PQRI Workshop:
TiO2 Use in Pharmaceuticals
Global Regulatory and Technical Challenges
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Impact of Film Coating Change on Product Quality

Analytical Tests, Specifications and Formulation Bridging

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Outline

- Impacted Quality Attributes (Tablets)
- Analytical Methods/Specifications
- Level of Change and Potential Impact on Product Performance
  - Innovator Company Perspective
- Formulation Bridging (new drugs)
  - Biopharm
  - Stability data set
- Remaining quuestions

Why is TiO_2 in film coat ?

- Appearance → patient compliance/ differentiation
- Protection from light → Appearance and impurities

- Manufacturing Change (“optimization”) should not lead to product with inferior quality compared to a “reference” (i.e., marketed product or product in clinical development)

Removal of TiO_2 and Drug Product Quality/Specifications: Solid Oral Dosage Forms

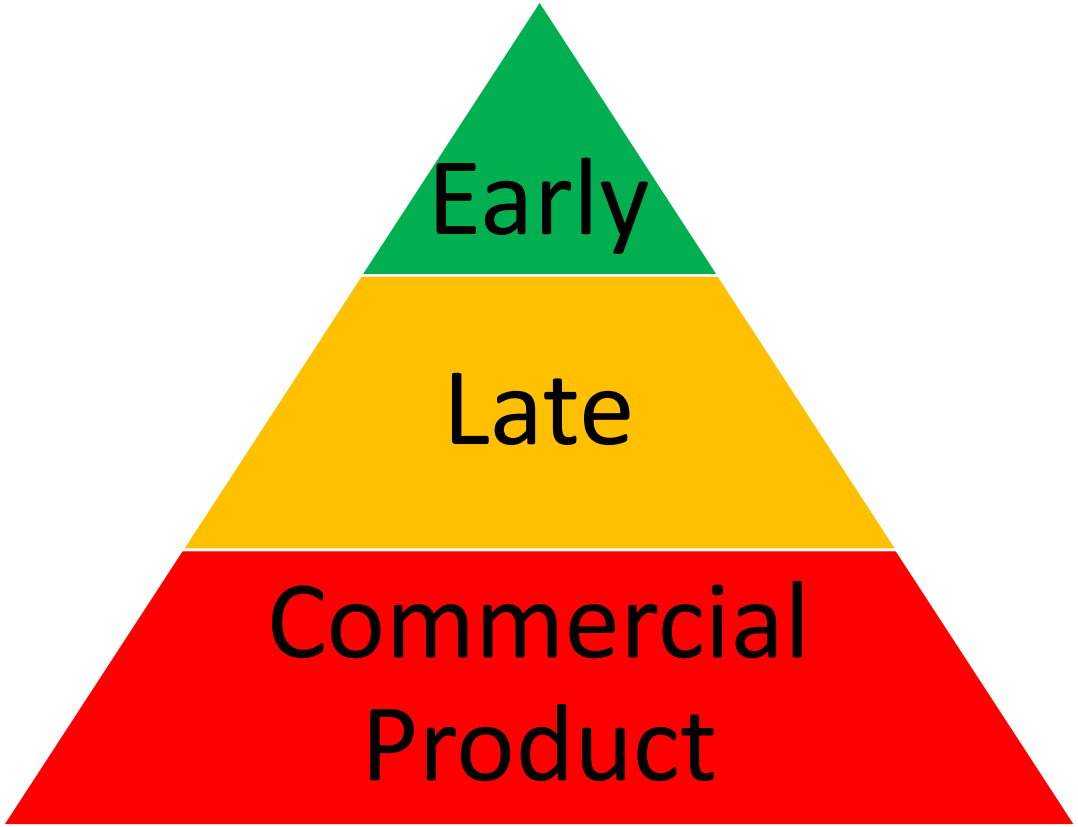
Test*	**Acceptance Criteria**	**Potential Risk** **Release**	**Shelf life***
Assay	90-110 % LC	Very Low	(Very) Low
Content Uniformity	Per Compendia	Very Low	NA
Appearance	As per approved product**	Low	Medium
Impurities	ICH Q3B(R2)	Low	Low/Medium
Dissolution	As per approved product**	Low/Medium	Medium/?
Moisture	As per approved product**	Low/Medium	Medium?
Microbial Enumeration Test	Per Compendia	Low	Low/Medium

Commercial product: Risk of failing one or more Product Specs at the end of shelf-life

- Other elements of QTPP may be impacted (e.g., taste/acceptability)
- ** May change in case approved product spec can't be met
- For products premarket approval requires up-dates in IND/IMPD

Impact on (existing) Analytical methods

- Early clinical development phase:
  - Impact Low -> methods are fit-for purpose and phase appropriately validated
    - No rework beyond typical development efforts
- Late-stage clinical development:
  - Impact Medium/High:
  - Methods usually “locked” – data consistency for CTM and registration stability
  - All elements of method validation need to be repeated
  - Methods transfers to manufacturing sites/ release and stability testing to be repeated
  - Methods and data need to be bridged if FSS already started
    - Low risk for appearance, assay, deg. but could be challenge for dissolution
      - May repeat all or part of FSS
- Commercial Products:
  - Impact high:
    - In addition to revalidation (demonstration of equivalency) , and methods transfer – including to countries requiring TOI, all changes must be filed in markets where products are approved
  - Magnitude depends on product portfolio (type of product, total number of products impacted) → available resources!



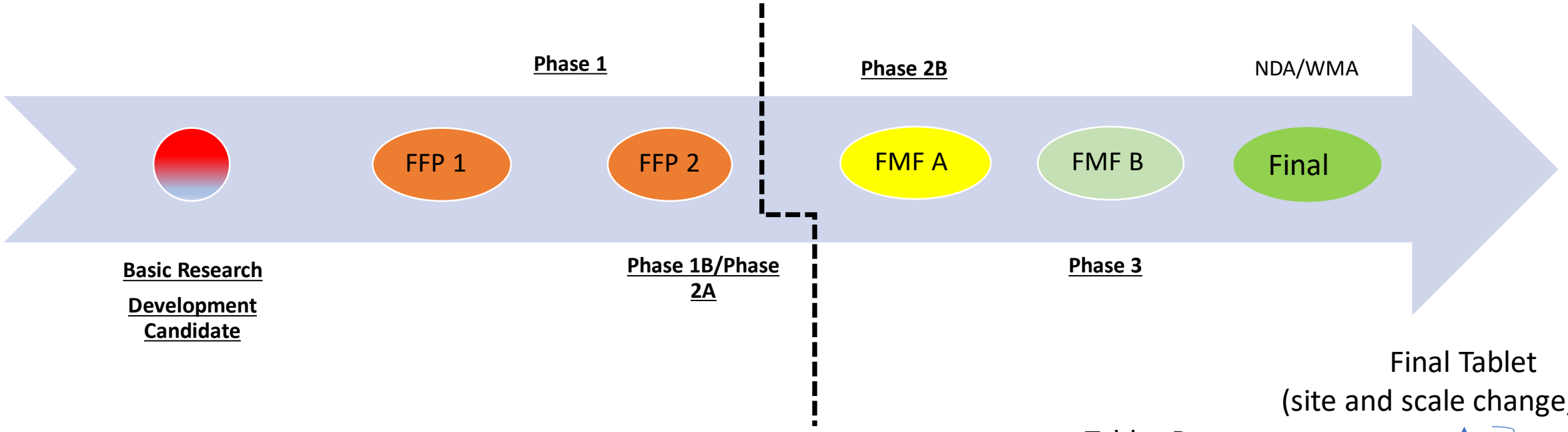
Analytical resources (internal, external) unlikely to meet demand

Drug product Stability Mitigation Strategy

- Long-term Stability of TF-coated solid oral dosage forms and TF-capsules with similar attributes compared to TiO_2 is sparse
  - Increased risk of Out-of-Trend and Out-of-Specification
    - Increased Quality oversight/ communications with agencies
- Potential Change to product with inferior stability may be effectively mitigated by:
  - changing storage conditions (store below 30°C, vs. store at controlled RT, protect from light, use immediately, etc.)
    - Tightly controlled shipping conditions
  - Changing the Packaging
  - Shorten shelf-life (supply chain issues)
  - Additional reformulation (ideally below SUPAC Level 3 and equivalent reg. guidance)
  - Change in Specifications

Increased filing/ review/approval process: AR→ PAS→ sNDA

Changes during Product Development – example bridging scenario



Final Tablet
(site and scale change, etc.)

Tablet B
(formulation + process change)

FFP: Fit-For-Purpose

Examples:

PIB → Capsule/ Tablet → Tablet A

Final Market Formulation

Film coating changes and impact on development timelines

- Products not at pivotal* clinical study stage:
  - → low/medium impact
    - Purposeful Changes are typically supported by *in vitro* and if needed *in vivo* data
      - Follow existing rBA/BE guidances in major markets
      - Adherence to strict BE criteria in some markets

- Products in pivotal clinical trials:
  - CTM in Phase 3 close to final formulation/ process
    - Uses the “to-be-commercial” manufacturing process (incl. composition)
  - Manufacturing Changes require demonstration of lack of *in vivo* impact
    - In addition to stability
  - Potentially considerable rework needed
    - Dependent of overall product filing strategy

* Phase 3/ JP: Phase 2b

New product filing options

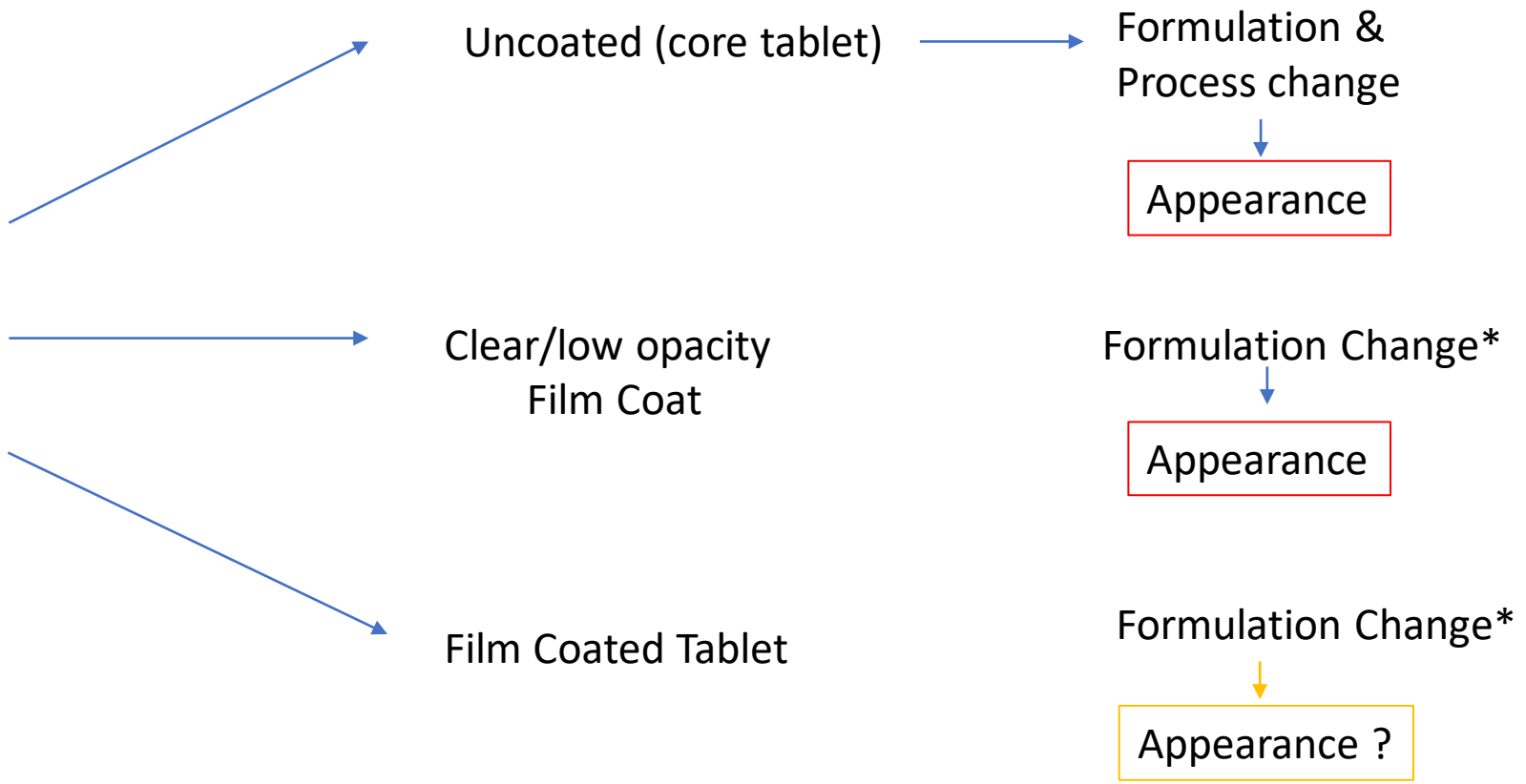
- One global market image – Titanium Dioxide Free (TF)
  - Benefit: lean manufacturing, product registration, and supply strategy
- Several (regional) market images – TiO_2 and TF
  - Benefit: only regional requirements need to be met
  - Draw-back: essentially doubles late-stage CMC development efforts:
    - Process scale-up (film coating only- if only change)
    - Multiple Formal (or bridging) stability studies
    - Complex (non-harmonized) *in vitro* bridging requirements
      - May lead to BE studies (or separate clinical trials → even more complex!)
    - Managing products with different Quality attributes

May question ethical standards (industry and health authorities)

Options for Changing to TiO_2 free Tablets

Late clinical development and commercial product

- Remove FC
- Remove TiO_2
- Remove & Replace TiO_2



* Assumes “no change” in process, no change in other specifications

Regulatory Requirements (in select regions)

Region	Remove FC	Remove TiO2	Remove and Replace	Comments
EU	Type 1A/1b: comparative dissolution in conjunction with reason not to conduct BE			No approved QC specs
US	Level 1 change; meet QC specifications		Level 3 change	No QC spec.
Japan	For Adult products: Level B change (intricate multi-pH media dissolution testing)			Pediatric products- if offered -may be Level C/D: BE
Korea	Changes may require BE study			No QC spec.
China	May require BE	May be considered minor/ disso testing		No QC spec.

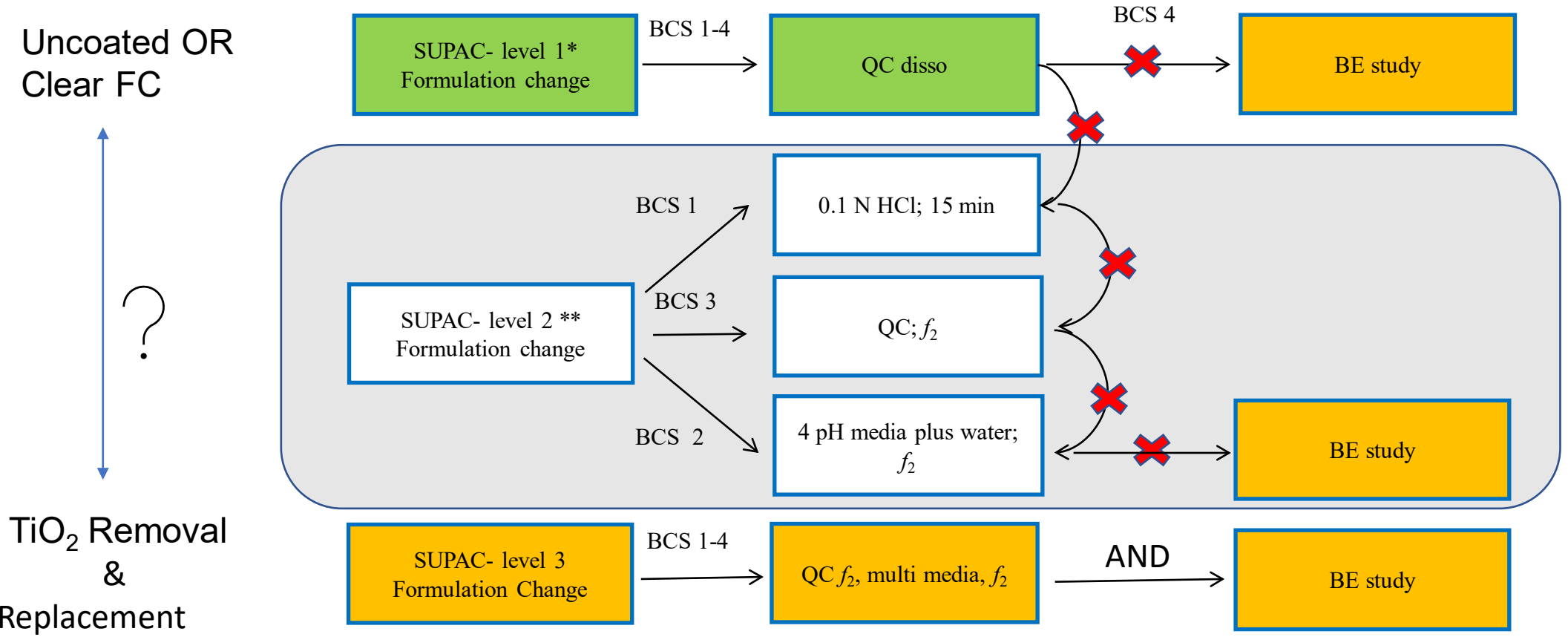
IR products: Assumes no other changes
Biopharmaceutics Classification System: Unlikely recognized at this stage – so can't be leveraged

Disharmonized Dissolution Similarity Acceptance Criteria major Risk for industry → BE studies

SUPAC IR - Interpretation of Reg. requirements:

- SUPAC IR:
- Changes would likely be > level 2 component/composition change
  - Provisions exists to allow removal/ replacement of colorant (FC)
    - Pigments/ dyes are ~ 10% weight of typical film coating systems
    - ***Level 1 change, file in AR for marketed products***
- Changes here may be in excess of 2% total tablet weight (i.e., not small removal of a “pigment”)
  - Minitablets: TiO_2 (~ 5% total weight) to $CaCO_3$ (more than 5% total weight)
    - “Non-functional” FC still affords taste masking
    - ***Plain removal Still Level 1 change***?
  - How to apply guidance in development?

In vitro bridging efforts within SUPAC-IR*



= not met

SUPAC MR - Interpretation of Reg. requirements:

- No “SUPAC IR Q&A” suggesting flexibility re-”minor” change
- MR is a complex product “group”:
  - DR: enteric coated product FC removal not an option
  - ER: FC maybe release controlling or not
- Changes would likely be > level 2 component/composition change
  - IVIVC may be available for some ER products (less likely for DR)
- Products in development have no approved QC method
  - So same dilemma as for IR: does one rely on more extensive disso testing?

In vitro (biopharm) bridging risks

- Failure to meet Disso spec (if one is approved):
  - IR :
    - BCS 4 will require BE
    - BCS 1-3: follow Level 2 change
  - MR:
    - Regulatory Flexibility uncertain/unknown → BE likely (or apply IVIVC)

- For Products in development: a regulatory approved QC specification doesn't exist
  - IR → multi-media dissolution even for minor changes
  - MR → most likely BE (or use IVIVC if successfully conducted and reg. approved)

Other solid Oral Dosage Forms

- Pediatrics: Taste/ smell/ color
  - Suspendability, in-use compatibility with (approved)soft foods
- ODT: disintegration Time may be impacted – FC weight increase, change in FC materials attributes…

Others……

Where does this lead to once a ban is in effect?

- Products Pre- Phase 3: most likely change to TiO_2 free (TF)
- In Phase 3, but before FSS: change to TF but continue clinical trials with TiO_2
  - Likely no impact on analytical specs (no change during long-term stab. studies)
  - Appearance specification of FMF still adjustable
  - Need to bridge bioperformance (*in vitro or in vivo)*
  - Final Methods validation may/ may not require substantial rework
- Phase 3/ FSS already under way:
  - Analytical specs to be up-dated
  - Not final image – additional registration stability data (“2 X FSS”)
    - New Packaging materials may also need to e identified…
  - Rework of analytical methods may require additional work
  - Formulation bridging
- Filed products:
  - Potentially all methods need to be revalidated and transferred to test labs (including those that do test on importation)

Summary

- Manufacturing changes should lead to superior product quality not inferior
  - If TiO_2 is “unsafe” it shall be addressed
- A ban will likely not be limited to just removal/ replacement of TiO_2
- In addition to new film coating process development all analytical methods are impacted
  - Major disruption in QC Testing labs– including government owned/operated labs
- Biopharm risk assessment/ mitigation without globally aligned requirements will inevitably lead to many unnecessary BE studies
- Regulatory filing (applicant) and filing review (agency) burden

When can someone can review our filing?

Acknowledgements

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