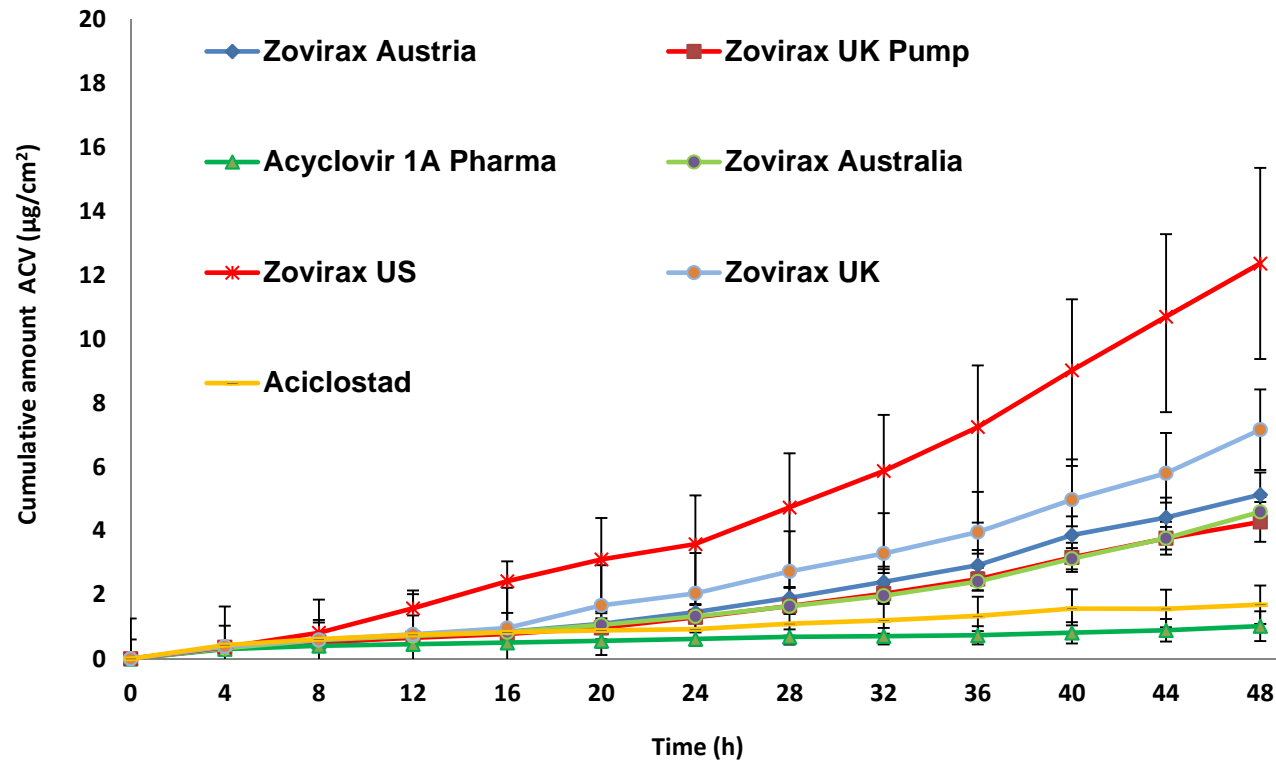


Fig. 4. Effect of propylene glycol content on the percutaneous permeation of aciclovir. 3/3 exclusion criteria met (standard error).

Here, the **40% PG cream delivered 10-fold more acyclovir** than the nearly identical formulation containing **15% PG** only.



# Our acyclovir IVPT findings for various products now used!



- Zovirax US best penetrating cream of those tested

**WHY?**

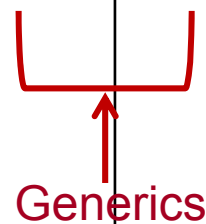
**LOOK AT CQA DIFFERENCES**

# 1. Excipients and Polymorphs

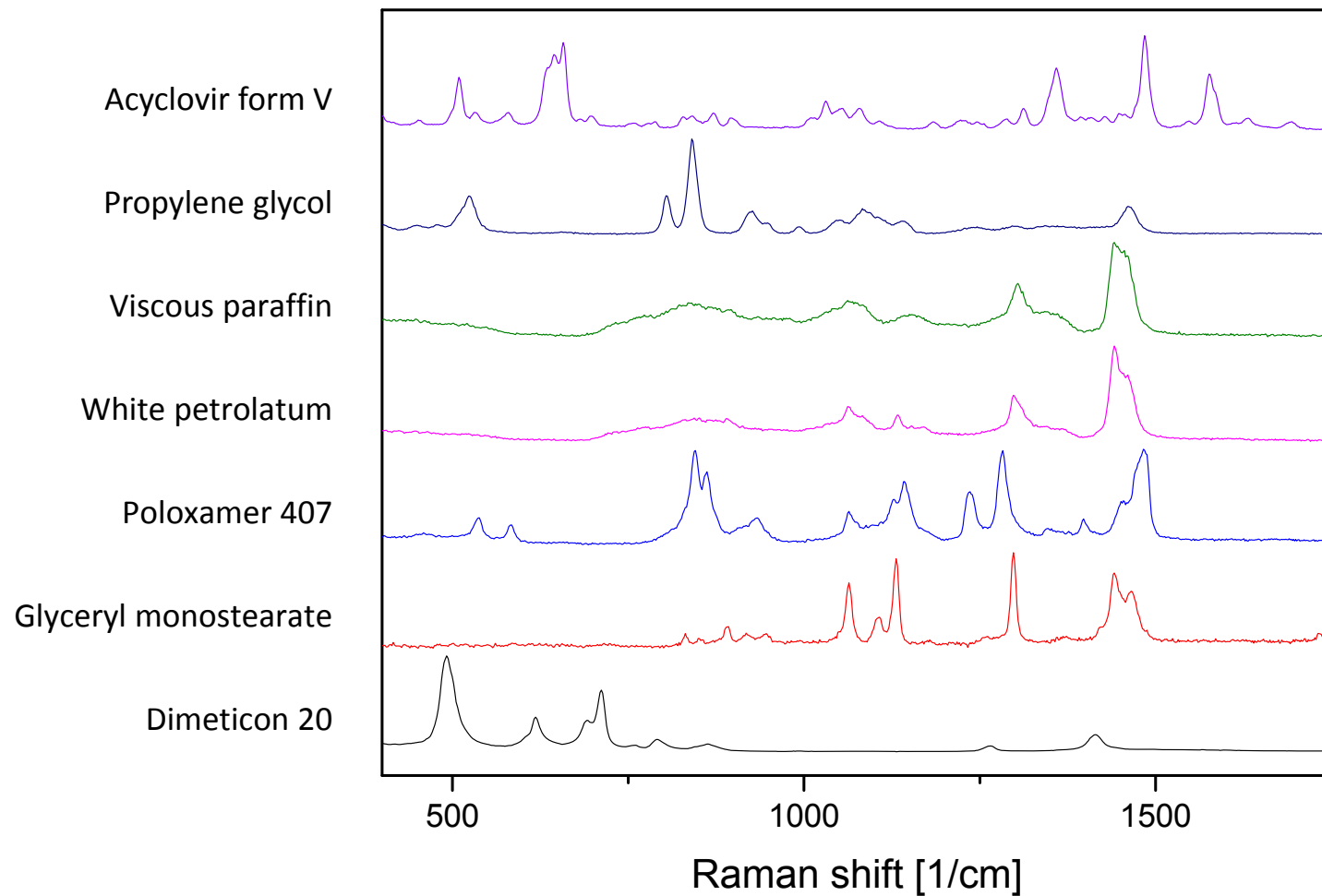
- ❑ All Zovirax creams have subtle differences
- ❑ Larger differences between generics and Zovirax Brand creams
- ❑ Confocal Raman used to identify formulation differences
- ❑ We also sought to generate a snapshot map of key ingredients within the formulation landscape

# Formulation differences

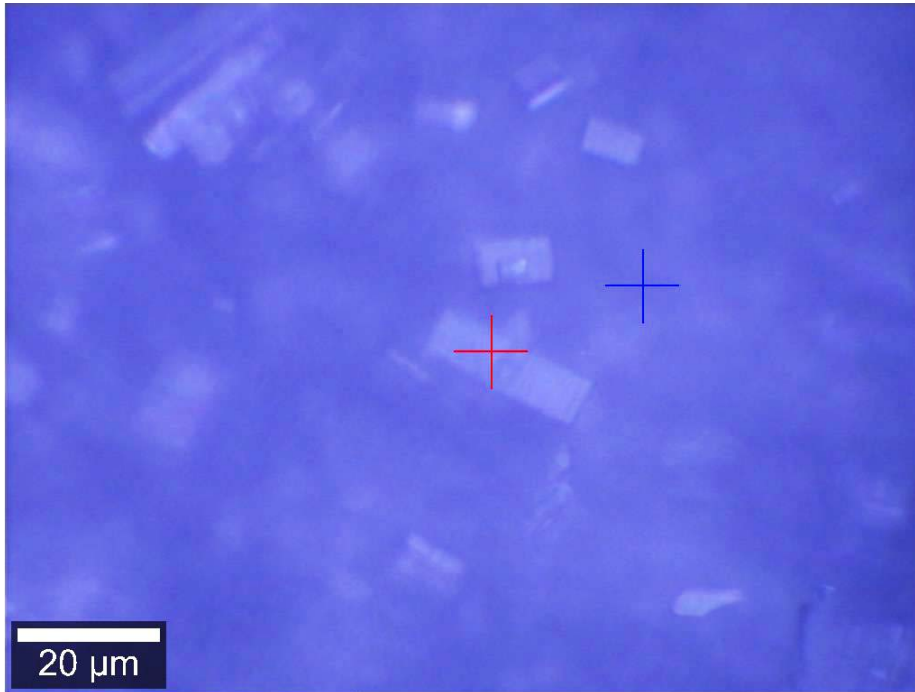
Cream Name	Zovirax (U.S.)	Zovirax (U.K.)	Zovirax (Austria)	Aciclostad (Austria)	Aciclovir 1A Pharma (Austria)	Zovirax (Australia)	Zovirax (Germany)
Approval number	N021478	PL 00003/0180 (Market Authorization Number)	1-18064	I-22973	1-22499	ARTG 55006	
Company name:	GlaxoSmithKline Research Triangle Park, NC 27709 Distributed by Valeant Pharmaceuticals	The Wellcome Foundation Ltd. Trading as GlaxoSmithKline UK	GlaxoSmithKline Pharma GmbH, Albert Schweitzer-Gasse 6, 1140 Wien, Österreich	STADA Arzneimittel GmbH, Muthgasse 36/2, 1190 Wien, Österreich	1A Pharma GmbH, Stella-Klein-Löw-Weg 17, 1020 Wien, Österreich	GlaxoSmithKline Australia	
Approval date	30.12.2002	28.10.1999	05.12.1985	13.04.1999	17.04.1998	04.09.1996	
ACV concentration	1 g = 50 mg ACV	1 g = 50 mg ACV	1 g = 50 mg ACV	1 g = 50 mg ACV	1 g = 50 mg ACV	1 g = 50 mg ACV	1g = 50 mg
Propylene glycol (PG)	Yes	400 mg/g	400 mg/g	150 mg/g	150 mg/g	Yes	Yes
Cetyl alcohol	No	No	No	50 mg/g	1.5 mg/g	No	No
Other Ingredients:	Cetostearyl alcohol Mineral oil Poloxamer 407 Sodium lauryl sulfate Water White petrolatum.	Poloxamer 407 Cetostearyl alcohol Sodium Lauryl Sulfate White soft paraffin Liquid paraffin Purified water Arlacel 165 (containing glycerol monostearate and polyoxyethylene stearate) Dimeticone 20	Cetostearyl alcohol White vaseline Liquid paraffin Poloxamer Sodium dodecyl sulfate Dimethicone Glycerol monostearate Macrogol-100-stearate Purified water	White vaseline Liquid paraffin Macrogol stearate Dimethicone Purified water	White vaseline Viscous paraffin Glycerol monostearate Polyoxyethylene stearate Dimethicone Purified water	Dimethicone Soft white paraffin Cetostearyl alcohol Liquid paraffin Poloxamer 407 Sodium lauryl sulfate Glycerol monostearate macrogol stearate Purified water	White petrolatum, Cetylstearyl alcohol Viscous paraffin Glycerol monostearate Macrogol stearate 100 Poloxamer 407 Sodium lauryl sulfate Dimethicone 20 Purified water
Prescription requirement	yes		yes	no	yes	no	
Site of application	Herpes labialis on the face or lips		Herpes genitalis and labialis	Herpes labialis	Herpes genitalis and labialis	Herpes labialis	


  
Generics

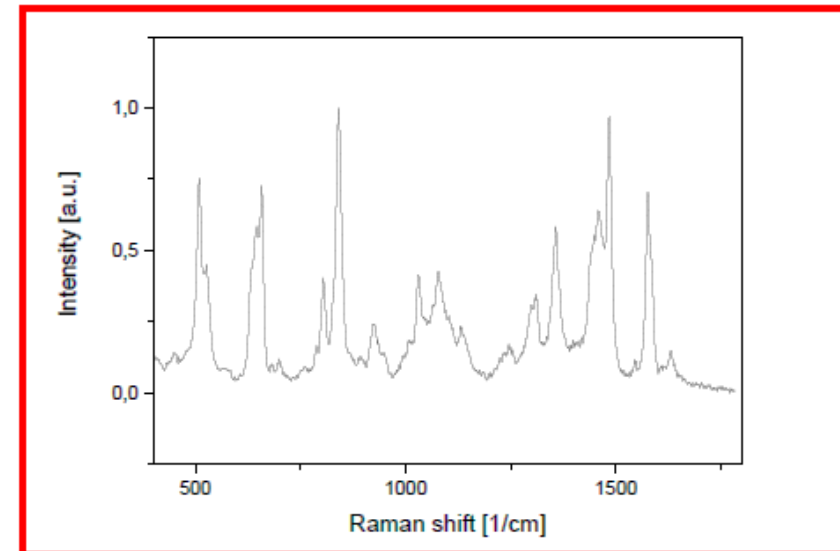
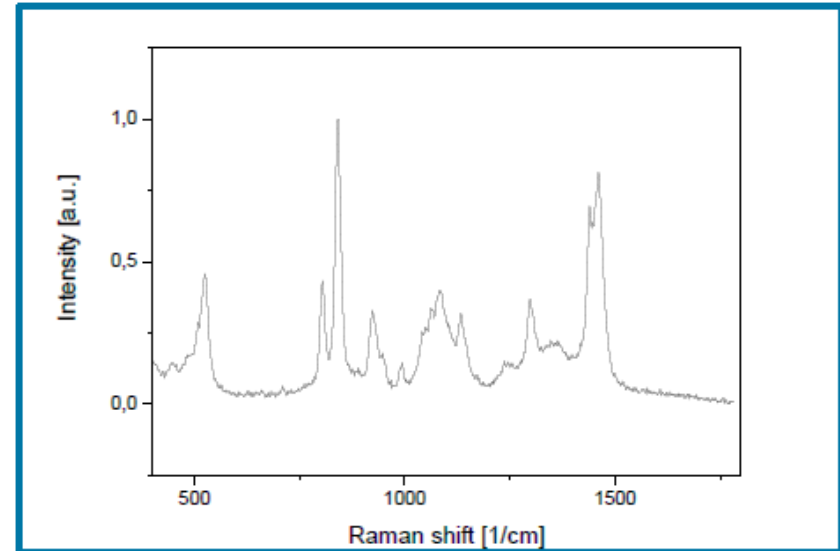
# Zovirax main excipients - individual Raman spectra



# Zovirax – individual Raman spectra



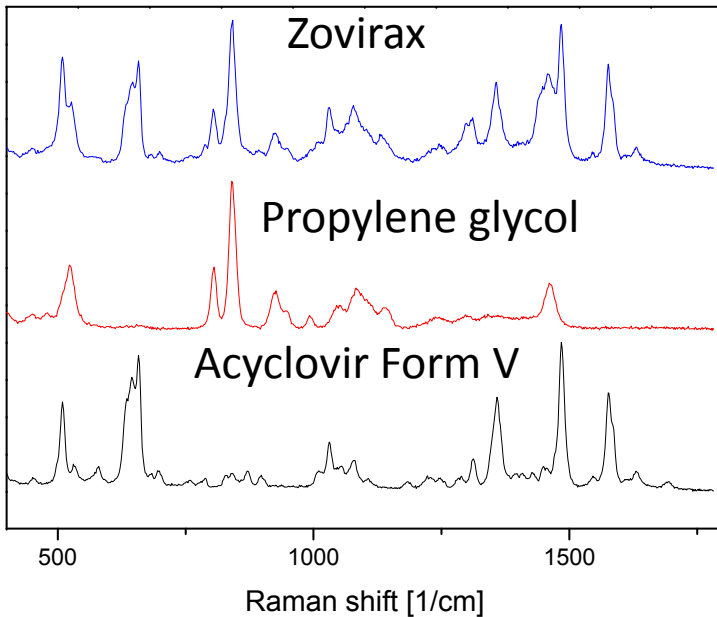
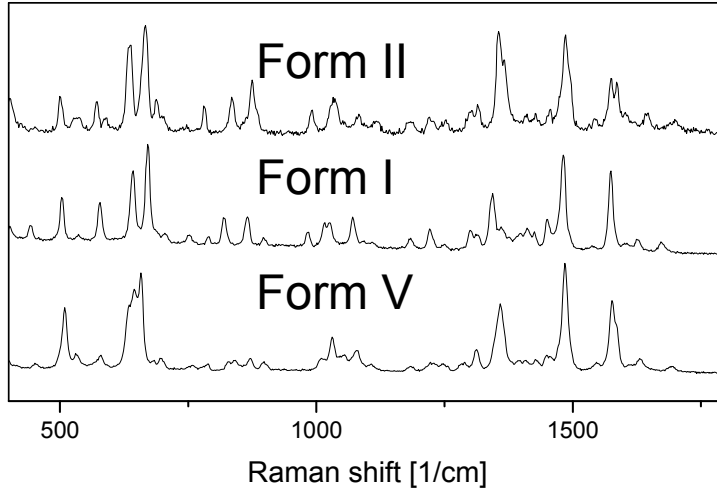
- Preliminary results suggest all commercial acyclovir creams contain Acyclovir polymorph form V



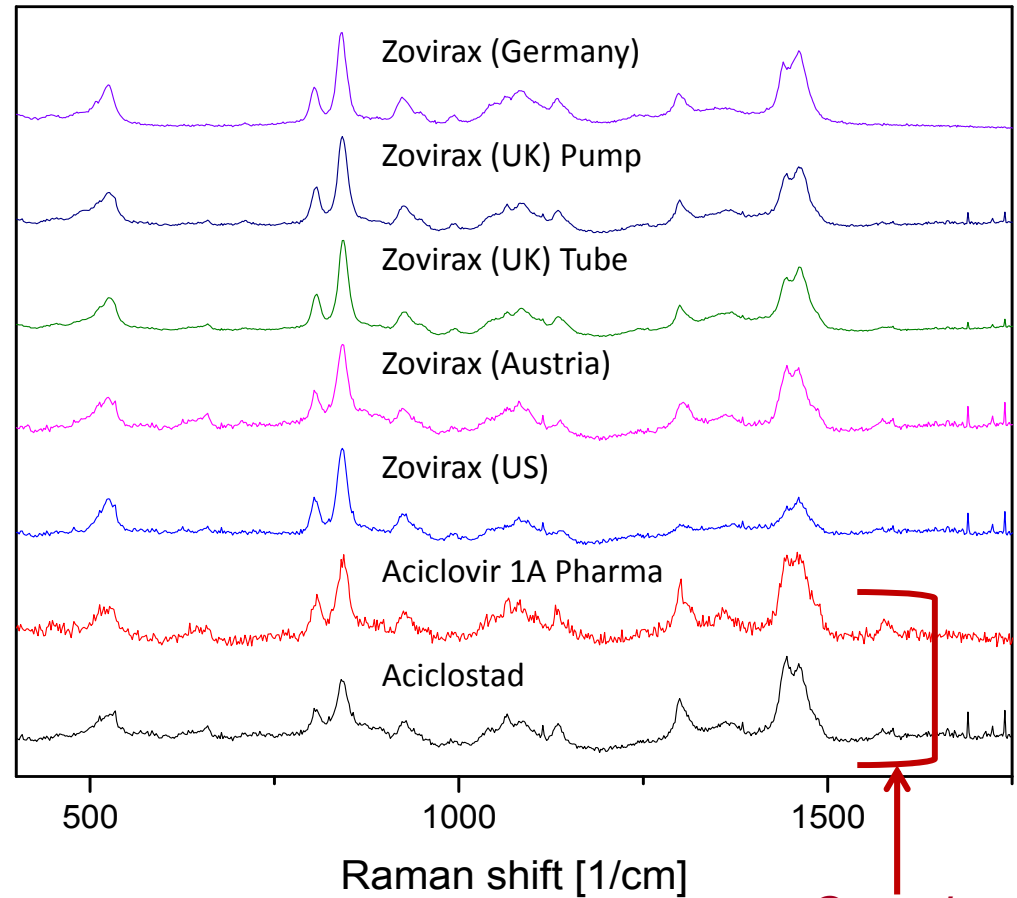
ACSD	Zov US	Zov UK
✓	✓	✓

# Raman of Zovirax & other products

Raman spectra of recrystallized acyclovir polymorphs



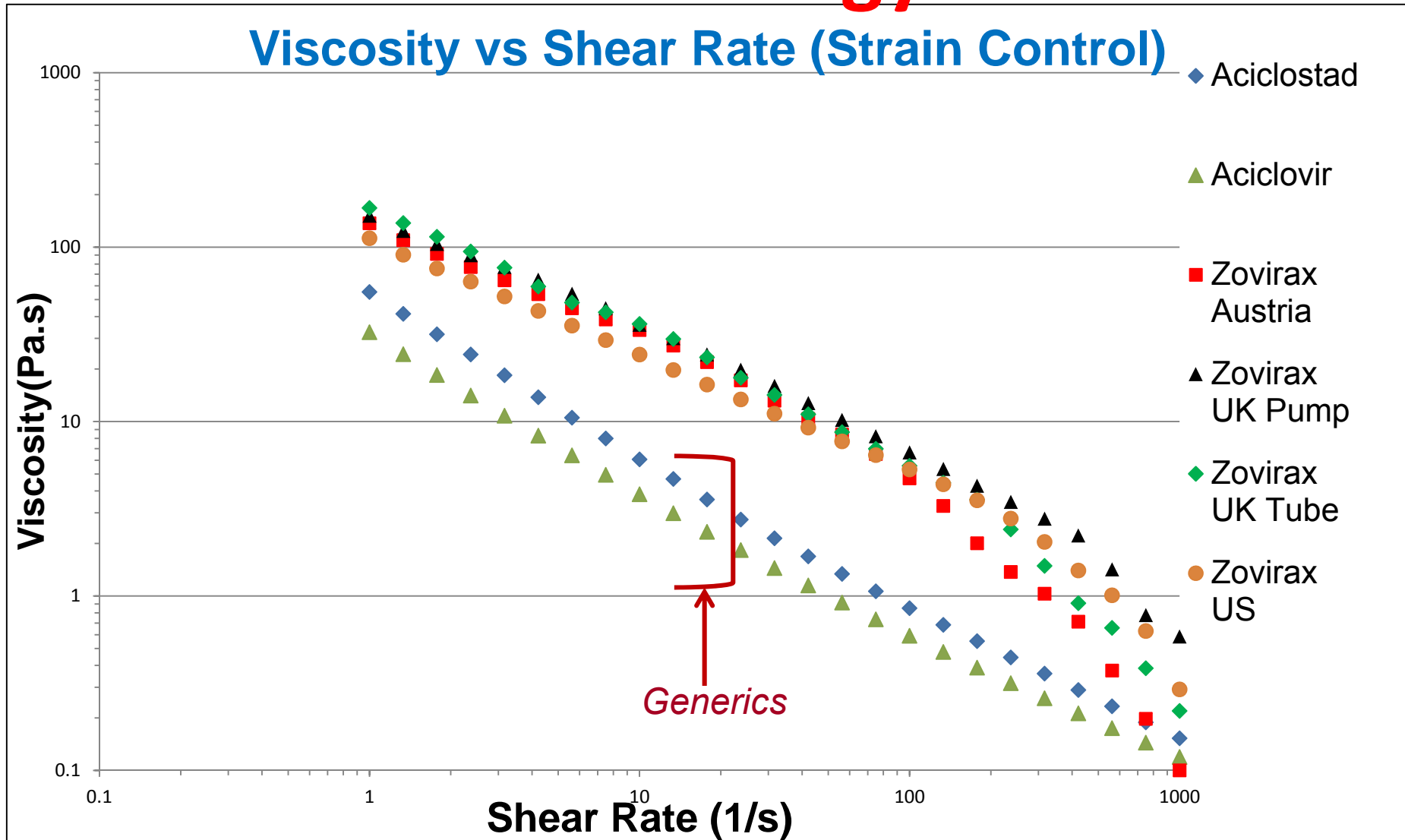
Raman spectra of all products



*Generics*



# 2. Rheology

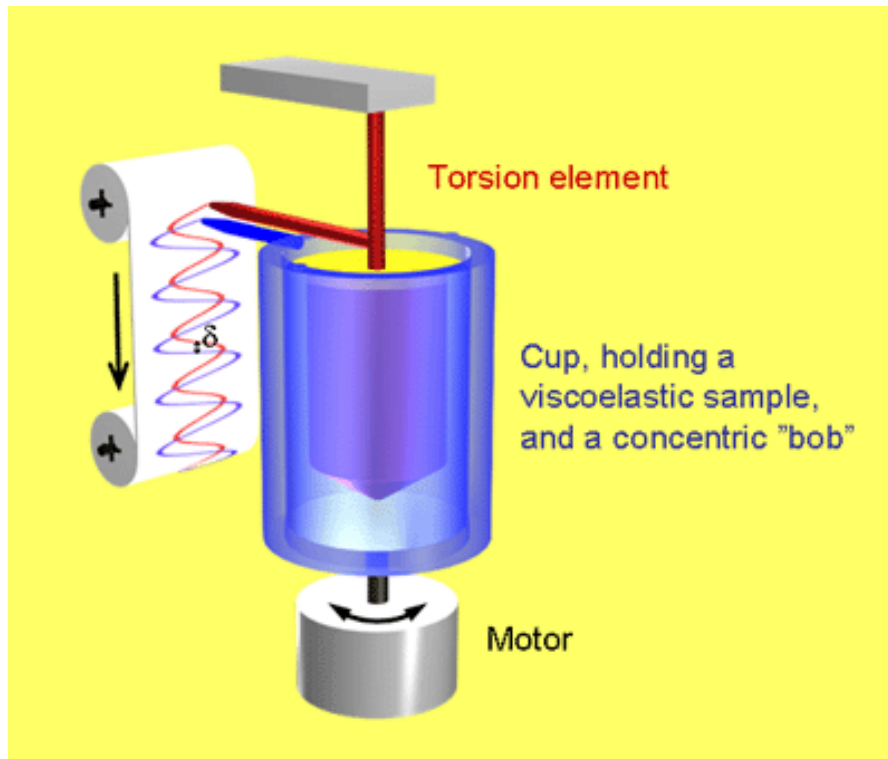


Strain rate is the deformation change, represented by shear rate sweep (range) for no change in product volume; With sinusoidal displacement with frequency  $\omega$ , complex modulus  $G^*$ =force/shear rate and complex viscosity  $\eta^* = G^*/\omega$ .

# Introductory viscoelasticity

Dynamic mechanical analysis from a wide gap - oscillatory amplitude sweep of a product defines its viscoelastic properties:

Complex modulus  $G^* = \text{solid (storage or elasticity modulus, } G') + i \cdot \text{liquid (loss or viscosity modulus, } G'')$ ; where  $i^2 = -1$  &  $\tan \delta = G'' / G'$



For a totally elastic material like steel,  $\delta = 0$ ; for a liquid  $\delta = 90^\circ$

[http://projekt.sik.se/rheology/Undre\\_rheobeginners2.htm](http://projekt.sik.se/rheology/Undre_rheobeginners2.htm)

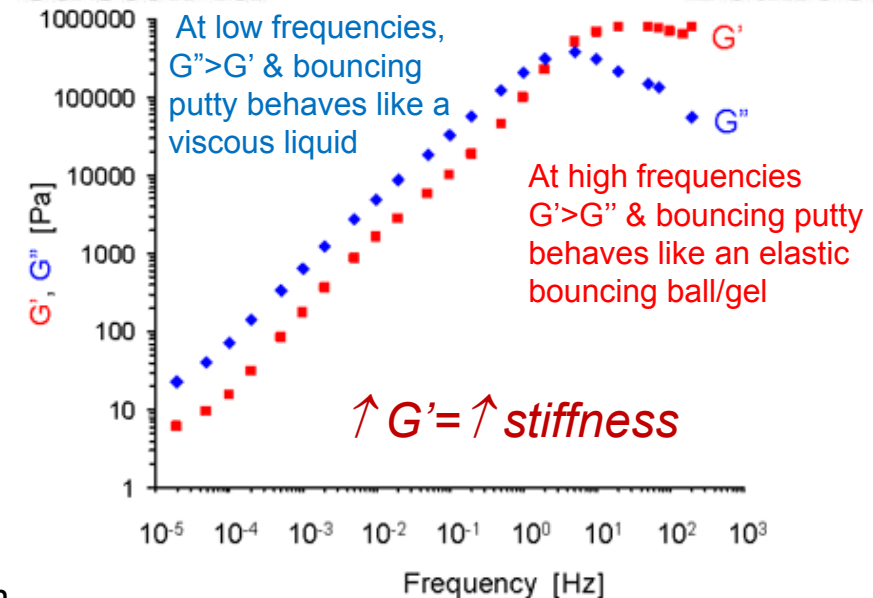


Bouncing Putty  
from polydimethyl-  
siloxane



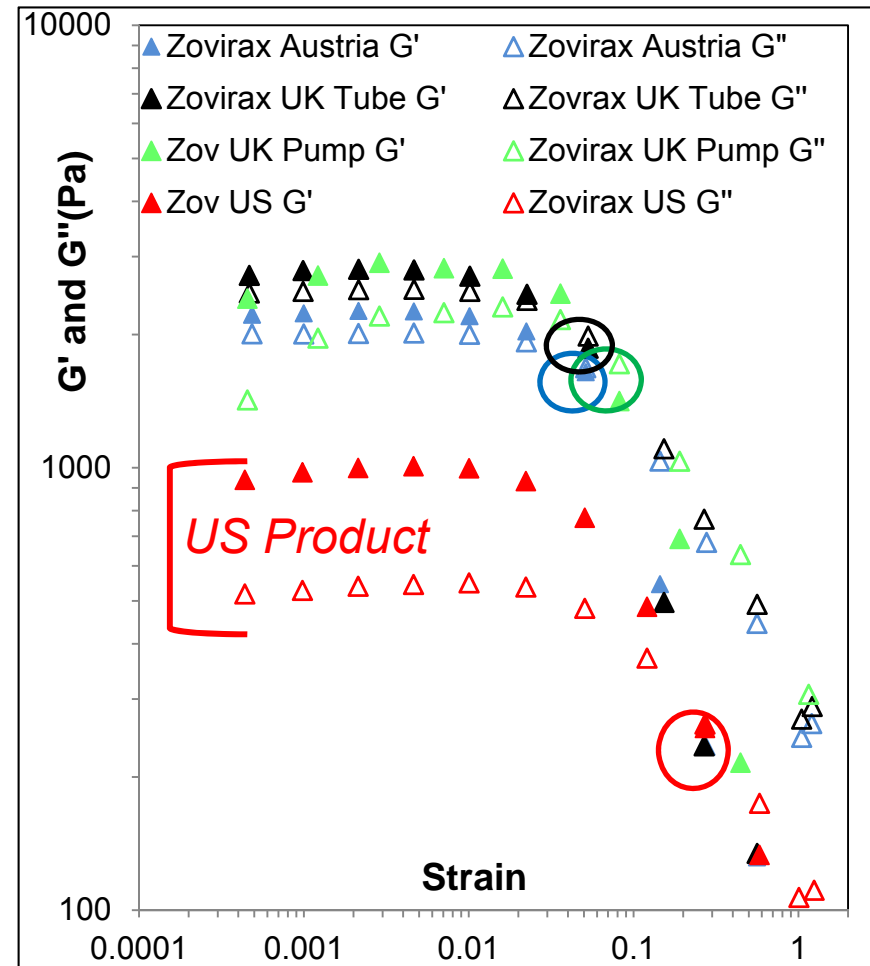
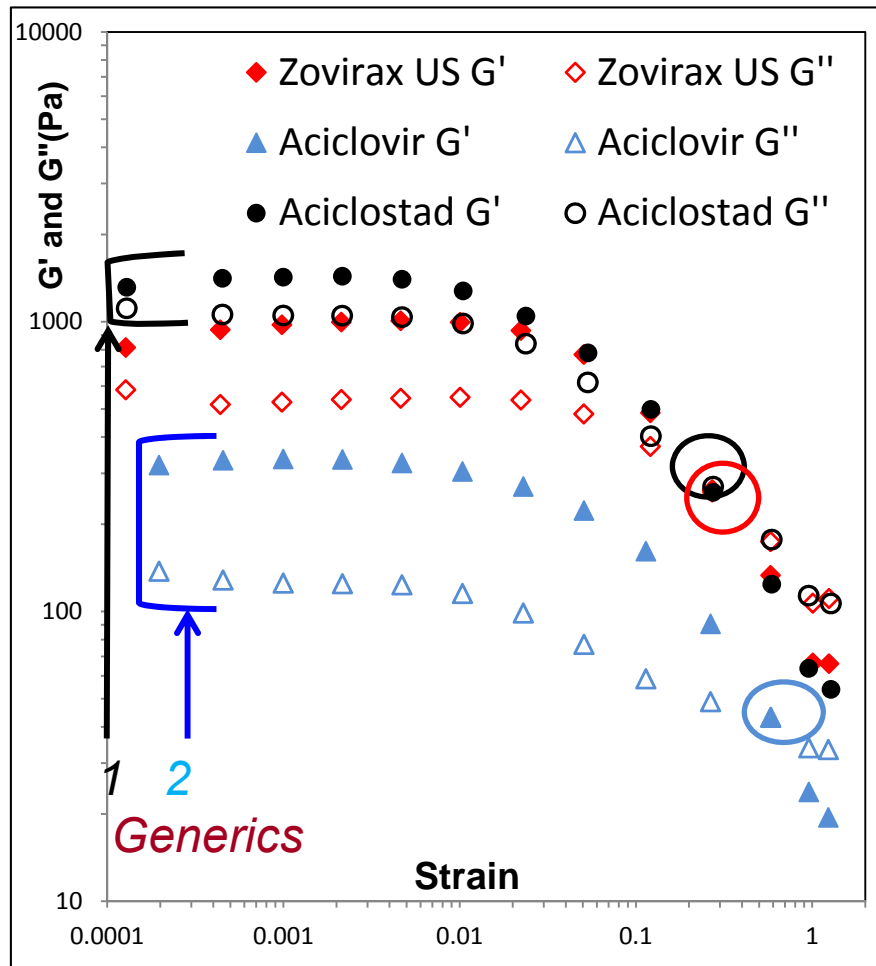
Stretch It!

Bounce It!



# Viscoelastic properties for our products

$G'$  = solid (storage or elasticity,) modulus;  $G''$  = liquid (loss or viscosity) modulus

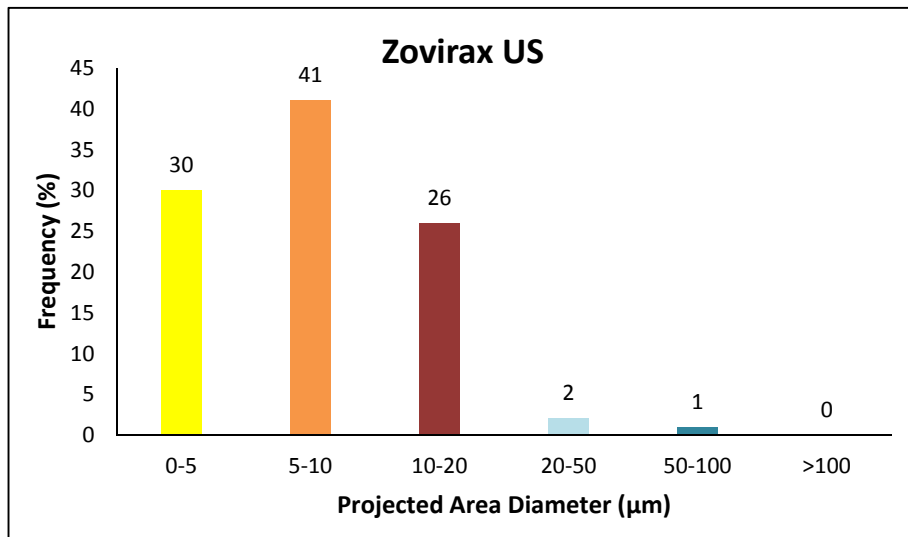
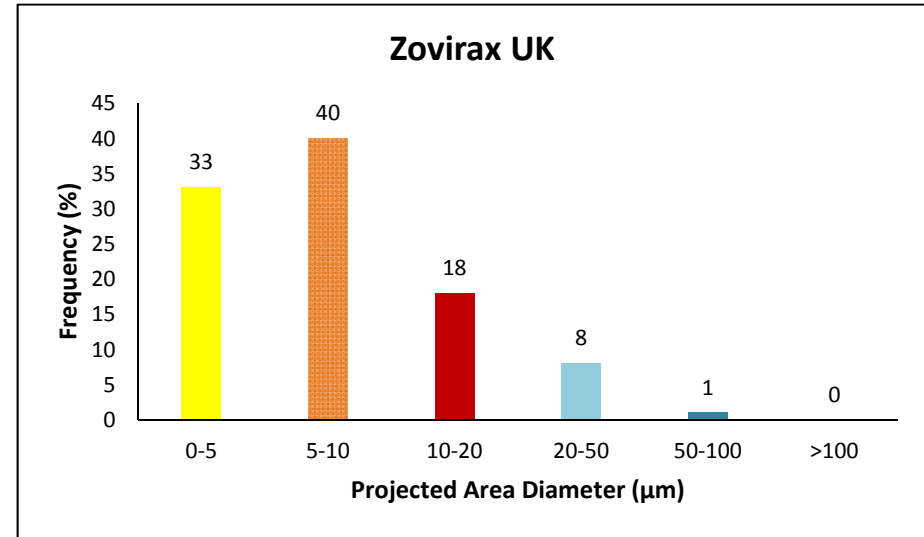
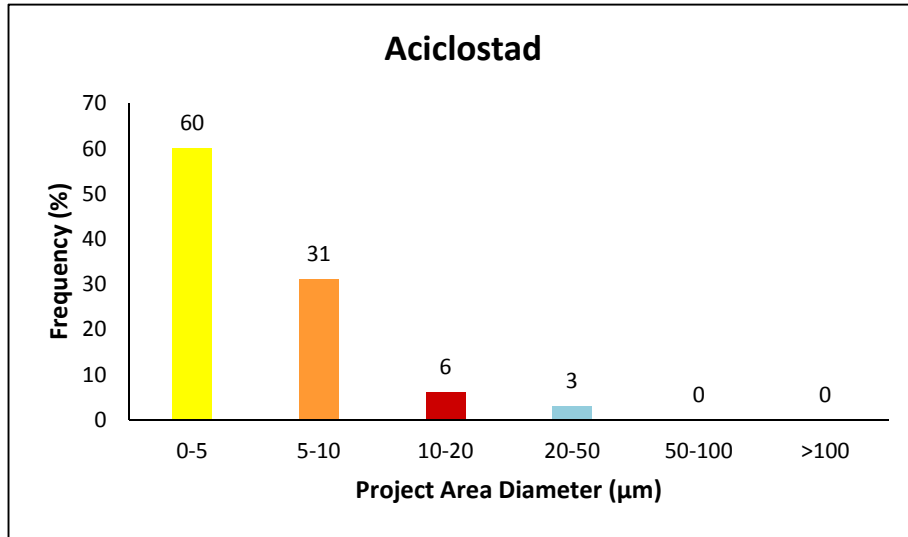


# Return to formulations tested

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Cetyl alcohol	No	No	50 mg/g
Other Ingredients:	Cetostearyl alcohol Mineral oil Poloxamer 407 Sodium lauryl sulfate Water White petrolatum.	Poloxamer 407 Cetostearyl alcohol Sodium Lauryl Sulfate White soft paraffin Liquid paraffin Purified water Arlacel 165 (containing glycerol monostearate and Polyoxyethylene stearate) Dimethicone 20	White vaseline Liquid paraffin Macrogol stearate Dimethicone Purified water
Prescription requirement	yes		no
Site of application	Herpes labialis on the face or lips		Herpes labialis

- **What else is different ?**

# 3. Particle size



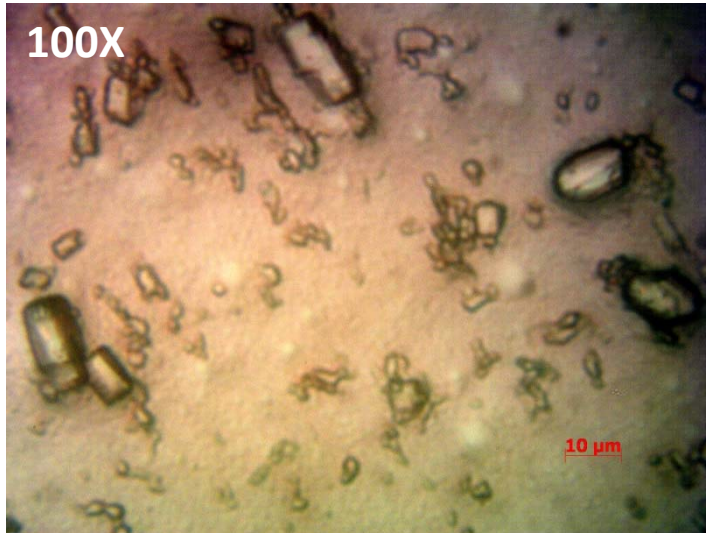
- All creams have particle sizes < 100 µm
- 70-90% size within 10 µm
- > 90% less than 20 µm
- Frequency distribution not significantly different

Not Significantly Different

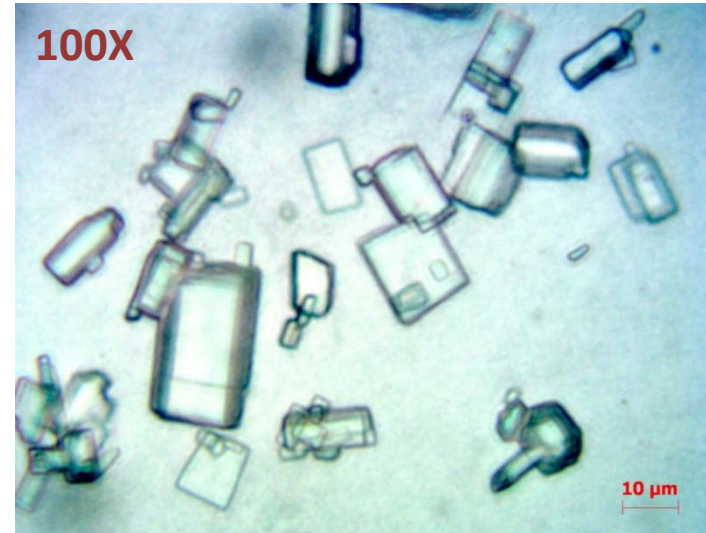
ACSD	Zov US	Zov UK
✓	✓	✓

# 4. Particle shape

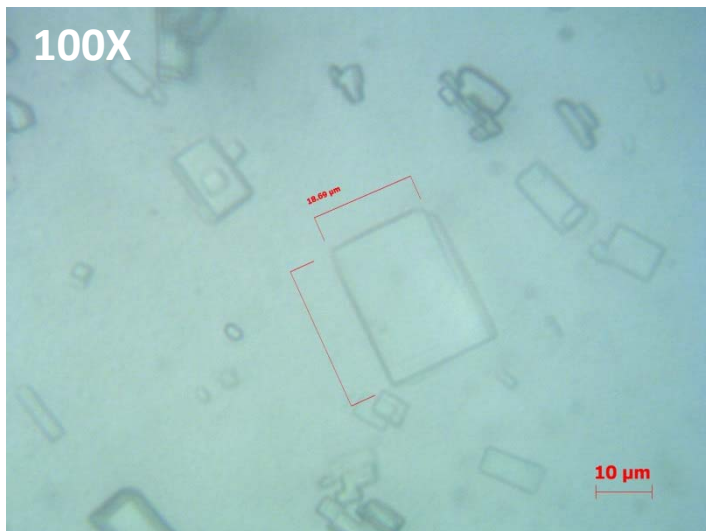
Aciclostad



Zovirax UK



Zovirax US



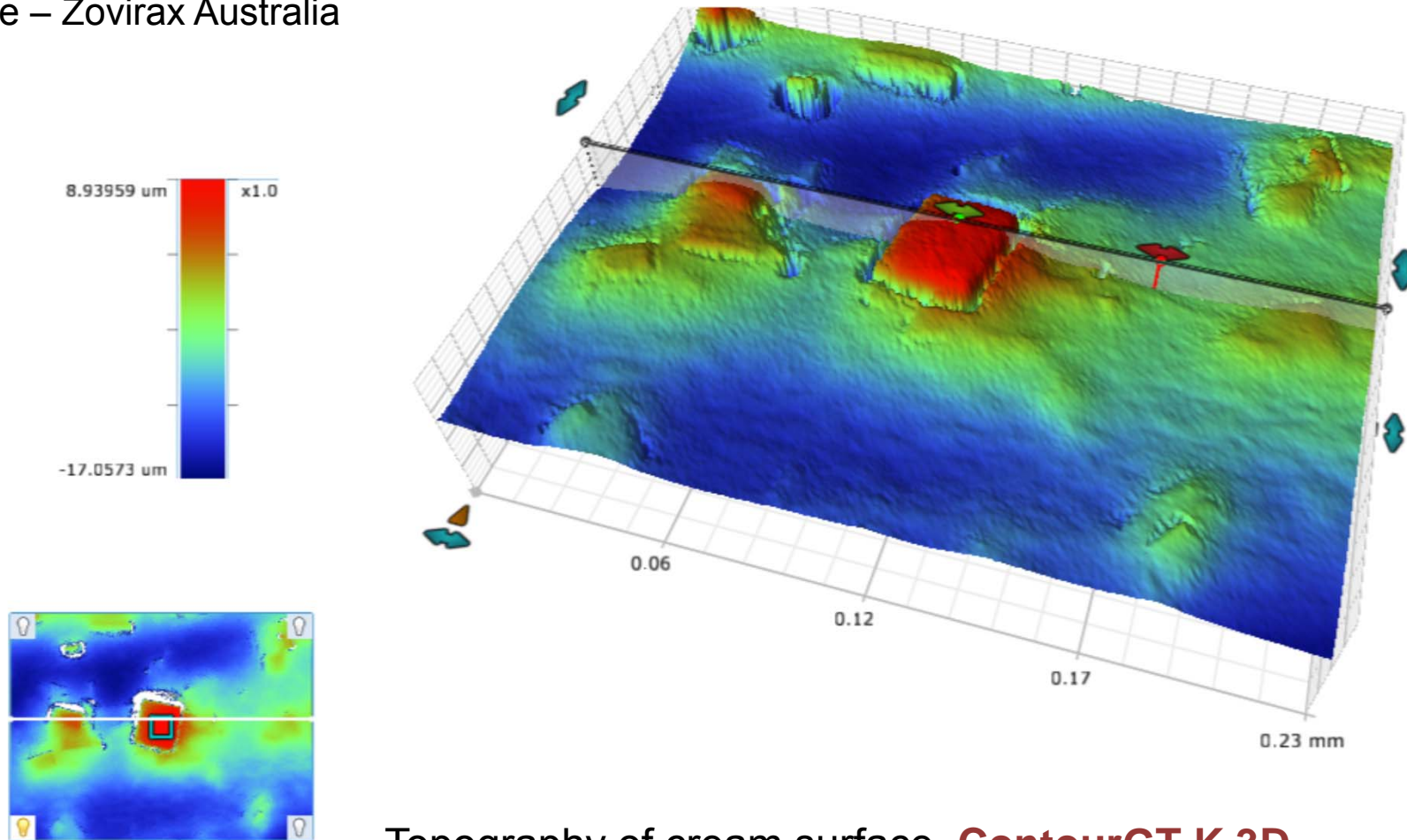
- Zovirax US and UK have similar shaped crystals
- ACSD has smaller and more irregular crystals
- Dissolution from these crystals needs to be assessed

ACSD	Zov US	Zov UK
x	✓	✓



# AFM and Profilometry imaging

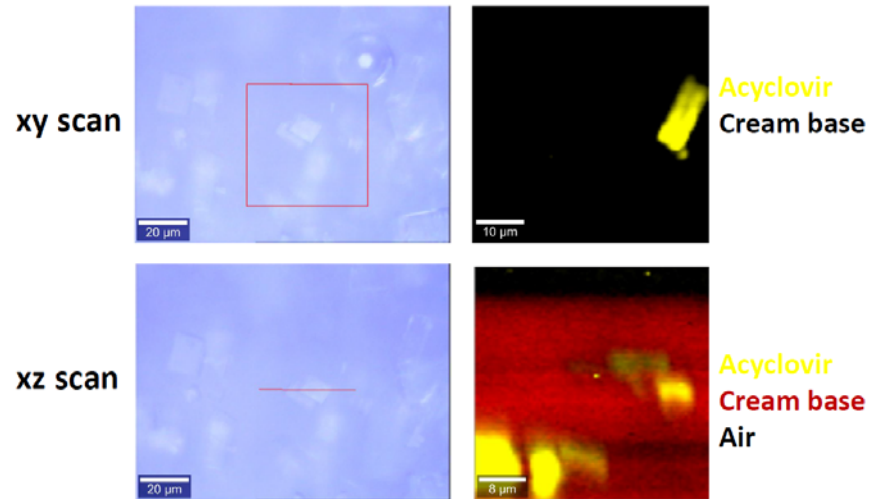
Cream sample depth profile – Zovirax Australia



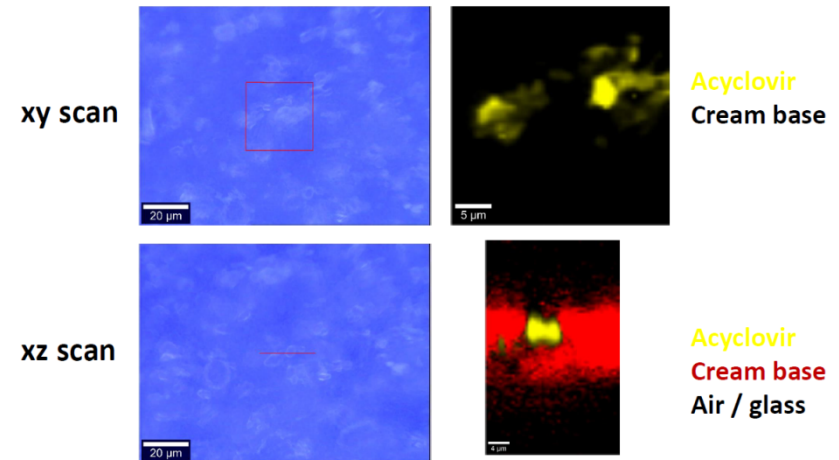
Topography of cream surface. **ContourGT-K 3D Profilometry Optical Microscope**  
Red to blue highest to lowest

# 3D Confocal Raman Imaging

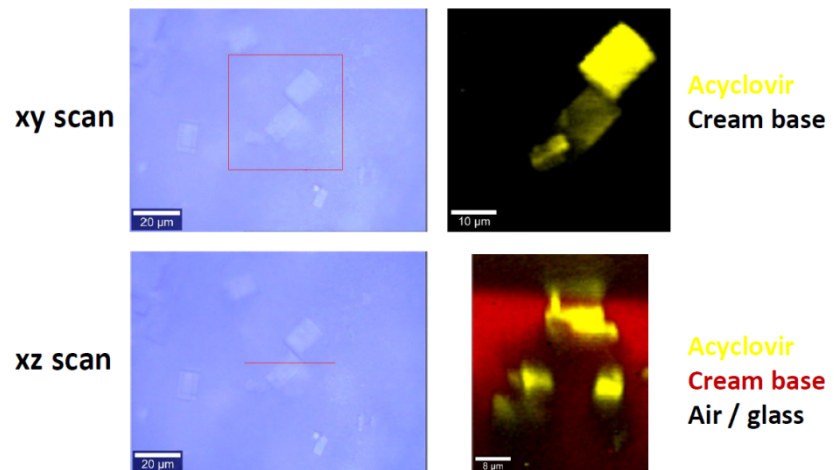
Zovirax US



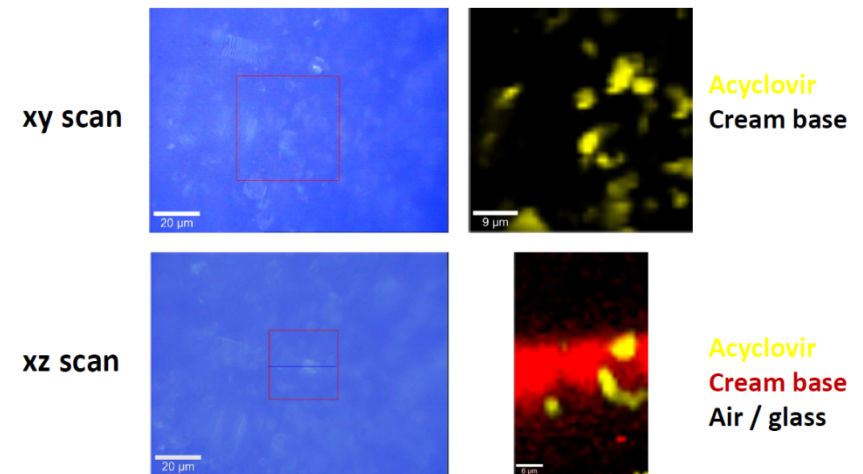
Aciclostad Austria



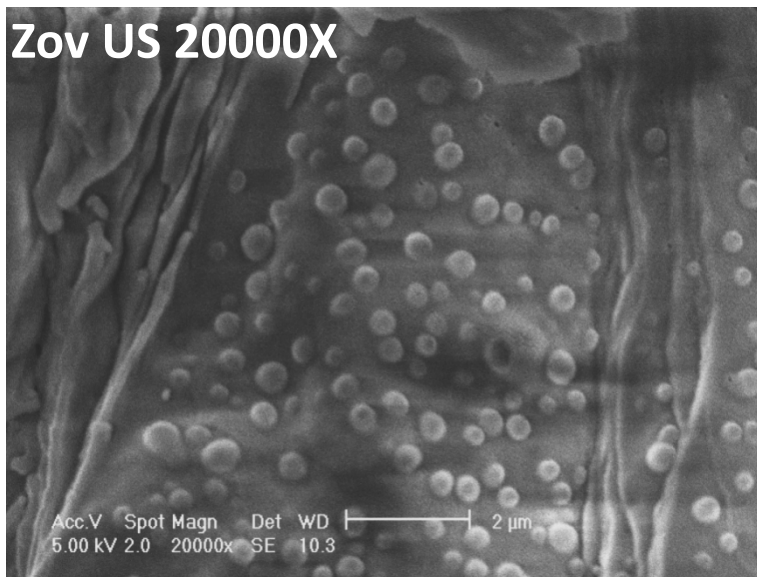
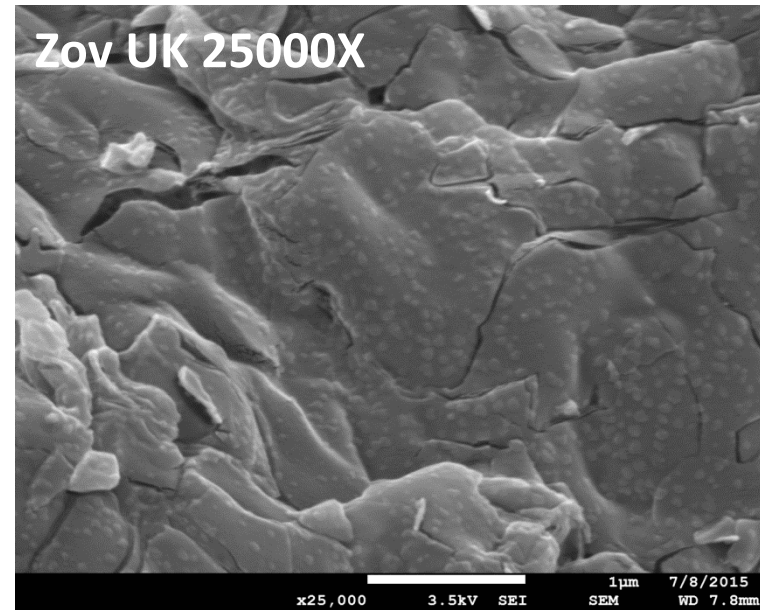
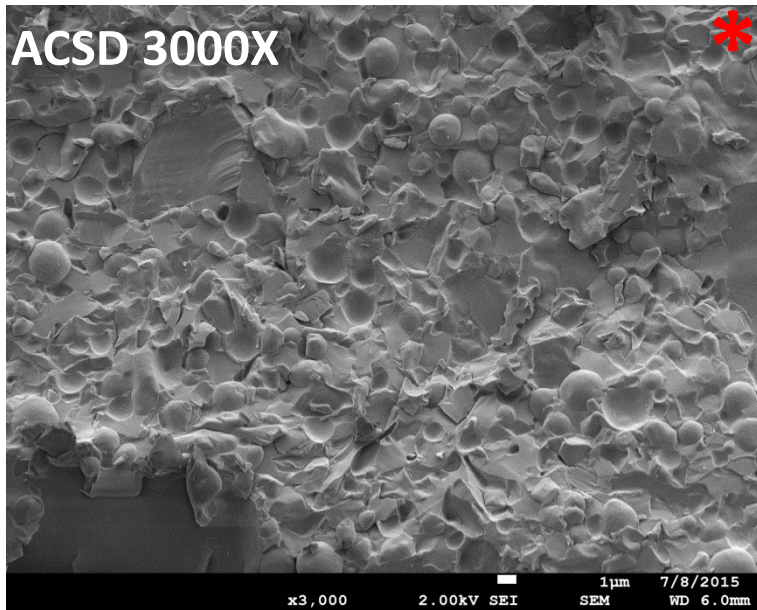
Zovirax Austria



Aciclovir 1 A Pharma Austria



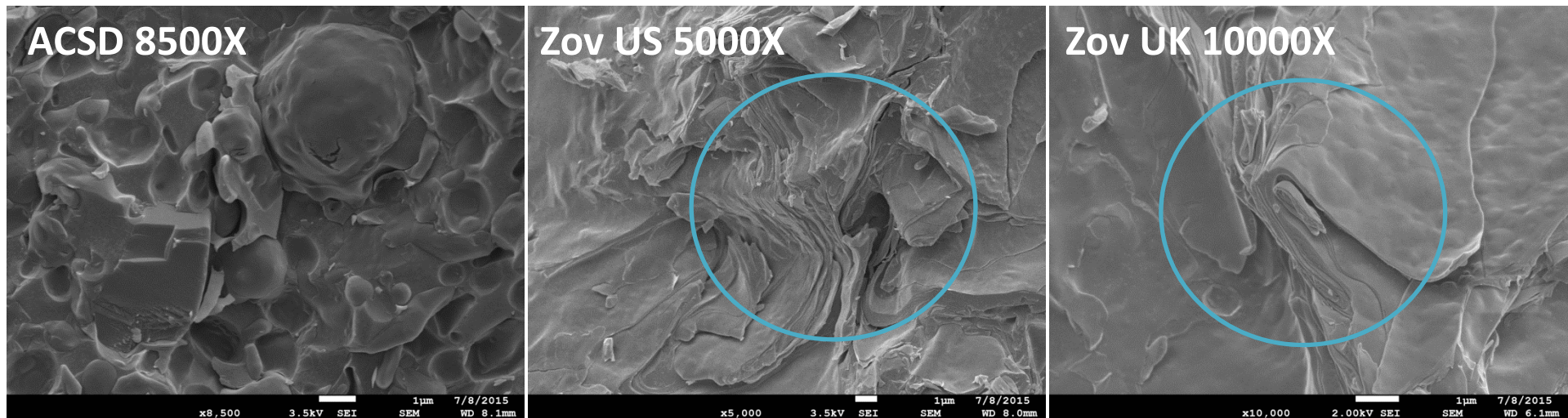
# 7. Globule size



\* Aciclostad image, magnification  
3000X



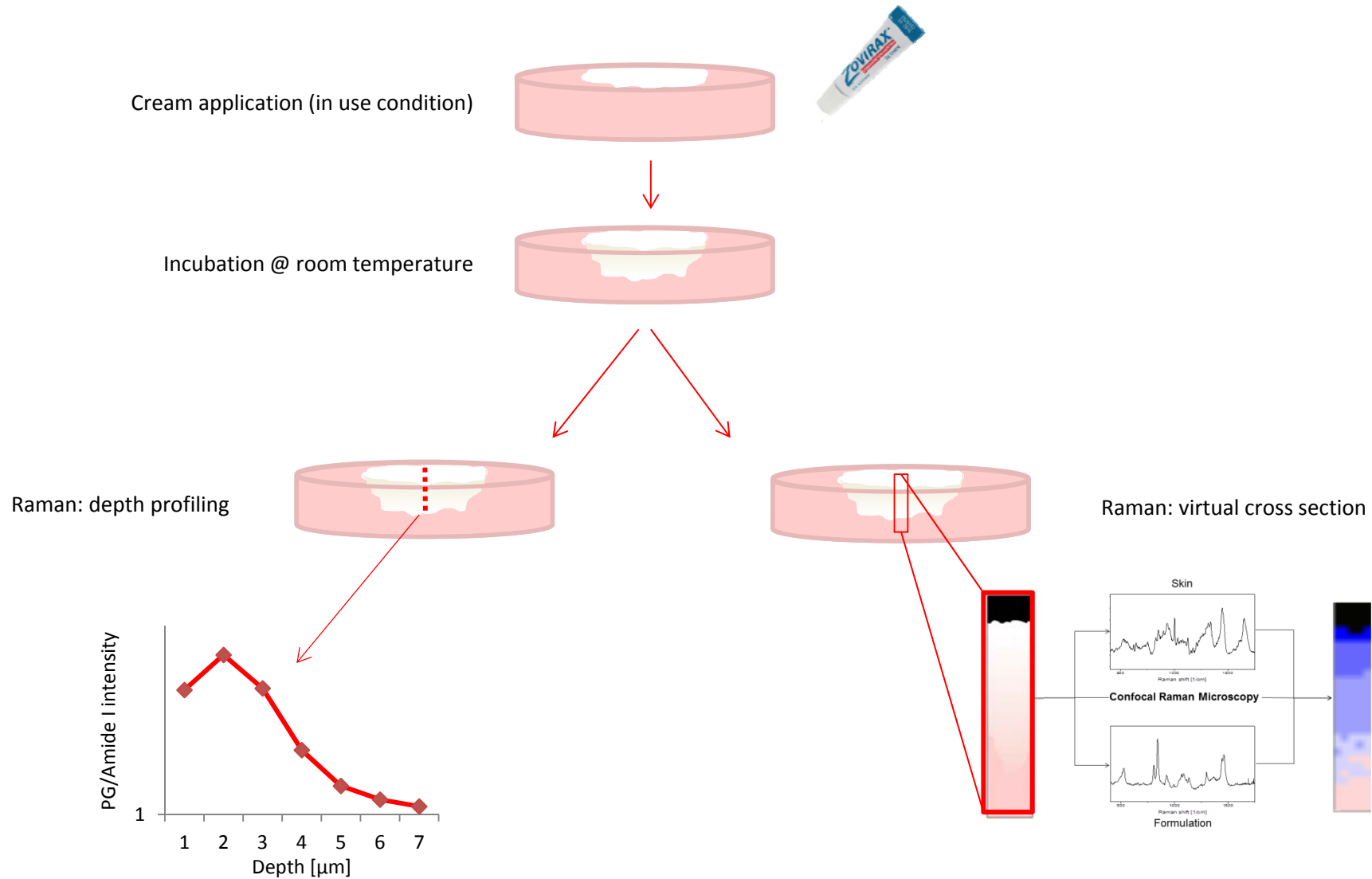
# 8. Formulation background microstructure (fabric of the cream)



- Both the Zovirax products have a defined microstructure **i.e. the fabric of the underlying cream without the crystals and globules** (Circles)
- Plates of the continuous phase were found to be tightly organised
- Aciclostad on the other hand did not show an observable microstructural pattern
- Further studies can help identify superior stability of the structured semi-solids

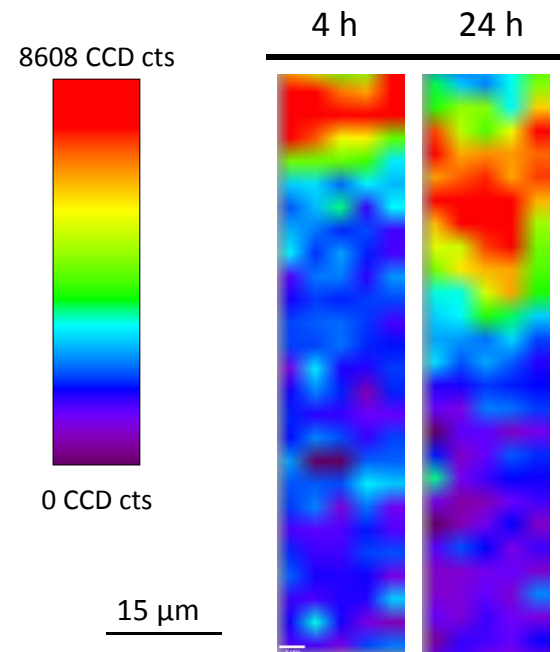
ACSD	Zov US	Zov UK
x	✓	✓

# 9. Penetration of PG – Confocal Raman experimental setup

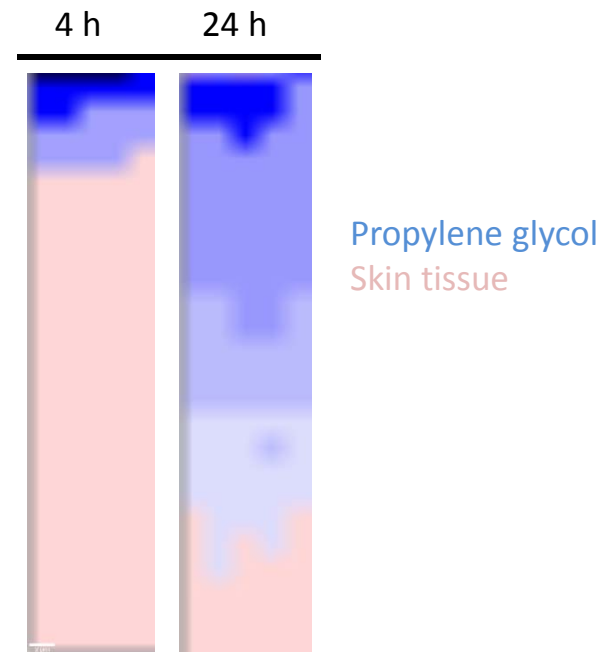


# Penetration of PG – Confocal Raman

Intensity map of propylene glycol



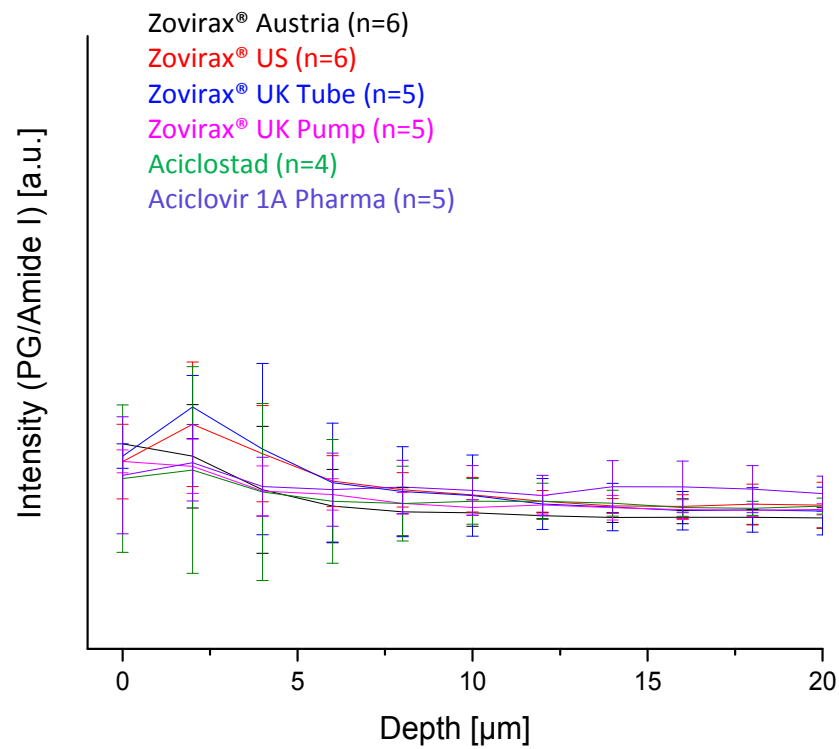
Hierarchical cluster analysis



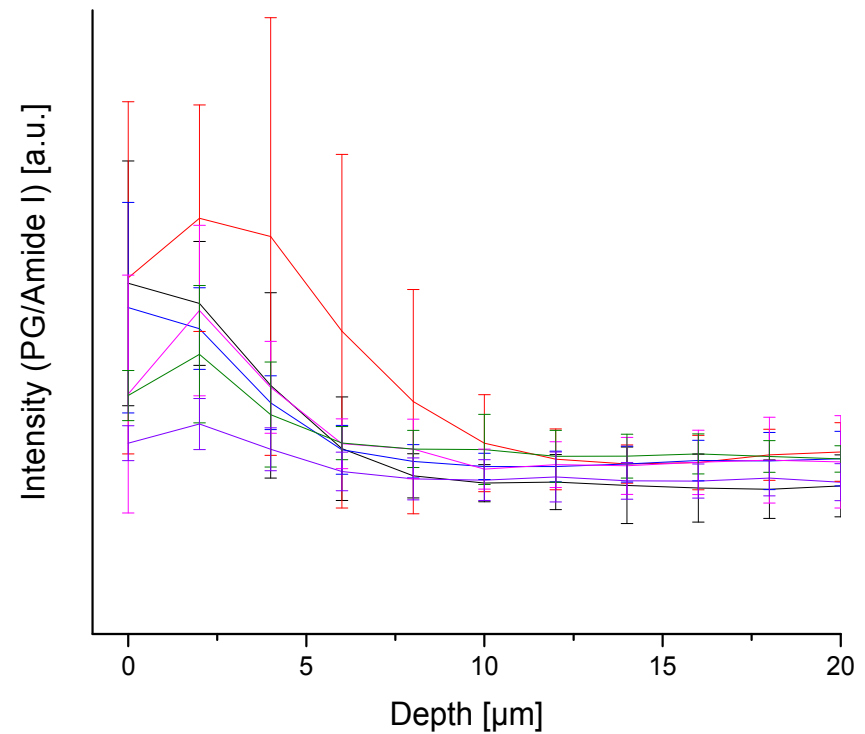


# Penetration of PG – Confocal Raman

4h



24h



# Summary

Test	ACSD	Zov US	Zov UK
pH	✓	✓	✓
Polymorphs	✓	✓	✓
Particle Size	✓	✓	✓
IVPT	✗	✓	✓
Excipients	✗	✓	✓
Zero Shear Rheology	✓	✓	✗
Particle Shape	✗	✓	✓
Loss of Water	✗	✓	✓
Globule Size	✗	✓	✓
Microstructure (Without inclusions)	✗	✓	✓

# Conclusion

- The generic product ACSD differs from the RLD in multiple tests, including IVPT
- ACSD may not be a therapeutically equivalent product?

## *Challenges going forward!*

- ❖ Defining failure modes &
- ❖ Critical quality attributes that cause them
- ❖ Testing for CQAs
- ❖ Parallel IVPT studies – recognise not the only way to assess bioavailability
- ❖ Relating test results to IVPT
- ❖ Regulations based on CQAs and IVPT
- ❖ Does lack of Q3 similarity in CQAs lead to an automatic failure ?
- ❖ Weighing up failure modes
- ❖ Does performance based failure supersede all other failures ?
- ❖ Is IVPT based BE really bioavailability & the best way to prove two products are same ?
- ❖ How to deal with CQAs differences ?
- ❖ Setting limits on test outcomes
- ❖ How close is close enough (upper limit) ?
- ❖ How different is too different (lower limit) ?

# Acknowledgments

- Associate Prof Maïke Windbergs and her student Natalie Jung
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- Dr Sarika Namjoshi
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- Associate Prof Heather Benson
- Associate Prof Jason Stokes, post-doc Dr Heather Shewan
- Dr Sam Raney and the FDA team

Special thanks to teams



Adelaide



Brisbane

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