PQRI Workshop:

TiO2 Use in Pharmaceuticals

Global Regulatory and Technical Challenges

Breakout Session 2: June 14, 2023

BREAKOUT ROOM #1

Experiences when Evaluating Alternatives (Materials or Approaches) for use in Pharmaceutical Drug Products

Moderators:

Jason Melnick

Notetakers:

Bram Baert

PQRI

Product Quality Research Institute

Questions for Breakout Room #1

1. Which alternatives to TiO2 are you evaluating and why were those specific alternative(s) chosen?
2. Are you concerned with the safety of any of the currently employed alternatives to TiO2? If so which alternatives and why?
3. What decision/acceptance criteria are being used to say an alternative is considered acceptable?
4. What specific technical challenges are being encountered during your evaluations of TiO2 alternatives?
5. Is a change in appearance considered a barrier for introduction of an alternative to TiO2 for your marketed product?
6. What unit dosage marking techniques do you currently employe and how does removal of TiO2 and use of alternatives impact those unit dose marking capabilities?

Notes for Breakout #2

- **General Comments - Let's say ban is in place. What do we need to know?**
  - Guidance from EU variation guideline if minor change.
  - But – as per EMA – rarely submitted as a type IA change
  - If major change, Up to the producer to decide which data.
  - But what about FDA?
    - If minor change, annual report (guidance)
    - If quality and spec change (e.g. appearance): major change
  - BE studies to run.
  - What is a spec: not necessarily what is in the file, but any change to product characteristics/properties such as roughness
  - Differences in interpretation between regulators and even between reviewers may cause inconsistencies.

Notes for Breakout #2

1. Which alternatives to TiO2 are you evaluating and why were those specific alternative(s) chosen?
   - Not a one-to-one swap
   - Combinations of various alternatives
   - CaCO3 is number 1

Notes for Breakout #2

2. Are you concerned with the safety of any of the currently employed alternatives to TiO2? If so which alternatives and why?

- Preference to remove TiO2 due to fear that alternatives may also not be safe and require a second reformulation later on.
- EFSA risk rather than safety risk

Notes for Breakout #2

3. What decision/acceptance criteria are being used to say an alternative is considered acceptable?

- More than just appearance, no impact on quality of product allowed (no inferior product)
- Consideration: are the alternatives suitable for continuous manufacturing (coating)?
  - Not yet explored for TiO2-free systems but may pose big issues (due to weight gain and variability). TiO2 allows for more variability (levels off).
  - Subsequent changes in production process needed. Post-approval change process?
- Share concerns with EMA (FDA) as it may be an argument in favor of TiO2 White paper?
- Q: Ability for dialogue with EMA? Not really, even EFPIA does not speak (a lot) with EMA
- Can USP committee members be more involved in the communication?

Notes for Breakout #2

4. What specific technical challenges are being encountered during your evaluations of TiO2 alternatives?

- Weight gain to achieve same opacity
- Water activity / more moisture impact on stability
- Debossing
- Printing
- Lack of opacity
  - are we being too strict in the requirements and have unrealistic expectations? Are the studies performed relevant for ‘real life’
  - consistency in appearance is important
  - Japan is very strict even for minor specs / color changes (for imported products).

Notes for Breakout #2

5. Is a change in appearance considered a barrier for introduction of an alternative to TiO2 for your marketed product?

- No change if not needed
- From what has been approved?
  - Change in approval alone not sufficient to not change if forced.
  - In nutrition, a change in appearance can even be beneficial even if it comes with a compromise in quality (e.g., specks) because of marketing considerations.
  - If the same shade is to be maintained, it may require more than one color to be changed.
  - Could be acceptable if no other quality characteristics are impacted.
- What if change is only needed for EU
  - Continue change and keep both options (EU and non-EU)
  - If two different product have the same color and shape, there is a risk for mix-up. May require different colors.

Notes for Breakout #2

6. What unit dosage marking techniques do you currently employ and how does removal of TiO2 and use of alternatives impact those unit dose marking capabilities?

- Printing comes with technical issues and is not preferred
- Debossing option 1
- Laser marking (quite new)
- Combination of print and debossing
- Capsules: off-set printing
- Note: overencapsulation in clinical trial must be able to hide print on tablet.

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BREAKOUT ROOM #2

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Moderators:

Andreas Abend

Notetakers:

Rohit Tiwari

PQRI

Product Quality Research Institute

Questions for Breakout Room #2

1. What unit dosage marking techniques do you currently employe and how does removal of TiO2 and use of alternatives impact those unit dose marking capabilities?
2. Is a change in appearance considered a barrier for introduction of an alternative to TiO2 for your marketed product?
3. What specific technical challenges are being encountered during your evaluations of TiO2 alternatives?
4. What decision/acceptance criteria are being used to say an alternative is considered acceptable?
5. Are you concerned with the safety of any of the currently employed alternatives to TiO2? If so which alternatives and why?
6. Which alternatives to TiO2 are you evaluating and why were those specific alternative(s) chosen?

Notes for Breakout #2

- **General Comments**
  - What are the expectations from regulators – what is valuable to the industry, any information from regulators? Lot of resources have been spent so far,
  - Is it clear what kind of data package is required? Some of the expectations are clear with respect to film coating, EMA has set of requirements, but different markets have different requirements,
  - Ideally, a harmonized protocol would be helpful (ideal scenario). However, new products are easier to get transitioned – come up with a formulation without TiO2 but products that have been approved the regulatory landscape is unknown with respect to transitioning into TiO2 free scenario, e.g.
  - EMA should open a channel for discussion with companies – engage with companies
  - Switching to TiO2 free formulation would cause supply chain snarls and thus not practical.
  - Generic pharma faces another hurdle of changing thousands of products to their corresponding TiO2 free formulations

Notes for Breakout #2

1. What unit dosage marking techniques do you currently employ and how does removal of TiO2 and use of alternatives impact those unit dose marking capabilities?
   - Adhesion issue is a game stopper, would lead to multiple film coat evaluations, almost gets in way of ability to deboss, imprinting doesn't offer to much of a solution;
   - May need to go back to older type of film coats that have other challenges. There are still a lot of studies which need to be done to understand about softgels, as they may not be amenable for dark colors and at times softgels may need TiO2,
   - There are inks with TiO2 in them (e.g. red ink, black, blue) but the contrast difference would be minimal for dark colored dosage forms. ---
   - Eventual implications of using darker colors for thousands of medicines may cause trouble at pharmacies with identification of the correct medicines (medication errors).
   - Changing the appearance of the dosage form may affect patient compliance;

Notes for Breakout #2

2. Is a change in appearance considered a barrier for introduction of an alternative to TiO2 for your marketed product?

- Results in change in specification – wont' be able to maintain the existing specification
- Would be considered as a major change, change in appearance is critical because end user notices it including pharmacists, doctors and health care workers.
- Patients may attribute their ill health to change in appearance of the products.

Notes for Breakout #2

3. What specific technical challenges are being encountered during your evaluations of TiO2 alternatives?

- Alternatives are not as elegant, requires more coating, black specs on tablets – increasingly difficult time covering black specs;
- Unknown risk with scale ups; uniformity issues with intratablets – belly bands, surface concavity;
- Uncertainty and not much commercial experience,
- No long-term supply experience, lot of unknowns that need to be dealt with.
- Did anyone try large scale manufacture with alternatives – not too much experience. So, there could be some learnings when the alternatives are scaled up.

Notes for Breakout #2

4. What decision/acceptance criteria are being used to say an alternative is considered acceptable?

- Teams go through formal film coating selection based on data, processability, moisture, uniformity – come up with something optimal.
- Are there any safety concerns anticipated that may entail from a change in spec tests or acceptance criteria?
- Would alternative meet aesthetic requirements for Japan? Expect the alternatives to be similar to the existing ones

Notes for Breakout #2

5. Are you concerned with the safety of any of the currently employed alternatives to TiO2? If so which alternatives and why?

- No data yet; would need to undertake lots of studies to understand the risk.
- For HPMC – two options – CaCO3, and iron oxide

Notes for Breakout #2

6. Which alternatives to TiO2 are you evaluating and why were those specific alternative(s) chosen?
   - Various CaCO3 alternatives and CaCO3/isomalt. No work on capsules yet – so far focused on tablets.