Development Strategies for Generic Topical products with formulation differences to Reference listed drug

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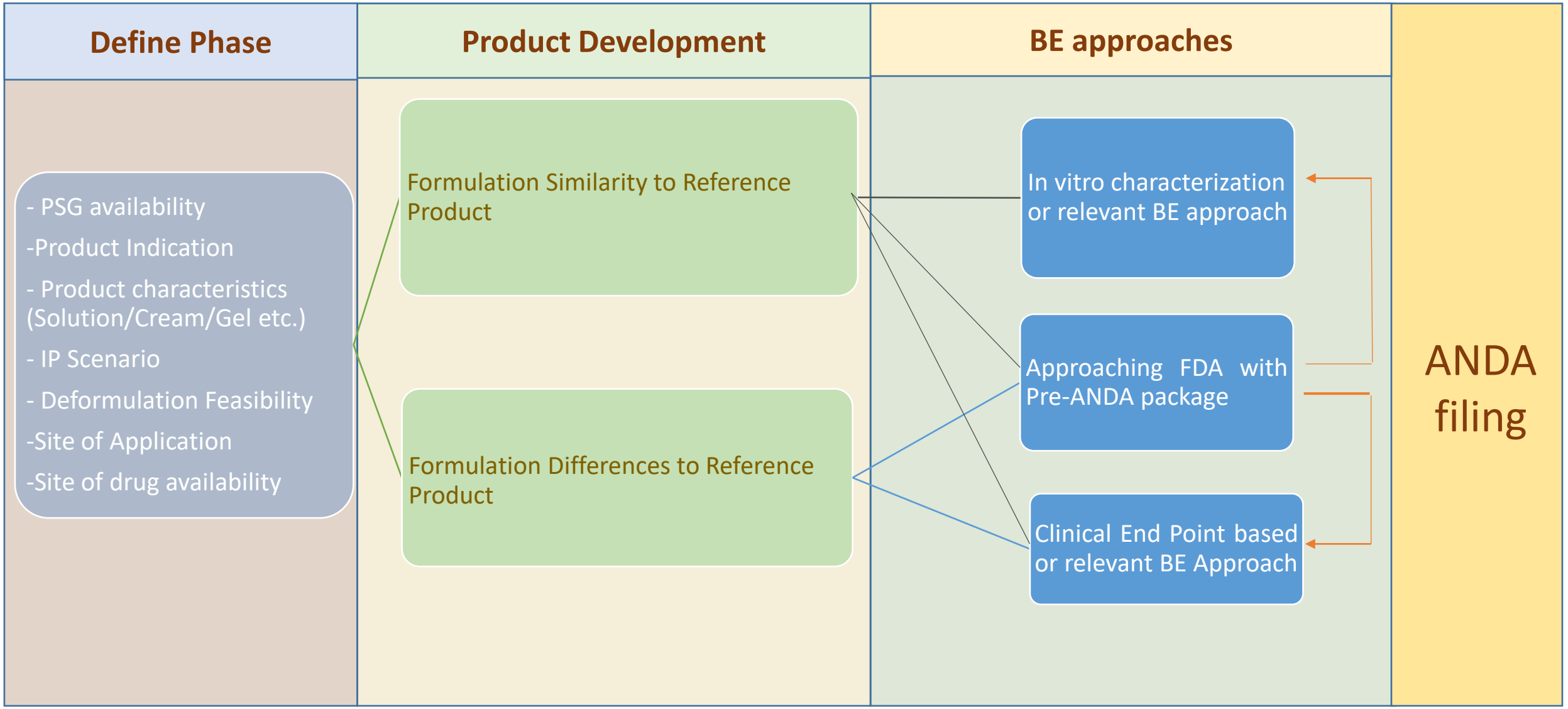

Development Strategies for Generic Topical products with formulation differences to Reference listed drug

Define Phase:

- Define Quality Target Product Profile (QTPP) for the product to be developed
- Studying multiple lots of RLD (Deformulation) to define the TPP for generic product and establishing a range for Q3
- Study component/ compositions of the Reference product
- PSG availability: *In vitro* characterization based approach vs. *In vivo* approaches
- Assessing risk based on current IP scenario, Ease of Deformulation and nature of BE study
- 'Develop product with formulation differences' in undermentioned cases
    - IP Scenario 'not clear'
    - 'Deformulation' not feasible
    - Non-availability of any 'Specific component' used in Reference product
    - Discontinuation of Reference Listed Drug (RLD) product and lack of clarity on Reference standard (RS)

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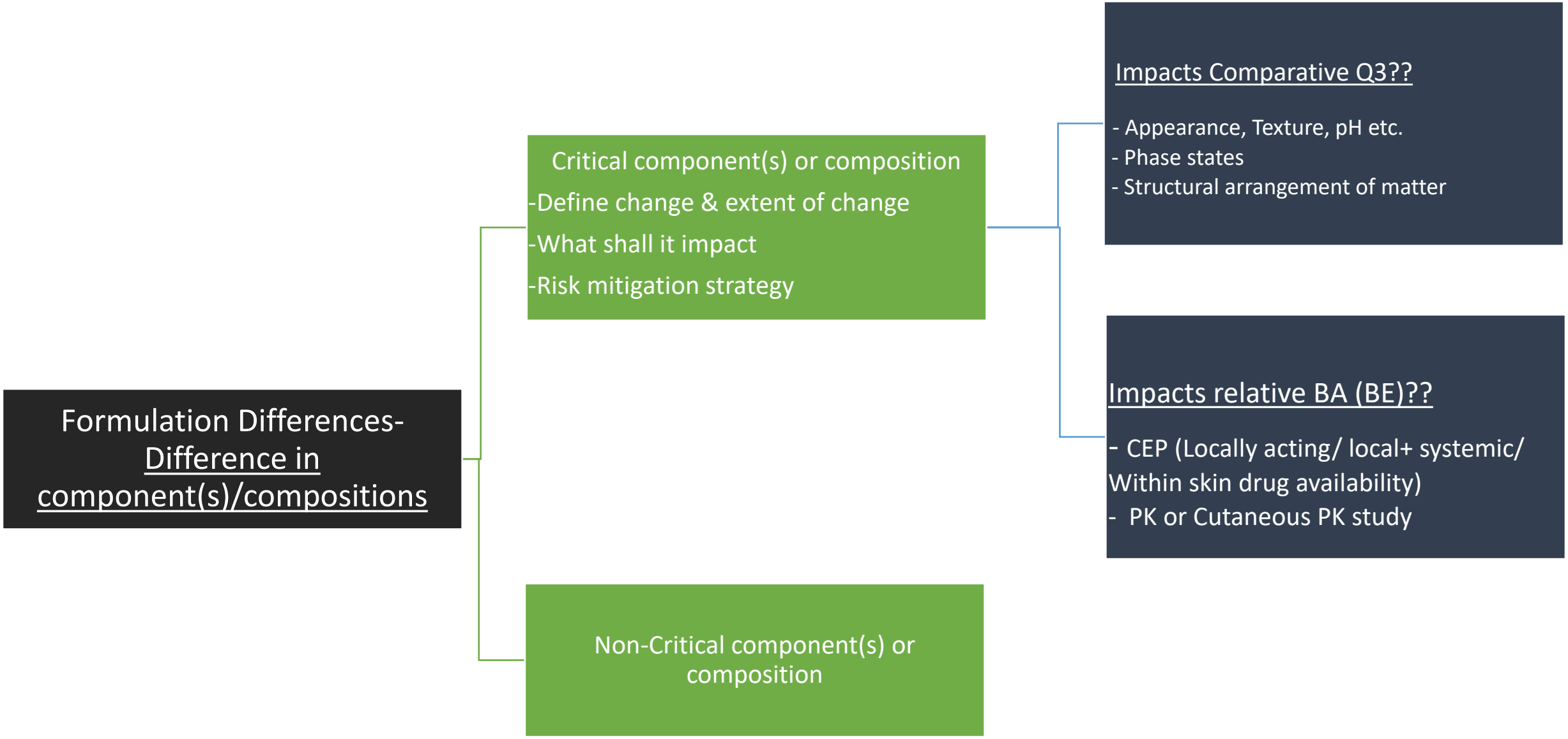

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CMC Development Phase: Case Study of a Topical Gel Product intended for drug availability within the skin milieu

Ingredients (%w/w)	RLD	Generic (Q1Q2)	Generic (With Q1 diff.)	Remarks
API	A	A	A	Same
Transcutol	B	B	B	Same
pH independent gelling agent (Polymer, disp. media, Surfactant)	C	C	-	Difference in Critical Excipient
pH dependent gelling agent	-	-	D	Difference in Critical Excipient
Surfactant	-	-	E	Similar in Qty. to RLD
Preservative	F	F	F	Same
Sodium Hydroxide	-	-	q.s.	May not be critical
Purified Water	G	G	H	Difference in Q2 of Critical Excipient varies Q2 of non-critical excipient

Q3 similarity is challenging; hence attributes that may affect BE needs to identified and "**relative similarity**" of such attributes with Reference product could be targeted for risk mitigation.

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Generic (Q1Q2)-Approach

Arrangement of matter	**Same**
Underlying matter • **Visual appearance and texture** • **Phase state, structural organization of matter** • **Rheological behavior** • **pH** • **Specific gravity** • **Other potentially relevant Q3 attributes**	**Same**

Option 1: IVRT+IVPT+PK

Generic (With Diff. Q1Q2)-Approach

Arrangement of matter	**Different**

Possible Difference
- Rheological features
- Appearance/Texture
- Specific gravity, pH
- Dissolved/Undissolved ratio

Possible Mitigation
- Range of Dissolved/Undissolved ratio
- Similar Polymorphic form to RLD
- Attaining near similar viscosity, visual appearance, water activity
- Developing an IVRT method which provide some confidence on similarity in drug release between generic and RLD

Option 2: Clinical End Point study

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Formulation Differences-

Same component/composition

but Q3 different (One or more attribute)

Impacts relative BA (BE)??

- CEP (Locally acting/ local+ systemic/ Within skin drug availability)
- PK or Cutaneous PK study
- Other approaches

Does not Impact Relative BA/BE

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CMC Development Phase: Case Study of a Topical Cream Product intended for drug availability within the skin milieu

Ingredients (%w/w)	RLD	Generic (Q1,Q2 same, Q3 different)	Remarks
API	M	M	Generic product has no difference in components or composition to the Reference product. "Q3" difference could be due to - Age differences in test and RLD - Manufacturing process variations - Other reasons
Structure forming excipient	N	N	
Oil Component-1	O	O	
Oil Component-2	P	P	
Non-ionic Surfactant	Q	Q	
Solubilizer	R	R	
Purified Water	q.s.	q.s.	

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Variable Q3 Attribute(s):

- ❖ RLD tends to depict decreased apparent viscosity during shelf life
  - ✓ Possible Mitigation:
    1. Age matching the test and RLD products closely, to have similar apparent viscosity attribute
    2. Comparative release from near similar age test and RLD product.
- ❖ Microscopic evaluation suggests certain typical structures present in different intensity in different lots of RLD
  - ✓ Possible Mitigation:
    1. 'Minimal Impact' of these structures on release profile, possibly suggesting this variation is not a critical attribute
    2. Defining process design space so that such structures are generated and are visible to an extent that neither release nor any other Q3 attribute is impacted.

BE approach

- no difference in inactive ingredients relative to reference product
- Same physicochemical and structural attributes (Q3)
- Acceptable IVRT
- Acceptable IVPT

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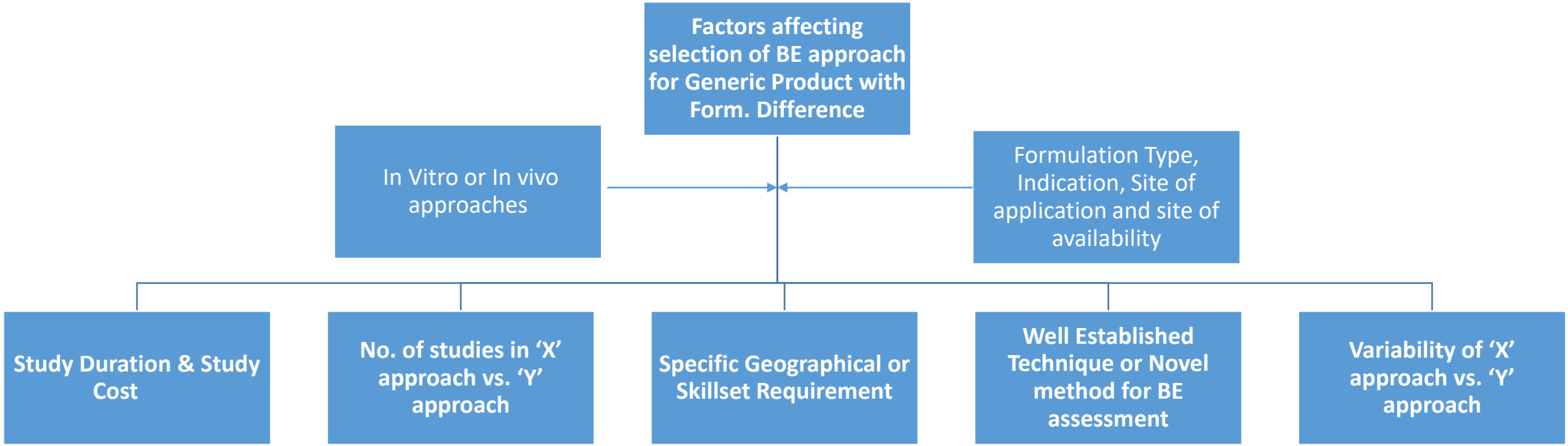
BE Phase: Selection of a suitable BE approach (Dependent on PSG availability, Pre-ANDA discussion etc.)



Conclusion

- Development Strategy for Generic product with form. differences to reference should be tailor made based on
    - Type of formulation
    - Product indication
    - Site of product application
    - Site of drug availability
    - Relative Similarity to RLD
    - Extent of change (viz. difference in critical component)

- Difference in component/ composition or Q3 attribute(s) should be studied well and correlated to product performance to support BE

- BE approach selection must be time and cost savvy, for early market entry as well as lower overall development cost.

THANKS

Disclaimer

Dr. Dubey contributed to this presentation in his personal capacity. The views expressed are his own and do not necessarily represent the views of Alembic Pharmaceuticals Ltd.