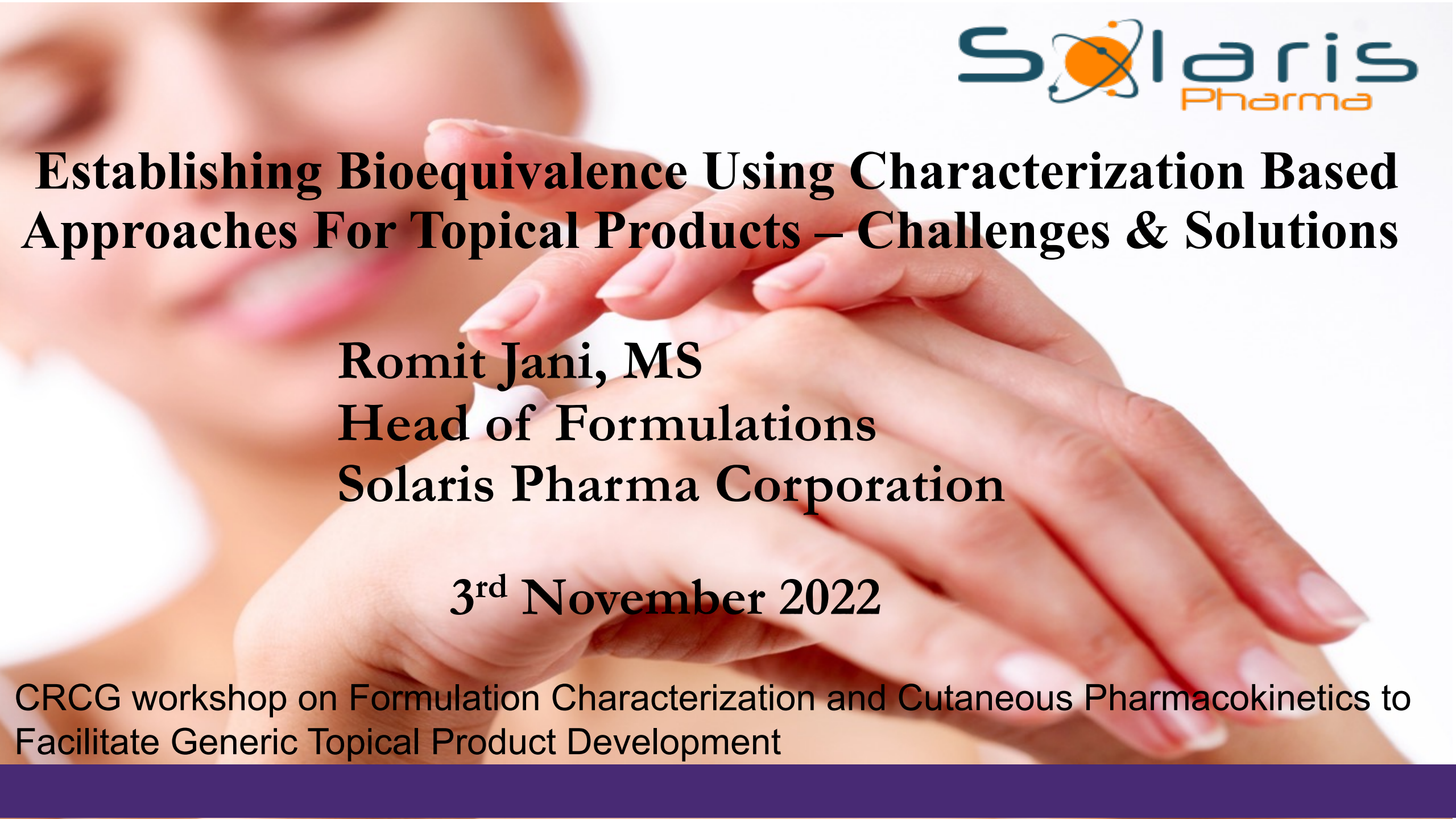

Establishing Bioequivalence Using Characterization Based Approaches For Topical Products – Challenges & Solutions

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CRCG workshop on Formulation Characterization and Cutaneous Pharmacokinetics to Facilitate Generic Topical Product Development

Presentation Outline

- Challenges and complexities in Q1 (Qualitative) and Q2 (Quantitative) sameness characterization
- A case study on polymer grade and impact on BE
- An alternative approach for non Q1/Q2 products for non-critical excipients
- Alternative approach for non Q1/Q2 products for critical excipients
- Summary

Topical Product Development – BE Characterization Challenges

- Reverse Engineering challenges
- Lack of availability of analytical techniques for identifying complex ingredients and smaller concentrations
- Availability of alternate approaches to establish bioequivalence for Q3 similar products

- <u>Q1/Q2 challenges – Reverse engineering, complex excipients, Excipients with different grades</u>
- RLD Lot to lot variability - impact on Q3, IVRT/IVPT
- IVPT challenges
- Particle size, globule size of products with low drug concentration

Challenges - Qualitative Sameness Characterization(Q1)

Ingredient

Combination of two or more ingredients/excipients

Listed in the Label as separate but they are single ingredient

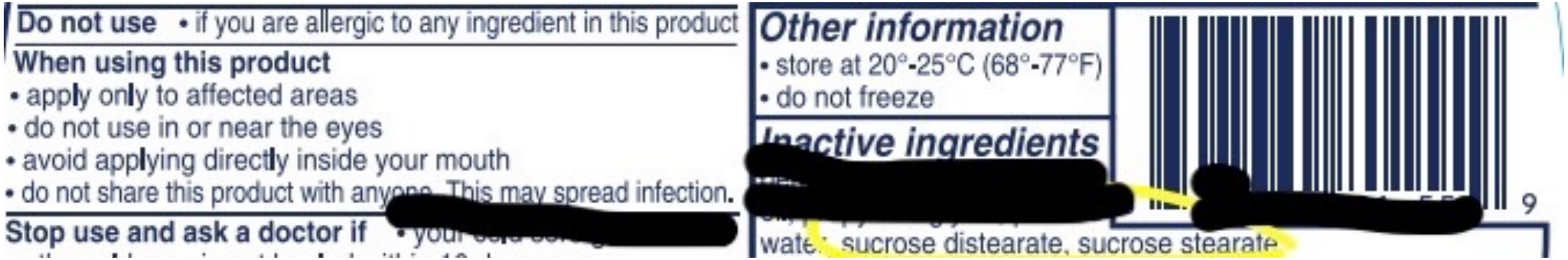
- Sepineo P 600 (Acrylamide/Sodium Acryloyldimethyl Taurate Copolymer/Isohexadecane & Polysorbate 80)
- Glyceryl Stearate /PEG 100 Stearate
- Sucrose stearate / Sucrose distearate
- Combination of Polymers, eg carbomers

Grade variations

- Petrolatum
- Carbomer Homopolymer
- Hypromellose
- Mineral Oil

Challenges – Qualitative Sameness Characterization - Q1

Example 1



Do not use • if you are allergic to any ingredient in this product

When using this product
- apply only to affected areas
- do not use in or near the eyes
- avoid applying directly inside your mouth
- do not share this product with anyone. This may spread infection.

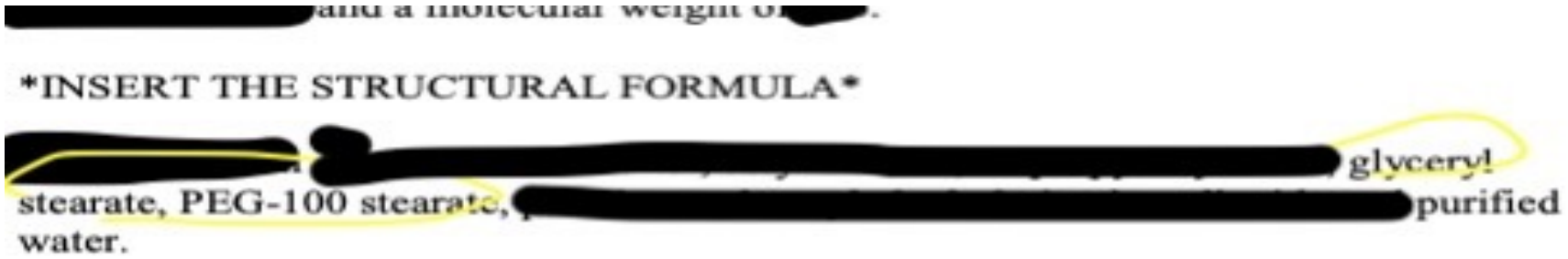
Stop use and ask a doctor if • your [redacted]

Other information
- store at 20°-25°C (68°-77°F)
- do not freeze

Inactive ingredients

[redacted] sucrose distearate, sucrose stearate

Example 2



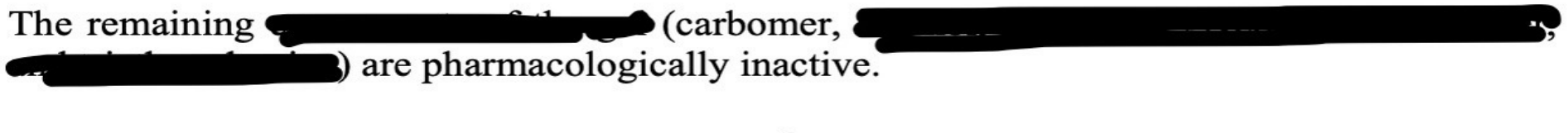
[redacted] and a molecular weight of [redacted].

INSERT THE STRUCTURAL FORMULA

[redacted] glyceryl stearate, PEG-100 stearate, [redacted] purified water.

CLINICAL PHARMACOLOGY

Example 3

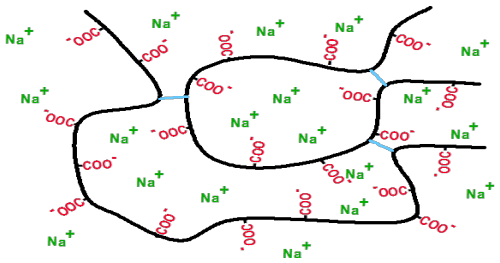


The remaining [redacted] (carbomer, [redacted]) are pharmacologically inactive.

CLINICAL PHARMACOLOGY

Challenges in establishing Quantitative sameness Q2

- Collection of molecules that can feature distributions in molecular size, chemical composition, functional groups, end-groups, branching, etc (eg., Carbomer)



Polymer

Oleaginous Compounds

- Either used as a single excipient or in combination– Lack of available analytical techniques.
- Eg., Petrolatum, Mineral, White wax

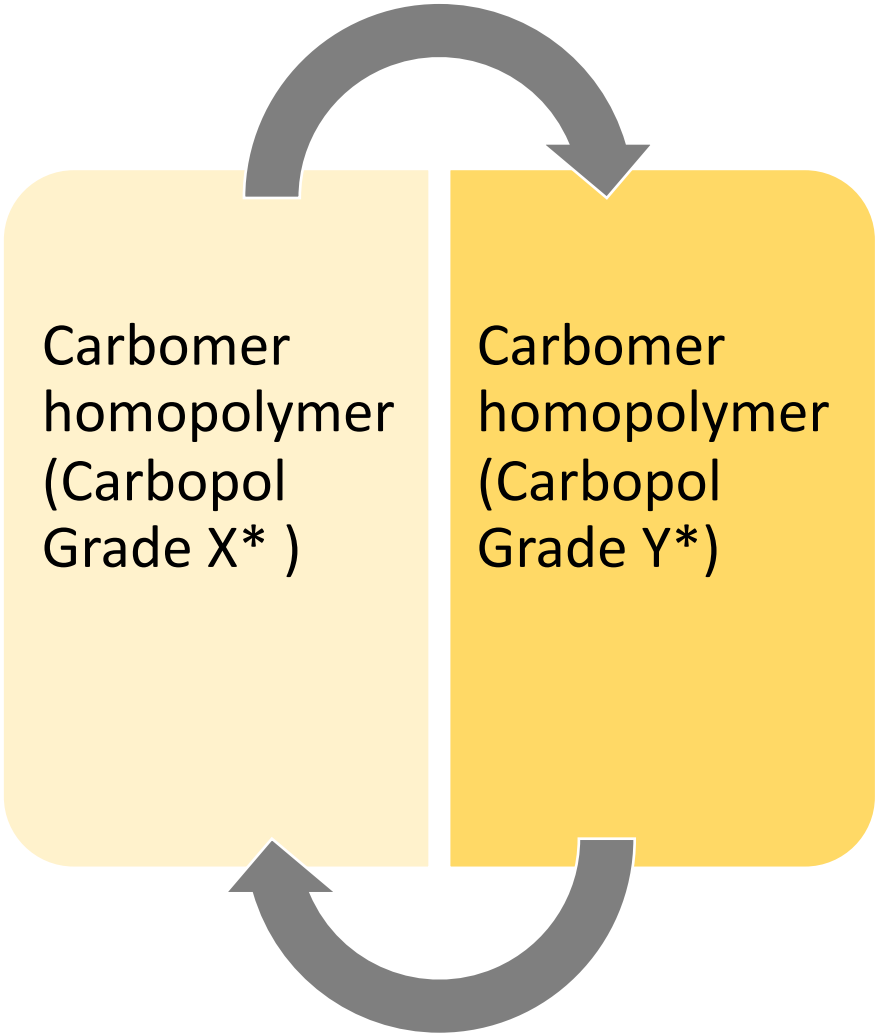
Buffering agent

- Single or multiple buffer system
- Challenge in quantifying individual components
- Eg., Citric acid/Na Citrate

Low concentration Excipient

- Polymers (HPMC, Carbomers) , Antioxidants and preservatives
- Surfactants and emollients (Polysorbate 80, Poloxamer)

Impact of Polymer Grade on demonstrating Bioequivalence – A Case Study



- Reference Product used Grade (Grade X*) which uses benzene in the process;
- Replaced with like-to like Grade (Grade Y*) which uses ethyl acetate in the process
- Both grades have same viscosity range at 0.5% concentration with pH adjusted to 7.5

* This is not a type of the grade. This was mentioned just to illustrate that both the grades were different.

Impact of Polymer Grade on demonstrating Bioequivalence – A Case Study

RLD – with Polymer Grade X

Test-1 – Polymer Grade Y

PHYSICOCHEMICAL PROPERTIES

CHARACTERISTIC		RLD*	Test-1
pH		6.50 - 6.62	6.6
Viscosity, cP (Brookfield)		28150 - 36830	30240
Viscosity, Pa.s (Discovery hybrid)		1.942 - 2.018	1.972
Flow curve - Viscosity (Pa.s) at Shear Rate (1/s)	1.09	99.61 - 118.93	110.26
	10.04	15.18 - 19.40	18.00
	115.3	2.65 - 3.31	3.18
Sp. gravity		0.854 - 0.891	0.86

* RLD data Range established with of multiple lots

Case Study : Impact of Polymer Grade on Pharmacokinetic data

An open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose bioequivalence study

Acceptance Criteria 80.0 %-125.0 %

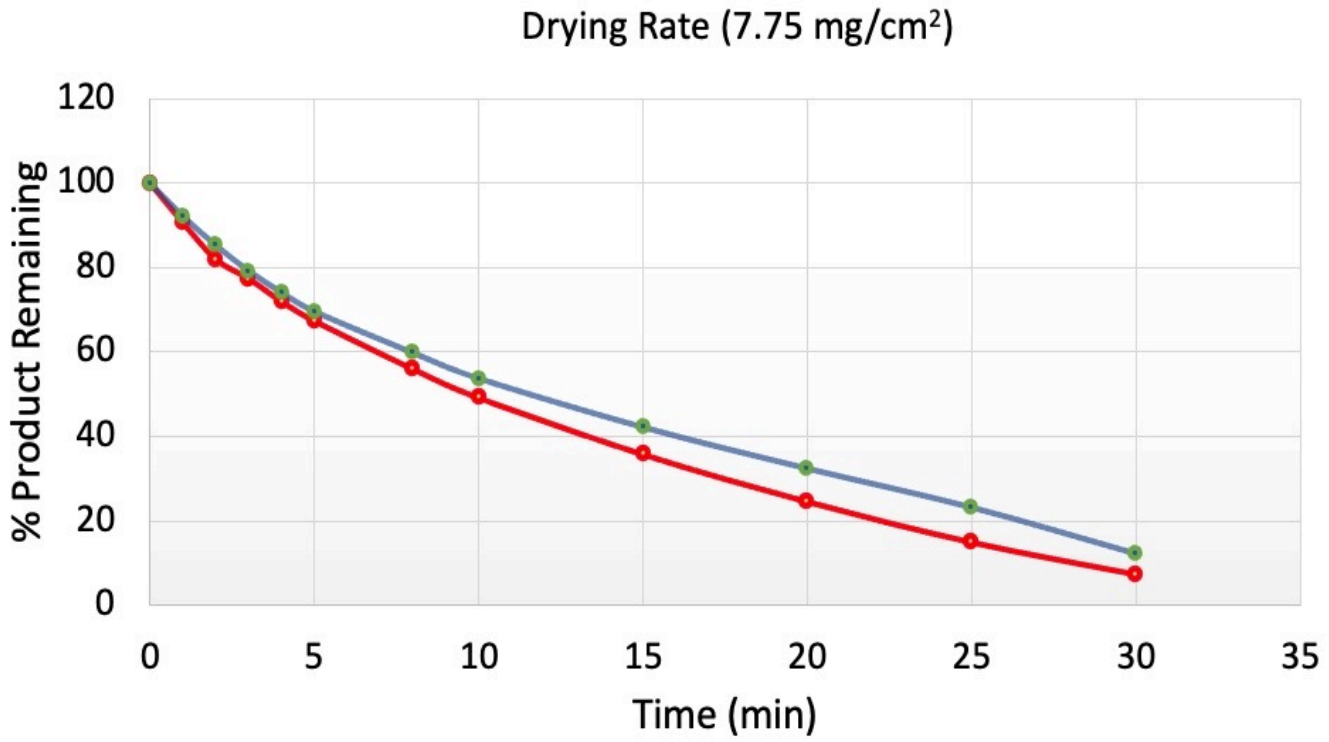
Dependent	Units	Test	RefGeoLSM	TestGeoLSM	Ratio_%Ref_	CI_90_Lower	CI_90_Upper	Power	IntraSubject_CV
Ln(Cmax)	pg/mL	T	31.386	45.312	144.37	103.24	201.89	0.0000	64.100
Ln(AUCt)	hr*pg/mL	T	1240.097	1376.414	110.99	91.06	135.29	0.1282	35.697
Ln(AUCi)	hr*pg/mL	T	1867.760	1816.640	97.26	73.19	129.25	0.0000	29.904
Note: The reported power is based on Schuirmann's TOST (Two One Sided Test) confidence interval approach.									

Data indicates that the failure is not only due to lack of sufficient power but also showed that the formulations are not the same.

IVRT comparison RLD and Test Product

Accumulated Amount Released (mg/cm^2)		
Time, $min^{0.5}$	**RLD (n=4)**	**Test -1 (n=4)**
5.477	3.225	3.125
7.746	8.006	8.881
9.487	12.781	15.231
10.954	18.125	21.462
12.247	23.293	28.700
13.416	28.518	35.35
In Vitro Release Rate (Slope; $mg/cm^2/min^{0.5}$)	3.2	4.1
%RSD	10.4	6.2

DRYING RATE



Test product Reference product

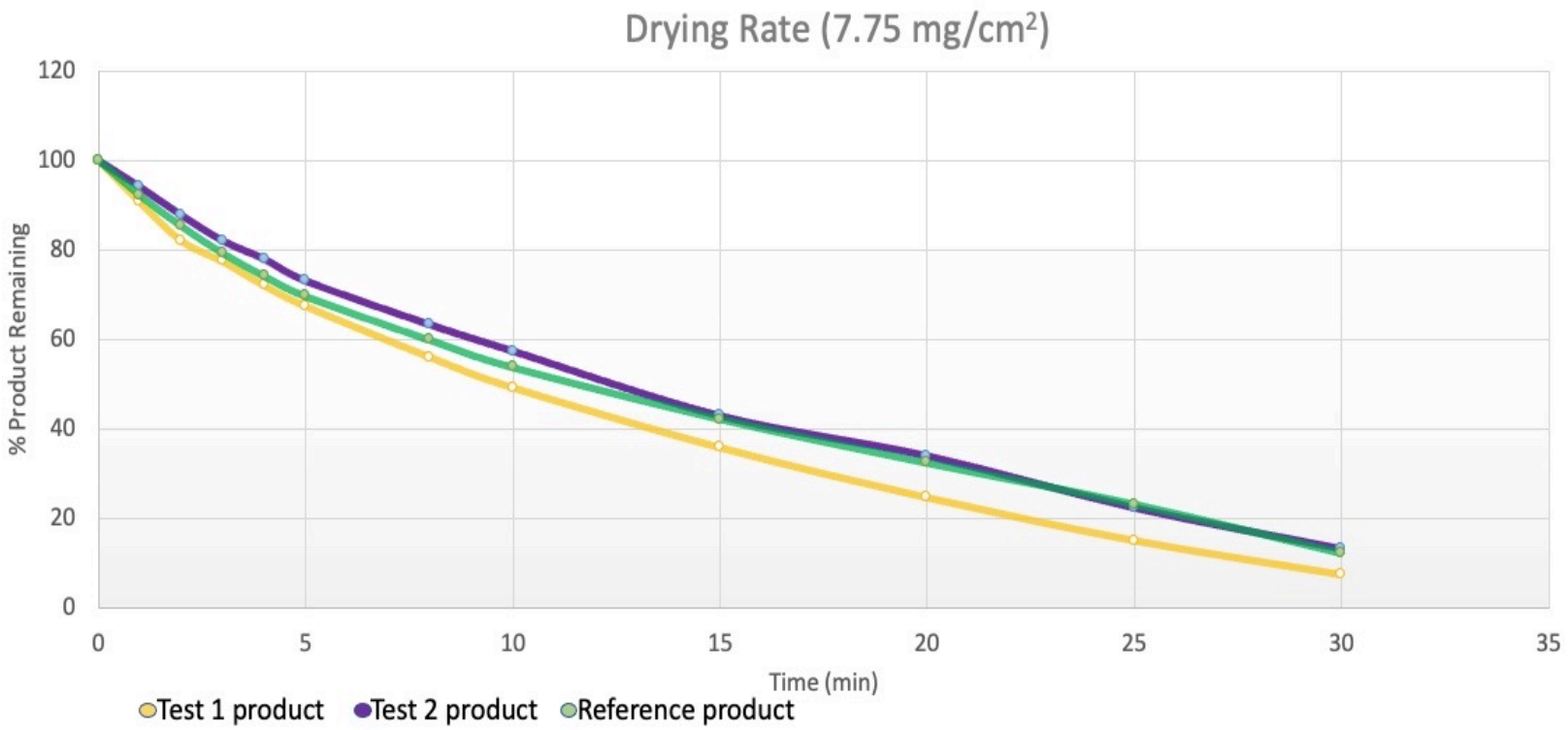
- Revisited formulation and RE information and finalized to increase the polymer content

PHYSICOCHEMICAL PROPERTIES

CHARACTERISTIC		RLD*	Test -1	Test -2 (approximate ~15 % Higher Polymer conc)
pH		6.50 - 6.62	6.6	6.5
Viscosity, cP (Brookfield)		28150 - 36830	30240	34093
Viscosity, Pa.s (Discovery hybrid)		1.942 - 2.018	1.972	1.934
Flow curve - Viscosity (Pa.s) at Shear Rate (1/s)	1.09	99.61 - 118.93	110.26	95.02
	10.04	15.18 - 19.40	18.00	16.82
	115.3	2.65 - 3.31	3.18	3.09
Sp. gravity		0.854 - 0.891	0.86	0.880

* Range established with multiple RLD lots

Drying rate comparison of Two Test products against RLD



Case Study : Impact of Grades of Polymer on Drug Release

IVRT – Test and RLD with higher polymer

Accumulated Amount Released (µg/cm^2)		
Time, min$^{0.5}$	RLD (n=6)	Test -2 (Higher Polymer conc) (n=6)
5.477	3.366	3.950
7.746	7.691	8.720
9.487	13.154	14.337
10.954	18.670	19.775
12.247	23.920	26.175
13.416	29.508	32.500
In Vitro Release Rate (Slope) (Slope; µg/cm^2/min$^{0.5}$)	3.3	3.6 (4.1 on Test-1)
%RSD	5.7	9.1

IVRT – Test 1 and Test 2 with RLD

Accumulated Amount Released ($\mu g/cm^2$)			
Time, $min^{0.5}$	**RLD (n=4)**	**Test-1 (n=4)**	**Test -2 (15% higher polymer conc) (n=4)**
5.477	1.725	3.133	2.733
7.746	5.581	8.583	6.283
9.487	9.968	15.4	10.750
10.954	14.681	21.6	15.783
12.247	19.631	28.358	21.533
13.416	25.262	35.925	27.566
In Vitro Release Rate (Slope; $\mu g/cm^2/min^{0.5}$)	2.9	4.1	3.1
%RSD	7.0	6.4	3.4

PK Study with the new formulation

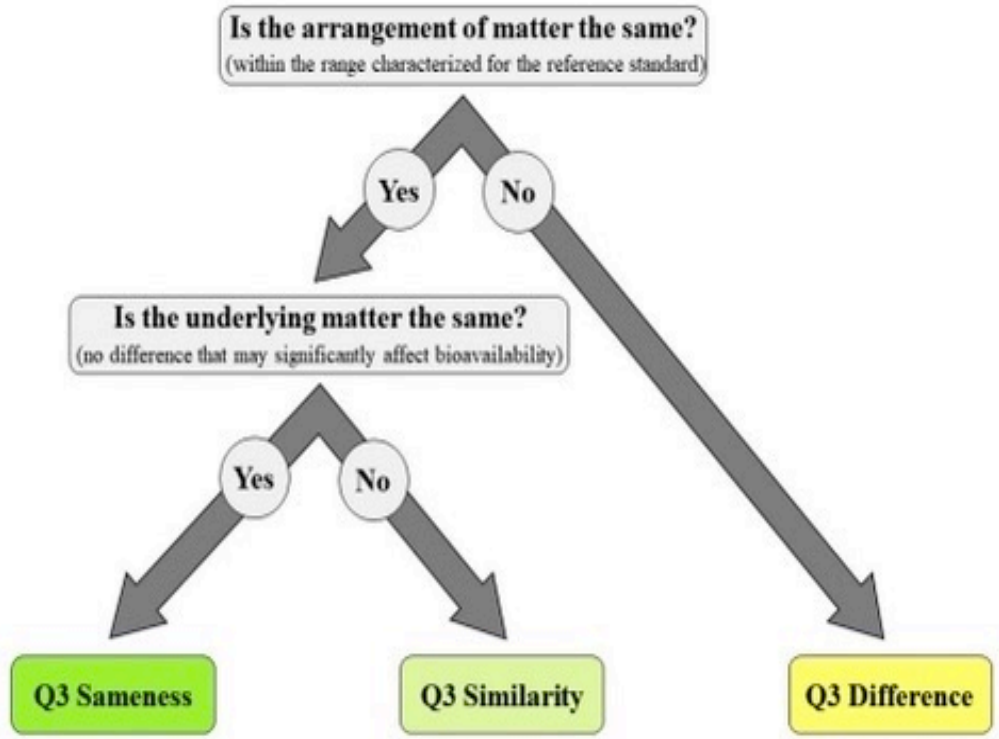
An open label, randomized, four-period, two-treatment, two-sequence, fully replicate, crossover, balanced, single dose bioequivalence study.

Pharmacokinetic data

PARAMETER	SWR	S^2WR	SWT	S^2WT	REFERENCE INTRA SUBJECT CV (%)	TEST INTRA SUBJECT CV (%)
Cmax	0.683	0.4666	0.546	0.2980	77.112%	58.917%
AUCt	0.486	0.2358	0.355	0.1261	51.564%	36.666%
AUCi	0.400	0.1601	0.349	0.1216	41.662%	35.959%
PARAMETER	T/R RATIO	THETA	95% UPPER CONFIDENCE INTERVAL			
Cmax	0.8976	0.7967	-0.2478			
AUCt	0.9730	0.7967	-0.1378			
AUCi	0.8966	0.7967	-0.0182			

Note: As SWR of Cmax, AUCt & AUCi is greater than 0.294, Scaled average BE approach has been applied. For determination of BE using Scaled average approach, 95% upper confidence interval must be less than or equal to zero and (T/R) ratio must be within [0.800, 1.250]

Q3 similarity approach



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A test topical product that meets the following criteria would generally be considered as *Q3 similar* to its reference standard:

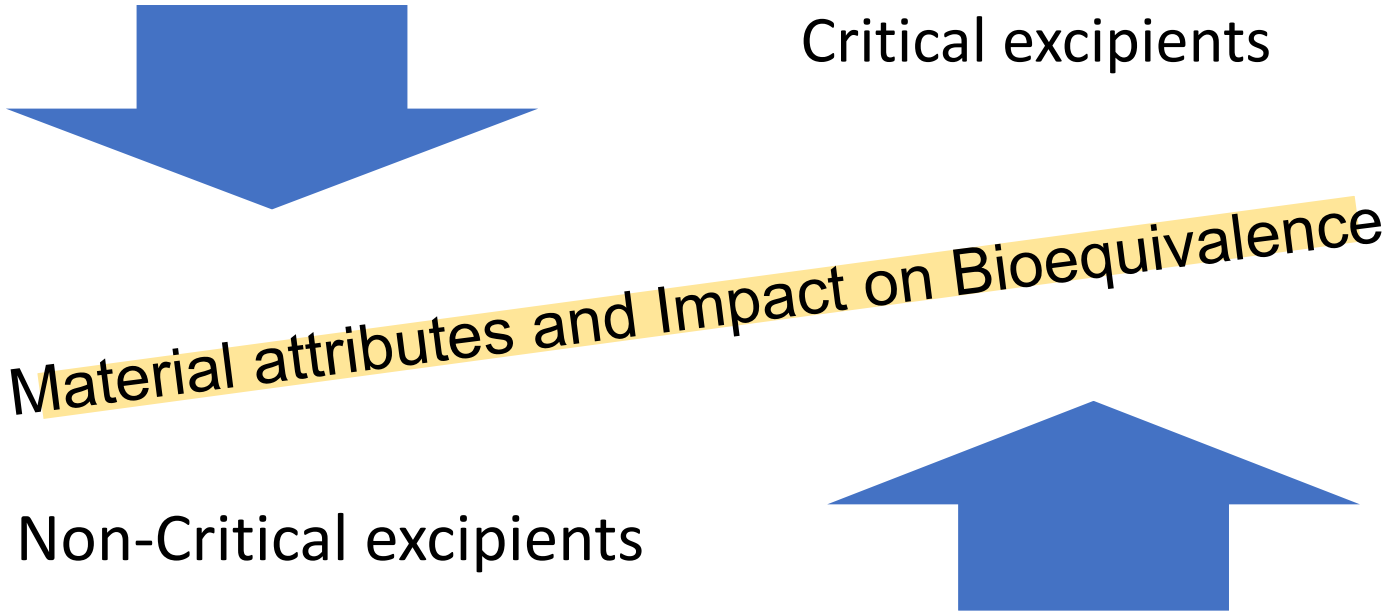
a. Each relevant Q3 attribute of the test topical product, characterized in multiple batches, is:

i. demonstrated by the applicant to be within the range characterized for that Q3 attribute of the reference standard for the topical product, potentially characterized in multiple batches, or

ii. determined by the Agency to be within the acceptable variability for the reference standard for the topical product; and

b. There is a difference in the components or composition of the test topical product and reference standard for the topical product that may significantly affect systemic or local availability.

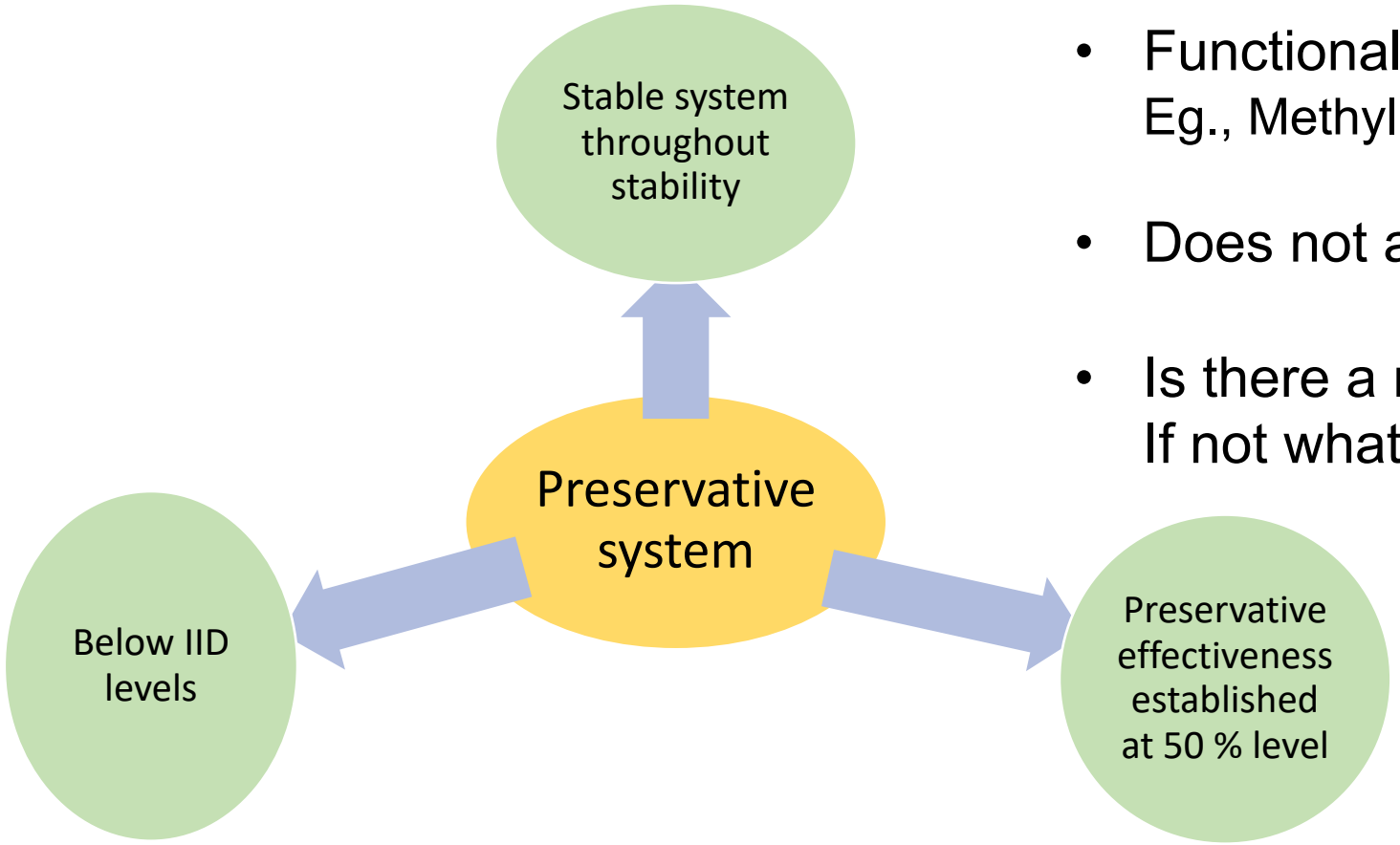
Reference: Draft Guidance published in October 2022 by the FDA . Topic: Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs Guidance for Industry



Critical excipients: Impact on the product performance in terms of establishing Bioequivalence --- High

Non-Critical Excipients: Impact on the product performance in terms of establishing Bioequivalence --- Low

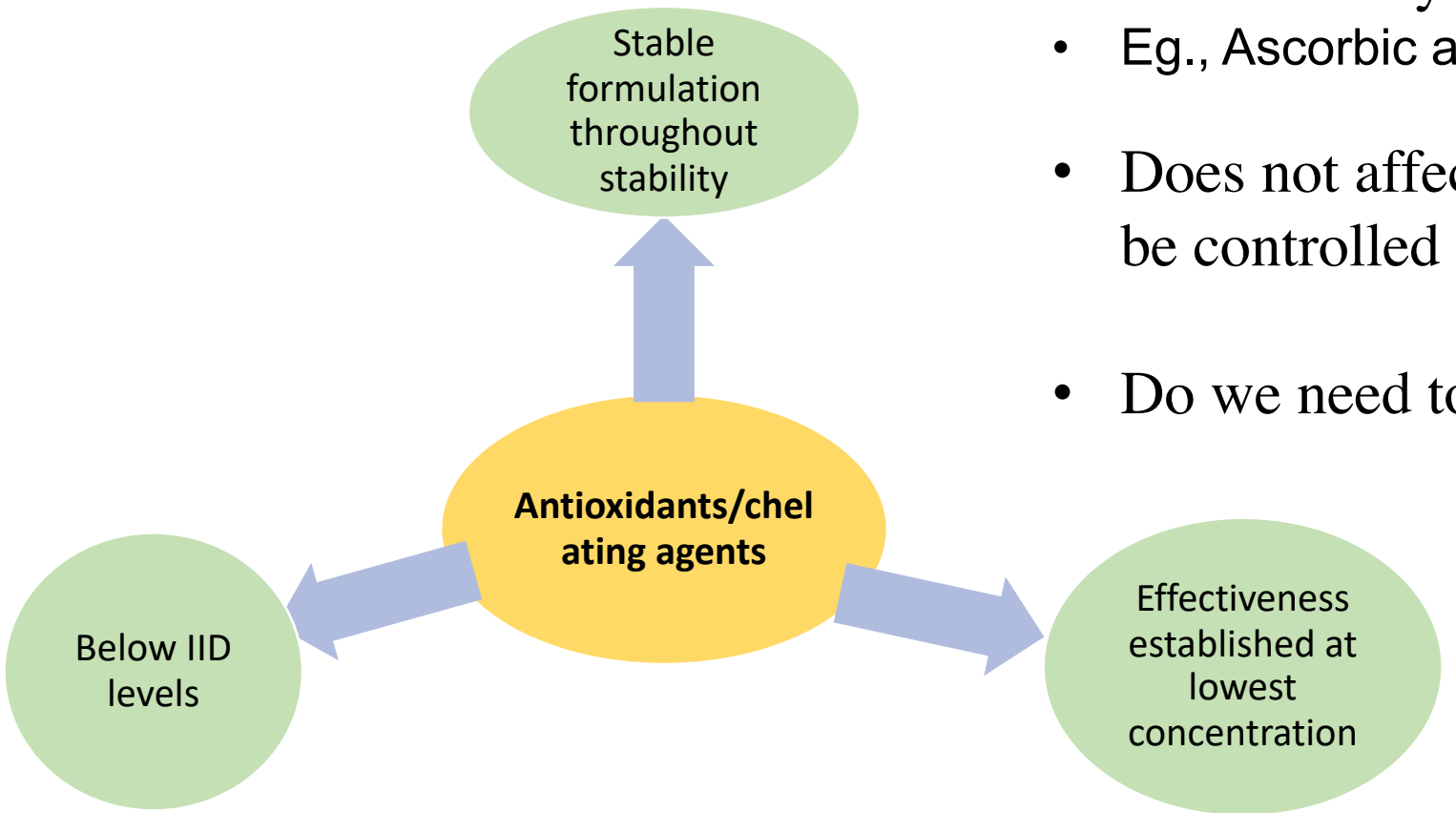
Q3 sameness/similarity for Non-critical excipients : Preservatives



- Functionality : Antimicrobial efficacy
  Eg., MethylParaben, Benzyl Alcohol
- Does not affect the product performance
- Is there a necessity to have Q2 within 5%?
  If not what would be the limit?

Product specification typically ~ 80.0 – 110.0%

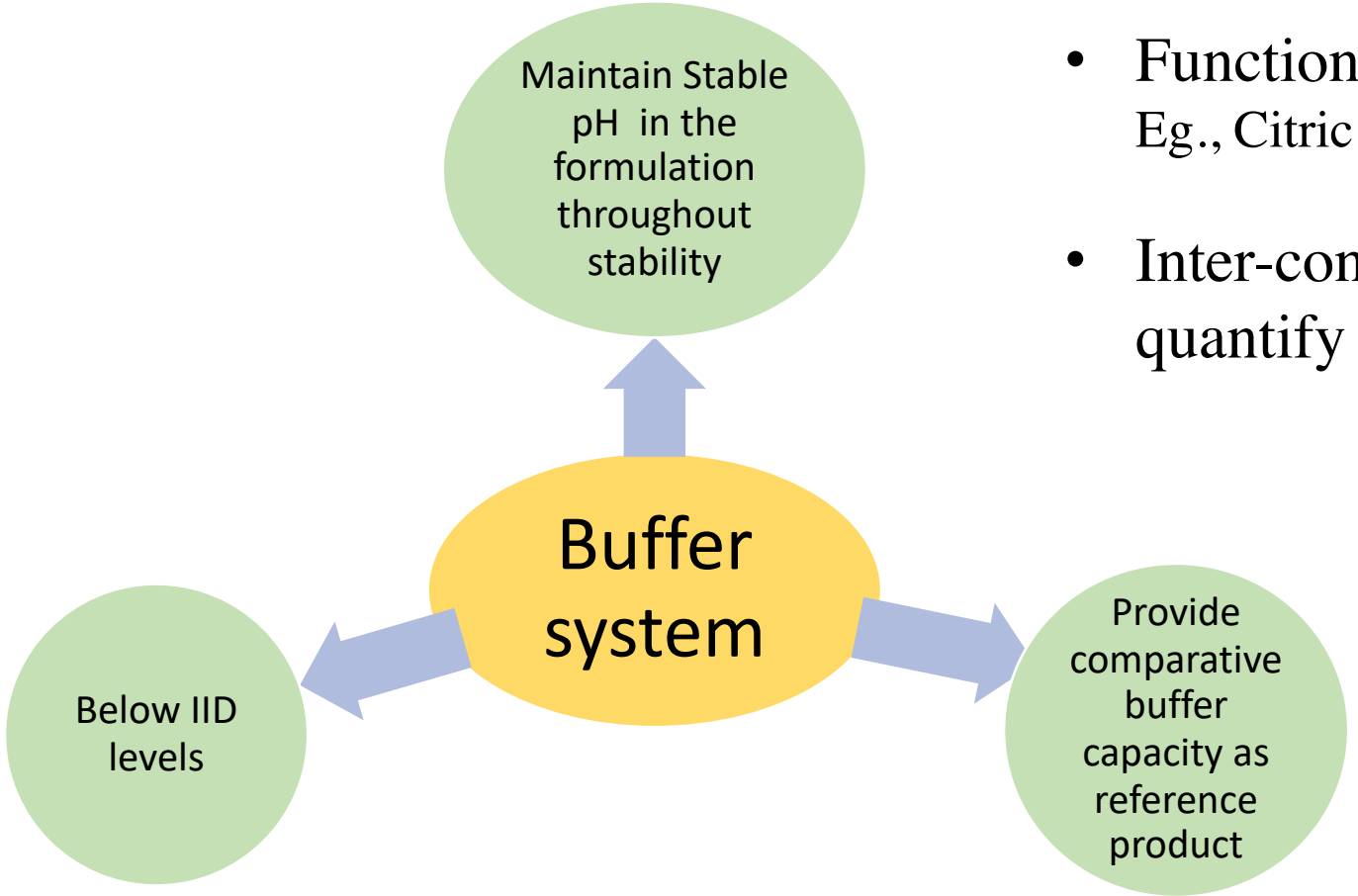
Q3 similarity for Non-critical excipients : Anti oxidants/chelating agents



- Functionality: Antioxidant/chelating agents
- Eg., Ascorbic acid, EDTA sodium
- Does not affect product performance; Can be controlled with specification.
- Do we need to be within 5% in such cases

Product spec typically depends on nature of excipient and shelf life stability but typically it is more than the 5% limit

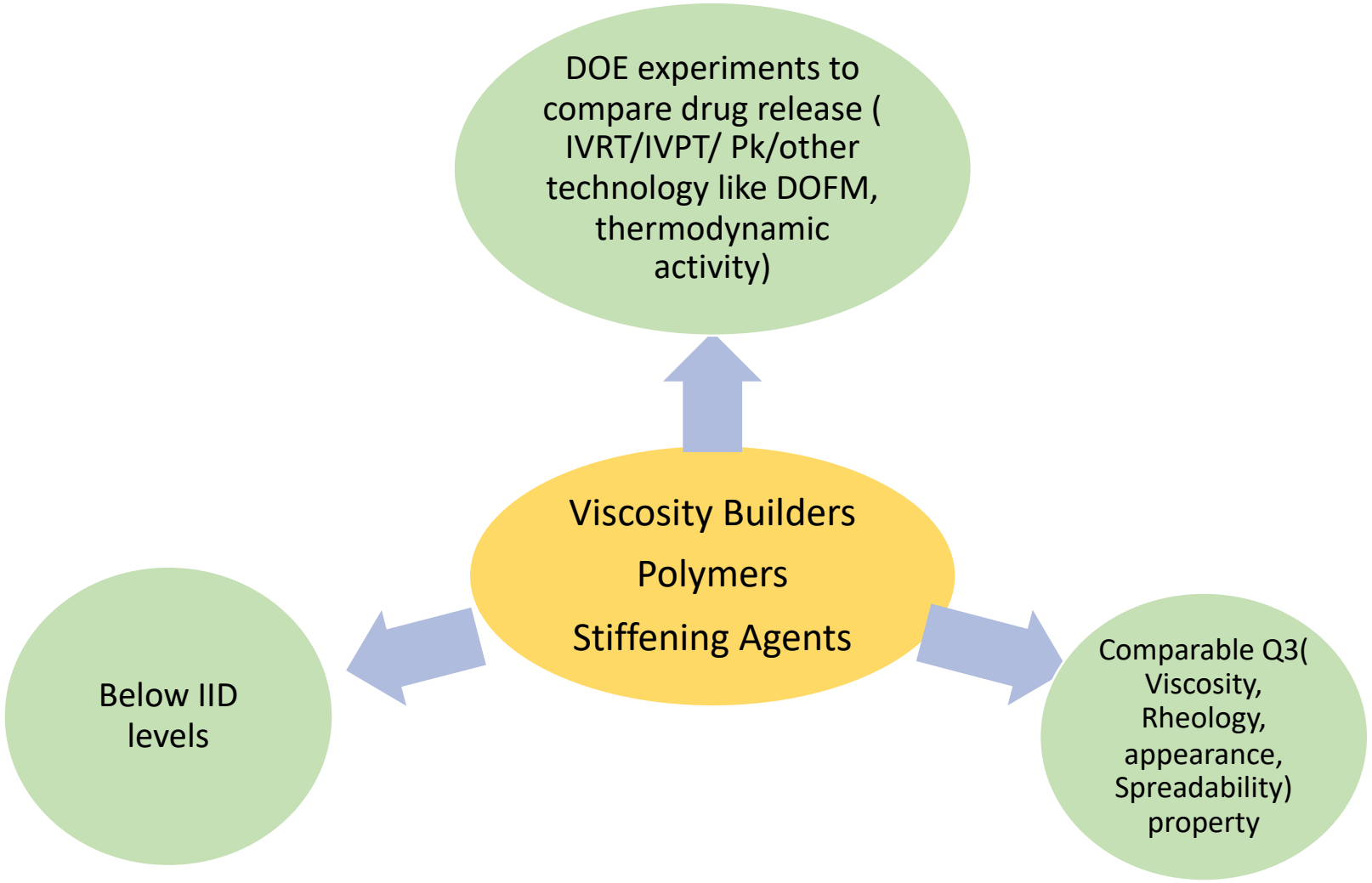
Q3 similarity for Non-critical excipients : Buffering Agents



- Functionality : Buffering agents
  Eg., Citric Acid, Na citrate, Boric acid/Na Borate
- Inter-conversion makes it challenging to quantify each buffer component

If we demonstrate buffer capacity and pH is maintained, Do we need individual composition of buffers as long as they are below IID limit??

Q3 similarity for Moderately Critical excipients : Polymers, Viscosity builders



The question is: Is this sufficient to establish product performance and BE?

Summary

- Characterization of excipients for Qualitative and Quantitative sameness is complex and challenging for many products.

- Can we use Non-critical excipients (Preservatives , antioxidants, Buffers) outside Q1Q2 ?

- Can we use critical excipients within acceptable limit (Established by DOE) and outside Q1Q2 with alternate bioequivalence approach?

- Alternate in vitro or in vivo techniques (alone or in combination) may need to be developed to establish bioequivalence!!

  Examples: DOFM, Microdialysis, Thermodynamic activity, Raman Spectroscopy techniques, IVRT, IVPT, Crystal habits, drying rate etc.

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Questions?

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