The Premise of Topical Drug Classification System as an Alternative to Clinical Endpoint BE Studies

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A Novel Approach for Overcoming Barriers to Improve Patient Access for Topical Drugs

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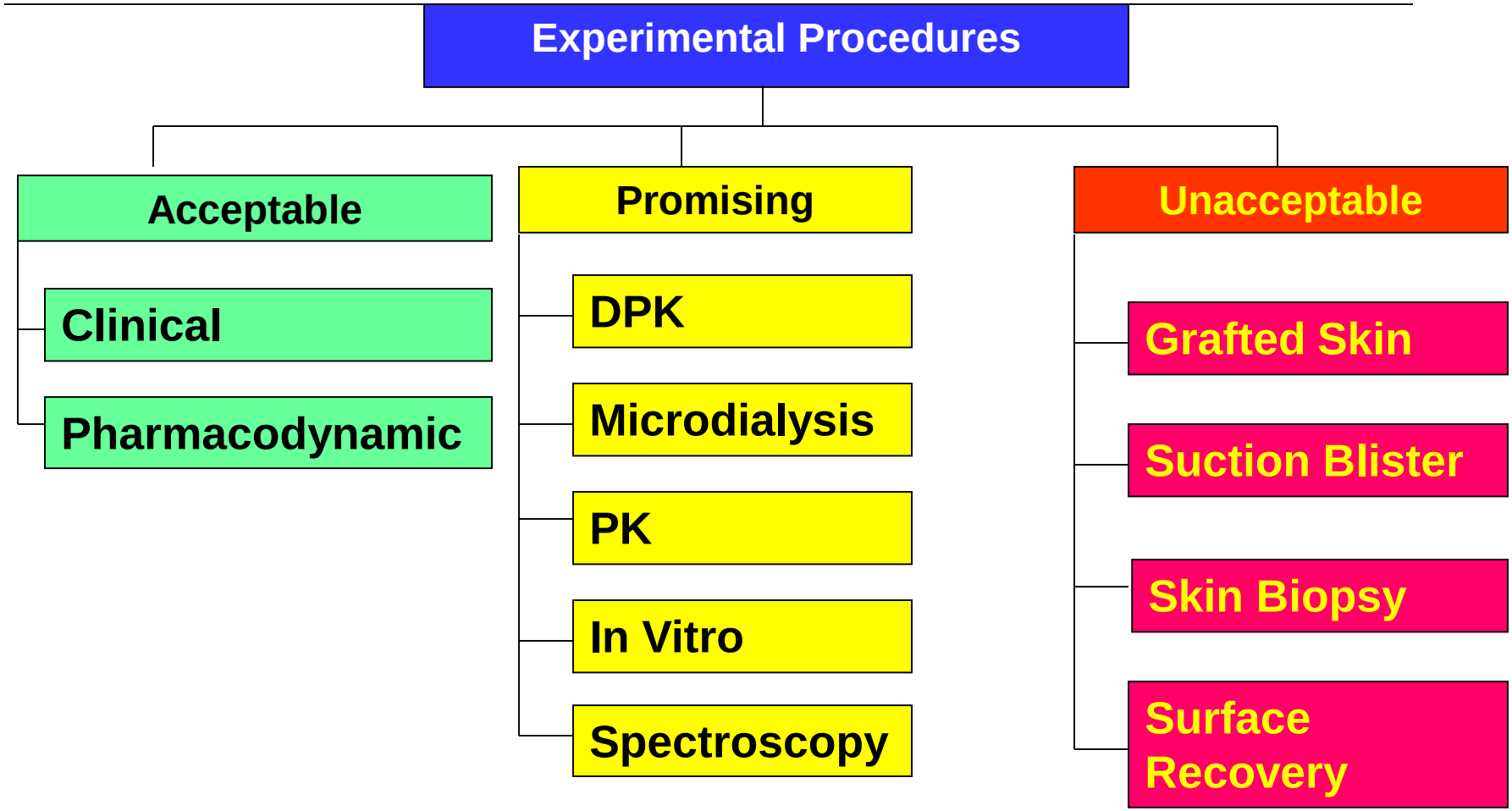
Outline

- BE methods
- Clinical - comparative clinical studies
- Topical Drug Classification System (TCS)
- Validation of TCS
- TCS – IVR – DPK
- Conclusion

Methods of BE of Topical Dermatological Drug Products



Ref: Adopted from VP Shah. Int. J Clin. Pharmaco. and Ther. 42(7): 379-381, 2004.

Acceptable Methodology

Comparative Clinical Trials

- Expensive
- Large patient population
- Time consuming
- Difficult to conduct – End points have high variability
- Less sensitive

Need alternative method to assure Bioequivalence and product quality

Bioequivalence via a Clinical Endpoint BE Study

- Usually Test vs. Reference vs. Vehicle
- Therapeutic equivalence only infers bioequivalence and not a true measure of bioequivalence
- Not sensitive due to significant placebo effect – Chance of success low
- Resource and Cost intensive - May require many subjects; typically more than 300
- There are no blockbusters in topical products. Almost all of them less than 200 million dollar market size.
- You must be sure of the quality of your (Test) product that matches with Reference product

Generic Product Approval

- For product approval: PE + BE = TE
- Determination of BE is the biggest barrier towards approval of dermatological generic topical drug products
- An alternative approach needs to be developed that will assure drug product quality, safety and efficacy.

Evaluation of BE for Topical Drug Products

A Modular Framework for In Vitro BE Evaluation

- Q1/Q2 sameness
- Q3 similarity
- IVRT (In Vitro Release Test)
- IVPT (In Vitro Permeation Test)

Multiple Approaches for BE Evaluation

- In Vivo Pharmacokinetic studies
- In Vivo Pharmacodynamic (Vasoconstrictor) studies
- In Vivo Clinical Endpoint BE studies
- In Silico Quantitative Methods, Modeling and Simulation

Promising Methodology

In Vitro Drug Release

- It is a measure of product quality and sameness with SUPAC related changes.
- With Q_1, Q_2 and Q_3, in vitro release method can be used for biowaiver
- **Draft Guidance utilizing IVRT:**
  - Acyclovir ointment – March 2012
  - Acyclovir Cream – December 2016
  - Silver sulfadiazine cream – July 2017
  - Ivermectin cream – September 2018
  - Dapsone Gel – September 2018

Regulatory Pathway

- A science based approach using **SUPAC-SS** principles – Q1, Q2, Q3 - and in vitro release similarity measurement is developed that can provide biowaiver for certain generic topical drug products, but at the same time maintaining safety, efficacy and quality of the product.

Topical Drug Classification System (TCS)

Topical Drug Classification System (TCS)

- **TCS** is a framework for classifying topical drug products based on
  - qualitative (Q1) and quantitative (Q2) composition,
  - the role of inactive ingredients,
  - microstructure arrangements of matter (Q3) and
  - *in vitro* release (IVR) similarity.
- **TCS** is a classification system of topical drug products, which when applied will help in approval of generic topical drug products, without conducting *in vivo* studies, but assuring product quality, efficacy and safety.

Topical Drug Classification System, TCS

Q1, Q2 Same Q3 Same	Q1, Q2 Same Q3 Different
TCS class 1	TCS class 2
Q1, Q2 Different Q3 Same	**Q1, Q2 Different Q3 Different**
TCS class 3	TCS class 4

Ref: VP Shah et al., Int J of Pharmaceutics. 491: 21-25, 2015.

Topical Drug Classification System (TCS)

TCS Class 1:

- If the product is Q1 and Q2, and if it meets IVR (same Q3) comparison criteria and confidence interval identified in SUPAC-SS, a biowaiver can be provided.
- This corresponds to the definition of Level 1 changes in the SUPAC-SS guidance. There is no reason to expect the generic product to perform differently than the RLD under such a scenario.

Topical Drug Classification System (TCS)

TCS Class 2:

- If the product is Q1 and Q2, but has different IVR (and different Q3), then a biowaiver cannot be granted, and an appropriate BE study should be required.

Topical Drug Classification System (TCS)

TCS Class 3:

- If the generic product is not Q1 and Q2, then it necessitates evaluation of the excipients, to determine if they are inert or not inert.
- Excipients can influence drug penetration and may have an effect on *in vivo* performance of the product, thereby changing the safety and efficacy profiles. It is therefore essential to evaluate the properties of the excipients with respect to safety and efficacy, as well as how excipients affect both the thermodynamic activity of the active pharmaceutical ingredient and the skin permeability.
- In addition, the IVR needs to be determined.
- If the excipients are inert and IVR turns out to be the same as the RLD, and meets the confidence interval criteria, then a biowaiver can be provided.

Topical Drug Classification System (TCS)

TCS Class 4:

- If the generic product is not Q1 and Q2, and IVR is different, then biowaiver cannot be granted, and an appropriate *in vivo* study will be required for topical drug product approval.

Topical Drug Classification System - TCS

Biowaiver

- **TCS Class 1:**

  Q1, Q2 and Q3 same → IVR

- **TCS Class 3:**

  Q1 and Q2 different, Q3 same → IVR

  - **May require additional in vitro studies**

  (e.g., particle size, pH, globule size, rheology)

  - Excipient evaluation

Bioequivalence Study

- **TCS Class 2:**

  Q1, Q2 same but Q3 different → BE studies

- **TCS Class 4:**

  Q1, Q2, Q3 different → BE studies

Validation of TCS Concept

- Validation requires manufacturing and studying of formulations that will fall into different TCS classes
- Determination of IVR and rheological (Q3) measurements and ultimately confirming TCS class with in vivo study in human.
- 12 formulations of acyclovir cream were prepared under GMP conditions by altering source of active ingredient, inactive ingredients and manufacturing process variables.
- Study IVR and rheology of 12 products
- Select 3 products for DPK studies

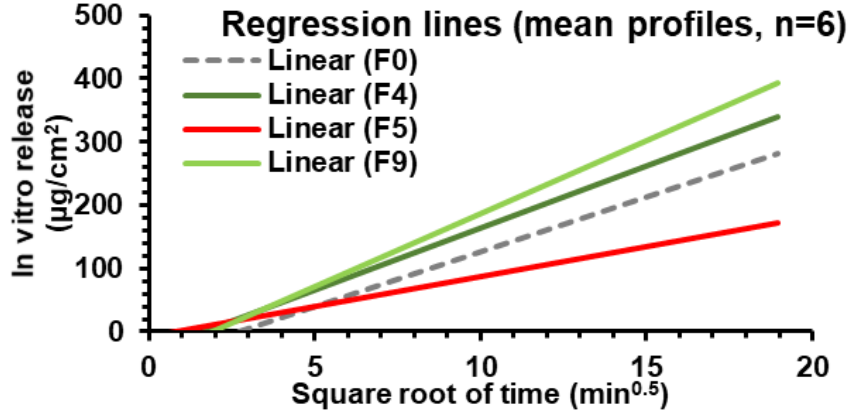
Manufacturing of Acyclovir Formulations

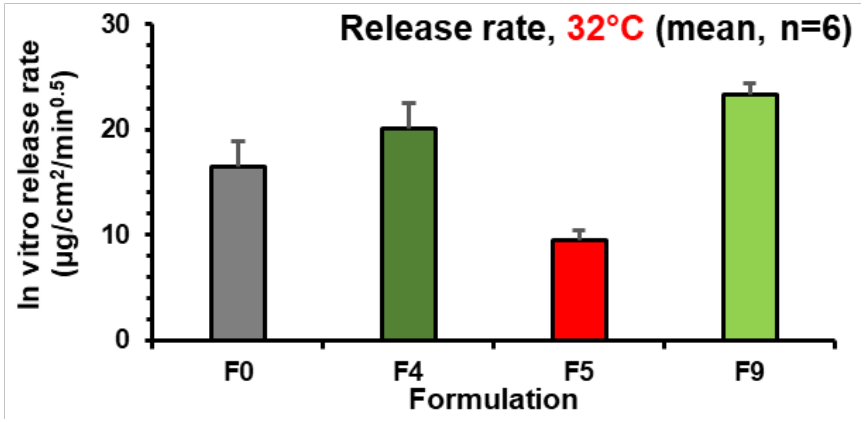
Drug / Excipient
Acyclovir
Cetostearylic alcohol (50:50)
Mineral oil / Liquid paraffin
Petrolatum / White soft paraffin
Polisorbate 80
Sorbitan oleate
Benzylic alcohol
Purified water
Propylene glycol

Subgroup	Code of the formulation	Ingredient / Parameter
A (manufacturing variables)	F1	Order of addition for phases
	F2	Cooling procedure (stirring)
	F3	Cooling procedure (temperature)
	F4	Mixing procedure
B (sources of row material)	F5	Cetostearylic alcohol (inert excipient)
	F6	Polisorbate 80 (non-inert excipient)
	F7	Acyclovir (active ingredient)
	F8	Petrolatum / White soft paraffin (inert excipient)
C (quantities / grade)	F9	Propylene glycol, 5% (non-inert excipient)
	F10	Propylene glycol, 40% (non-inert excipient)
	F11	Cetostearylic alcohol (30:70) (inert excipient)
	F12	Cetostearylic alcohol (110%) (inert excipient)

Acyclovir - IVR

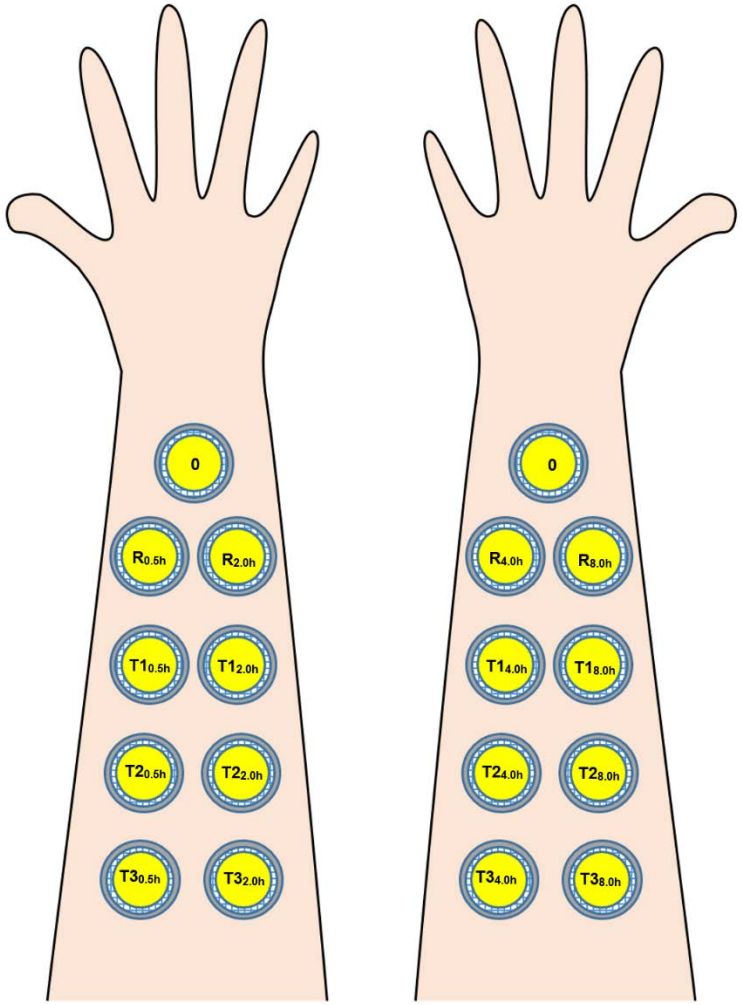
- IVR of products selected for DPK Analysis.
- F0, F4, F5 and F9.





- In vitro similarity concluded only for F4 vs. F0, according to SUPAC-SS methodology.

Schematic representation of drug application area for DPK Study



Number of spots:
9 on each forearm (including 1 for blank), with application sites un-occluded after t=0.

R is ref standard
T1, T2, T3 are formulated products.

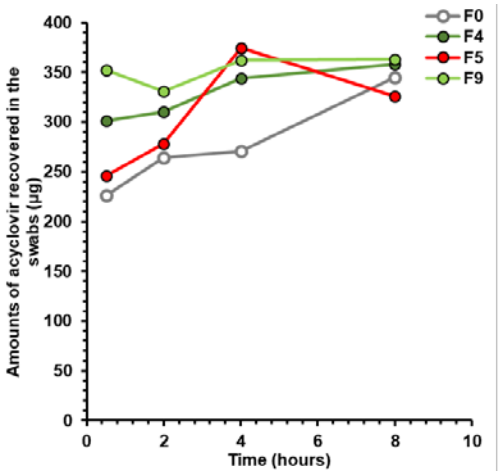
Acyclovir Cream – DPK Study

- **DPK study with 4 products in 8 subjects**
  - F0 – Internal reference
  - F4 – Q1, Q2 same as F0 but manufactured with different process (TCS class 1)
  - F5 – Q1, Q2 same as F0 but different source of raw materials (TCS class 2)
  - F9 – Q1 same, but not Q2, change in non-inert excipient (TCS class 4)
- **DPK Samples**
  - Absorption phase – 0.5, 2.0 hrs.
  - Elimination phase (after 3.0 hrs absorption) 4.0 and 8.0 hrs.
- **Total samples**
  - 1 swab + First two strips + 3-12 strips x 9 spots x 2 arms x 8 subjects = 432 samples - analyzed using validated LC/MS/MS.

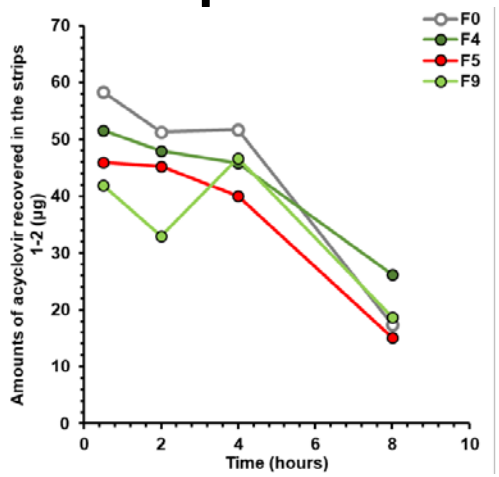
Acyclovir - DPK Data

- **Comparative presentation of the amounts of acyclovir (n=8)**

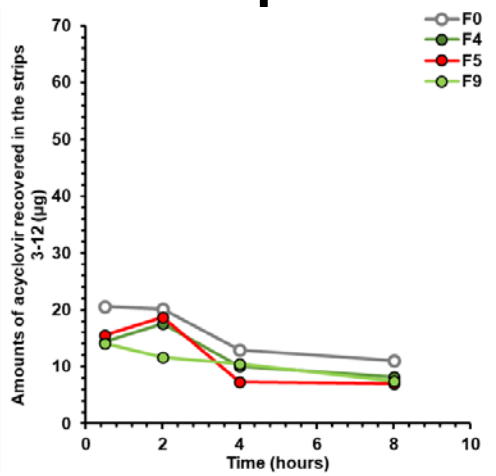
Swabs



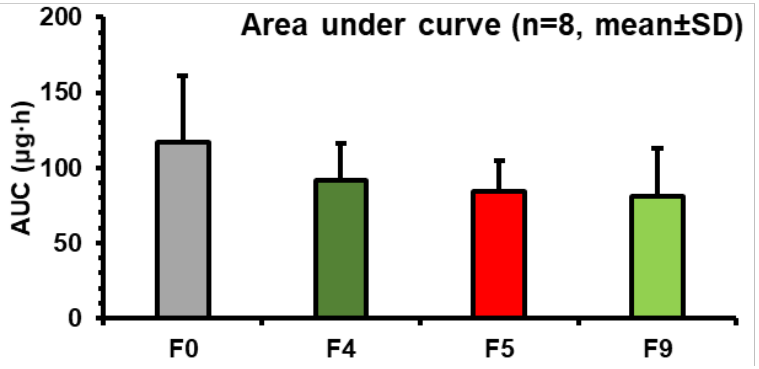
Strips 1-2

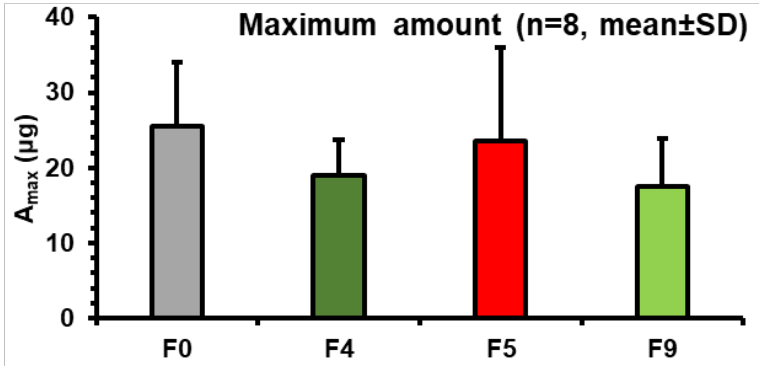


Strips 3-12



- **Comparative presentation of the mean in vivo DPK parameters**





Acyclovir: DPK Analysis

- Pilot study with 8 subjects, High variability.
- Comparison of the internal reference (formulation **F0**) with the other three formulations (**F4**, **F5** and **F9**) using amounts recovered in strips 3-12.
- Calculation of areas under curve using trapezoidal rule.
- ANOVA performed using subject and formulation effect (p=0.0023).

Comparison	Ratio of means	Lower limit, 90%CI	Upper limit, 90%CI
F4 vs. F0	0.8419	0.7287	0.9726
F5 vs. F0	0.7576	0.6558	0.8753
F9 vs. F0	0.6997	0.6057	0.8084

Acyclovir: Data Analysis - TCS

TCS Class 1 **IVR similar** **Biowaiver** **Formulation F4** **Confirmed with DPK/in vivo**	**TCS Class 2** **IVR not similar** **No biowaiver** **Require in vivo study/DPK** **Formulation F5** **DPK – Not BE to Reference** **Not approvable based on IVR**
TCS Class 3 **IVR Similar** **Biowaiver** **Unfortunately no manufactured product fell in this group**	**TCS Class 4** **IVR not similar** **No biowaiver** **Require in vivo study / DPK** **Formulation F9** **DPK – Not BE to reference** **Not approvable based on IVR**

Impact of TCS

- It will help in developing appropriate regulatory guidance.
- It will help in updating/modifying existing guidance.
- It will validate the application of IVR beyond the current SUPAC-SS framework.
- It will facilitate in product development, reduce regulatory burden and assure product quality.
- It will increase the availability of topical drug products to patients and consumers at a more affordable cost.

Conclusion

- **A practical and science based approach for simplifying Regulatory Pathway for a Complex Generics – Creams – using IVRT is proposed.**

Topical Drug Classification System - TCS

- **TCS will facilitate:**
  - ❑ Generic product development, reduce the regulatory burden and assure product quality across all therapeutic classes.
  - ❑ Availability of topical drug products to patients and consumers at a more reasonable cost.

Thank you for your Attention