A Science Based Approach to Simplify Regulatory Pathway for A Complex Generics using IVRT

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6th International Annual Symposium on Dissolution Science and Application

Strategic Advantage through Dissolution Testing

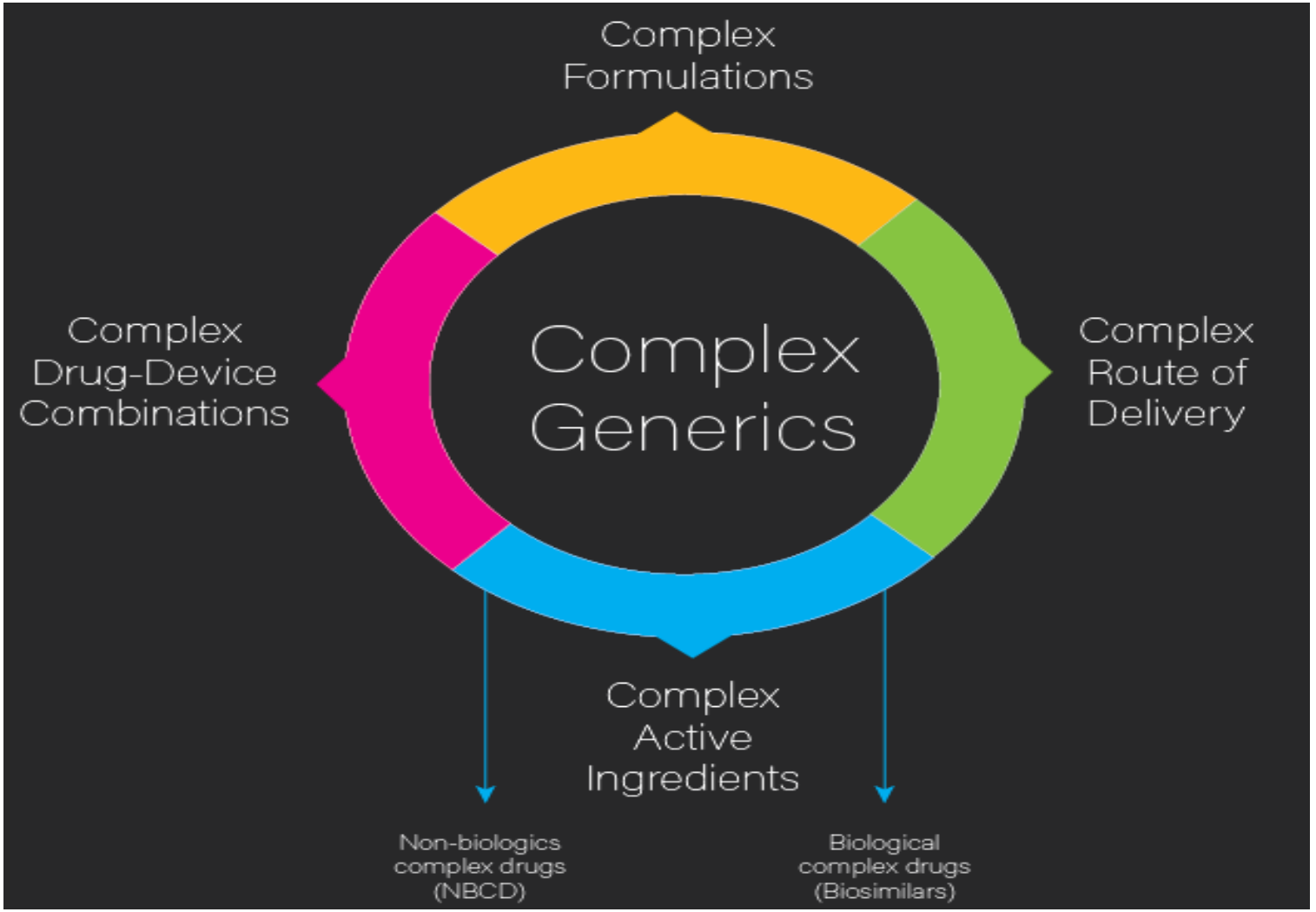
Disso India – Hyderabad, 2018

India. June 28, 2018

Outline

- What are Complex Generics ?
- A Regulatory Pathway for Generic Topical Drugs
- Topical Drug Classification System (TCS)
- IVR and Q3 Measurements in Support of TCS
- In vivo studies
- Conclusions

Complex Generics



Source: OGD/FDA Workshop: Demonstrating Equivalence of Generic Complex Drug Substances and Formulations, Oct 6, 2017.

Complex Formulations / Dosage Forms

- Long acting parenteral drug products
  - Microparticles
  - Implants / inserts
  - Multivascular liposomes
  - Suspensions
- Injectable drug products with nanotechnology
  - Nanosize liposomes
  - Iron complex
  - Nanosuspensions
- **Semisolids**
  - **Lotions**
  - **Ointments**
  - **Creams**
- Emulsions
- Inhalation drug products

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.

Regulatory Pathway

- A science based approach using **SUPAC-SS** principles and in vitro drug release measurement is developed that can provide biowaiver for certain class of topical drug products.

Topical Drug Classification System (TCS)

SUPAC-SS

- ***Level 1 Changes***: Changes in excipients up to 5% - unlikely to have detectable impact on quality/performance
- ***Level 2 Changes*** include:
  - (i) changes of > 5 and ≤ 10% of excipients,
  - (ii) change in equipment to a different design / different operating principles; process changes including changes in rate of mixing, rate of cooling, operating speeds and holding time,
  - (iii) change in batch size beyond a factor of 10.

SUPAC - SS

- *"The physical properties of the dosage form depend upon various factors, including the size of the dispersed particles, the interfacial tension between the phases, the partition coefficient of the active ingredient, between the phases, and product rheology. These factors combine to* ***determine the release characteristics*** *of the drug, as well as other characteristics, such as viscosity."* … **SUPAC-SS**
- *"An in vitro release rate can reflect the combined effect of several physical and chemical parameters, including solubility and particle size of the active ingredient and rheological properties of the dosage form."* … **SUPAC-SS**

Topical Drug Classification System (TCS)

- **TCS** is a framework for classifying topical drug products based on its qualitative and quantitative composition, microstructure arrangements of matter and *in vitro* release (IVR).
- **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 efficacy.
- **TCS** considers the qualitative (**Q1**) and quantitative (**Q2**) composition, the role of inactive ingredients and microstructure arrangement of topical semisolid products (**Q3**).

Topical Drug Classification System, TCS

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

- Based on composition (**Q1** and **Q2**) and **IVR** properties, the topical drug products are classified as **TCS** class **1**, **2**, **3** and **4**.
- Under the proposed classification:
  - ❑Only **TCS class 1** and **TCS class 3** drug products are eligible for biowaiver;
  - ❑ **TCS class 2** and **TCS class 4**, are not eligible for biowaiver and will require *in vivo* BE studies for drug approval;
  - ❑The nature and type of *in vivo* BE study will depend on the therapeutic class and dosage form category.

Topical Drug Classification System, TCS

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

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

Acyclovir Cream

Current Study Findings

- 21 generic products and 6 RLD (from Europe, US) were analyzed.

Findings indicate that:

- The formulations (excipients/composition) are markedly different, the *in vitro* release and microstructure, rheology are all different.
- A good relationship was observed in these studies between microstructure (Q3) (rheology) and *in vitro* release.
- Changes in microstructure reflected in different release rate. **Q3 → IVRT**

Validation of TCS Concept

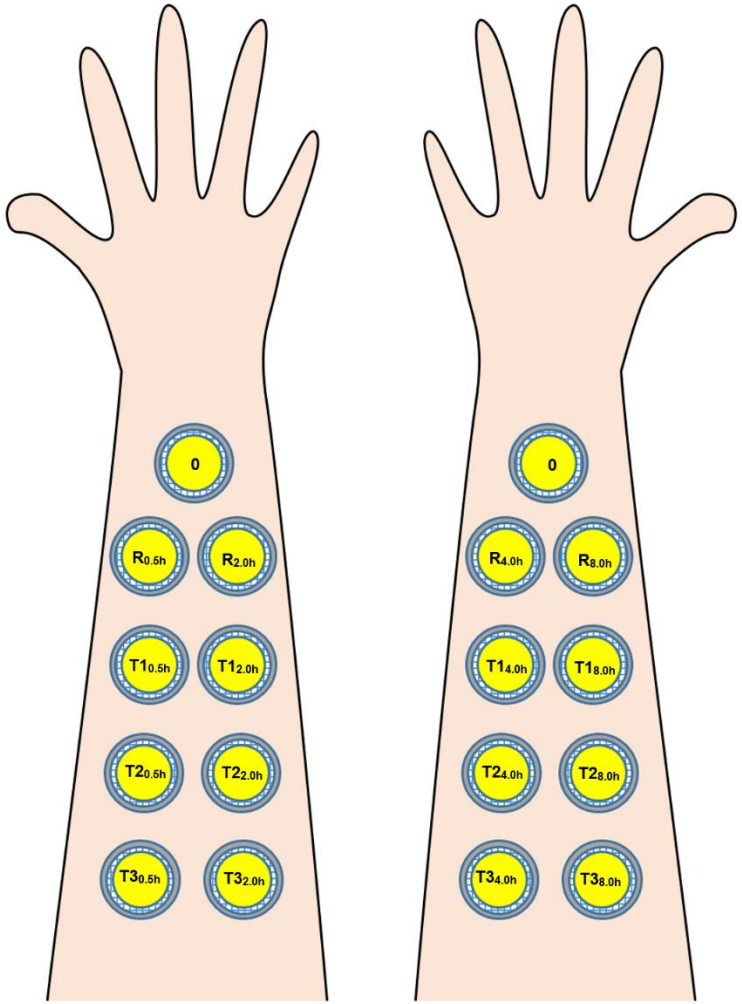
- Validation requires manufacturing and studying of formulations that will fall into different TCS classes
- Determination of IVR and rheological (Q3) measurements and ultimately confirming TCS class with in vivo study in human.
- 12 formulations of acyclovir cream were prepared under GMP conditions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

Formulations under evaluation

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)

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.

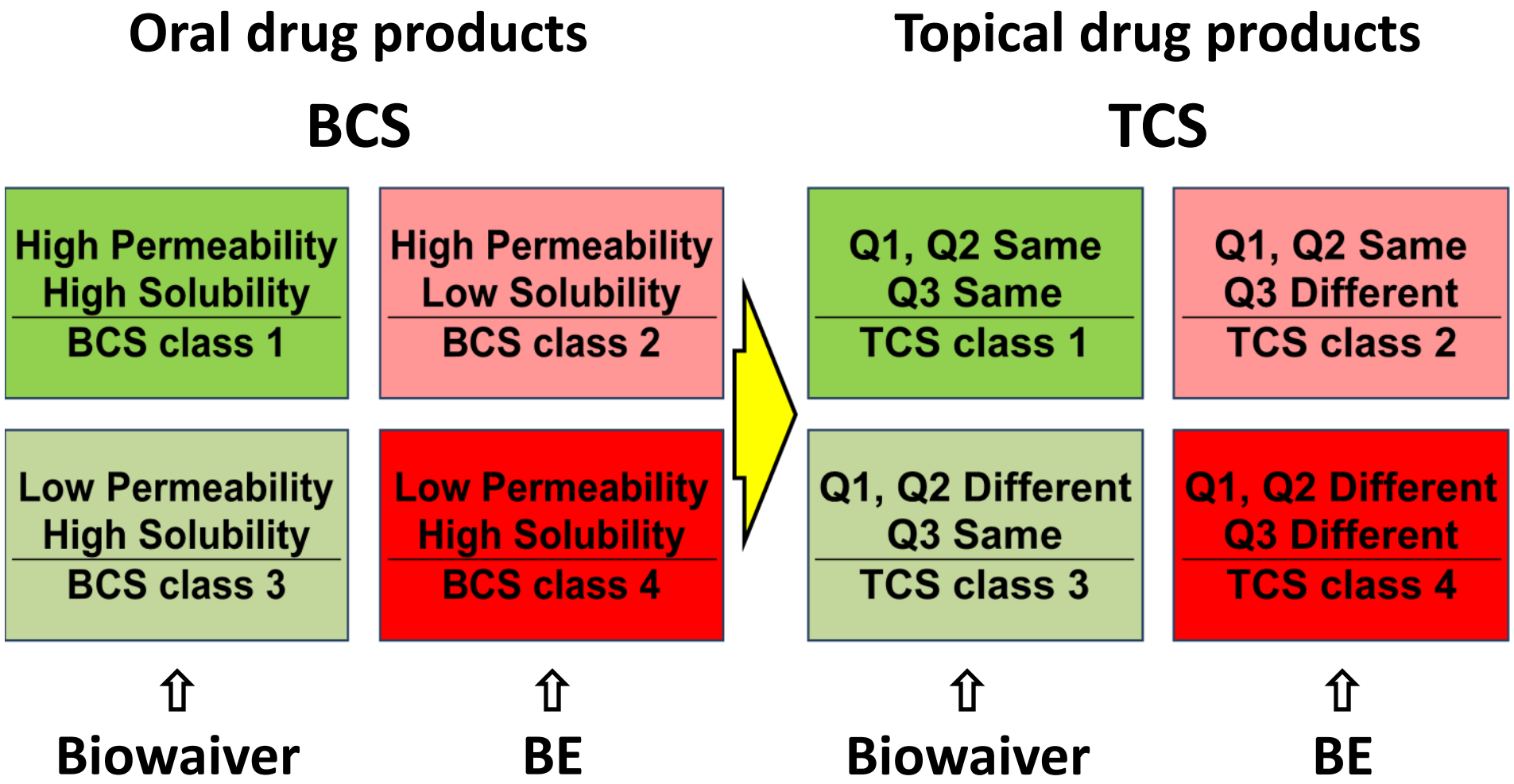
R is ref standard
T1, T2, T3 are formulated products.

Stay tuned for final results !!!

Topical Drug Classification System (TCS)

- TCS is based on SUPAC-SS, Q1 & Q2 principles and IVR measurements.
- IVR reflects Q3 measurements.
- There is a good similarity between BCS and TCS. In both the cases, biowaiver is based on dissolution/in vitro release comparison.
- In both the cases, class 1 drug products are eligible for biowaiver, and class 3 products require stricter criteria or addition testing for biowaiver.

BCS and TCS



Ref: VP Shah et.al., Int J Pharmaceutics. 509 : 35-40 (2016).

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.

Acknowledgement

- Product Quality Research Institute (PQRI) for partial funding.
- Romanian National Research Grants
- Dr. Flavian S Radulescu and Dr. Dalia S Miron of Faculty of Pharmacy, University of Medicine and Pharmacy “Carol Davila”, Bucharest, Romania.
- Dr. Avraham Yacobi for valuable discussions on the TCS concept.

Thank you for your Attention