Impact on a Large Global Pharmaceutical Manufacturer: Manufacturing, Supply, & Patient Implications of a TiO2 Ban in Pharmaceuticals

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PQRI Workshop:
TiO2 Use in Pharmaceuticals
Global Regulatory and Technical Challenges
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Pfizer

Outline of presentation

1. Options for phasing out TiO2
2. Global supply strategy
3. Challenges in replacing TiO2 in medicines
4. Criteria for alternatives
5. Importance of suppliers
6. How much effort & time will this take?
7. The great unknowns

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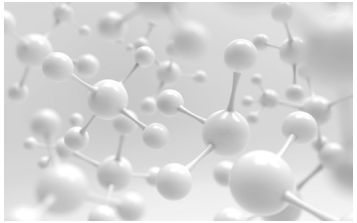
Drivers for current use of TiO2 (E171)



- Globally acceptable
- High purity & consistency
- Chemically inert
- Well tolerated by patients
- Highly precedented
- Low levels needed
  - high refractive index
- Freely available
- Low cost

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Options for phasing out TiO2 from existing medicines

- Remove TiO2 from the product
  - Likely not feasible in many cases due to product quality & patient acceptability issues
- Reduce TiO2 levels
  - To levels that can be agreed to be ‘safe’
  - Justify ‘lowest effective level’ with experimental data (similar to preservatives)
  - Not currently being considered by regulatory agencies, but could be a practical approach
- Replace TiO2 with alternative excipients
  - No single solution currently available
  - Significant patient impacts expected (appearance, taste, mouthfeel, shelf life, cost, etc)
  - Difficult technical challenges (especially with capsules)
  - Potential for major business impact (reduction in new medicines development & shortages of existing products)
- Withdraw product from the market
  - Loss of access to important medicines for European patients

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Global supply considerations (new & existing medicines)

1. Go all-in on a TiO2-free formulations for all global markets
   - ✓ A single global formulation (reduced supply chain complexity)
   - X Very little experience with TiO2-free formulations & processes, so puts non-European supply at risk for no good reason

2. Maintain *status-quo* in non-European markets & develop special TiO2-free formulations for Europe
   - ✓ Isolates business/regulatory risk to European market
   - X ~2x resources needed for formulation development, ICH stability & validation
     - Estimated additional cost of up to $50MM for a new product
   - X Bioequivalence needs to be demonstrated between TiO2-free and conventional formulations
   - X Adds significantly to complexity of commercial supply chain (2x # of SKUs)

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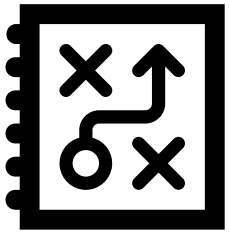
Challenges in replacing TiO2 in medicines

Technical challenges

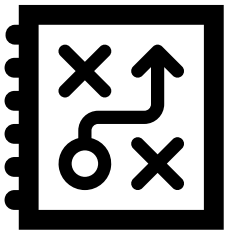
Business challenges

Patient impacts



Technical challenges in replacing TiO2 in medicines

- Lots of proposed solutions, but no proven track record for TiO2-free formulations
  - Product stability (over the long term)
  - Manufacturing process robustness
  - Long term safety (better than TiO2)
- Many products need to be considered at the same time
- Complex process required for re-approval of existing products
  - Likely to involve significant product composition and process changes
  - May require re-development & re-validation of analytical methods
  - May involve clinical studies to demonstrate bioequivalence
  - One-product-at-a-time regulatory review/approval process in place today



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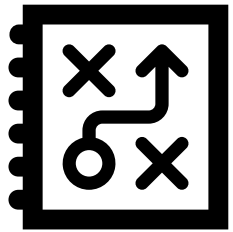
Business challenges in replacing TiO2 in medicines

- Large numbers of products impacted
  - Hundreds for every company
  - Tens of thousands for the industry
- Insufficient capacity
  - R&D labs
  - Manufacturing facilities
  - Regulatory reviewers
- No longer able to have a single product for all markets
  - Significant added business complexity (2x # of SKUs)
  - Potential for global supply chain disruption
- Significant added costs



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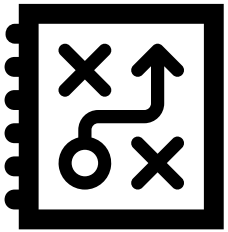
Patient impacts in replacing TiO2 in medicines

- Increased costs
- Supply shortages
- Product withdrawals
- Product quality changes
- Appearance changes



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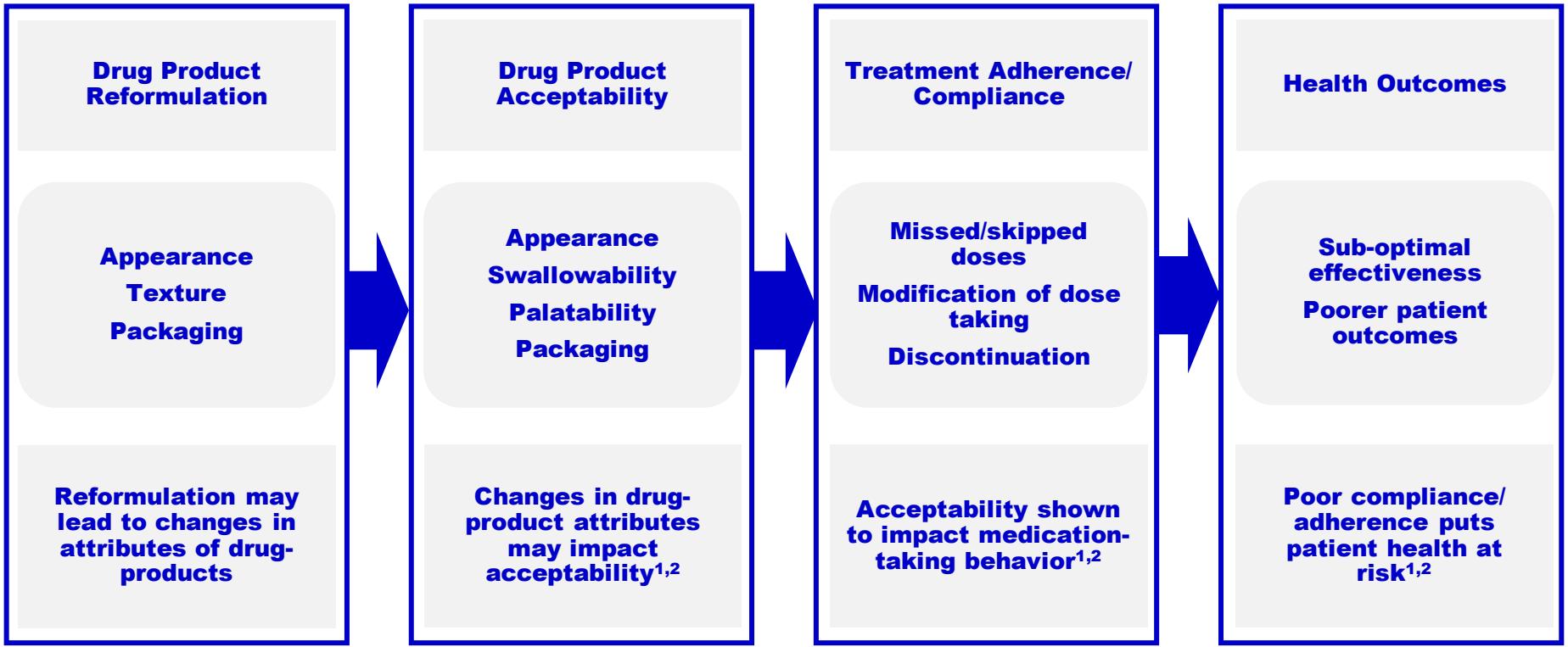
Reformulation's potential impact on patients



[1] Guideline on pharmaceutical development of medicines for paediatric use (europa.eu)
2 https://www.fda.gov/files/drugs/published/Size--Shape--and-Other-Physical-Attributes-of-Generic-Tablets-and-Capsules.pdf

Criteria for alternative materials

- Contemporary/complete safety data package
  - Inferior safety is not acceptable
- Satisfactory appearance
- Adequate mechanical properties (of films)
- Low chemical reactivity
- Globally acceptable
- Freely available (in pharma grade(s))
- Non-proprietary / freedom to operate
- Moderate to short processing times
- High processing performance/robustness
- Moderate to low cost

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Importance of suppliers

- Film coating pre-mixes and capsule shells are almost always purchased from 3rd party vendors
- Medicines manufacturers are reliant upon these suppliers to develop TiO2-free options
- Many of these suppliers are small companies with limited resources
- Developing new film coating and capsule formulations requires highly specialized skills which are in limited supply
- A close partnership is needed to establish which coatings or capsules will work for each different product

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Initial steps for new products in development (1 of 2)

- Evaluate technical feasibility of using TiO2-free alternatives
  - Manufacturability
    - Changes to product attributes, critical process parameters, etc
  - Stability
    - Updating of analytical methods, impact on dissolution, etc
  - Bio-performance
    - Focused on modified release and BCS 2/4 products
- Confirm safety data package of proposed alternatives
  - Assess literature data & data from suppliers
  - Run new toxicology studies (if needed)

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Initial steps for new products in development (2 of 2)

- Assess impact on
  - Ongoing global clinical studies
  - Patient experience (blinding, palatability, compliance, etc)
  - Performance (bioavailability, shelf life, etc)
  - Manufacturing capacity / efficiency
  - Time to market
  - Global supply chain (single global formulation preferred, CMO capacity, etc)
  - Cost of goods
- Negotiate supply agreements with suppliers
  - Materials may not be initially available in commercial quantity or quality
- Manufacture supplies to bridge to current formulation & begin bridging studies (clinical & stability)
- Continue to support existing formulation until bridging data is available & regulatory approval is obtained

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Additional steps for marketed products

- Understand make-up of commercial product portfolio
  - How many & which products are in-scope?
  - Function of TiO2 in each product?
  - Confirm composition information with suppliers
  - Centrally vs. nationally registered?
  - Product volumes & economics?
  - Remaining exclusivity (patent life)?
  - Essential medicines?
  - Internal vs. external manufacturing?
- Develop high-level plans to ‘remediate’ each product
  - Technical feasibility?
  - Patient impact?
  - Global supply chain impact?
  - Economics?
  - Decision: Withdraw / remove / reduce / replace?
- Understand capacity to make formulation changes across multiple products
  - R&D, manufacturing, laboratory, regulatory & distribution capacity

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How much effort & time will this take?

- More than 60% of marketed tablets and capsules contain TiO2
  - For large companies, hundreds of current products are in scope
- For each marketed product, a detailed assessment of the business, technical, medical and regulatory risks is needed (>6 months)
- Acceptable alternatives need to be available from suppliers
  - Complete contemporary safety data package
  - Meeting minimum product quality standards
  - Freely available in commercial quantities at a reasonable cost
- A staged approach to transition would be needed (>>5 years)
  - To allow suppliers to innovate
  - To address global manufacturing capacity constraints
  - To allow regulators time to review proposed dossier changes
  - To minimize impact to patients (medicines supply, appearance changes, etc)

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The great unknowns

- What is the EU/EMA expectation for safety data on other excipients?
  - Especially nano materials & TiO2 replacements
- Will existing approved products be ‘grandfathered’ in? Or will their marketing approvals be revoked?
- Under what circumstances can TiO2 continue to be used as an excipient in European medicines? (benefits>>risks)
- What are EMA’s plans & timelines for reviewing hundreds of updated MAAs?
- Will plans be put in place to minimize medicines shortages in Europe?
- Will any other major markets restrict the use of TiO2 in medicines?

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Thank You

Recap: Function of TiO2 in tablets & capsules

TiO2 acts:

- As a pigment or color
- As an opacifier
- To create a smooth surface texture

Benefits:

- Unique and consistent product appearance
  - easy recognition & blinding
- Protection from light induced chemical degradation
- Ease of swallowing

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Evaluation of new film coatings

- Establish global acceptability & safety of new coating formula
- Characterization of coating solution properties
  - Viscosity, surface tension, use-period, etc
- Mechanical property testing (on cast or sprayed films)
  - Tensile strength, modulus, adhesion, wear, smoothness, etc
- Spray-trials to establish optimal spray conditions
  - spray rate, atomization air flow, etc
- Film coating trials to establish processing conditions for target appearance and performance
  - Drying temperature, etc
- Color & opacity matching trials
- Stability studies
  - Physical, chemical & photo
- Bioperformance studies

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Evaluation of new capsule shells

- Establish global acceptability & safety of new capsule formula
- Characterization of solution properties
  - Viscosity, surface tension, use-period, etc
- Capsule manufacturing trials
  - Drying, release, weight uniformity, etc
- Mechanical property testing
  - Brittleness, adhesion, wear, smoothness, etc
- Encapsulation trials
  - Cracking, # of rejects, speed limits, etc
- Color & opacity matching trials
- Stability studies
  - Physical, chemical & photo
- Bioperformance studies

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	Existing Products				New Products
	Withdraw / divest	**Remove TiO2**	**Replace TiO2**	**Retain / Reduce TiO2**	**TiO2 free**
Toxicology	• Divest - buying company may require support	• Toxicology studies not required	• Which replacement(s)? • Toxicology studies required? (industry consortium?) • Data ready by 2025?	• Toxicology studies required (industry consortium?) • Data ready by 2025?	• Surrogate part of the regular safety data pack for global new product
Technical Considerations	• Divest - buying company may require support	• Understand the purpose of TiO2 in the formulation • Data needed to support (stability, manufacture)	• Understand the purpose of TiO2 in the formulation • Identity suitable replacements • Data needed to support (stability, manufacture, bioequivalence?)	• Understand the purpose of TiO2 in the formulation • Data needed to support (stability)	• Which replacement(s)? • PharmSci workflows generate the necessary data package • All new products to have TiO2-free option • Max one TiO2 coating as back-up?
Regulatory	• Regulatory comms of withdraw/ divest plans • If Withdraw not allowed need plan for retain/ replace	• Regulatory fillings needed for changes	• Regulatory fillings needed for changes • Expectation to contemporize older products? • Downstream impact to other markets	• Regulatory comms to justify continued use • Early engagement with regulators to establish acceptable approaches	• Use of precedented/ compendial excipient preferred (to avoid delays)
External Advocacy		• Develop case study to explain why even removal may not be straightforward • Seek alignment for simple changes (color) first and more complex changes or retention of TiO2 later	• Regulatory certainty needed on content of submission package for replacement • Consider bundling post approval changes (platform approach vs individual products) • Advocacy for a more reasonable timeline for replacement • Engagement with suppliers and competitors for safety & technical data	• Focussed advocacy on safety issues leveraging key groups like IMI, IHI, HSI, UK COM	• Influence Regulatory bodies (e.g. ICH) for harmonized requirements and solutions • Education of patients/HCPs on expected changes • Influence Supplier networks (e.g. DMF topic) • Networking / Benchmarking progress and approaches with peer companies
Business and Portfolio	• Divest – manage any Legal implications • Manage portfolio and loss of revenue	• Manage appearance changes (customer communications, complaints, etc)	• Manage appearance changes (customer communications, complaints, etc)	• Assess benefit-risk for products retaining TiO2	• Update development and launch strategies (as needed) • Manage appearance limitations, patient acceptance