

A Science Based Approach for Topical Drug Classification System

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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

Topical Drug Classification System (TCS)

- TCS is based on established scientific principles specifically developed for semisolid topical products (SUPAC-SS) and is combined with the IVR of the drug product.
- TCS considers the qualitative (Q1) and quantitative (Q2) composition of inactive ingredients and microstructure arrangement of topical semisolid products (Q3).

Outline

- Principle of TCS
- Q1, Q2, and Q3
- SUPAC-SS
- In Vitro Release (IVR)
- Classification of TCS
- BCS and TCS comparison
- Impact of TCS
- Conclusions

Topical Dosage Forms

- Transdermals - For systemic effect
- **Topical drug delivery** - For local action (in skin)
- Topical dosage forms - Generic drugs
 - Generic Product: $PE + BE = TE = TI$
 - Topical: Q1 and Q2
 - Bioequivalence testing - Challenge
Case-by-case approach
 - In Vitro testing

Generic Topical Drug Product

- According to 21 CFR 314.94 the generic topical drug product will need to have the same excipients, qualitatively (Q1) and quantitatively (Q2) as the brand name drug (RLD).
- If the generic product is not Q1 and Q2 compared to RLD, the applicant must provide adequate proofs that the differences will not impact the safety and efficacy profiles of the product.

Ref: Chang, R.K., et al, AAPS Journal 2013;15(1):41-52.

In vitro Release Test (IVR)

- Assures product sameness after SUPAC changes
- Reasonable test
- Batch-to-batch uniformity
- QbD emphasizes development of a meaningful drug development specification based on clinical performance. IVR is the first step towards this goal.
- **To be implemented as a required drug product release and stability test.**

Ref: R-K Chang, A Raw, R Lionberger and L Yu. Generic development of topical dermatologic products: Formulation development, process development, and testing of topical dermatologic products. AAPS Journal, 15 (1), 41-52, 2013.

SUPAC - SS

- The SUPAC-SS guidance was developed to address:
 - Changes in the component or composition,
 - Changes in the manufacturing process and equipment,
 - The scale-up/scale-down of manufacture, and/or
 - Change in site of manufacture.

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 $\leq 10\%$ 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

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Q1, Q2 and Q3. In vitro Release

- Q1 – Same ingredients/components as RLD
- Q2 – Same ingredients/components in the same concentration as RLD
- Q3 – Same ingredients/components/in the same concentration with same arrangement of matter (microstructure) as RLD → Same IVR
- Acceptable comparative physicochemical characterization and equivalent in vitro release (Q3) to RLD
- Biowaiver may be granted with supportive data to demonstrate Q1 and Q2 same and similar physicochemical characteristics (Q3 – IVR)

Ref: R-K Chang, A Raw, R Lionberger and L Yu. AAPS Journal, 15 (1), 41-52, 2013.

IVR and Q3

- Adequately developed and validated, IVR methodology can provide information on the combined role of several physico-chemical characteristics, including the particle or droplet size, viscosity and diffusional resistance of the vehicle.
- The IVR reflects the microstructure, arrangement of the matter and the state of aggregation of the dosage form (Q3). **Q3 → IVR**
- IVR methodology for the evaluation of Q3 similarity is used in TCS classification for application of biowaiver.

Microstructural Similarity(Q3)

- Microstructure similarity: Particle/droplet size measurements - similar distribution, similar rheological properties
- Microstructure non-similarity: differences in physical characteristics, in rheology (even for similar particle size) and in IVR rates
- Rheology: Shear stress vs. strain rate measurements; Evaluation of linear viscoelastic response; Yield stress (σ_0) - inversely proportional to spreadability.
- Validation of Q3 must be related to Therapeutic Equivalence

Ref: L Yu. FDA Pharm Sci Advisory Committee meeting. 2003.

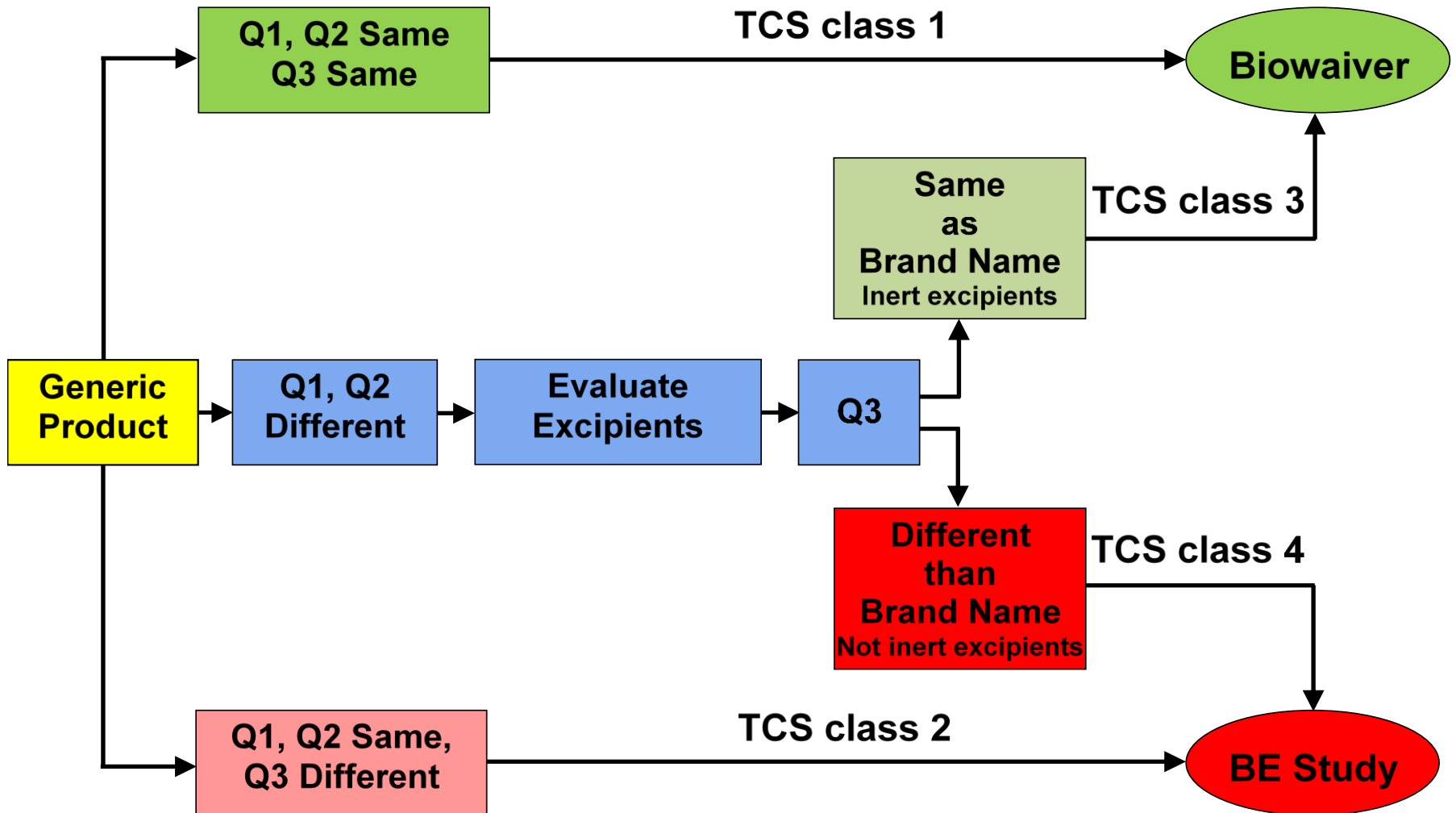
Excipients in Topical Drug Products

- Excipients may have significant impact on drug release from topical dosage form, skin barrier properties and/or drug penetration directly affecting rate and extent of exposure at site of action, and may have an effect on *in vivo* performance of the product, thereby changing the safety and efficacy profiles.
 - If all three parameters, Q1, Q2 and Q3 are the same between the RLD and the generic product, the generic product may be suitable for a biowaiver.
 - If they are not the same, a biowaiver cannot be provided and additional studies or a biostudy will be required.
- Using these scientific principles, a Topical Drug Classification System (TCS) is proposed to simplify the regulatory requirements.

Topical Drug Classification System - TCS

- Based on composition (**Q1** and **Q2**) and IVR similarity (**Q3**), 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



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

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TCS class 4

Topical drug Classification System (TCS)

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Review

A science based approach to topical drug classification system (TCS)



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ABSTRACT

The Biopharmaceutics Classification System (BCS) for oral immediate release solid drug products has been very successful; its implementation in drug industry and regulatory approval has shown significant progress. This has been the case primarily because BCS was developed using sound scientific judgment. Following the success of BCS, we have considered the topical drug products for similar classification system based on sound scientific principles.

BCS and TCS

- BCS is based on the solubility and permeability characteristics of the drug substance.
- TCS system is based on established scientific principles specifically developed for semisolid topical products (SUPAC-SS) and is combined with IVR of the drug product.
- TCS considers the qualitative and quantitative composition of inactive ingredients and microstructure arrangement of topical semisolid products.
- In both the classification systems, BCS and TCS, their applicability for biowaiver granting **relies on the use of *in vitro* testing** as key decision tools.

BCS

Publications:

Pharm.Res. 12:413-420, 1995.

BCS Guidance:

Aug. 2000 (class 1)

BCS Guidance update (Draft):

May 2015 (class 1 and 3)



Requirements:

API

Solubility and Permeability

Dosage form

Class 1 - Dissolution

Class 3 with Q1 + Q2

Dissolution

TCS

Publications:

SUPAC-SS Guidance:

May 1997

AAPS J. 15:41-52, 2013.

AAPS J. 15:674-683, 2013.

Int.J.Pharm. 491:21-25, 2015.



Requirements:

Dosage form

Q1 + Q2

Inert excipients

Microstructure

In vitro release

BCS and TCS

Oral drug products

Topical drug products

BCS

TCS

High Permeability
High Solubility
BCS class 1

High Permeability
Low Solubility
BCS class 2

Q1, Q2 Same
Q3 Same
TCS class 1

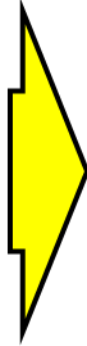
Q1, Q2 Same
Q3 Different
TCS class 2

Low Permeability
High Solubility
BCS class 3

Low Permeability
High Solubility
BCS class 4

Q1, Q2 Different
Q3 Same
TCS class 3

Q1, Q2 Different
Q3 Different
TCS class 4



Biowaiver



BE



Biowaiver



BE

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



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Mini review

Commonality between BCS and TCS



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ABSTRACT

Both biopharmaceutics classification system (BCS) and topical drug classification system (TCS) are based on sound scientific principles with the aim of providing biowaiver and reducing regulatory burden without lowering the quality requirements and standards of approval for the drug products. BCS is based on the solubility and permeability properties of the active pharmaceutical ingredient (API, or drug substance) whereas the TCS is based on the qualitative and quantitative composition of the dosage form and the *in vitro* release rate of the active ingredient as key decision tools. Both BCS and TCS take drug release and dissolution as their guiding principle for providing biowaiver, increasing the availability and affordability of safe and effective medicines to the consumers and at the same time maintaining the drug product quality.

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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 classification system, TCS, for topical drug products is proposed.
- 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***