PQRI Workshop:
TiO2 Use in Pharmaceuticals
Global Regulatory and Technical Challenges
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Challenges to Providing Essential Drugs if a TiO2 Ban takes place: Generic Drug Manufacturer Perspective

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Overview

- Uses of Titanium dioxide
- Alternatives & Costs to change
- Impacts

Much of this Presentation

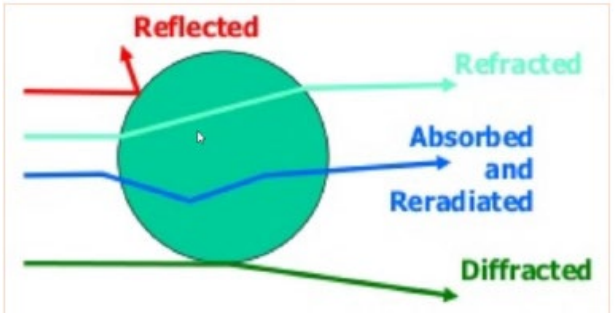
Collaboration between these organizations

- **Medicines for Europe**
  - Represents the European generic, biosimilar and valued added pharmaceutical industries.
  - Supplies over 67% of all medicines in Europe
    - https://www.medicinesforeurope.com/medicines-for-europe/

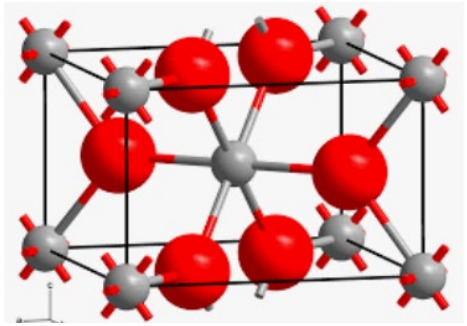
- **European Federation of Pharmaceutical Industries and Associations** (EFF
  - Represents the biopharmaceutical industry operating in Europe.
  - Voice of the research-based pharmaceutical industry operating in Europe
    - 37 national associations & 39 leading pharmaceutical companies
    - https://www.efpia.eu/about-us/
- **Association of the European Self-Care Industry, (AESGP)**
  - Voice of the manufacturers of non-prescription medicines, food supplements, and self-care medical devices in Europe, an area also referred to as “self-care” or “consumer healthcare” products.
  - https://aesgp.eu/who-we-are

Why is TiO2 used in so many pharmaceutical products?

- Key functions of TiO2: Full masking of capsule fill / tablet core



- Key characteristics of TiO2
  - Protects the ingredients susceptible to light degradation
  - High refracting index (not matched by any other opacifier)
  - Chemically inert -> no interaction with other ingredients
  - Insoluble in water
  - Highly stable to heat, light and weathering



TiO2 is present in almost all coating/capsule shells of solid drug products to inhance stability of the product and have clear, white appearance

Why is TiO2 in pharma – used in so many products?

- Industry are not aware of any material that has the properties that are unique to titanium dioxide such as:
  - opacity, whiteness, inertness, protection from UV light and the finish/smoothness of the resulting product.
- Alternative colorants to achieve an acceptable opaqueness of the product or coating will likely require greater amounts.
- Alternatives (especially if used in greater amounts) may have greater reactivity with API or other excipients
- *"no system or material which could address both current and future toxicological concerns of Regulators and the functional needs of the pharmaceutical industry and patients has been identified. This takes into account the assessment of materials such as calcium carbonate, talc, isomalt, starch and calcium phosphates"*
  - From: Blundell et al., The Role of Titanium Dioxide (E171) and the Requirements for Replacement Materials in Oral Solid Dosage Forms: An IQ Consortium Working Group Review*, J. Pharm. Sci,* 2022

Uses of Titanium Dioxide

Because of its opacity, whiteness, inertness, protection from UV light and the finish/smoothness it gives, it is very commonly used:

- Titanium dioxide is used in **~70% of oral solid dose medicines**
  - Used in ~90% of tablets/capsules that are colored or coated
    - Source: Survey on TiO2 in medicines, AESGP, EFPIA and Medicines for Europe, August 2020.
  - **Vital for appearance of tablets and capsules**, and therefore plays a **significant role in patient compliance**.

Possible alternatives for TiO_2 in pharmaceuticals

- **Calcium Carbonate**
  - Calcium carbonate is sourced by **mining**
  - Due to it alkaline properties, may react with Active Pharmaceutical Ingredients.
  - To achieve acceptable coverage higher amount and longer coating time needed
  - Few suppliers globally are able to comply with GMP certification and maintain the quality

Possible alternatives for TiO_2 in pharmaceuticals

- **Talc**
  - Mined material.
  - Managing its elemental impurity levels and ensuring the absence of asbestos adds complexity

- **Starch**
  - Corn Starch
  - Preferred over other starches due its whiteness.
  - Obtaining GMO-free certified corn starch will be a challenge for products going to the EU
    - >90% of US Corn is GMO (USDA, 9/2022)
    - https://www.ers.usda.gov/data-products/adoption-of-genetically-engineered-crops-in-the-u-s/recent-trends-in-ge-adoption/

Impacts

- **Removal of titanium dioxide** – if feasible - is a **reformulation** and will take years per product (depending on the need for e.g. stability, bioequivalence studies)
  - Does removal change efficacy by impacting:
    - Absorption during food consumption?
    - Delayed release?
    - Bioavailability in other ways?
  - Does removal change quality and stability?
  - May take 30-60 months
  - **Each individual reformulation** would cost the companies **between 500.000 and 1.5 million Euros** (without considering the EU manufacturing capacities required for EU only products).
- 50% of products impacted are multiregional

- If a product requires 2X the coating, requires double the time to coat

Impacts – Testing Required for Re-formulations

Stress Testing (ICH Q1A and Q1B)

- Effect of temperatures (in 10°C increments (e.g., 50°C, 60°C, etc.) above that for accelerated testing)
- Humidity (e.g., 75% RH or greater)
- Where appropriate, oxidation, and photolysis on the drug substance
- Hydrolysis across a wide range of pH values when in solution or suspension
- Photostability

- Other Considerations (Quality Attribute Considerations for Chewable Tablets, FDA, 2018)
  - Tablet hardness
  - Disintegration
  - Dissolution
  - Performance in Simulated Physiological Media

Impacts

- Removal of titanium dioxide from use in medicines will require new formulations to be developed for the majority of oral solid dose products for EU only, with titanium dioxide continuing to be used in the majority of medicines globally.
- Drug shortages are already a problem in the EU
  - 2022 survey of groups representing pharmacies in 29 European countries found almost a quarter of countries faced shortages of more than 600 drugs and 20 percent reported 200-300 drug shortages
    - https://www.politico.eu/article/health-care-pharma-why-is-europe-running-out-of-medicines-and-whats-being-done-about-it/
    - https://www.pgeu.eu/wp-content/uploads/2023/01/Medicine-Shortages-PGEU-Survey-2022-Results-1.pdf
  - A TiO2 ban will likely significantly increase the **risk of shortages of medicines**.
- **Decision to restrict TiO2 in medicines should be based on robust considerations of benefit/risk considering public health and patient compliance**

Ongoing Safety testing by authorities and other industries

Message from Industry

- Industry is investigating potential alternatives to titanium dioxide, with a clear plan to ensure there is no impact on patients from any replacements
- Industry would like common alignment with EU institutions on clear targets and deliverables to be achieved prior to EMA evaluation (April 2024)
- Investigation of safety is key, to ensure less safe alternatives are not introduced and to inform an appropriate benefit/risk assessment of titanium dioxide
- Many potential alternatives to coatings have been developed but there is no evidence yet that these are generally applicable as alternatives
- Evidence generated to-date, suggests that, unless amounts of coating are increased, titanium dioxide containing materials generally deliver products of superior appearance and protection
- Particular concerns about the impact on appearance, light resistance and/or the need for increased film coating quantities
- Premature to revise the EMA conclusions from September 2021 EMA/504010/2021

  "[…] The feasibility of replacing TiO_2 cannot be confirmed at this stage

  Any requirement to replace TiO_2 in medicines will almost certainly cause significant medicines shortages and discontinuations/withdrawals of medicines from the EU/EEA market with major implications for patients and animals […]"