USE OF TITANIUM DIOXIDE AS EXCIPIENT IN HUMAN AND VETERINARY MEDICINES AND IDENTIFICATION OF ALTERNATIVES

INDUSTRY FEEDBACK TO QWP EXPERTS/EMA QUESTIONS FINAL REPORT FEB 2024

efpia
European Federation of Pharmaceutical Industries and Associations

TiO_2 Alternatives Consortium

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VOICE OF EUROPEAN SELF-CARE INDUSTRY

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iPEC EUROPE 30 YRS

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The yellow text represents the updates versus previous document.

NEW PROVISIONS

Below we identify the pages where we have included new provisions since our interim report of November 2023. Each of these changes is highlighted in yellow throughout the text. Where further cosmetic changes have bene made (change in word, table number etc) these are also highlighted throughout the text however not noted in the table below.

Page	Headline	Comment
8	Table 1: Outreach and engagement touch points, final row	Reference to the Interim report submitted to the EMA in November 2023
12	Summary and timeline of industry activities to identify and assess alternative coatings and capsules	Diagram updated
Question 1		
17 - 19	3. Manufacturing and Quality Summary of TiO_2 Alternatives Consortium Assessment of Alternatives	Section 3 updated: text and revised Table 2. It further references 2 extensive annexes to be shared as separate documents (due to their size): ANNEX 2: Alternatives to Titanium Dioxide in Tablet Coatings ANNEX 3: Alternatives to Titanium Dioxide in Hard Shell Capsules.
20 - 21	4.Safety Assessment of Alternatives	Section 4 text updated and Table content. References annex to be shared as a separate document: ANNEX 4: Safety assessment of alternatives and comparison with Titanium Dioxide as an opacifier and colorant for oral administration
22 - 24	Table 3: Current status of the safety assessments of TiO_2 alternatives	Content of Table 3 updated
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25		For full details, reference to ANNEX 2: Alternatives to Titanium Dioxide in Tablet Coatings and ANNEX 3: Alternatives to Titanium Dioxide in Hard Shell Capsules.
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45-46	1.Recent Global Safety Evaluations of TiO_2	Includes 2 new updates: - Ministry of health, Labour and Welfare of Japan 2023 - Joint FAO/WHO Expert Committee on Food Additives (JECFA) 2023

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47	3. Recently Published TiO2 Quality Evidence	New Section including reference to newly published paper
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56	Conclusions and Recommendations	New text has been added
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	Annex 4 (Separate document)	Safety assessment of alternatives and comparison with Titanium Dioxide as an opacifier and colorant for oral administration

Introduction

This document is submitted on behalf of the European associations representing the human medicines manufacturers, veterinary medicines manufacturers and excipient producers. It is the interim feedback to the European Commission, EMA Quality Working Party (QWP) and Non-Clinical Working Party (NcWP) experts in relation to the requirement of the Regulation amending Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council as regards the food additive Titanium Dioxide (E 171) (2022/63/EU). It aims at providing written answers to both the questions posed by QWP on 11 September 2023 and by QWP and NcWP experts at the QWP drafting group and industry associations meeting on Titanium Dioxide meeting of 16th October 2023.

The questions posed by the QWP to industry with the deadline of 2nd November 2023 were as follows:

A. TiO_2 possible alternatives

1. Please list the alternatives to replace / remove TiO_2 without negatively impacting the quality, safety and efficacy of medicine that you have investigated to date with the advantages and disadvantages and if applicable, any additional potential alternatives that are planned to be investigated in future.

2. Please supply a summary of the evidence /results from the ongoing studies comparing alternative formulations (for different dosage forms as available) with those containing TiO_2.

3. In 2021, you provided QWP with information on the methodology and timeline estimates on investigating potential alternatives to replace/remove TiO_2 without negatively impacting the quality, safety and efficacy in medicinal products. Please provide the updates to this information versus the last analysis.

B. Industry impact assessment of the situation on the pharmaceutical sector and timelines

4. In case an alternative to replace/remove TiO_2 is identified, please indicate approximate timelines to prepare and file for such a change (for subset of products/which ones/are there different issues for different products or dosage forms/types of products?).

5. Please, supply an updated summary of the calculated impact on availability, shortages, and costs of any requirement to replace/remove TiO_2 from medicines in Europe, considering the global nature of product development and supply.

Overview

Titanium Dioxide as a ubiquitous excipient in medicines globally

Titanium Dioxide (TiO_2, E171, anatase) is primarily used in medicinal products as a white colourant and opacifier in coatings and capsules. It has unique properties, such as providing light protection to many active ingredients and formulations and to ensure uniform appearance when used in in minimal quantities.

TiO_2 is ubiquitous in medicines globally. Although an exact number i difficult to establish, it is estimated that at least 100 000 human medicinal products and 1600 veterinary medicinal products in the EU contain TiO_2. The true number globally is likely to be significantly higher (EMA/504010/2021). Reformulation of even a proportion of these products would provide an enormous and unprecedented challenge which will be discussed in detail within this report.

TiO_2 has played a key role in the safety, efficacy and compliance for the majority of medicines in Europe for over 50 years; and as a pure mineral, TiO_2 meets the most stringent of requirements governing the safety of medicines, including those set by the European Pharmacopoeia, Japanese Pharmacopoeia and US Pharmacopoeia.

Timeline of Developments

1. EFSA 2021

On the 6th May 2021, the European Food Safety Authority (EFSA) published their opinion on the safety assessment of E171 Titanium Dioxide, which states that it can no longer be considered safe when used as a food additive. EFSA found that, on the basis of a reassessment of the available safety data, a concern for genotoxicity "*could not be ruled out*" and, consequently, a "*safe level for daily intake of the food additive could not be established*". EFSA has previously reviewed the use of TiO_2 as a food additive in 2016, 2018 and 2019, however, all three previous EFSA investigations found no evidence indicating TiO_2 could present a risk to human health.

2. Industry Assessment and EMA report (EMA/504010 2021)[1]

On the 30 June 2021, three European associations representing the human medicines manufacturers (AESGP, EFPIA, Medicines for Europe) prepared a report[2] to feedback to the European Commission and EMA experts in relation to the opinion of EFSA on TiO_2 and its impact on human and veterinary medicinal products. The report provided written answers to the group of QWP experts on the use of titanium dioxide as an excipient and address three area: quantitative and qualitative presence of TiO_2 in medicinal products in EU/EEA, possible alternatives, and an impact assessment of a theoretical requirement to replace TiO_2.

Likewise, the two associations representing the Veterinary medicines sector (AnimalhealthEurope and Access VetMed (formerly EGGVP) also submitted a report[3] to feedback on the impact on veterinary medicines sector to the EMA updated on the 8th July 2021, the report included quantitative and

[1] https://www.ema.europa.eu/en/documents/report/final-feedback-european-medicine-agency-ema-eu-commission-request-evaluate-impact-removal-titanium_en.pdf

[2] https://www.ema.europa.eu/en/documents/other/annex-i-use-titanium-dioxide-excipient-human-medicines-industry-feedback-qwp-experts/ema-questions_en.pdf

[3] https://www.ema.europa.eu/en/documents/other/annex-ii-use-titanium-dioxide-excipient-veterinary-medicines-industry-feedback-qwp-experts/ema-questions_en.pdf

qualitative presence of TiO_2 in medicinal products in EU/EEA, possible alternatives and impact assessment of a theoretical requirement to replace TiO_2.

The EMA subsequently published their final feedback to the EU Commission request to evaluate the impact of the removal of TiO_2 from the list of authorised food additives on medicinal products in October 2021. It included the following conclusions:

- TiO_2 is extensively used as an opacifier and colourant in medicines due to its multiple functionalities.
- TiO_2 is used very frequently in oral solid dosage forms and in oral semi-solid dosage forms. TiO_2 is also present in dosage forms administered via routes other than oral.
- It is present in many essential medicines.
- To date [2021], no single material had been identified that provides the same combination of properties that are unique to TiO_2. Separating out the different functionalities of TiO_2 for those medicinal products in which it serves more than one function is difficult or might not be possible at all.
- Possible alternatives identified so far [2021] have a number of disadvantages versus TiO_2.
- The feasibility of replacing TiO_2 could not be confirmed at this stage. Each affected medicinal product will need an individual review and assessment.
- Europe would potentially be the only region globally to ban TiO_2 as excipient in medicines, which would require industry to develop new formulations.
- An acceptable transition period for phasing-out TiO_2 was difficult to envisage or estimate considering the scale of the use of this excipient, the time and costs involved in the reformulation and the volume of products impacted.
- Replacing 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. Particular concerns arise in relation to certain vulnerable classes/types of products such as paediatric medicines, orphan medicines or low sales volume products.

3. Legislative requirements

On 14 January 2022, the Commission adopted a ban on the use of Titanium Dioxide as a food additive (E171), amending Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council as regards the food additive Titanium Dioxide (E 171) (2022/63/EU. Since 2022, TiO_2 is not authorised in the food categories (with a transition period of 6 months (implemented 7 August 2022).

Regulation 2022/63 provisionally maintains the inclusion of E171 in the list of approved colours allowed for use in medicines. The recitals note that this is to avoid shortages of medicinal products containing TiO_2 as this could impact public health and animal health and welfare. It is also noted that the replacement of TiO_2 requires investigation and testing of suitable alternatives to ensure that quality, safety and efficacy of medicines are not negatively affected.

The Commission will review the necessity to maintain TiO_2 or to delete it from medicines by February 2025 based on a re-evaluation by EMA in April 2024.

Summary of outreach and engagement between industry, EU institutions and the EU regulatory network

The industry has engaged extensively throughout the process with the EU institutions and EU Regulatory Network to build a good dialogue and align on the expectations from industry on the scientific investigation of TiO_2 and potential alternatives. Table 1 below outlines the dialogue since 2021.

Table 1: Outreach and engagement touch points

Date	Engagement	From	To/With	Focus of interaction
5 August 2021	Letter	AESGP, EFPIA, Medicines for Europe	European Commission	• Request for scientific dialogue with the goal to arrive at an overarching risk assessment for the use of E171 in pharmaceuticals
31 August 2021	Letter	European Commission	AESGP, EFPIA, Medicines for Europe	• Response to letter of 5 August 2021 • Informed on no room for a separate scientific assessment on the use of TiO_2 in medicines • Informed industry that on the 17 May 2021, the EC requested EMA to provide an analysis with the aim to define the technical purpose of TiO_2 in medicinal products.
17 February 2022	Letter	EMA, European Commission, HMA	AESGP, EFPIA, Medicines for Europe, AnimalhealthEurope, Access VetMed	• Informing industry of Reg 2022/63 • Informing industry of requirement to accelerate R&D of alternatives to TiO_2
25 February 2022	Letter	AESGP, EFPIA, Medicines for Europe	EMA, European Commission, HMA	• Acknowledging receipt of letter 17/2 • Acknowledging the continued use of TiO_2 in medicines • welcome the continued dialogue opportunities and the EU Regulatory Network
2 May 2022	Meeting	AESGP, EFPIA, Medicines for Europe	Commission, EMA, HMA	• Presentation and discussion with the Commission on the human pharmaceutical association's activities on TiO_2 and alternatives

3 May 2022	Meeting	AESGP, EFPIA, Medicines for Europe, EUCOPE, AnimalhealthEurope, Access VetMed	QWP of EMA	• Presentation and discussion on the planned approach of industry on the scientific investigation of TiO_2 and potential alternatives
24 June 2022	Letter	AESGP, EFPIA, Medicines for Europe	EMA, HMA, cc European Commission	• Follow up from QWP meeting in May • Requesting close collaboration on TiO_2 and alternatives • Requesting support for the industry proposed integrated and technical plan to assess the safety of alternatives and establish the feasibility of replacing TiO_2 in medicinal products. • Clarification of the EU Regulatory Network's expectations under Commission Regulation 2022/63 and EMA Q&A 384135/2021
23 September 2022	Letter	EMA	AESGP, EFPIA, Medicines for Europe	• Acknowledged receipt of the letter of 24/6/22 • Welcomed the pharmaceutical industry's commitment to seeking safe potential alternatives to TiO_2
4 October 2022	Meeting	AESGP, EFPIA, Medicines for Europe, Eucope	NcWP of EMA	• Presented on the Scientific Investigation of TiO_2 & Potential Alternatives
27 February 2023	Letter	AESGP, EFPIA, Medicines for Europe	EMA, HMA	• Industry thanked EMA for opportunities in 2022 for engagement and discussions with the EMA within the context of the QWP (May) and NcWP (October) on TiO_2 and alternatives • Reiterated the need for close collaboration and request for a meeting
18 April 2023	Letter	EMA, HMA	AESGP, EFPIA, Medicines for Europe	• Responded to letter dated 27/2/23 • Recommended companies continue to explore possible alternatives to TiO_2 and the feasibility of such alternatives. • Agreed to include the topic at the next QWP IP meeting however reiterated the need for a safety discussion

				• Requested information on the EMA re-evaluation processes
26 May 2023	Letter	AESGP, EFPIA, Medicines for Europe + TiO_2 Alternatives Consortium	EMA, HMA	Requested further clarifications from the EMA: • Welcomed opportunity to discuss at the QWP • Noted related article (27) of the adopted commission proposal for a directive of the EU general pharmaceutical legislation
27 June 2023	Meeting	AESGP, EFPIA, Medicines for Europe, EUCOPE, AnimalhealthEurope, TiO_2 Alternatives Consortium, IPEC	QWP of EMA	• Presentation and discussion updating on the approach of industry on the scientific investigation of TiO_2 and potential alternatives
16 October 2023	Meeting	AESGP, EFPIA, Medicines for Europe, EUCOPE, AnimalhealthEurope, TiO_2 Alternatives Consortium, IPEC	QWP, NcWP, Commission	• Presentation and discussion with industry associations to discuss the 5 proposed questions of the EMA
10 November 2023	Report	AESGP, EFPIA, Medicines for Europe, EUCOPE, AnimalhealthEurope, TiO_2 Alternatives Consortium, IPEC	EMA	• Industry Feedback to the QWP experts/EMA questions Interim report Nov 2024

Investigation of Alternatives to Titanium Dioxide in Capsules and Coatings

Industry is continuing to address the requirements of Commission Regulation 2022/63 to assess alternatives to Titanium Dioxide. At the outset of investigations, it was established that alternatives to TiO_2 must:

1. Deliver products of equivalent or superior safety to those using TiO_2.
2. Deliver products of equivalent or superior efficacy and quality to those using TiO_2.
3. Be available and sustainable.

It was identified that although some materials had become commercially available (e.g., coatings and capsule shells) which did not contain TiO_2, there was lack of evidence to show whether these provided viable alternatives (e.g., assessing impact on medicine appearance, stability, light protection and/or the need for increased film coating quantities which can impact efficacy).

Most importantly, the safety of such alternatives (in general terms and relative to TiO_2) may not have been appropriately established. At the same time industry also noted that currently approved colours may also undergo EFSA re-assessment, particularly regarding assessment of the safety in relation to nanoparticles (see Annex 1).

Excipients industry efforts to identify alternatives to Titanium Dioxide

The excipients industry has created a number of options for TiO_2 free coatings and capsules which are currently being evaluated by medicinal product manufacturers. The best options available are a culmination of each individual excipient company evaluating numerous excipients in different combinations over the last 2-3 years. It is estimated that over 2000 different combinations of excipients have been evaluated by suppliers. In the opinion of IPEC Europe, there is no 'like for like' replacement for TiO_2, and this document will illustrate some of the issues the pharmaceutical industry will face should TiO_2 be no longer be available as an excipient in Europe. IPEC Europe also notes the likelihood that in such an eventuality, the demand for replacement materials (eg titanium dioxide-free coatings and capsules) will surge and the time and costs required for any capacity expansion to meet this need must be taken into account.

TiO_2 is an inert material that gives film coatings and capsules an effective opacity and protection from UV light, it allows the rapid development of consistent colour regardless of the core colour and condition, and regardless of the process parameters used or the scale of production. One of its hidden values is that it makes the coating process and resulting product much more consistent and predictable. In order to find a suitable replacement, the material must meet as many of these characteristics as possible, otherwise the quality of the resulting drug product is likely to be negatively impacted.

Process to assess alternatives to Titanium Dioxide

Film coating and capsule companies start by screening potential materials to assess their performance as an opacifier. Once a suitable material is identified different grades of the same material from different suppliers are screened to determine the most effective opacifier or the whitest source. The next step is to see how any material performs in film coating or capsule shell formulations compared to TiO_2. Depending on time pressures and demand some of these simple replacement coating or capsule shell formulations were made available commercially, but these remain non-optimised and

there are significant compromises that need to be evaluated. Once a viable material is identified the next step is to optimise that formulation and this may involve removing or adding additional excipients to counteract the lack of performance versus TiO_2 in one aspect or another. In all cases there are still compromises that need to be balanced against performance and quality of the coating or capsule, these will then be evaluated more closely and made into commercially available products if they are acceptable from a regulatory compliance standpoint (see General Compliance assessment below). It is only at this stage that these optimised coatings and capsules can be fully evaluated (opacity, stability, process parameters, scale, availability, safety and quality) in finished drug products, and which needs to be repeated for each dosage type and API. The optimised coating or capsule shell formulations being evaluated are the result of over 2000 different combinations of excipients being evaluated by excipient companies.

Generally speaking, IPEC Europe believes that there is no excipient that is the equivalent of TiO_2. TiO_2 free coatings and capsules are commercially available, but they are more sensitive to scale effects, process parameters, UV protection is lower, and colour is not as predictable. These formulations also tend to have more excipients added to them making any licence variation more complex. These points are further discussed later within this report.

Titanium Dioxide Alternatives Consortium

To coordinate activities and deliver an industry-aligned assessment, a grouping of (>20) pharmaceutical companies was formed in 2022 to collectively address this via a new pre-competitive industry Consortium. **The aim of the Alternatives Consortium was to generate evidence that can be used by the EMA to support the re-evaluation of the feasibility of removing TiO_2 from the list of excipients for use in medicines.**

What:

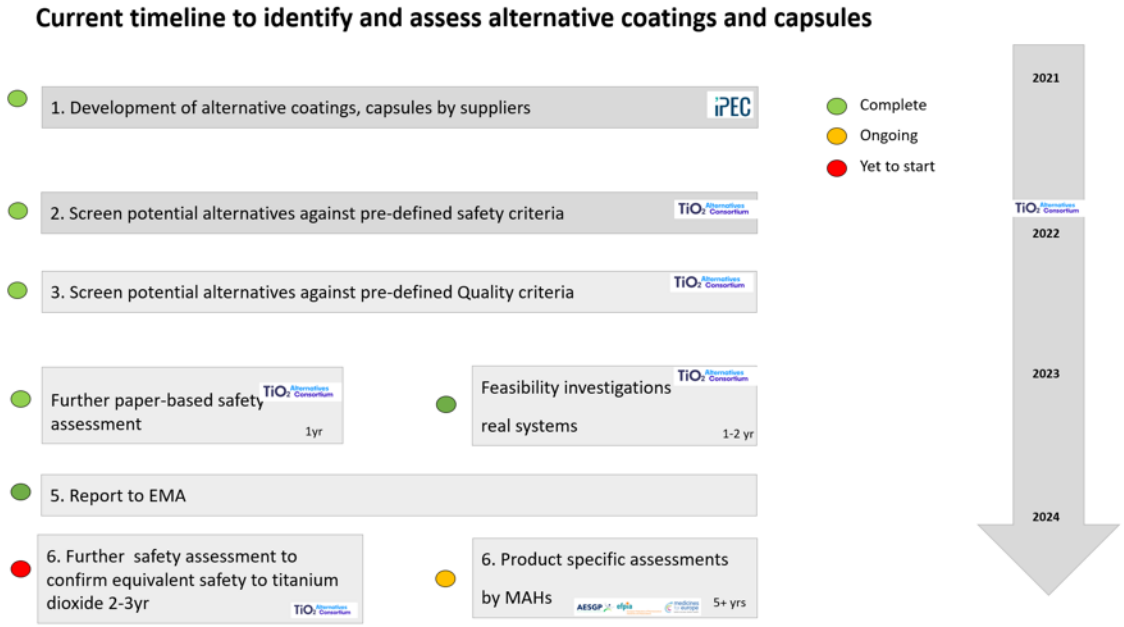
- These activities have been carried out by one, or several, Contract Research Organisations (CROs).
- They will be responsible for managing the work activities, and the associated financials, of this new consortium.

How:

- *Phase 1:* Comprised the technical evaluation of alternatives and manufacturing feasibility study running until approximately end 2023. Collect data and prepare final reporting to EMA IN February 2024.
- *Phase 2:* If required, in collaboration with the excipient industry and with input from EMA safety experts, would comprise *in-vivo* safety studies for the three most promising alternative candidates to complete their safety data set and would run beyond 2024.

Summary and timeline of industry activities to identify and assess alternative coatings and capsules

The summary below presents an illustrated summary of the industry activities to identify alternative, TiO_2-free coatings and capsules, and to evaluate the safety and use of these in medicines.



EMA Questions to Industry - 2023

A. TiO_2 possible alternatives

Question 1

Please list the alternatives to replace / remove TiO_2 without negatively impacting the quality, safety and efficacy of medicine that you have investigated to date with the advantages and disadvantages and if applicable, any additional potential alternatives that are planned to be investigated in future.

Assessment of TiO_2 alternative materials in film coat systems and hard capsule shells

The Consortium has undertaken a comprehensive assessment of alternative excipients to replace TiO_2 in film coats and hard capsule shells. The objective of the consortium has been to assess the potential impact of these alternative materials on the performance of immediate release film coated tablets and hard shell capsules. Immediate release products were selected for the evaluation as the impact on dissolution and disintegration would be easier to assess compared to the evaluation of controlled release dosage forms where any potential changes may have to be assessed through *in-vivo* studies.

The consortium has not evaluated the impact of alternative materials to TiO_2 in specialised dosage forms such as oral suspensions and soft capsules (softgels), where specialised manufacturing equipment and formulations which are designed for specific fill material result in a non-universal capsule shell formulation.

Selection of Alternative TiO_2 Film Coat and Hard Capsule Shell Systems

To perform the assessment of these TiO_2-free alternatives, the consortium obtained ready-made coatings and hard capsules directly from the manufacturers. The manufacturers have the know-how and intellectual property related to the component selection, compositions, and manufacturing processes to match customer requirements.

For coatings and hard capsules there is several standard formulations depending on the film-forming polymer, structural additives (plasticizers, gelling agents), colorants and opacifiers and sometimes process aids. For coatings the main groups are Hypromellose (HPMC) versus polyvinylalcohol (PVA) polymers combined with different plasticizers. For capsules the main groups are Hypromellose (HPMC) versus gelatin with or without gelling agent.

During pharmaceutical development, multiple coatings or capsules are typically tested in parallel to determine the compositions yielding the most stable and robust drug product.

The following selection criteria for the TiO_2-alternatives were applied:

- **Suppliers:** all global suppliers known to the consortium were consulted, and included in the program if they offered alternatives.
- **Alternatives were selected based on**:
    - **Commercial readiness**: the alternatives had to be ready in terms of raw materials and manufacturing process. It was not a requirement that the alternative is effectively used in a commercial product.
    - **Compliance:** the alternatives and their components had to have a minimum compliance level with food or pharma quality monographs.

- For colored alternatives, the suppliers were consciously asked to avoid the use of organic dyes to avoid interferences in analytical and stability studies.

General Compliance Assessment

Forty systems were studied (27 coats, 13 capsules). Key compliance considerations for alternative opacifying systems:

- Calcium carbonate ($CaCO_3$) and rice starch are included in 32 out of 40 systems, but for 15 systems the grades used have not been proven to meet multicompendial requirements limiting the potential for developing global formulations.
- Novel systems containing chemicals such as zinc oxide (ZnO) or sodium pyrophosphate are not globally approved for food use in oral medicines.
- Only calcium carbonate (white) and iron oxide (coloured)(Fe_2O_3) are approved food colourants
- ECHA has submitted a dossier proposing 'suspected carcinogen' labelling for Talc, which is a component for all 8 PVA-coats out of various 27 coating systems studied.
- EFSA is re-evaluating the safety of iron oxides and hydroxides potentially affecting its status as approved food additive and colourant, which might impact all coloured coatings and capsule shells under evaluation.
- For 20 out of 40 alternatives, the system consists of an opacifier (e.g. calcium carbonate) and a component which boosts performance (e.g. isomalt). Most of the alternatives are used as an opacifier, not as colourant. The applicability of the food colourant requirement for these alternatives (opacifier, booster) is therefore unclear.

1. Tablet Film Coats – Compliance Assessment

Based on offerings from 8 global suppliers, the predicted best and most diverse TiO_2-free alternatives were selected.

These consisted of either Hypromellose, HPMC, (19 systems) or Polyvinyl alcohol, PVA, (8 systems) as these are the two most commonly used polymers in film coating. The coatings were initially assessed for compliance risks including food legislation (E-number, food colorant approval), investigation for nano-risk by EU-member states, global pharma approval for oral use, compliance to European Pharmacopoeia and to USP/NF & JP ('Other Pharm'), presence of talc and iron oxide (Fe_2O_3).

None of the 27 selected coat systems are considered risk-free with 24 out of 27 coats (~90%) considered to have 2 or more risks as shown in Figures 1 and 2.

Figure 1: Compliance risk for hypromellose coatings

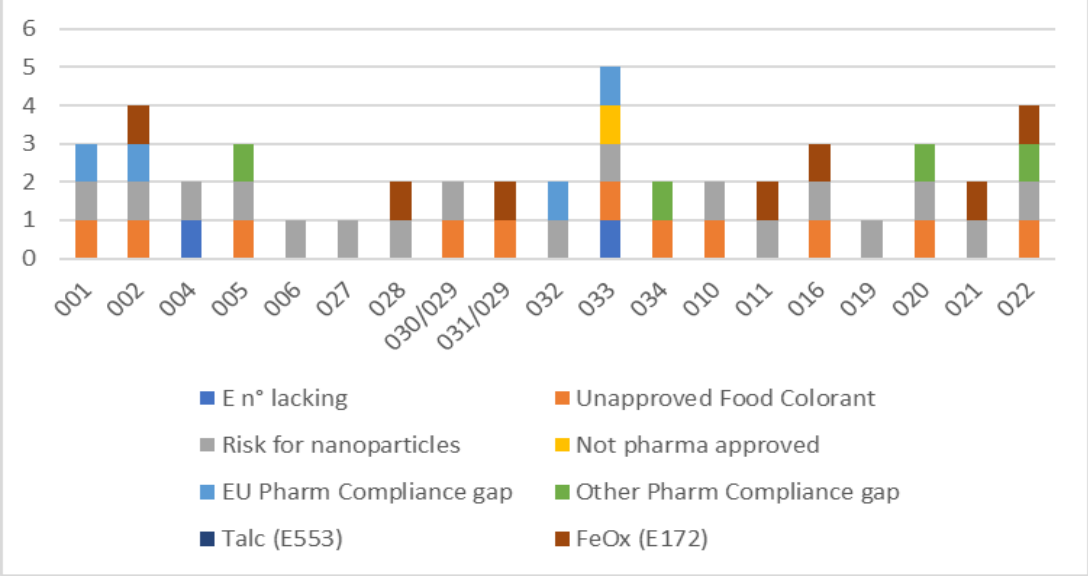
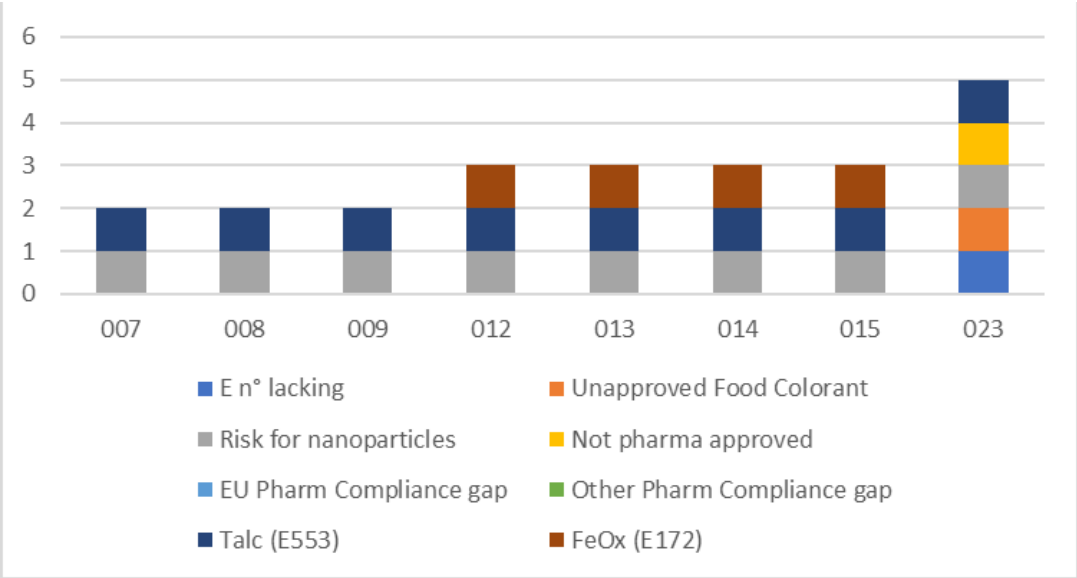


Figure 2: Compliance risks for PVA coatings



Note: supplier coat systems have been anonymised with random numbers

2. Capsule – Compliance Assessment

Based on offerings from 4 global suppliers, the predicted best and most diverse TiO_2-free alternatives were selected. The capsule shells with these alternatives include 8 HPMC & 5 gelatin capsules. The capsules were initially assessed for compliance risks including food legislation (E-number, food colorant approval), investigation for nano-risk by EU-member states, global pharma approval for oral use, compliance to European Pharmacopoeia and to USP/NF & JP ('Other Pharm'), presence of iron oxide.

None of the 13 selected systems are considered risk-free with 12 out of 13 capsules considered to have 2 or more risk as shown in Figures 3 and 4. For Iron Oxide (Fe_2O_3) exposure must be limited:

WHO-ADI E172 0.5 mg/Kg BW, JPN $Fe(OH)_3$ 5.67 mg/day, FDA 5 mg Fe/day. This typically limits the daily dose to 3 standard size #0[4] capsules per day.

Figure 3: Compliance risks for hypromellose capsules

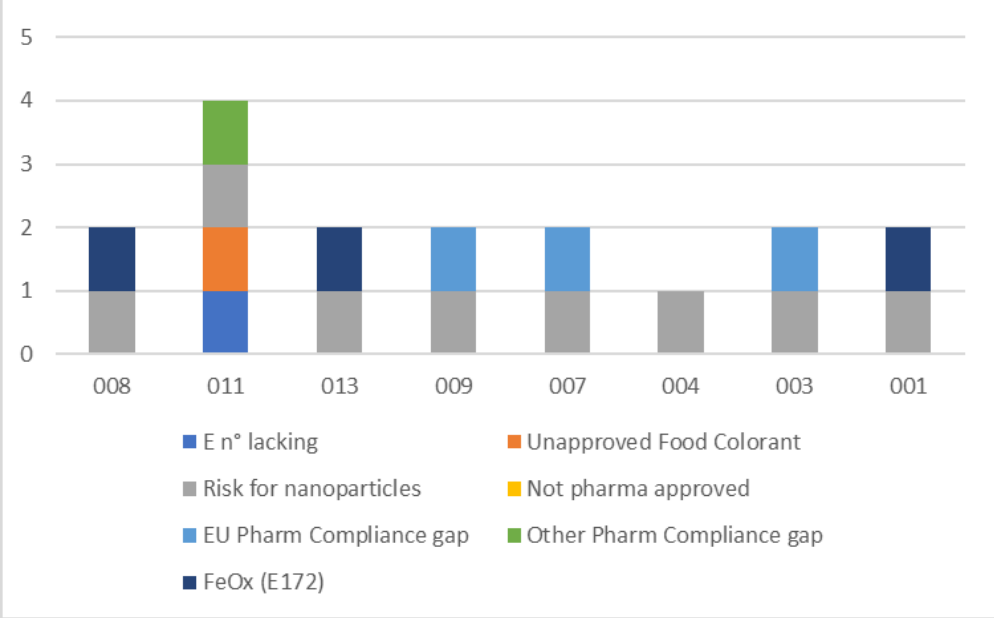
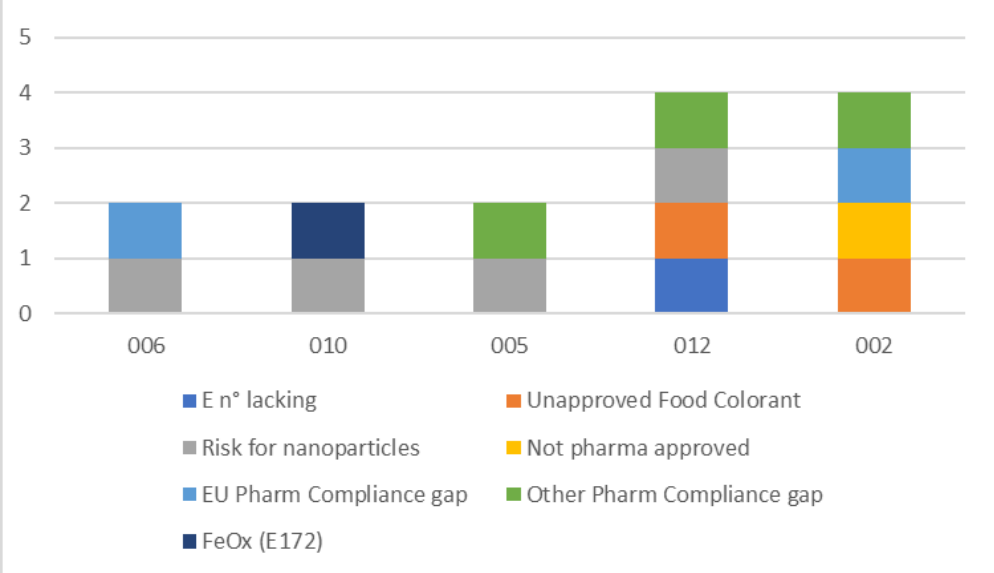


Figure 4: Compliance risks for gelatin capsules



Note: supplier capsules have been anonymised with random numbers

[4] Size 0 capsule corresponds to a capsule with a closed length of approximately 21.5 mm

3. Manufacturing and Quality Summary of TiO_2 Alternatives Consortium Assessment of Alternatives

The consortium has completed its activities, evaluating a significant number of film coat and capsule systems comparing their performance to reference TiO_2 containing systems. The detailed results and the conclusions of this analysis is provided in **(1) ANNEX 2: Alternatives to Titanium Dioxide in Tablet Coatings** and **(2) ANNEX 3: Alternatives to Titanium Dioxide in Hard Shell Capsules**.

From these activities the following conclusions can be determined:

Film Coating

Table 2 List of coating materials selected for evaluation

Consortium Coat Reference	TiO_2-Free (Yes/No)	Color	Film Former A	Film Former B	Opacifier(s)[e]	Target[b] %Solids
COAT-001	Yes	White	Hypromellose (HPMC)[d]	HPC[d]	Magnesium carbonate ($MgCO_3$) + A + B	16 (15-17)
COAT-002	Yes	Pink	HPMC	NA	Rice starch + A+B+D + (Fe_2O_3)	16 (15-17)
COAT-003	Yes	Clear	Polyvinyl Alcohol (PVA)	NA	Talc	20
COAT-004	Yes	White	HPMC	NA	Calcium carbonate ($CaCO_3$) + C	11
COAT-005	Yes	White	HPMC	NA	Magnesium oxide (MgO)	11
COAT-006	Yes	White	HPMC	NA	$CaCO_3$ + D	20
COAT-007	Yes	White	PEG- PVA graft copolymer[d]	PVA	$CaCO_3$ + Talc	30
COAT-008	Yes	White	PVA	NA	$CaCO_3$ + Talc	20
COAT-009	Yes	White	PVA	HPMC	$CaCO_3$ + Talc	20
COAT-010	Yes	White	HPMC	NA	Rice starch + D	20
COAT-011	Yes	Pink	HPMC	NA	$CaCO_3$ + D + Fe_2O_3	20
COAT-012	Yes	Pink	PEG- PVA graft copolymer	PVA	$CaCO_3$ + Talc + Fe_2O_3	30
COAT-013	Yes	Pink	PVA	HPMC	$CaCO_3$ + Talc + Fe_2O_3	20
COAT-014	Yes	Pink	PVA	NA	$CaCO_3$ + Talc + Fe_2O_3	20
COAT-015	Yes	Pink	PVA	NA	$CaCO_3$ + Talc + Fe_2O_3	20
COAT-016	Yes	Pink	HPMC	NA	Rice starch +D + Fe_2O_3	20
COAT-017[a]	No	White	HPMC	NA	TiO_2	15
COAT-018[a]	No	White	PVA	NA	TiO_2 + Talc	25
COAT-019	Yes	White	HPMC	NA	$CaCO_3$ + D + E	17
COAT-020	Yes	White	HPMC	HPC	Rice starch + D	15
COAT-021	Yes	Pink	HPMC	HPC	$CaCO_3$ + D + Fe_2O_3	15
COAT-022	Yes	Pink	HPMC	HPC	Rice starch + D + Fe_2O_3	15
COAT-023	Yes	White	PVA	NA	F+ Talc	18.5 (17-20)
COAT-024[a]	No	White	HPMC	NA	TiO_2	15
COAT-025[a]	No	Pink	PVA	NA	TiO_2 + Talc + Fe_2O_3	18.5 (17-20)

COAT-026[a]	No	Pink	HPMC	NA	TiO_2 + Fe_2O_3	15
COAT-027	Yes	White	HPMC	NA	$CaCO_3$ + D	16.5 (15-18)
COAT-028	Yes	Pink	HPMC	NA	$CaCO_3$ + D + Fe_2O_3 + FD&C Red #40	16.5 (15-18)
COAT-029	Yes	White	HPMC	NA	B + G	12
COAT-030	Yes	Clear	HPMC	NA	B + E	12
COAT-031[c]	Yes	Red	HPMC	NA	B + Fe_2O_3	12
COAT-032	Yes	White	HPMC	NA	$CaCO_3$ + H	17.5
COAT-033	Yes	White	HPMC	NA	$CaCO_3$ + D + F	18
COAT-034	Yes	White	HPMC	NA	Rice starch	18

[a]TiO_2 reference coating materials bTarget or range %solids based on the manufacturers' recommendations.

[c]COAT-031 is a ready-to-use solid coloring agent preparation for addition to other film-coating admixes e.g., COAT-030.

[d]Hypromellose is described as hydroxypropylmethylcellulose (HPMC) hereafter in this report and macrogol-PVA graft copolymer as polyethylene glycol (PEG)-PVA graft copolymer. HPC = hydroxypropylcellulose

[e]Fe_2O_3 is not an opacifier per se but contributes to opacification through its colorant properties.

All of the 20 TiO_2-free coatings studied in detail were inferior to the TiO_2 reference coats based on the entire set of Key Performance Indicators (KPI). Some performed well when assessed against certain criteria but not others. Many did not achieve surface coverage and opacification at a 6% weight gain and those, which did, required a significantly higher coating level than the TiO_2 reference coats. In general, the performance of the coloured TiO_2-free coatings was poorer than the white TiO_2-free coatings.

In conclusion, none of the TiO_2-free coatings could match the properties of TiO_2. Their use will result in longer, more expensive and potentially less robust coating processes and may also impact on the stability and shelf-life of products. Colour matching between marketed products and TiO_2-free coatings will be extremely difficult and the colour palette available for product identification and anti-counterfeiting measures will be reduced due to the poor performance of the coloured coatings. There is also a risk to patient adherence due to the colour changes seen in some TiO_2-free coatings and to patient safety as a result of the limited colour palette available to distinguish between different products/strengths.

Hard Shell Capsules

The Consortium studied 13 TiO_2-free hard capsule shells and compare them with 4 TiO_2 reference capsule shells.

The results show that for white capsule shells, all of the TiO_2-free capsule shells have inferior properties to TiO_2 containing reference shells in terms of opacity and ability to camouflage the capsule shell contents. In some cases, they had reduced mechanical integrity than the TiO_2-containing counterparts. The gelatin-based TiO_2-free capsule shell, CAP-002's opacity varied significantly in response to changes in relative humidity. Therefore, none of the white TiO_2-free capsule shells evaluated were considered suitable replacements for TiO_2 containing capsule shells.

The red/orange TiO_2-free capsules containing the colorant, Fe_2O_3, performed well in the battery of tests. The capsule shells are opaque and therefore capable of camouflaging any colour differences in the capsule contents. Fe_2O_3 is not an opacifier per se but imparts opacification through its intense red colour. The intensity of colour makes it difficult for the human eye to detect colour changes in the capsule shell e.g., following accelerated stability storage, even though colorimetry data showed that

changes had occurred. However, exact colour matching for the purposes of reformulating an existing product as TiO_2-free may be difficult as CAP-014, the TiO_2 reference and the TiO_2-free CAP-001 from the same supplier, product line and tradename had colour difference values of above 2.

This pink semi-translucent capsule shell was the only non-red/orange coloured capsule shell evaluated. It does not contain Fe_2O_3. Its pink colour bleached to white in the photostability studies and it was found to be very brittle. In addition, its semi-transparency would not hide the colour and appearance of its contents. For the above reasons it is not considered a replacement for TiO_2 containing pink capsule shells. TiO_2-free capsule shells of other colours were not evaluated as part of the Consortium's work due to lack of availability at the start of the project.

Based on the results, only TiO_2-free red/orange capsule containing Fe_2O_3 could be suitable replacements for TiO_2 containing capsules. If TiO_2 was banned in medicines, this would severely restrict the colour palette available for new medicines or reformulating commercially available ones to be TiO_2-free, with a down-stream impact on the ability to identify medicines and prevent counterfeiting. In addition to a reduced colour palette caused by the darker colours imparted by iron oxides to the capsule shell, finding an imprinting ink with sufficient contrast to the capsule shell colour will be difficult because the lighter ink colours, e.g. white ink, contains TiO_2. The daily intake of iron oxide (E172) is restricted by authorities such as the World Health Organization, the FDA and the Japanese authorities for safety reasons. These limits translate approximately to the equivalent of 3 x Size 0 capsules per day. Based on these limitations, Fe_2O_3 would not be a suitable replacement for TiO_2 as it would not have global regulatory acceptability and could not be used in medicines developed for global markets, especially those involving multiple dosing or chronic use

4. Safety Assessment of Alternatives

The safety team of the consortium evaluated the potential colourants/opacifiers included in the TiO_2 alternative film coating and capsule systems assessed. A detailed safety report is attached as **ANNEX 4: Safety assessment of alternatives and comparison with Titanium Dioxide as an opacifier and colorant for oral administration**

All selected alternative colorants, which also serve as opacifiers, are already in use in medicinal product formulations and food supplements. The safety team considered all alternatives as safe, with comprehensive safety data sets in some cases and health authority assessments available. As with TiO_2, these opacifiers and colourants have been safely used in products for decades. However, some of the colourants/opacifiers have data gaps with regard to toxicity data (including genotoxicity, chronic toxicity, carcinogenicity, reproductive and developmental toxicity) compared to TiO_2, but given their history of safe human use, these non-clinical data gaps are not considered as being relevant.

- For a few opacifiers the presence of nanoparticles is unclear. Guidance from EMA/EFSA is needed to understand how to take into account the nanoparticle portions of opacifiers and if further safety testing is required to characterize those fractions. A critical review on the nanoparticle discussion in particular on the classification and the presence is attached in Annex 1 and is considered by the consortium as a basis for potentially seeking scientific advice from the EMA NcWP. However, current investigations demonstrated that the alternatives Zinc Oxide (ZnO), Calcium sulphate ($CaSO_4$), Calcium carbonate ($CaCO_3$), Magnesium carbonate ($MgCO_3$) and Magnesium oxide (MgO) may contain nanoparticles, but all are soluble at pH 1.2, therefore not falling under the EFSA definition of nanomaterials. In addition, Isomalt, Maltodextrin are freely soluble and do not pose a nanoparticle concern as well as Microcrystalline Cellulose and Rice Starch.
- There is an extensive data set for TiO_2 available, assessed by different authorities and expert groups ensuring its safety. Most notably, the carcinogenicity study (NCI TR-097, 1979) on TiO_2 using comparable material to the material used in medicines provided a robust conservative No Observed Adverse Effect Level (NOAEL) of 2250 mg/kg/day. Additionally, the JECFA concluded that there is no identifiable hazard for INS171 (similar to E171) and consequently no requirement for an ADI. However, the TiO2 Alternatives consortium have proposed establishing an oral permitted daily exposure (PDE) of 2250 mg/day which will reassure patients that TiO_2 use is actively monitored and controlled at safe levels. Also, the oral PDE can be applied to compare the safety of TiO_2 with the safety of alternative colourants/opacifiers.

Safety evaluations by Agencies are ongoing for some of the opacifiers and excipients, e.g.:

- *Talc:* ECHA is evaluating talc as a potential Category 2 carcinogen. The safety experts of the consortium concluded that talc (pharmacopoeia grade) can be considered as safe by the oral route. Furthermore, an EFSA opinion was published in June 2018 on talc as a food additive.
- *Fe_2O_3*: Currently, an EFSA re-evaluation is ongoing.

Of note, the risk assessments performed to date by the safety team of the consortium (see table below) have not taken into account that daily exposure of the selected opacifiers in the formulations will, in most cases, be higher compared to TiO_2 levels to reach the same effect (e.g. iron oxide (Fe_2O_3) would generally be 2-3 times higher than TiO_2).

It has to be mentioned and reiterated, that e.g., Fe_2O_3 exposure is limited: WHO-ADI E172 0.5 mg/Kg BW, JPN Fe(OH)3 5.67 mg/day, FDA 5 mg Fe/day. This typically limits the daily dose to 3 standard size #0 capsules per day from a safety perspective.

Overall, the consortium considers there is no relevant difference between the safety profile of TiO_2 and the investigated alternatives based on available data.

Table 3: Current status of the safety assessments of TiO_2 alternatives

Chem Name CAS	Used in Food	Used in Drug Formulations	Other Assessments	Unintended Nanoparticles Present	Summary and potential safety Data gaps
Calcium Carbonate $CaCO_3$ 471-34-1	E170	FDA IID	JECFA 1965), SCF (1990) EFSA (2011, 2023)	Yes, but fast dissolution in the acidic environment of the stomach demonstrated (EFSA, 2011, 2023). Considered as no concern.	Comprehensive toxicology data package available, except chronic toxicity and carcinogenicity. However, for use in food, the EFSA Panel concluded that there is no need for a numerical acceptable daily intake (ADI) for calcium carbonate and that, in principle, there are no safety concerns with respect to the exposure to calcium carbonate per se at the currently reported uses and use levels in all age groups of the population, including infants below 16 weeks of age. No ADI specified
Calcium Sulfate $CaSO_4$ anhydrous: 7778-18-9 hemihydrate: 10034-76-1 dihydrate: 10101-41-4	E516	FDA IID, US and EU Pharmacopoeia	GRAS, SIDS (2003), JECFA, (1973)	Yes, but soluble at pH1.2	Basic toxicological data are available for calcium sulphate but long-term and carcinogenicity data in animals are lacking. In the available studies, the test item has often not been well characterised and i.e., information on particle size (i.e., nanoforms) is missing. Calcium sulphate has a long history of safe use, an ADI was not specified, the tolerable upper intake limit is 2500 mg/d based on calcium intake. High doses of sulphate result in transient gastrointestinal effects.
Isomalt 64519-82-0	E953	FDA IID, US and EU Pharmacopoeia	GRAS, BfR (2014), SCF (1984, 1989), JECFA (1985)	No (freely soluble in water)	Extensive toxicological data, including repeat-dose (up to chronic) toxicity studies, multigeneration and teratogenicity studies, genotoxicity and carcinogenicity studies are available for isomalt. Even though many of the published studies are from 1970's to 1980's and may not fully comply to current standards, and no formal fertility and peri- and postnatal development studies are available (the multigeneration study covered many of the relevant endpoints). Overall, no relevant data gaps regarding toxicity data are seen. In humans, isomalt is well tolerated at doses <20 g/day. Gastrointestinal effects, in particular flatulence and diarrhoea, were observed at ≥20 g/day.

Magnesium Carbonate $MgCO_3$ 546-*93*-0	E504	FDA IID	Magnesium: JECFA (1986), EFSA (2015) SCF (2006), BfR (2017)	Yes, but soluble at at pH 1.2 and 4.5	Taking into account all available data, both the existing toxicological studies with magnesium carbonate and other Mg salts and that Mg is an essential trace element, it can be concluded that the use of magnesium carbonate as an excipient in pharmaceutical products is safe. The in vitro genotoxicity battery is missing, although there is no indication of a genotoxic potential for $MgCO_3$.
Magnesium Oxide MgO 1309-48-4	E530	FDA IID, EU Pharmacopoeia	Magnesium: JECFA (1986), EFSA (2015), SCF (2006), BfR (2017) MgO (GRAS)	MgO readily dissociates after a reaction with gastric HCl under formation of magnesium chloride ($MgCl_2$).	Considering the high NOAEL and relatively mild toxic effects associated with Mg intake, the available upper limit of 250 mg/day derived by regulatory authorities seems sufficient and it can be concluded that MgO is of low toxicity and concern. Whilst several routes of synthesis for MgO NP have been described, data on the particle size distribution of MgO for the use as a pharmaceutical excipient is lacking. Safety data of those MgO NP is rare and current studies do not fulfil the requirements by EFSA Guidance on risk assessment of nanomaterials to be applied in the food and feed chain [EFSA, 2021]. However, based on the dissociation of MgO in gastric fluid MgO is not considered a NP
Maltodextrin 471-34-1	E1400	FDA IID	GRAS EFSA (2013)	No (freely soluble in water)	Maltodextrin is widely used across the food, cosmetic and pharmaceutical industry. Based on its metabolic profile, it has been considered non-hazardous by health authorities and is either an approved food additive or is considered safe but not classified as a food additive. No carcinogenicity studies or reproductive and developmental toxicity studies could be found for maltodextrin.
Microcrystalline Cellulose 9004-34-6	E460-E469 indirect food additive (US FDA 2018)	FDA IID	JECFA (1998, 2000), EFSA 2018	No	The available data set and toxicity information with cellulose and derivative forms is extensive. Physical properties or particle size (including the nanoparticulate fraction) and distribution are not always available and represent a data gap. In alignment with US authorities, EFSA determined no numerical ADI for microcrystalline cellulose and based on the available toxicological dataset, considered no safety concern at the reported use levels (estimated exposure 660-900 mg/kg bw day) with unmodified and modified celluloses (EFSA, 2018).
Rice Starch	Nutrient	FDA IID	GRAS	No	Starch is GRAS listed and considered to be safe. It is already in use as an excipient for pharmaceuticals in different regions and REACH and EFSA reports are coming to the same conclusion. No genotoxicity and chronic toxicity data are available.

Tetrasodium pyrophosphate 7722-88-5	E450	FDA IID	GRAS EFSA (2019), SCF (1997), JEFCA (2006)	TBD, No data on solubility in gastric fluid	The available toxicological information for each phosphate salt is limited and the overall phosphate assessment as a pharmaceutical excipient is based on read-across approaches and a group-specific toxicity assessment for several phosphate salts. While not assuming that there would be significant differences in toxicity, different salts could express different oral bioavailability or solubility in water. The EFSA derived a group ADI for phosphates and its salt of 40 mg/kg bw per day (expressed as P). Both phosphates, E339 and E450, are considered to be of low toxicity concern for human exposure as pharmaceutical excipient.
Trisodium phosphate 7601-54-9	E339	FDA IID	GRAS EFSA (2019), SCF (1997), JEFCA (2006)	TBD, No data on solubility in gastric fluid	
Zinc Oxide ZnO	FDA Substances added to food list	FDA IID UK, EU and US Pharmacopoeia	GRAS SCF 2003 EFSA 2016	Yes, fast but dissolution expected in the acidic environment of the stomach (EFSA, 2016), and soluble at pH 1.2 and pH 4.5	For zinc oxide, no specific safety information was found in the open domain. However, as a food additive, zinc oxide is generally recognised as a safe substance. For zinc, detailed toxicological information can be found in the public space. In general, no adequate experimental studies are available to evaluate the carcinogenic potential of zinc or zinc compounds. In addition, the safety of zinc (oxide) nanoparticles is less well understood.

Question 2

Please supply a summary of the evidence /results from the ongoing studies comparing alternative formulations (for different dosage forms as available) with those containing TiO_2.

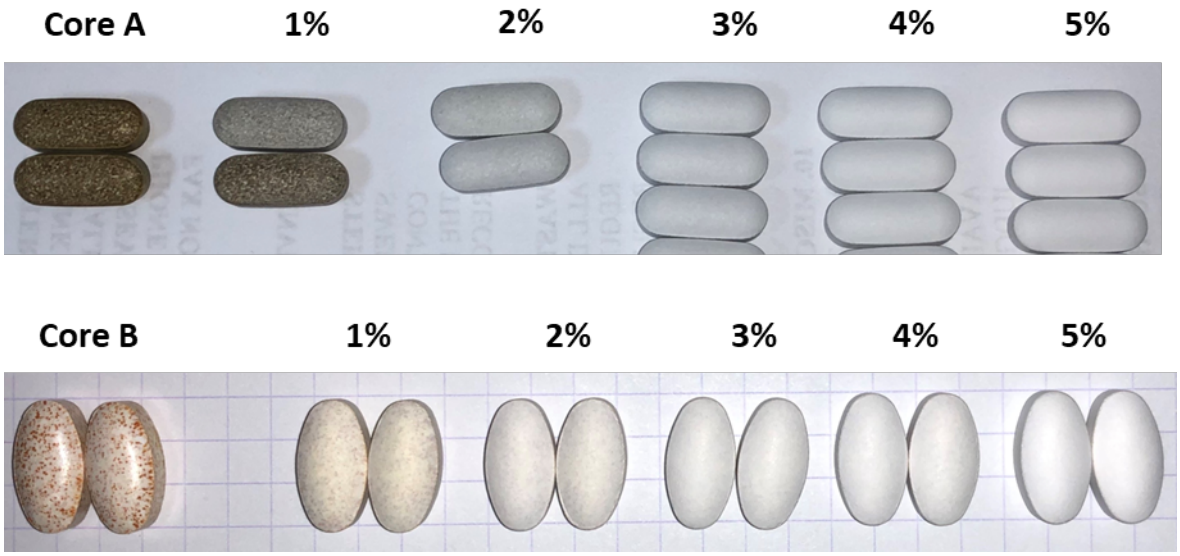
In the following sections examples of the performance of alternative materials to TiO_2 used in film coat systems and hard capsule shells is provided. As the TiO_2 Alternatives Consortium activities are still ongoing, some of the examples have been provided by individual pharmaceutical companies or material suppliers. Full detail is provided in **(1) ANNEX 2: Alternatives to Titanium Dioxide in Tablet Coatings** and **(2) ANNEX 3: Alternatives to Titanium Dioxide in Hard Shell Capsules**.

Film Coating Systems

1. Appearance: Opacity (Industry experience)

Two different coloured cores (Core A and Core B) were coated using a TiO_2 free film coat system to assess the ability for the system to mask the core appearance. The cores were coated to a weight gain of up to 5% w/w. Samples were taken throughout the coating process and were visually assessed for the coats ability to provide acceptable coverage. The results are presented in Figure 5.

Figure 5: Visual appearance of different coloured cores coated with a TiO_2-free film coating system

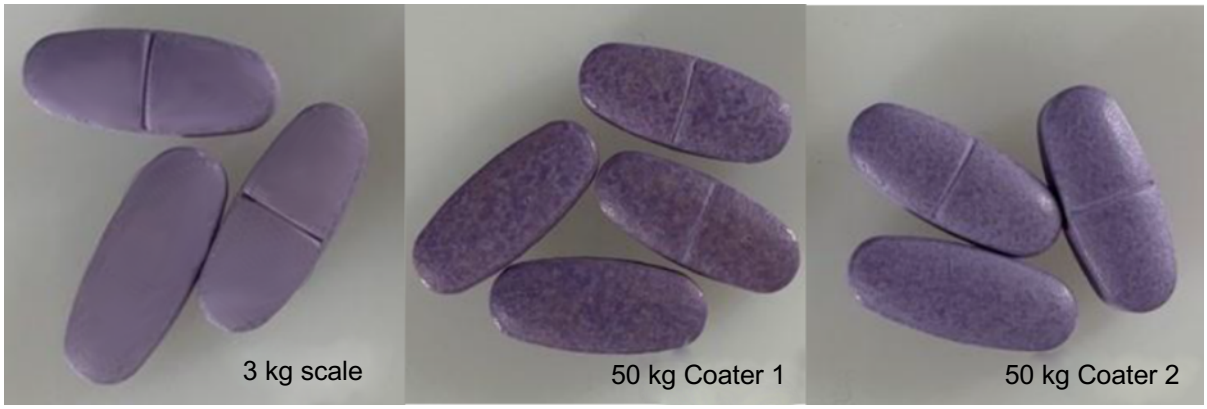


From this study it was observed that due to decreased opacity of the TiO_2-free system more coating needs to be applied to achieve an acceptable appearance. Also, any discolouration in the core and core defects were more challenging to cover.

Manufacturability: Scale-Up (Industry Experience)

A multivitamin tablet core was coated using a coloured (purple) TiO_2 free film coat system at small scale (3 kg) and at representative commercial scale (50 kg) using different types of coating equipment. The purpose of this study was to evaluate the impact of scale and the use of different coating equipment on the visual appearance of the coated tablets. The results are provided in Figure 6.

Figure 6: Evaluation of the visual appearance of a multivitamin tablet core coated with a purple TiO_2 free coating system at different scales and equipment type



In this study it was observed that at the 3 kg scale the visual appearance of the tablets was acceptable with no significant defects noted. However, at the 50 kg scale the visual appearance was poor with poor colour uniformity. Also, it was observed that there was a difference in the visual appearance between tablets coated in the two different types of equipment. Based on this study it was concluded that the coating scale can have an impact on the final coating appearance. Differences in the coater design (coating pan, spray gun positioning, air flow limitations, etc.) can impact the final film coating appearance.

Colour Matching Capability (Industry Experience)

A visual assessment of two TiO_2 free coating systems to match the colour of a TiO_2 based film coat system was performed. The results are presented in Table 4 below. Both the coating systems (TiO_2-free and the TiO_2 Based) were supplied from the same supplier.

Table 4: Visual assessment of TiO_2 free film coating systems to colour match to a TiO_2 containing film coat system

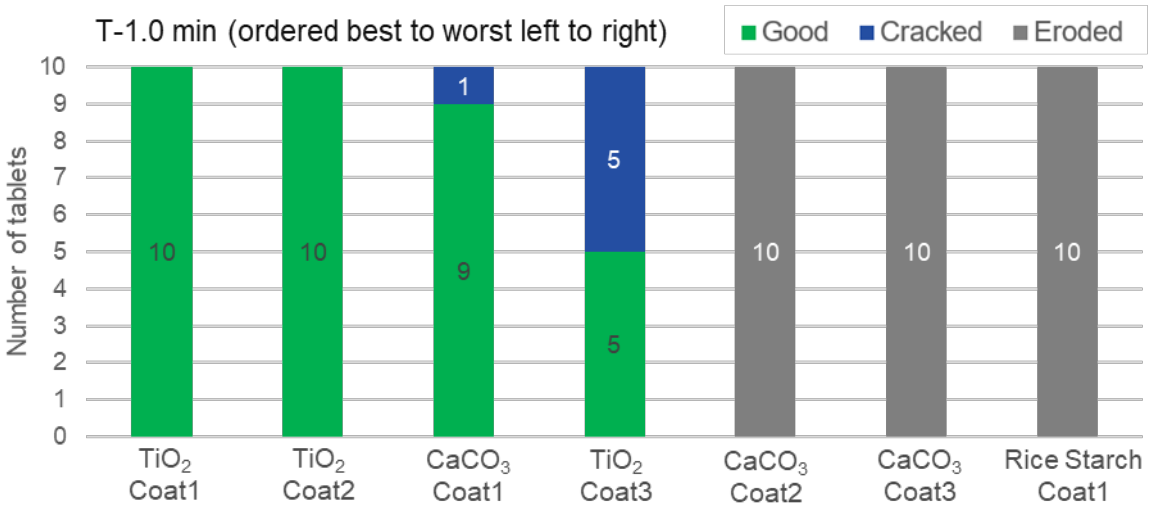
Type (HPMC)	Colourants	Colour Match (3-4 % w/w gain)	Photo
TiO2 (Control)	Iron oxide	Control: Purple	
CaCO3		No	
Rice Starch		No	

At equivalent film coat weight gains, it was not possible to match the visual appearance of the TiO_2 based film coat using the TiO_2 free alternatives. The film coating supplier confirmed that this was due to the removal of the TiO_2.

2. Mechanical Strength (industry experience of coat adhesion)

To-date, commercial scale experience of performance remains limited. As an example, film coats containing TiO_2, calcium carbonate ($CaCO_3$) and rich starch were assessed for their coat adhesion. Tablet cores were coated to a weight gain of approximately 3.5% w/w and then assessed for their friability using a Friabimat SA-400 (Born friabiliator). The results are provided in Figure 7.

Figure 7: Bar chart representation of coated tablet defects after 1.0 min Friabimat® testing



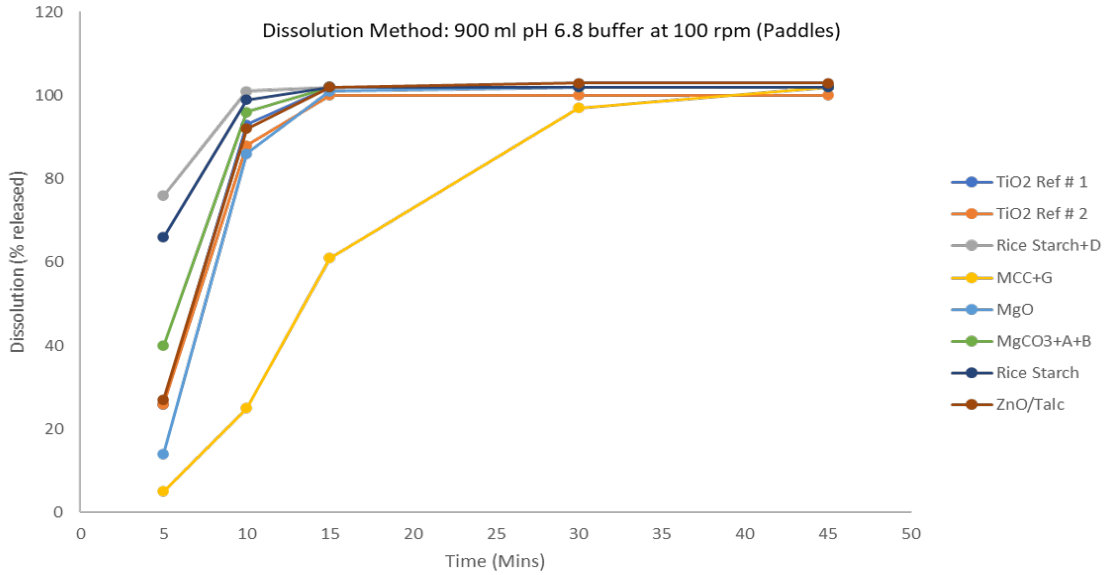
After 1 minute of using the friabiliator only the TiO_2 (coat 1 and coat 2) based film coats showed no erosion and cracking of the coat. One of the CaCO3 (Coat 1) film coating system showed minor erosion. The $CaCO_3$ coating systems (Coat 2 and Coat 3) and the rich starch showed significant erosion and cracking, with all the tablet samples failing. An example of the degree of failure is provided in Figure 8. However, it should be noted that one of the TiO_2 based film coat systems demonstrated a 50% failure rate for erosion and chipping (coat 3).

Figure 8: Example of erosion and film cracking of a CaO_3 film coated tablets

3. In-vitro Performance: (Consortium experience of impact on dissolution)

To assess the potential impact of the TiO_2 alternative film coating systems on dissolution performance, Rosuvastatin 10 mg cores were coated with a range of alternative systems and their dissolution performance was evaluated and compared to TiO_2 based film coat reference systems. The results are presented in Figure 9.

Figure 9: Dissolution performance of Rosuvastatin tablet cores 10 mg coated with different film coating systems



Compared to the TiO_2 references, most of the alternative systems demonstrated similar performance at 15 mins. The MCC based system demonstrated slower release compared to the other systems but was comparable by 30 minutes.

4. Chemical Stability: (Consortium experience)

Samples of Rosuvastatin tablet cores 10 mg were coated with different TiO_2 free and TiO_2 based film coating systems. The coated tablets were then placed on accelerated stability conditions (50°C / 30 % RH and 70°C / 75 % RH) in HDPE bottles. Samples were taken after 7, 14 and 21 days and tested for assay content. The results are presented in Figures 10 and 11.

Figure 10: Assay of Rosuvastatin 10 mg tablets stored at 50°C/30% RH after 7, 14, & 21 days

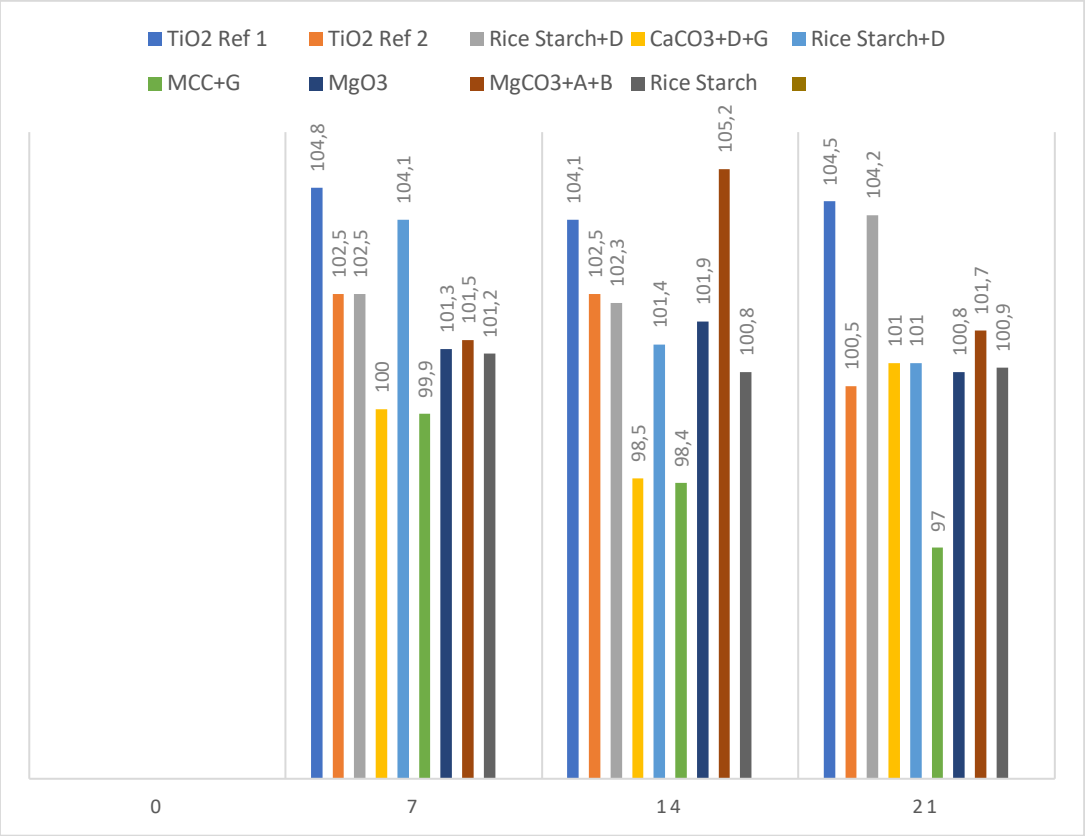
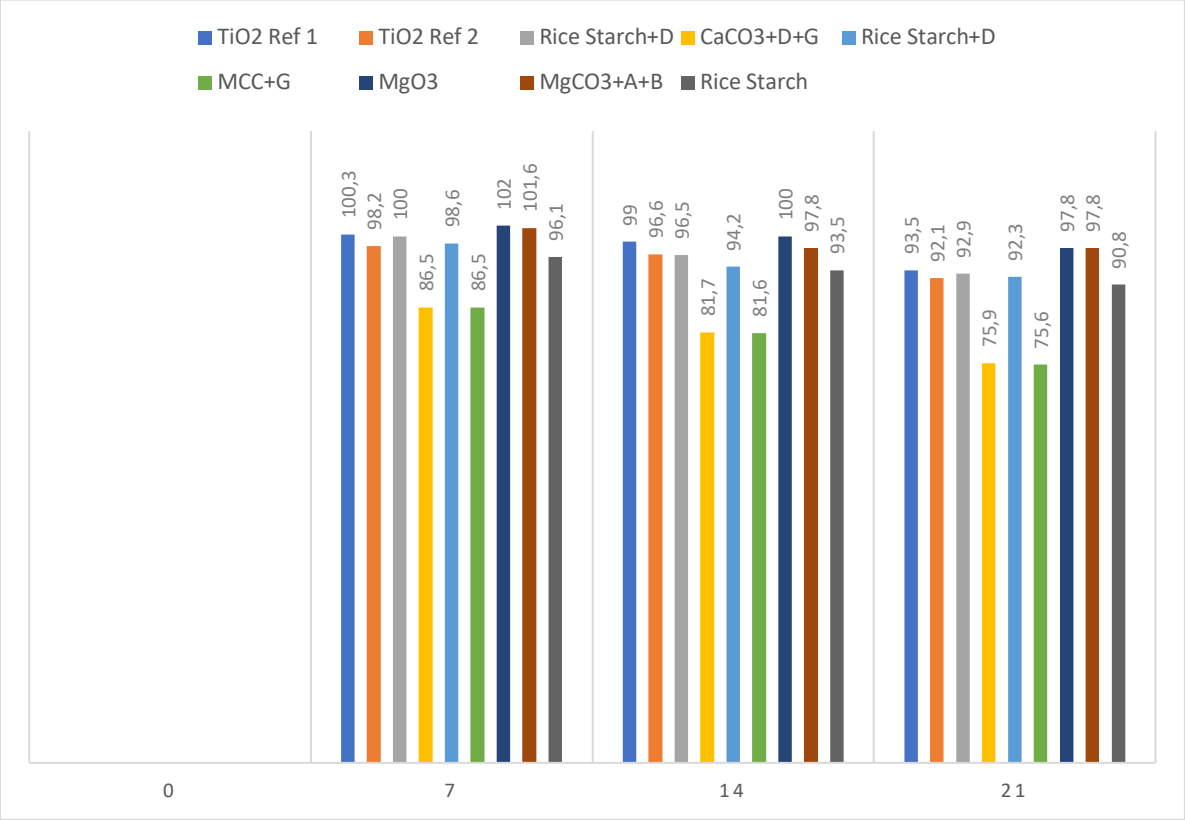


Figure 11: Assay of Rosuvastatin 10 mg tablets stored at 70°C/75% RH after 7, 14 & 21 days



Except for coating systems that contained material “G”, no trends in assay values were observed under all conditions and testing periods. Systems that contained material “G” demonstrate a comparable decrease at 70°C /75 % RH over the testing period compared to the TiO_2 references.

5. Photostability (Chemical) (Industry Experience)

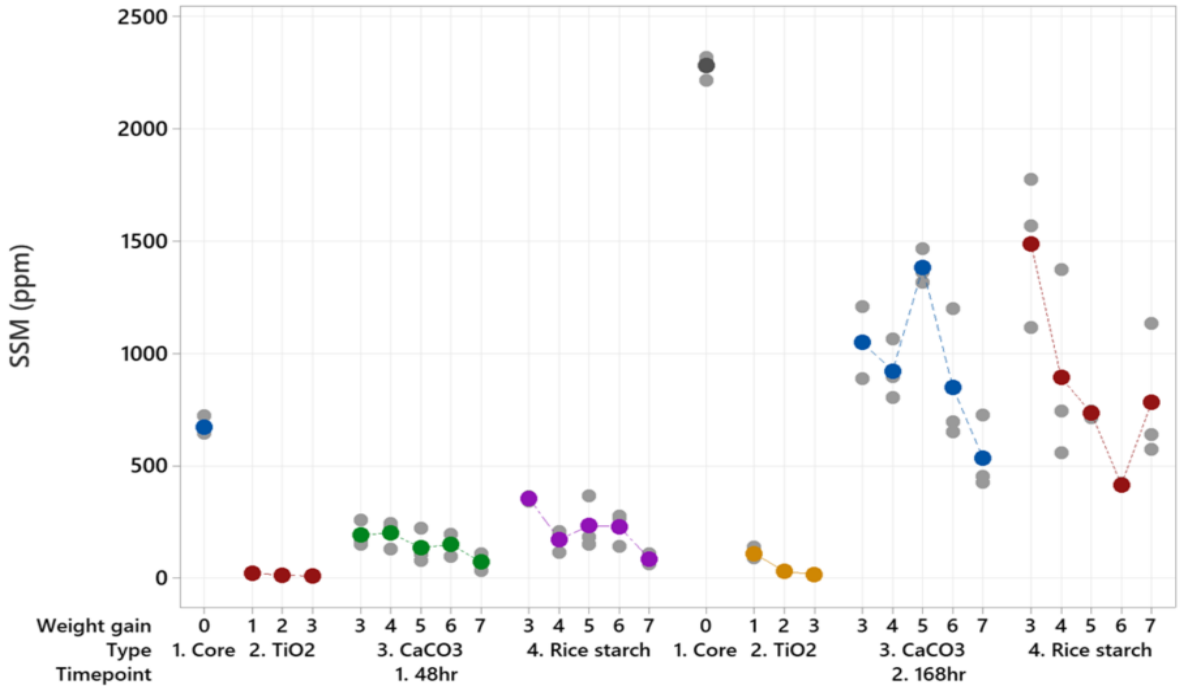
Tablets containing sodium stearyl fumarate were coated with TiO_2, $CaCO_3$ and rice starch-based coating systems. The weight gains applied are summarised in Table 5.

Table 5: Amount of TIO_2 based $CaCO_3$ and rice starch film coat systems applied to tablets containing sodium stearyl fumarate

Film Coat	Coverage per tab (ug/mm^2)						
	1% w/w	2% w/w	3% w/w	4% w/w	5% w/w	6% w/w	7% w/w
TiO_2	5.61	11.21	16.82	n/a	n/a	n/a	n/a
$CaCO_3$	n/a	n/a	18.84	25.12	31.40	37.68	43.96
Rice Starch	n/a		18.84	25.12	31.40	37.68	43.96

Coated tablet Samples of the different weight gains from the TiO_2, $CaCO_3$ and rice starch-based film coat systems were placed on photostability (using ICH option 2) for 48 and 168 hours. Samples were tested for photodegradant sodium stearyl malate (SSM). The results are presented in Figure 12.

Figure 12: Formation of SSM after exposure to ICH photostability (Option 2) conditions of tablets containing Sodium Stearyl Fumarate coated with different film coat systems.



Compared to the core, the amount of SSM formed with the TiO_2 based system was significantly less after 48 and 168 hours of exposure compared to core. After 48 hours both the $CaCO_3$ and rice starch systems demonstrated similar SSM formation which was less than the core and slightly higher than the TiO_2 system. After 168 hours both $CaCO_3$ and rice starch system demonstrated significant SSM formation compared to the TiO_2 system but less than the uncoated core. A relationship between coat weight gain and SSM formation can be established for all systems evaluated.

Hard Capsule Shells

1. Mechanical Strength of Capsules (Consortium Experience)

Empty capsules (gelatin & HPMC) were assessed for their brittleness under a wide range of environmental conditions. Brittleness can be used as a surrogate how the shells may behave during encapsulation, long term stability and patient use. The results of the study are presented in Figure 13 and Figure 14.

Figure 13: Brittleness assessment of empty gelatin capsule shells stored at different relative humidities for 72 hours

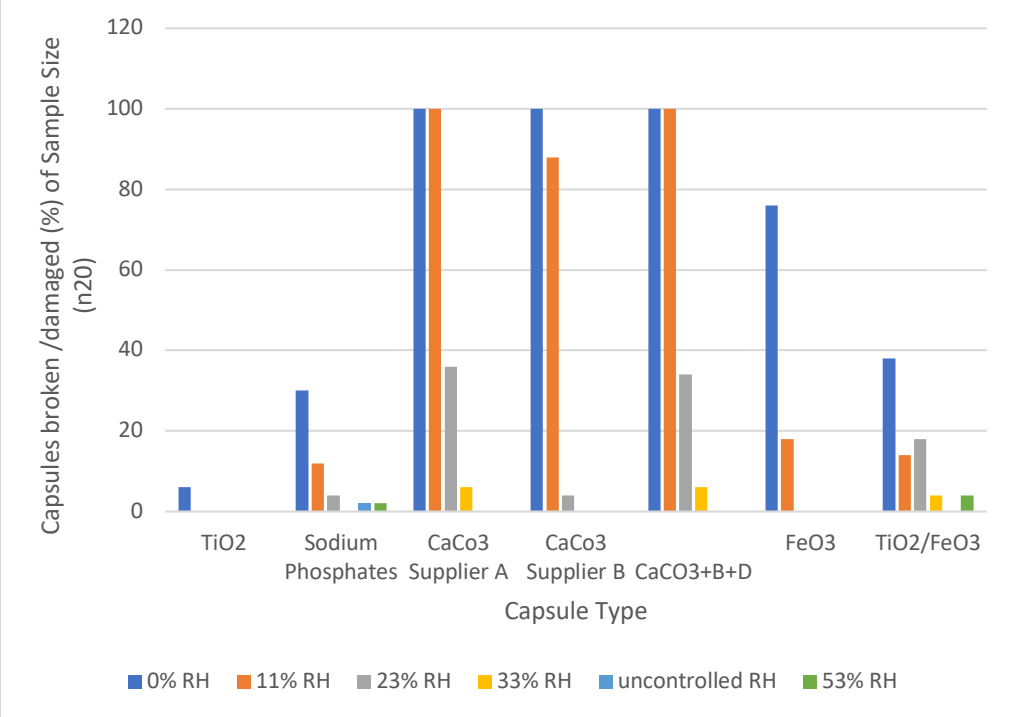
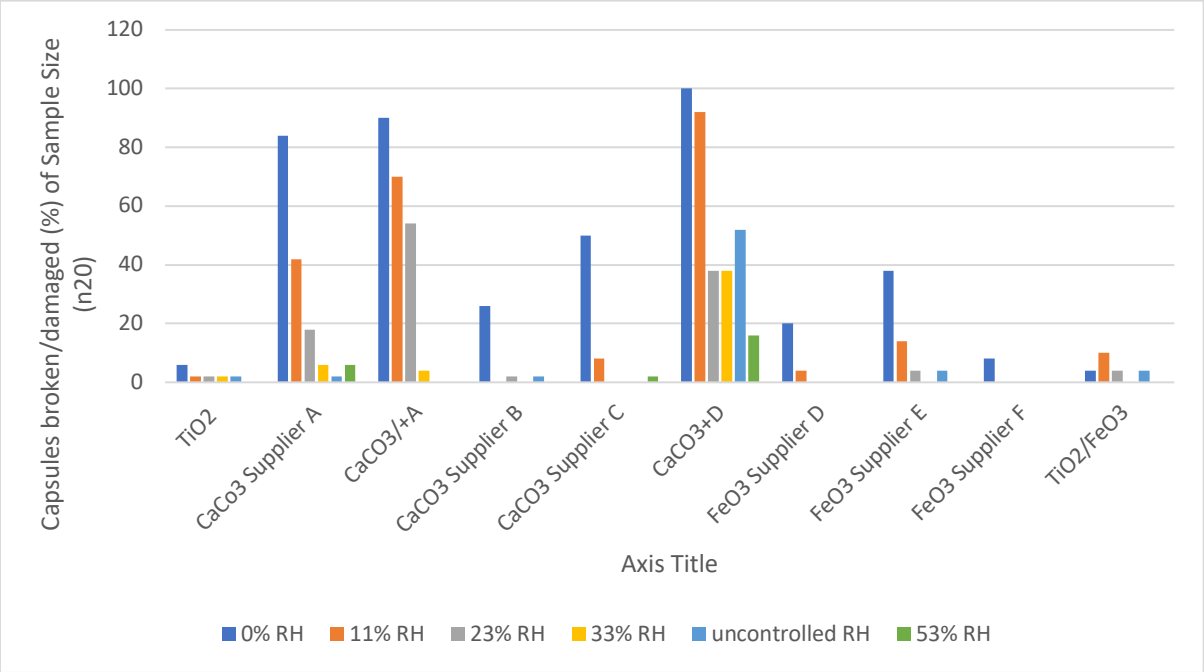


Figure 14: Brittleness assessment of empty HPMC capsule shells stored at different relative humidities for 72 hours

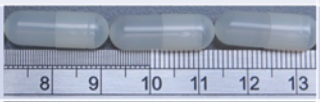
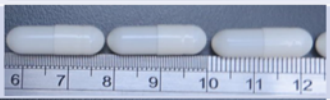
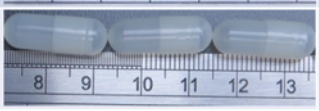


At lower humidities, $CaCO_3$ containing capsules were more brittle regardless of capsule shell evaluated (gelatin or HPMC). At uncontrolled and higher levels of humidity, >33% all the capsules demonstrated comparable brittleness except the $CaCO_3$+D HPMC. HPMC capsules showed less propensity for brittleness at the low humidities as expected when compared to gelatin comparator.

2. Appearance: Capsule (Industry Experience)

Empty $CaCO_3$ and Sodium Phosphates capsule shells placed under different storage conditions (open dish) for 7 days and compared for visual appearance with a TiO_2 reference capsule. The results are provided in Figure 15.

Figure 15: Visual Appearance of TiO_2, $CaCO_3$ and Sodium Phosphate Based Capsule Shells Under Different Storage Conditions

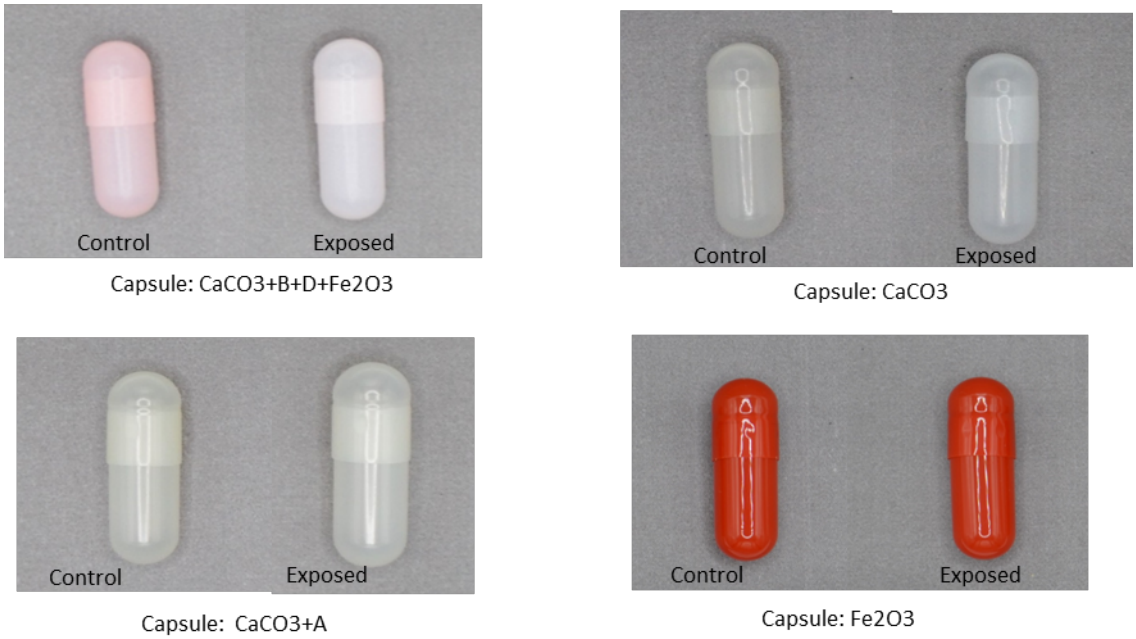
Conditions	TiO2 Capsule (Ref)	CaCO3 Capsule	Sodium Phosphates
40°C 10% RH			
25°C 11% RH			
Ambient			
30°C 75%RH			

Under all conditions the $CaCO_3$ capsule remained more translucent than the TiO_2 reference. At Low %RH the Sodium Phosphates capsule demonstrated comparable appearance to the TiO_2 reference. However, at high humidity (30°C / 75% RH) the capsule became translucent. The change in opacity may have an impact on patient acceptability.

3. Photostability: Capsule Shell Appearance (Consortium Experience)

Empty TiO_2 free capsule shells using different opacifiers/components were assessed for their visual appearance stability under ICH photostability conditions (2.4 million Lux) and compared to a dark control sample. The results are presented in Figure 16.

Figure 16: Visual appearance of empty capsule shells using alternative TiO_2 opacifier/components after exposure to 2.4 million lux with dark control for comparison

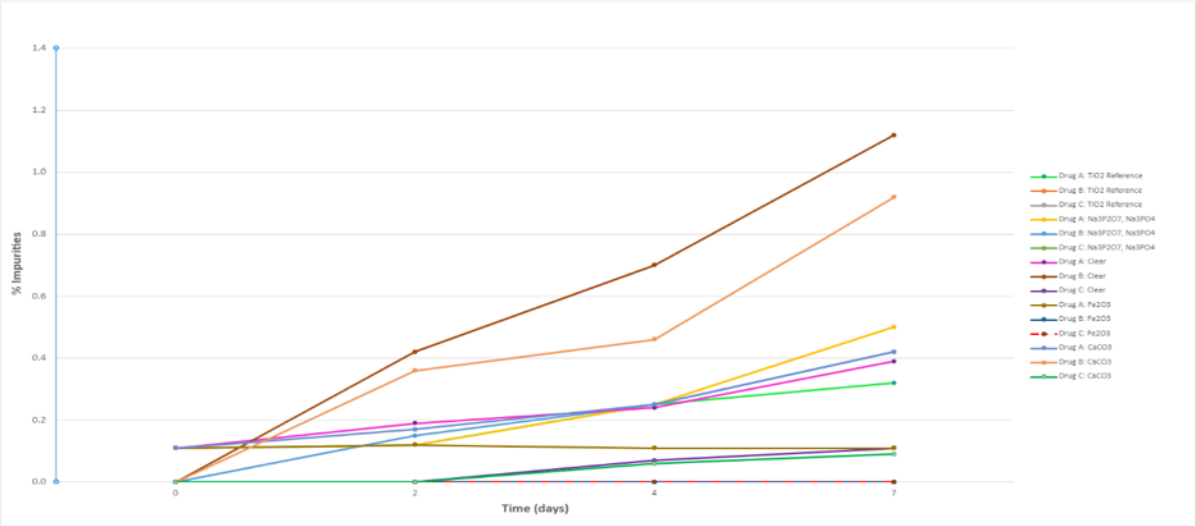


The Fe_2O_3 based capsule demonstrated no significant change under the stress conditions compared to the dark sample. Predominately $CaCO_3$ based capsules appear to become whiter/lighter under the stress conditions compared to the dark sample. The multicomponent opacifier system demonstrated significant loss of colour under the stress conditions compared to the dark sample.

4. Photostability (Chemical) of Capsules (Industry Experience)

Three model drugs (A, B, C) with different photo sensitivities were filled into gelatin capsules using Fe_2O_3, $CaCO_3$ and Sodium Phosphates as the primary opacifier. The capsules were then exposed to ICH Photostablity conditions (Option 2) for 7 days. Samples of the different capsule shell types were then assessed for the formation of each compounds impurities and compared to TiO_2 and clear gelatin capsule shells filled with the same model drugs and stored under the same conditions. The results are summarised in Figure 17.

Figure 17: Formation of impurities for model compounds A, B and C filled into TiO_2, Fe_2O_3, $CaCO_3$, Sodium Phosphates based gelatin capsule shells and clear gelatin capsules shells after exposure to ICH photostability (Option 2) conditions for 7 days



Under the conditions used, different amounts of photodegradation were observed for the different model compounds in the different capsule shell types. The Fe_2O_3 based capsule shell provided equivalent or improved photo protection for the 3 model drugs compared to the TiO_2 reference capsule shell. For model drug A; the Sodium Phosphates and $CaCO_3$ capsule shells demonstrated similar impurity profiles after 4 and 7 days but higher compared to the TiO_2 reference capsule shell. For model drug B; $CaCO_3$ capsule shell demonstrated significant degradation observed compared to TiO_2 reference capsule shell but less than the clear capsule shell reference. For model drug C: Sodium Phosphate and $CaCO_3$ capsule shells demonstrated comparable degradation but were higher than TiO_2 and Fe_2O_3 capsules shells. Based on this study it was possible to rank order the different capsule shell performance to inhibit the formation of the model compounds' impurities:

TiO_2 = Fe_2O_3 capsule shells> Sodium Phosphates capsule shell > $CaCO_3$ = Clear capsule shells

Question 3

In 2021, you provided QWP with information on the methodology and timeline estimates on investigating potential alternatives to replace/remove TiO_2 without negatively impacting the quality, safety and efficacy in medicinal products. Please provide the updates to this information versus the last analysis.

Timeline estimates

The TiO_2 Alternatives Consortium timelines for the planned assessments of film coating systems and hard capsule shells using alternative materials as potential replacement for TiO_2 are provided in Figures 18 and Figure 19. This has been completed to plan and the outcomes are summarised in **(1) ANNEX 2: Alternatives to Titanium Dioxide in Tablet Coatings** and **(2) ANNEX 3: Alternatives to Titanium Dioxide in Hard Shell Capsules**.

Figure 18: Timeline of TiO_2 Alternatives Consortium activities to assess film coating systems with different components as opacifiers

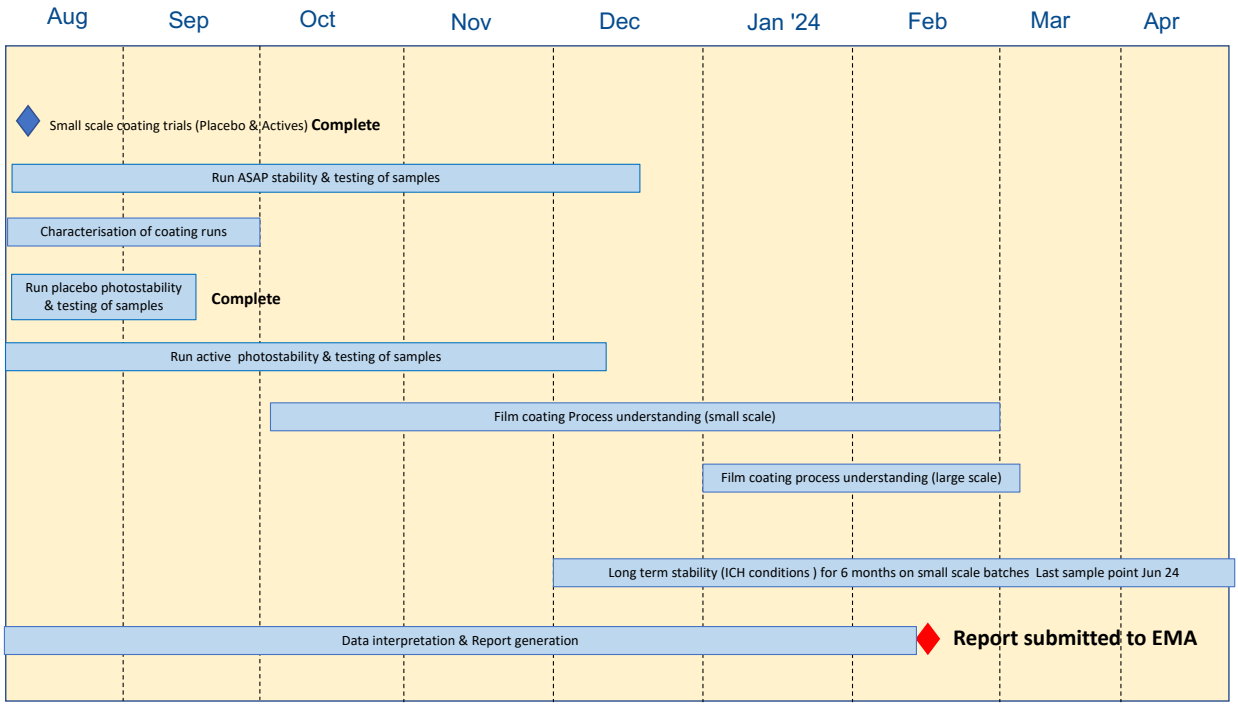
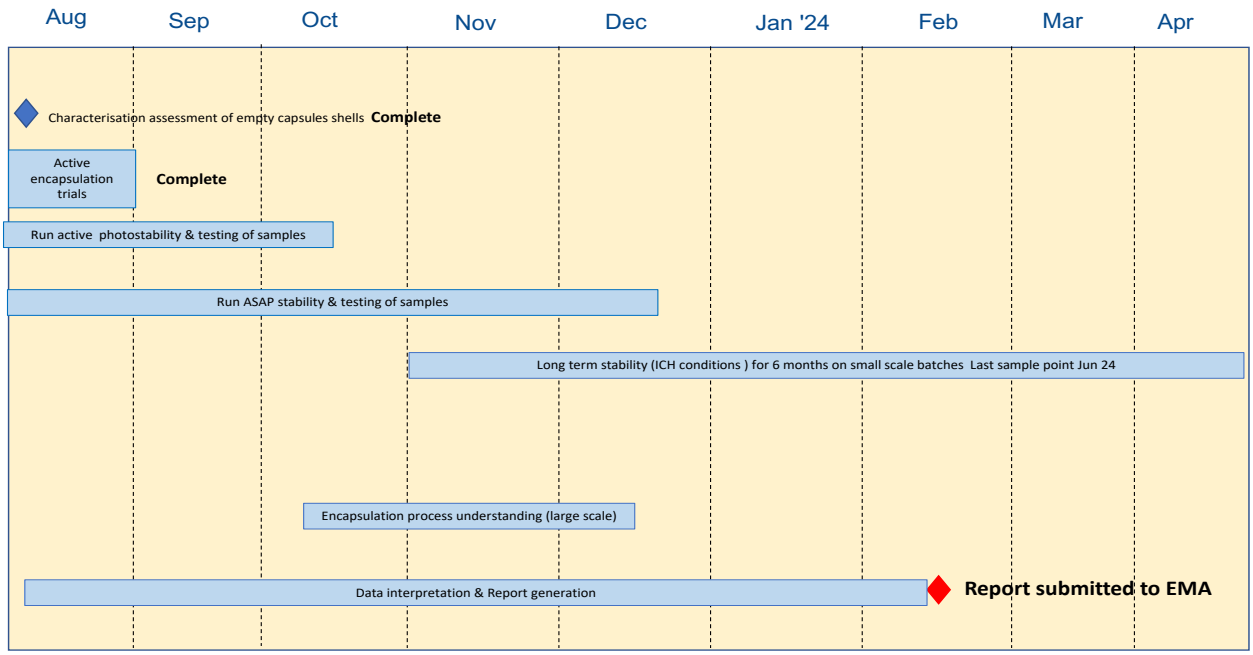


Figure 19: Timeline of TiO_2 Alternatives Consortium activities to assess hard capsule shells with different components as opacifiers



Some of the real-time and modelled stability data will be available but, due to the nature of long-term real time ICH stability studies, the full 6 m data will only be available from April 2024.

B. Industry impact assessment of the situation on the pharmaceutical sector and timelines

Question 4

In case an alternative to replace/remove TiO_2 is identified, please indicate approximate timelines to prepare and file for such a change (for subset of products/which ones/are there different issues for different products or dosage forms/types of products?).

1. Introduction

Since late 2021, industry has been evaluating the potential impact of a TiO_2 ban and the challenges of switching to coatings and capsules containing potential alternative excipients. Specifically, industry have been looking at the technical feasibility for different types of medicines, the potential impact on patients and healthcare providers, the global regulatory impact, and supply chain challenges (such as capacity, timelines, and cost). The following section describe the results of an in-depth evaluation with a focus on the processes and timelines needed to remove or replace TiO_2 in European medicines. This description builds upon the preliminary estimates provided to the EMA in 2021.[2]

The summary herein of the industry evaluations describes the risk factors medicines suppliers must consider in reformulating different products and dosage forms and the various possible reformulation options. The assessment of timelines is then presented in two parts:

- The timelines for registering a single product considering the added complexity of TiO_2-alternative formulations (for both new products and marketed products).
- The estimated timelines for the reformulation of the thousands of products currently on the market in Europe considering business, regulatory and supply chain factors.

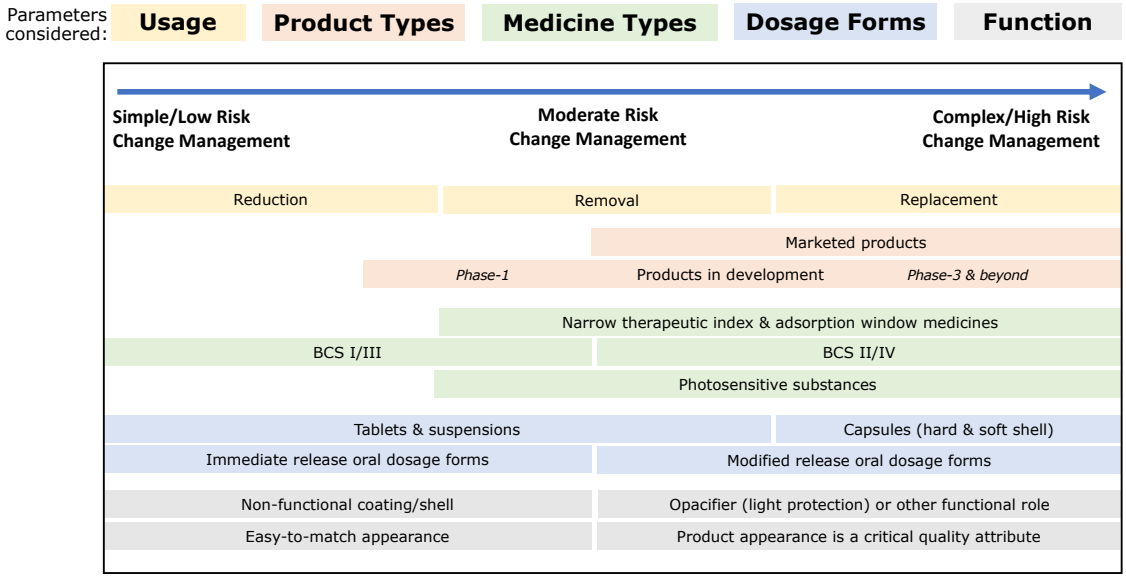
2. Risk Factors for Reduction / Removal / Replacement

Initially, it is important to note which factors were considered in the evaluation of the timelines for the reformulation of European medicines to eliminate the use of TiO_2. These are summarized in Figure 20 Depending on the product type, dosage form, usage, and function, the complexity and risks associated with the reformulation effort can vary considerably.

On the left side of Figure 20 those factors that create a lower risk, relatively simple, reformulation scenario are shown. Moving to the right of Figure 20, the factors that add significant complexity and risk to reformulation are illustrated.

It is estimated that more than half of the medicines currently marketed in Europe would map to the higher risk, right-hand side of Figure 20. For these higher complexity products there are currently no generally proven alternatives to the use of TiO_2 as an excipient and successful reformulation of these products is not guaranteed. If reformulation were not technically feasible or economically viable, potentially such medicines would have to be withdrawn from the European market, even though they may continue to be marketed elsewhere in the world.

Figure 20: Summary of the factors considered when estimating the timelines for the removal or replacement of TiO_2 in European medicines.



- It is estimated that complex products comprise a significant percentage (>50%) of the medicines currently marketed in Europe.
- There are currently no proven TiO_2 alternatives for these complex products. Successful reformulation is not guaranteed.

More details on each of the risk factors illustrated in Figure 20 are provided in Table 6. It is important to note that for many of these risk factors there are no proven technical solutions (for example, for most capsule products) or the reformulation approach has to be customized for each individual product and then tested to ensure no impact on critical products attributes (such as drug release rate, product shelf-life, patient acceptability, *etc*).

Table 6: Detailed description of the risk factors considered by industry in their timeline analysis

Risk factor	Description of issue
Narrow therapeutic index & limited adsorption window drugs; BCS II/IV compounds	• Bio-performance of alternative coatings and capsules is still quite poorly understood currently for these types of medicines. • Minimal clinical experience with TiO_2 -free coatings and capsules.
Photosensitive products	• Currently available TiO_2 -free coatings and capsule shells do not provide a sufficiently high level of protection from light. • Protective primary packaging not always a suitable alternative (e.g., for in-use stability).
Capsules (hard & soft shell)	• Globally acceptable alternative capsule shell options are not available (e.g., FeO2 levels). • Available alternatives demonstrate lack of robustness (e.g., brittleness).
Modified release products	• Impact of alternatives on medicine release performance is not predictable and thus each product needs to be studied on a case-by-case basis.
Coloured tablet cores or capsule fills	• Masking or colour matching is very challenging, and subsequent change of product appearance can lead to non-compliance.

Globally registered products	• Formulation and process changes are slow to be approved in some regions or are contingent on prior EMA approval. • Criteria for demonstration of equivalent performance may vary between regulatory agencies.
Long-established products	• For some long-established products, developed via traditional approaches, a lack of product or process knowledge may make changes to formulation or manufacturing process highly challenging.
Patient Access	• Costs of changing formulation composition or manufacturing process may exceed revenues for many generic products.

3. Reformulation Options Considered

The scenarios considered for reformulation were **replacement**, **removal** or **reduction** of the TiO_2 content in medicines. The EMA and European Commission have emphasized removal and replacement as their preferred approaches, but for completeness (and in the light of potential future scientific advances to establish a safe "permitted daily exposure" (PDE) for TiO_2) the possibility of reducing the amount of TiO_2 in medicines has also been considered as a potential approach.

- Replacement

After analyzing the current offering of medicines in Europe it is clear that there are very few cases where a simple 1:1 substitution of TiO_2 with another material would be possible. The work of the TiO_2 Alternatives Consortium has clearly shown that in almost every case a more extensive change in the formulation composition and concomitant manufacturing process changes would be required, even for the simplest formulations. For example, changes will often be needed to the film forming polymer, plasticizers, extenders, and the final film thickness in addition to replacing the opacifier or pigment. Similarly processing conditions (such as coating solution spray rate) will also need to be modified in many cases.

For each product the impact of these composition and process changes on the performance and stability of the medicines needs to be studied in detail. In addition, any downstream impact on analytical methods (such as specificity) and packaging configurations (such as tablet size and thickness) would need to be evaluated.

It is important to note that the replacement of TiO_2 with alternative materials will in most cases increase the thickness of the tablet coating or capsule shell. This is expected to lead to longer processing times and increased manufacturing capacity demands beyond today's norms.

Finally, in cases where clinical bioequivalence study is required to demonstrate comparable *in-vivo* performance, reformulation timelines would be extended significantly.

- Removal

Non-adherence to medications is a common problem and the WHO estimate that fifty percent of patients with chronic conditions deviate from their initial treatments. TiO_2 is crucial for the optimum appearance of tablets and capsules, and plays a significant role in patient compliance by enabling the differentiation of different dosage forms and different product strengths.

The Consortium experimental studies have shown that removal of TiO_2 from most film coated tablets and encapsulated products results in a significant impact on product appearance. The product color, smoothness and elegance can all change markedly, and thus patient acceptability and adherence can be negatively affected.

Thus, this reformulation approach (that is, removal of TiO_2) is only likely to be feasible for a very small percentage of existing products (estimated to be <<5%).

- Reduction

Based on the initial guidance of the EMA and the European Commission, *reduction* in TiO_2 levels in European medicines is not generally being considered for any product. However, this is a potentially valuable approach that could minimize patient exposure to TiO_2 whilst maintaining product performance and minimizing product shortages. A similar approach to that used for preservatives might be feasible, with manufacturers being required to demonstrate the need for a certain level of TiO_2 to provide the necessary functionality (light protection, *etc*). To enable this approach, a permitted daily exposure (PDE) would need to be established based on toxicological data.

4. Timeline for elimination of TiO_2 from European medicines

In 2021 the industry provided a preliminary estimate of the costs and timelines for eliminating TiO_2 from European medicines. This was communicated in the table shown below (Table 7) and the estimated time varied from 31 to 63 months per product based on the complexity of the reformulation project.

Table 7: Preliminary estimate of costs and timelines for eliminating TiO_2 from European medicines

Type of Product	Type of Regulatory Variation	Timing for R&D per formulation (months)	Timing to produce validation/stability batches per formulation (months)	Stability Requirements per formulation (months)	Batch analysis and regulatory documentation preparation per formulation (months)	Bioequivalence study (months)	High level project costs per formulation (excluding API) (€)	Fees/MA (€) per marketing authorisation	Regulatory Assessment Timetable (realistic) per marketing authorisation	worst-case total per marketing authorisation (months)
SIMPLE Hard Capsule / Coated Tablet – coating non-functional i.e. differentiation strategy	IAIN	9 to 12	3 to 6	3 to 6	6	0	500.0000	pan EU RMS with 1 strength product: 16,000 + 9,000 per additional strength	30 days acceptance/rejection	31
COMPLEX Coated Tablet – coating functional i.e. gastro resistance	II	12 to 18	6 to 9	6 to 12	9	9	1.500.000	pan EU RMS with 1 strength product: 118,000 + 30,000 per additional strength	3 - 6 months	63

Where companies decide that the only viable supply option is to replace titanium dioxide globally costs and timelines will be significantly increased (eg 3-4 years)

These preliminary estimates have been refined by industry following a more in-depth analysis and the updated estimates will be presented in the next few paragraphs. These updated timeline estimates have been confirmed by recent experiences with reformulation for the purposes of nitrosamine reduction in products developed for the European market.

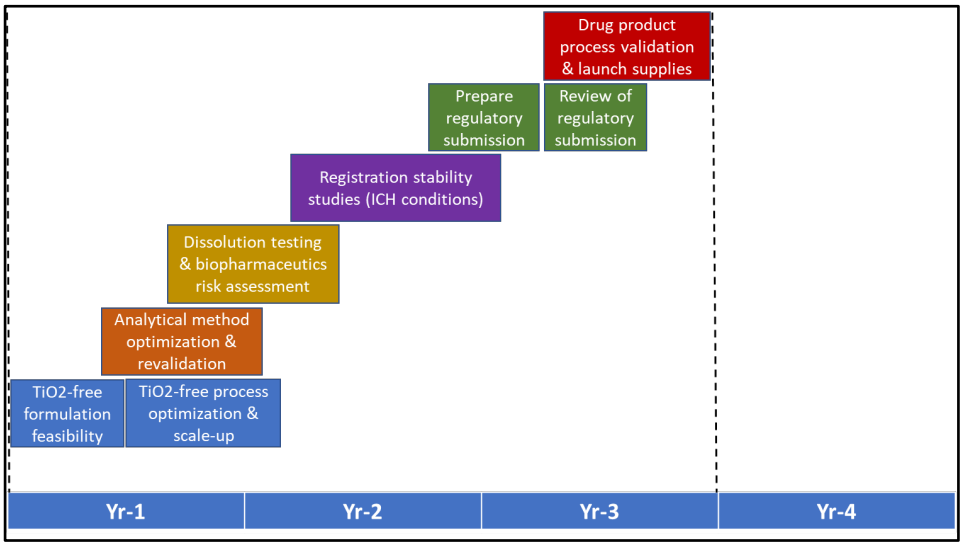
For ease of understanding, the timelines for reformulating individual products will be presented first, and after that the timelines for reformulation an entire product portfolio (one company's products) will be presented.

Low-risk / Simple case

For a low-risk (or relatively simple) reformulation project the estimated EU submission time is about three years per product (Figure 21). This scenario would be for a typical immediate release tablet

where reformulation is possible with standard excipients and the formulation and manufacturing changes are minor. These changes would need to have a minimal impact on product appearance, stability and performance, and no bioequivalence study would be required to demonstrated similar in-vivo functioning (hence, probably a BCS Class 1 or 3 product).

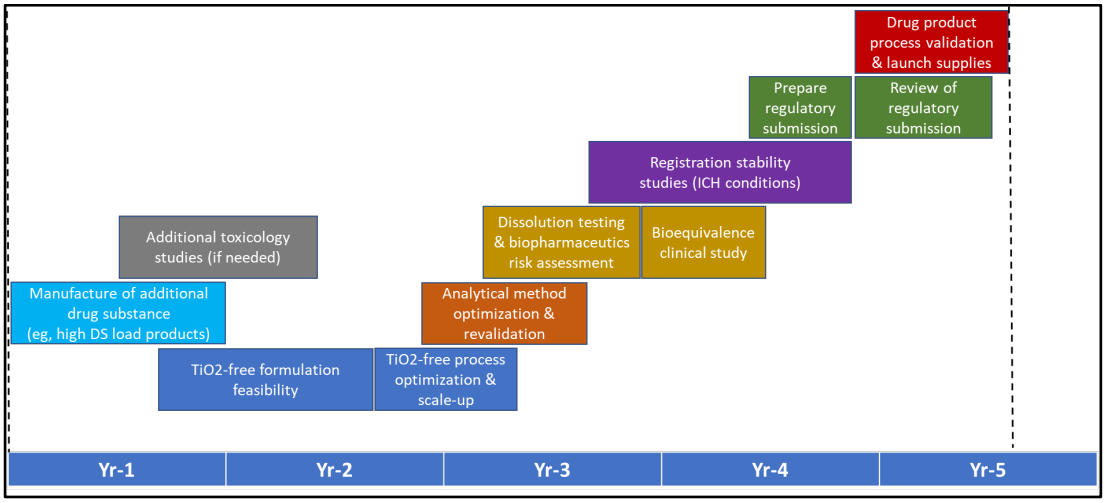
Figure 21: Estimated timelines for the reformulation of a single low-risk/simple product



High-risk / Complex case

In the case of a high-risk or more complex formulation scenario, the updated timeline for an individual product to be reformulated is about five years (Figure 22). This would be the case when supplies of the active drug substance are limited, or additional toxicology data needs to be collected on the alterative material(s) in the formulation. The added complexity could also be driven by the need to provide extensive light protection, or for a modified release dosage form where the film coating controls the drug release rate. If significant formulation or process changes were required, or if they had a marked impact on the product appearance, stability, or performance, then these could all increase the time needed to develop a TiO_2 -free medicine. The need for bioequivalence studies (perhaps in patients) could also extend the timelines for reformulating a complex product.

Figure 22: Estimated timelines for the reformulation of a single high-risk/complex product



5. Timelines for reformulating multiple products

Over 100,000 authorized medicinal products in Europe currently contain titanium dioxide. Reformulating all of these products would be the biggest reformulation effort ever undertaken by the pharmaceutical industry and there is a high probability that the supply of some medicines would be disrupted.

If business and supply chain factors are taken into account, it is possible to roughly estimate the time required for a typical medicines manufacturer to reformulate their entire product portfolio. However, there are many unknown variables or external influences that could have an impact on the timelines for remediation, therefore a detailed schedule for eliminating TiO_2 from European medicines cannot be provided at this time. These unknowable factors include the following:

- Cost and availability of commercial quantities of TiO_2 -free film coatings and capsule shells
- Long term stability and process robustness for TiO_2 -free medicines
- Patient responses to changes in the appearance of their medicines
- Speed of regulatory approvals in Europe and other markets
- Global economic factors (such as pandemics, recessions, regional conflicts, etc)
- Competing regulatory priorities (such as nitrosamine remediation and EG/DEG testing)
- Availability of contract manufacturing capacity for reformulation activities
- Ability to recoup reformulation costs by raising prices
- What competitor companies are doing
- Patient / consumer sentiment regarding continued use of TiO_2 (in Europe and other regions)

For most medicines manufacturers, remediation of multiple products concurrently would need to be staged over multiple years due to R&D and manufacturing capacity limitations. The consortium studies have demonstrated that thicker film coatings will be needed and this will equate to longer processing times and reduced manufacturing throughput for each company. There is also a finite and limited capacity for stability sample storage, analytical testing, and bioequivalence testing within the industry as a whole. The reformulation efforts for existing products would have to compete for these facilities with new products that are being developed to meet unmet medical needs. Even if new facilities for manufacturing and testing are commissioned immediately it would take several years for these GLP/GMP facilities to come online.

Other factors that need to be considered include the need to continue to supply existing products to patients (in Europe and the rest of the world) whilst the reformulation efforts are underway. There may also be a finite capacity at EMA/national competent authorities for the review of updated regulatory dossiers. It will be very important to minimize the impact on patients (due to product appearance changes, taste changes, package changes, *etc*) by education and outreach via pharmacists and doctors. In some regions, pandemic supply chain issues continue.

Finally, there may be unintended or unexpected impacts on global product registrations that cannot be easily 42foreseen. Many companies develop globally standardized products to simplify their supply chains and regulatory obligations, and any requirement to provide different products for the European market will add technical, commercial and regulatory complexity which could have unintended negative impacts on the supply of medicines for Europe.

In conclusion, it is conservatively estimated that for it would take between 7 and 12 years for a typical company to reformulate their entire portfolio of new and existing medicines. For some large multi-national companies, it would take even longer and lack of a long enough transition period would likely increase product withdrawals and/or lead to shortages of some medicines.

6. Summary of potential timelines

Based on studies completed with TiO_2-alternatives to date the feasibility of replacing TiO_2 in every European medicine still cannot be confirmed at this stage. Consortium studies confirm that certain subsets of products (such as capsules, photosensitive actives, narrow therapeutic index medicines) will be very challenging to reformulate. Based on previous reformulation experiences (e.g., to reduce nitrosamine levels) the industry confirms its initial estimate that reformulation of individual products will likely take from 3 to 5 years (and this could be longer for certain products).

Taking individual product timeframes, capacity constraints, unknowable risk factors, and the large number of products involved into account, the industry also estimates that removal of TiO_2 from all European medicines should be expected to take more than a decade. Based on analysis of the technical, commercial, and regulatory complexity of reformulating global products, the industry also confirms that the banning of titanium dioxide from European medicines could result in the withdrawal of hundreds (or possibly thousands) of products from the market and supply shortages for a significant number of medicines.

Also of note is that, at present, the majority of medicines suppliers have not yet developed any detailed plans for reformulation en-masse of medicines' portfolios, and that only approximations such as those described in this report, achievable at this stage. This is due to critical factors outlined in this report, including:

- That generally usable and suitable alternative coating and capsules have not been identified that give medicines of proven equivalent quality, safety and efficacy.
- That the safety of titanium dioxide has been evaluated by many groups and regulatory authorities as presenting no concern.
- That many alternative materials on coating and capsules do not yet have the same cumulative evidence of safety as titanium dioxide.
- That complexity on scale for such a multi-product activity (which requires technical, safety, manufacturing capacity and commercial assessment, including considerations of global considerations) is such that clarity is first required on timelines, available capacity and scope

Question 5

Please, supply an updated summary of the calculated impact on availability, shortages, and costs of any requirement to replace/remove titanium dioxide from medicines in Europe, considering the global nature of product development and supply.

1. Recent Global Safety Evaluations of TiO_2

A key factor effecting the calculated impact on availability, shortages and costs is the status of titanium dioxide globally. This is due to the fact that many medicines are developed with global supply chains in mind, and without specific manufacture or formulations for the EU market. As such, in updating industry's summary, it is essential to first outline the updated assessment made by other countries of the safety of titanium dioxide. This summary is provided below:

UK FSA 2022

COT (2022) Interim position paper on titanium dioxide[5]. Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment, UK:
The UK's Food Standards Agency (FSA) published after reviewing the evidence of the data, that no safety concerns have been identified, and that the weight of evidence does not support the EFSA conclusion. Consequently, there will not be a change to regulation in England and Wales. Food Standards Scotland (FSS) reached the same conclusion. In essence, they do not agree with the EFSA assessment and do not see a need to replace TiO_2 in pharmaceuticals. It is anticipated that UK COT will publish the outcome of the evaluation in Q4 2023/Q1 2024 based on a further analysis of the UK COM (Committee on Mutagenicity).

Health Canada (HC) June 2022:

The Food Directorate's comprehensive review[6] of the available science of TiO_2 as a food additive summarized:

- HC re-evaluated the cancer study with new data on compound characteristics that were not available for the EFSA evaluation. Unitane 0-220 particle size and purity is highly comparable to recent food grade TiO_2, E171 and HC concluded there was no evidence of cancer in mice and rats exposed to high concentrations of food-grade TiO_2.
- HC concludes that there were no changes to DNA in various animal studies after treatment with TiO_2. In addition. No adverse effects on reproduction, development, immune, gastrointestinal or nervous systems, or general health when rats were exposed from pre-conception to adulthood.
- Whilst HC acknowledged the uncertainties in the database that would benefit from further research, the weight of evidence (WoE) suggests that these gaps are not significant enough to warrant a precautionary approach.
- In summary, the Food Directorate's position is that there is no conclusive scientific evidence that the food additive TiO_2 is a concern for human health.

[5] https://cot.food.gov.uk/2021-statementsandpositionpapers (Accessed on October 29, 2023)

[6] https://www.canada.ca/en/health-canada/services/food-nutrition/reports-publications/titanium-dioxide-food-additive-science-report.html (Accessed on October 29, 2023)

USA FDA

The FDA reviewed the findings of EFSA's 2021 Opinion on titanium dioxide. The FDA notes that EFSA's 2021 Opinion continued to confirm no general and organ toxicity, as well as no effects on reproductive and developmental toxicity. Based on this evaluation, FDA published in the Code of Federal Regulations. Title 21, Volume 1 (21CFR73.575] updated in June 07 2023, the acceptable use of TiO_2 in food up to 1% (w/w)[7].

Australian / New Zealand September 2022

The Authorities (FSANZ) highlighted in their risk assessment[8] that absorption of food-grade titanium dioxide following ingestion in food is very low. Recent studies with food-grade titanium dioxide in rats suggest that less than 0.01% of the amount eaten is absorbed. FSANZ discussed that pre-neoplastic lesions in the colon were observed in a drinking water study with sonicated food-grade TiO_2 at 10 mg/kg bw/day, but these findings were not replicated in two studies in which food-grade TiO_2 was administered via the diet up to considerably higher doses (up to 267 or 1000 mg/kg bw/day).

They considered the results of feeding studies a being more relevant than studies after sonification.

In addition, they mentioned that the observations of pre-neoplastic lesions are also inconsistent with the findings of a 2-year bioassay of TiO_2 in rats and mice conducted by the US NCI. No evidence of toxicity or carcinogenicity was observed at dietary concentrations up to 50,000 ppm in this study.

A recent OECD TG-compliant EOGRT study in rats with food-grade TiO_2 administered via the diet at doses up to 1000 mg/kg bw/day found no evidence of systemic toxicity, developmental or reproductive toxicity or developmental neurotoxicity. and no evidence of developmental immunotoxicity was observed with TiO_2 in this study.

In conclusion, based on the data currently available, FSANZ concludes there is no evidence to suggest that dietary exposures to food-grade TiO_2 are of concern for human health.

Ministry of Health, Labour and Welfare of Japan 2023

National Institute of Health Sciences (NIHS) experts stated it is difficult to support the EFSA opinion. Additionally, based on the results from Agaki et al. 2023[9], it is thought that the absorption of TiO_2 from the gastrointestinal tract is extremely low. Therefore, it is difficult to rationally explain the EFSA interpretation, which assumes that orally administered TiO_2 reached target tissues such as the bone marrow at a concentration that would explain its induction of genotoxicity.

Joint FAO/WHO Expert Committee on Food Additives (JECFA) 2023

The JECFA discussed all available data in its Ninety-seventh meeting (Safety evaluation of certain food additives) from 31 October–9 November 2023[10]. In this meeting, the Committee considered additional toxicological studies relevant to the safety assessment of INS171 that investigated the toxicokinetics, acute toxicity, short-term toxicity, long-term toxicity and carcinogenicity, genotoxicity, and

[7] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=73.575 (Accessed October 29, 2023)
[8] https://www.foodstandards.gov.au/consumer/foodtech/Documents/FSANZ_TiO2_Assessment_report.pdf (Accessed October 29, 2023)
[9] Akagi, J. et. al. (2023) Oral toxicological study of titanium dioxide nanoparticles with a crystallite diameter of 6 nm in rats. Akagi et al. Particle and Fibre Toxicology. https://doi.org/10.1186/s12989-023-00533-x
[10] https://cdn.who.int/media/docs/default-source/food-safety/jecfa/summary-and-conclusions/jecfa97-summary-and-conclusions.pdf?sfvrsn=1b8ecced_5&download=true (Accessed February 2024)

reproductive and developmental toxicity, as well as special studies addressing the short-term initiation/promotion potential for colon cancer.

JECFA also evaluated estimates of dietary exposure to TiO_2, estimating the maximum 95th percentile to be 10 mg/kg bw/day, which was used for the risk evaluation of INS 171 in the diet.

INS 171 consists of uncoated TiO_2 anatase particles including a minor fraction of nano size particles. Food-grade TiO_2 is identified and labelled as E171 by the EU. INS 171 and E171 are equivalent except that INS 171 does not include the TiO_2 coating of pearlescent pigments (INS 176). Therefore, in line with the HC review, the JECFA also considered the historical carcinogenicity data from the NCI to be relevant for the risk assessment of INS 171 and by extension, E171.

The JECFA took into account that INS 171 was not carcinogenic in an adequately conducted 2-year study in mice and rats at gender-averaged doses of up to 7500 mg/kg bw/day for mice and 2500 mg/kg bw/day for rats, the highest doses tested.

The JECFA confirmed the assessments of other agencies that there was no evidence of reproductive or developmental toxicity in studies in rats at INS 171 doses of up to 1000 mg/kg bw/day, the highest doses tested.

JECFA stated that they reviewed all available research on genotoxicity risk and determined that the evidence is insufficient, owing mostly to the lack of suitable testing methodologies for nanoparticles." This indirectly implies, that value of the indicator assays like the comet assay in vitro is not relevant to describe the genotoxic potential, at least in the current format.

Therefore, JECFA recommended more research to address the current uncertainty about the distribution of TiO_2 particle sizes in food and to develop genotoxicity tests that are more appropriate for nanoparticles.

Finally, the JECFA concluded that considering the very low oral absorption of INS 171, and in the absence of any identifiable hazard associated with INS 171 in the diet, i**t was appropriate to reaffirm the ADI "not specified"** established at the Thirteenth meeting in 1969.

2. Further EU assessments on TiO_2 safety

Scientific Committee on Consumer Safety (SCCS) 2023

The expert panel concluded:

- There exists insufficient evidence to exclude the genotoxic potential of almost all TiO_2 particles, with the exception of the two nano-grades RM09 and RM11, where a negative hypoxanthine-guanine-phosphoribosyl-transferase test (HPRT) and micronucleus test (MNT) *in vitro* confirmed the absence of a genotoxic potential,
- In line with this interpretation, SCCS felt unable to recommend any safe levels for TiO_2 (including pigmentary grade) in cosmetics,
- Overall, the SCCS evaluation is in line with the EFSA statement but acknowledges that the situation for cosmetics is different from food ingredients in that oral uptake of cosmetics is usually incidental and thus quantitatively much lower, and primarily via oral buccal exposure versus through the GIT,
  - In contrast to others, their assessment is based on *in vitro* data from the Comet Assay, whereas elsewhere this assay is given much less weight as an indicator test as it is not equivalent to stable mutations or chromosome damage,

- A valid *in vitro* micronucleus or chromosomal aberration test (assuring all nanotoxicology state-of-the-art principles are applied) with adequately selected E171-equivalent material(s) would be needed to overrule the current conclusion,
- A lot of weight is given to the Kirkland et al. (2022)[11] review and the SCCS conclusions are in agreement with the Kirkland et al. conclusions ("the profile of genotoxicity results from the most robust studies with titanium dioxide does not fit the response pattern which would be expected for a genotoxic carcinogen"),
- SCCS is of the opinion that the Applicants should draw up a proposal for specifications of the different TiO_2 grades used in cosmetics.

Thus, SCCS is the only committee that follows EFSA's opinion that a genotoxic potential of TiO_2 cannot be excluded. However, in both cases this interpretation is based on data from assays that are considered by most other groups as not providing data reliable enough for such a conclusion. Of note, the SCCS suggest that well conducted OECD-compliant in vitro tests (micronucleus or chromosome aberration test) would adequately mitigate the genotoxicity concern (data that is currently lacking). In addition, the suggested to draw up a proposal for specifications for the different grades of TiO_2 used in those cosmetic products that could lead to oral and inhalation exposure. The SCCS will be able to assist the Commission in reviewing the proposal.

3. Recently Published TiO_2 Quality Evidence

Titanium Dioxide (E171 Grade) and the Search For Replacement Opacifiers and Colorants: Supplier Readiness Survey, Case Studies and Regulatory Perspective[11]

In a comprehensive review published in 2023, the IQ Consortium summarised a number of surveys and practical assessments conducted with alternative materials by IQ member companies. In this, review, they note that a range of technical challenges and regulatory hurdles were identified which mean that, in the short term, it will be difficult to replace titanium dioxide with the currently available alternative materials while readily achieving the same drug product quality attributes. The assessment summarised that this was linked to higher variability, colour fading and identified scale up risk, of E171 free film coatings[12], and the consequent negative impact on development costs and timelines and product quality. The review also highlighted the regulatory and supply chain hurdles that would have to be overcome if a titanium dioxide replacement was required for the EU market but was not mandated by others.

4. Recently Published TiO_2 Safety Evidence

The conclusions from non-EU regulators' assessment are further supported by assessments and published since the EFSA Assessment. These are summarised below:

Chronic Toxicity Study in rats with genotoxicity endpoint conducted at the National Institute of Health Sciences, Japan, 2023[13]

[11] Bruno Hancock, et al 2023 Titanium Dioxide (E171 Grade) and the Search For Replacement Opacifiers and Colorants: Supplier Readiness Survey, Case Studies and Regulatory Perspective, Journal of Pharmaceutical Sciences, ISSN 0022-3549, https://doi.org/10.1016/j.xphs.2023.12.006. https://www.sciencedirect.com/science/article/abs/pii/S0022354923005154

[12] https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/film-coating

[13] Akagi, Ji., Mizuta, Y., Akane, H. et al. Oral toxicological study of titanium dioxide nanoparticles with a crystallite diameter of 6 nm in rats. Part Fibre Toxicol 20, 23 (2023). https://doi.org/10.1186/s12989-023-00533-x

- *In June* 2023 an Oral toxicological study of titanium dioxide nanoparticles with a crystallite diameter of 6 nm in rats was published
- Overall, the result of the study demonstrated that there were no toxic changes, including general toxicity, induction of colonic abnormalities, DNA-damaging potential, and accumulation of TiO_2 in the liver, kidney, or spleen following the oral administration of anatase TiO_2 NPs with a crystallite size of 6 nm for 28 or 90 days.
- The NOAEL in both 28- and 90-day studies observed was 1000 mg/kg bw/day. The results provide further evidence for evaluating the safety of oral exposure to TiO_2 that may contain very small crystallites because Immunohistochemical analysis of colonic crypts showed no extension of the proliferative cell zone or preneoplastic cytoplasmic/nuclear translocation of β-catenin either in the male or female 1000 mg/kg bw/day group.
- In addition, no significant increase in micronucleated or γ-H2AX positive hepatocytes was observed, demonstrating an absence of double strand breaks.
- This is in particular important as the induction of γ-H2AX was not observed at the deposition sites of yellowish-brown materials.
- Overall, the authors concluded there are NO safety concerns even with these extremely small nano-sized particles of 6 nm.

Expert Review of the genotoxicity of titanium dioxide (TiO_2), 2022

A panel of experts (not employed by companies that manufacture and sell TiO_2, was convened to perform the review of the genotoxicity of TiO_2 (expertise in genetic toxicology, general toxicology, bioavailability, carcinogenicity, and nanoparticle characterisation)[14].

- Only Studies with Genetic Toxicology endpoints covered by validated OECD protocols were reviewed.
- From 337 datasets with available genotoxicity data on TiO_2, by using a structured WoE approach, taking into account the relevant endpoints, study protocols and material characterizations, only 34 (10.1%). Studies eventually provided relevant data.
- Of these 34, 10 were positive, all of which were from studies of DNA strand breakage or chromosome damage. All the positive findings were associated with high cytotoxicity, oxidative stress, inflammation, apoptosis, necrosis, or combinations of these. Considering that DNA and chromosome breakage can be secondary to physiological stress, it is highly likely that the observed genotoxic effects of titanium dioxide, including those with nanoparticles, are secondary to physiological stress.
- Expert Panel re-evaluated the data in each dataset included in the final assessment (and sometimes did not confirm the authors findings), whereas EFSA accepted the authors' conclusions without further review for datasets included in the final assessment.
- "Existing evidence does not therefore support a direct DNA damaging mechanism for titanium dioxide (nano and other forms)"
- However, carefully designed studies of apical endpoints (gene mutation, MN or CA), following OECD recommended methods, performed with well characterised preparations of TiO_2, would allow firmer conclusions to be reached.

[14] Kirkland, D., et al A weight of evidence review of the genotoxicity of titanium dioxide (TiO_2), Regulatory Toxicology and Pharmacology (2022), doi: https://doi.org/10.1016/j.yrtph.2022.105263

In addition, two TiO_2 cosmetic grades were tested negative in the in vitro gene mutation assay (HPRT) and MNT vitro assay (data presented at the Genetic Toxicology Association (GTA) Meeting 2023), in accordance with the published EFSA protocol for testing of Nanomaterials.

5. Ongoing safety testing

In addition, several safety evaluations considering the different grades of TiO_2 are planned or ongoing outside the pharmaceutical industry, involving high quality OECD compliant studies with TiO_2/E171, adequately designed to assess the nanomaterial fraction via:

- in vitro gene mutation assays (SCCS reported two negative in vitro assays for cosmetic grade TiO_2)
- In vivo Comet assay
- Transgenic animal mutagenicity studies

For example, the HESI GTTC MGRA working group is working on and Adverse Outcome Pathway for TiO_2 to support Risk assessment based on Mode of Action[15].

It should be noted that the different TiO_2 grades showed different physicochemical properties that may lead to different biological consequences.

6. Safety Summary and Industry Assessment of the EFSA Opinion

TiO2 has an extensive toxicological data set, demonstrating no evidence for potential hazard to human health. Since the EFSA Evaluation, new data were generated and should be considered in an updated risk:benefit assessment. These data provide supportive evidence to consider TiO_2 as non-mutagenic/carcinogenic.

So far, authorities outside EU assessing the available data considered TiO_2 as no risk for medicinal products. Some non-EU authorities followed the EFSA recommendation without their own assessments. Recently SCHEER followed also the EFSA conclusion, but only for nano-grade materials (<100 ng/day), i.e., toys containing pigmentary grade TiO_2 can be used with no or negligible risk.

Industry concludes in their assessment that there is no evidence that TiO_2 (E171) has mutagenic potential in vitro or in vivo. Genotoxic effects observed are primary DNA damage (stand breaks) and chromosomal damage (clastogenicity) mainly in indicator assay like the comet assay in vitro which have limitations in their relevance for hazard identification. However, these genotoxic effects seem not to result in gene mutation. The effects were observed at cytotoxic doses and/or considered to be secondary to oxidative/physiological stress. Several modes of actions inducing primary DNA lesion may exist, including formation of reactive (oxygen) species (induced directly, via inflammation or mitochondrial dysfunction) and direct DNA interaction only in vitro, but there is no proof for covalent binding of TiO_2 to DNA, no proof that TiO_2 enters the nucleus and no proof this results in gene mutations. Occurrence of primary DNA damage and clastogenicity in the absence of mutation induction is not novel and has been identified for situations where primary DNA damage is efficiently repaired and does not result in tumour induction.

Emergent data of the material characterisation (including the nanoparticulate fraction) that was representative of Unitane-0-220 used in the negative oral carcinogenicity studies conducted by the NTP are key (consequently, carcinogenicity data were accepted by HC, FSANZ, FDA). These carcinogenicity data are essential for informing the biological significance of in vitro and in vivo genotoxicity study results for the benefit:risk assessment of medicinal products, providing a NOAEL of 2250 mg/kg/day. With this NOAEL it should be possible to calculate a PDE supported by the new data

[15] https://hesiglobal.org/genetic-toxicology-gttc/

from Agaki et al[16], highlighting that Immunohistochemical analysis of colonic crypts showed no extension of the proliferative cell zone or preneoplastic cytoplasmic/nuclear translocation of β-catenin either in the male or female 1000 mg/kg bw/day group. Regarding genotoxicity, no significant increase in micronucleated or γ-H2AX positive hepatocytes was observed. Additionally, the induction of γ-H2AX was not observed at the deposition sites of yellowish-brown materials.

Overall, Industry does not agree with the EFSA assessment and considers TiO_2 as being safe when used as an opacifier or colorant in medicinal products. Industry requests the opportunity to work with EMA on any potential new safety studies with TiO_2 and/or potential alternatives.

The TiO_2 Alternatives Consortium Safety team examined the data on the potential health hazards of TiO_2. A review of the many decades of data on TiO_2 found that:

- Any genotoxicity observed with TiO_2 is likely secondary to physiological stress and not due to direct DNA damage.
- One study that suggested TiO_2-related effects, i.e., Bettini et al., 2017, is flawed and not reproducible.
- Nearly all regulatory agencies have reached a different conclusion compared to the EU and state that the food additive E171 does not pose a human health concern.
- The National Cancer Institute (NCI, 1979) carcinogenicity study is considered valid and is the most appropriate study for assessing the long-term effects of TiO_2 and setting an oral PDE. Although a PDE is not normally necessary for low hazard substances, a PDE for TiO_2 was determined and Scientific Advice requested. Scientific information and establishment of the PDE will serve for risk-benefit evaluation on the use of low amounts of TiO_2 contained in tablets and capsules in oral medicinal products and will reassure patients that TiO_2 use is actively monitored and controlled at safe levels.

7. Availability & shortages following a requirement to replace/remove titanium dioxide from medicines

The requirement to produce TiO_2 -free medicinal products in Europe, considering the global landscape wherein it remains fully available in other countries, creates the need for separate EU-only supply chains, and a greater likelihood of unforeseen issues leading to EU medicines shortages.

Many pharmaceutical companies supply or subcontract production to supply chains producing medicines for global markets. There is still uncertainty on whether these MAHs or their subcontractors would be supportive of reformulation to remove TiO_2 only in EU medicines, considering the effort required on regarding human resources and material resources.

Availability of TiO_2-free excipients is already problematic following the EU-wide ban in food, with suppliers having limited capacities to provide these excipients. Alternative options, regardless of suitability, currently available on the market cannot at present satisfy the volumes required by all the EU Pharmaceutical industry. Considering there is no 'one size fits all' alternative available today each reformulation has its own special consideration. Any requirement to replace TiO_2 would certainly lead to supply chain shortages.

Furthermore, a negative shelf-life impact is foreseen for many products following the removal/replacement of TiO_2. This will lead to further strains on the supply chains impacting availability.

[16] https://particleandfibretoxicology.biomedcentral.com/articles/10.1186/s12989-023-00533-x (https://doi.org/10.1186/s12989-023-00533-x)

For some products it will likely not be possible technically to remove TiO_2 from their formulation. These products may need to be withdrawn from the market.

The pharmaceutical industry does not have the capacity to reformulate all impacted medicines in parallel. Considering the findings of the Alternatives Consortium, companies will likely have to prioritize certain products above others for any reformulation work, leading to some low margin products either disappearing from the market for a certain period of time or even being completely removed, depending on the commercial perspective.

All reformulations will have to undergo regulatory variation procedures. Considering the hypothetical number of reformulations required delays from Competent Authorities are expected in this scenario, which can only lead to additional shortages of medicinal products. (to keep in mind the recent QRD template update and issues created for veterinary medicines) – bottleneck for both companies and authorities.

8. Costs of reformulation for the pharmaceutical industry

Considering the previously presented technical disadvantages created by the removal of TiO_2 from medicinal products, each point has a cost associated with it which varies from product to product. As an industry we cannot produce exact numbers associated with each of these points as every company has its own specificities when it comes to manufacturing distribution and overall efficiency of these steps, but it is unanimously agreed that each of the cost-producing arguments are not negligible. It is possible to split the costs into two different categories: **one-time costs** and **additional running costs**.

One-time costs

One-time costs include all the R&D (reformulation, production, stability testing etc) costs and the authorization costs. It is worth noting that depending on the function TiO_2 serves in each individual product, the R&D one-time costs vary by a ten-fold factor or even more in some cases. Gastroresistant coatings are much more expensive to reformulate compared to products where TiO_2 has an opacifier function.

In some cases, the additional drug substance costs needed for reformulation development, repetition of stability studies, and repetition of drug product validation costs could add up to millions of euros. We have a similar situation for toxicology studies.

Inventory write-off is also something to be taken into account, for stocks of products not yet placed on the market that cannot be sold anymore.

For nationally approved products all authorization costs will be multiplied by the number of Member States where these products are available, in some cases also by strength and species in case of veterinary medicines.

Looking at these one-time costs from a broad perspective, considering the number of products impacted it is easily estimated that the financial impact is well into billions of Euros.

Additional running costs

Additional running costs will be generated by:

- Raw material/excipients prices and fluctuations of pricing based on additional demand;
- Production costs associated with the de-coupling of EU production from the rest of the world;
- Longer film-coating processing times;

- Shelf life and overall medicines' stability and costs implied by trying to reverse these negative impacts (changes in packaging for example, or additional requirements in the distribution chain).

All such costs will have to be absorbed by manufacturers considering that medicines pricing is most often regulated from a reimbursement perspective in Europe. Even in free pricing pharmaceutical market settings, there may be measures that limit the possibility to increase prices (i.e., maximum price caps/minimum rebate levels in procurement or other civil contractual arrangements having a similar effect).

In the case of over-the-counter (OTC) products, the reformulation costs may result in price increase and may discourage people to practice self-care and push them to seek healthcare and reimbursed medication, thus adding additional costs and strain on the health systems

Summary

Summary of Evidence on Alternatives

Industry is continuing to investigate potential alternatives to titanium dioxide (TiO_2) with a clear plan to ensure there is no impact on patients from any replacements. Since 2021 there has been significant investigation and investment by suppliers of coatings and capsules and MAHs. A substantial amount of evidence has been generated and there have been many peer-reviewed publications. Industry's summary of the evidence is that:

- **For Coatings:** For many products alternative coating can replace TiO_2, although significant increased amounts will be required and appearance matching will not generally be possible. It may not be possible to replace for complex, modified release dosage forms and products sensitive to light may be at risk of increased impurities and lower quality and safety.
- **For Capsules**: the overall evidence generated to-date, suggests that it will be challenging to identify alternatives that can deliver products of the appropriate quality.
- Overall, the evidence confirms that for some medicines, use of TiO_2 as an excipient can be critical to safety and efficacy (e.g. as an opacifier to protect from light and prevent degradation, or to ensure that the minimal amount to coating is used to enable tablet dissolution).

Many international regulatory authorities have reviewed the safety of TiO_2 and concluded there is no safety concern in food or medicines. Furthermore, many alternative coatings and capsules contain colourants and opacifiers that do not have the same evidence of safety as TiO_2.

Industry refers to the 2022 article in J Pharm Sci as a review of all currently available literature on alternative coatings and the unique properties of TiO_2[17]. This document provides significant scientific assessment and concludes that:

> *"At the time of writing, in the view of the authors,* ***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. In this paper an IQ Consortium team outlines the properties of titanium dioxide and criteria to which new replacement materials should be held"*

A further detailed review, including a summary of surveys of capsule and coating supplier readiness and case studies on the use and issued encountered in real systems was published by the IQ Consortium in Dec 2023. This further supports the conclusions summarised in this report.[18]

Based on the existing comprehensive safety package for titanium dioxide, in particular, as additional scientifically sound data has been made available, industry is of the opinion that a permitted daily exposure (PDE) for titanium dioxide can be calculated. This PDE will provide a safe exposure limit and will finally support the comparison of Safety Data of the alternatives and will ensures the use of titanium dioxide as an excipient in pharmaceuticals. Industry asked EMA NcWP for scientific Advice

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[17] Blundell et al *J. Pharm. Sci*, **2022** The Role of Titanium Dioxide (E171) and the Requirements for Replacement Materials in Oral Solid Dosage Forms: An IQ Consortium Working Group Review DOI: 10.1016/j.xphs.2022.08.011

[18] *Titanium Dioxide (E171 Grade) and the Search For Replacement Opacifiers and Colorants: Supplier Readiness Survey, Case Studies and Regulatory Perspective,* Hancock, Melnick et al*, J Pharm Sci,* Dec **2023**, https://doi.org/10.1016/j.xphs.2023.12.006

on this topic. Taking all currently available data (low bioavailability, negative in vivo mutagenicity and carcinogenicity) and calculations together, Industry is proposing an oral PDE of 2250 mg/day to support the risk-benefit assessment of E171 as an excipient in oral pharmaceutical products, despite the fact that no hazardous properties have been identified for this material. Establishing the PDE will reassure patients that TiO_2 use is actively monitored and controlled at safe levels. Request on Scientific Advice from EMA was submitted on January 31, 2024 by Sanofi.

Summary of Potential Impact on EU Medicines Supply of Restrictions on the Use of Titanium Dioxide

Depending on the unique requirements of each medicine, any individual reformulation (if possible) may take 3-5 years from lab to patient. Furthermore, it is conservatively estimated that for it would take between 7 and 12 years for a typical company to reformulate their entire portfolio of new and existing medicines.

Wholesale changes to medicines' formulations in Europe will be a significant and unnecessary resource drain for companies supplying medicines to Europe and to the European medicines regulatory authorities and will require significantly more than a decade to implement.

At the same time, Titanium dioxide continues to be assessed outside of Europe as having **no safety concern** (e.g. following assessment by Health Authorities in Japan, UK, Canada, Aus/NZ and the preliminary review of US). Titanium dioxide also continues to meet the most stringent of requirements governing the safety of medicines, including those set by the European pharmacopoeia, Japanese pharmacopoeia and US pharmacopoeia.

For products with global supply chains, consideration as to the viability of any new EU-only formulation would need to be assessed on a case-by-case basis, and many products could be discontinued for the EU. In addition, many clinical programs for innovative drugs are ongoing via multi-region clinical trials with titanium dioxide-containing formulations (eg in EU, US, China, & Japan simultaneously)

Overall, an isolated, EU-only restriction on titanium dioxide use for medicines in the EU will likely have a significant impact on medicines supply and innovative clinical programs.

Colours permitted for use in human and veterinary medicinal products other than those included in the Union list of authorised food additives

Industry has reviewed the recently adopted proposal for a directive of the EU general pharmaceutical legislation[19] and notes with interest Directive Article 27 and the process wherein the Commission may establish a new list of colours permitted for use in medicinal products, other than those included in the Union list of authorised food additives.

Industry welcomes this important new element in the legislation, given the different benefit/risk considerations for medicines versus food and the impact on patient access of changing colours in medicines. Industry's interpretation is a similar process should apply to titanium dioxide, and that, following the assessment of the EMA, the Commission could potentially add titanium dioxide to the new list of colours permitted for use in medicinal products.

Industry also notes that the provisions of regulation 2022/63 (14) apply **only to the use of titanium dioxide as a colourant** (eg not as an excipient/opacifier) and that considerations per the *2007 CHMP opinion on CMR aspects of excipients*[20] should apply to titanium dioxide when used as an opacifier or

[19] https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en

[20] https://www.ema.europa.eu/en/documents/other/chmp-scientific-article-53-opinion-potential-risks-carcinogens-mutagens-substances-toxic_en.pdf

any other excipient uses than colourant. Industry also noted the EMA position that "*TiO_2 is monographed in the European Pharmacopoeia and is considered to be suitable for use in the medicinal products as an excipient*." (EMA/504010/2021).

Conclusions and Recommendations from Industry

Evidence to-date supports the ongoing use of TiO_2 in medicines:

There is a long experience of safe use of TiO_2 in medicines and scientific evaluation of the currently available safety data does not raise any safety concerns.

To date, for some alternatives to TiO_2, there is no such level of evidence and safety risks cannot be assessed with the same level of confidence as for TiO_2. Moreover, EMA conclusions from September 2021 (EMA/504010/2021) are still valid:

- *"[…] 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 […]"*

As is clear from the assessment and data generated by the Alternatives Consortium, no alternative system or material to TiO_2 has been identified for use as an opacifier in coatings and capsules with the functional requirements to ensure that the same high-quality medicines can be supplied to patients.

As such, and based on the current understanding, industry recommends that, in order to ensure ongoing supply of medicines to EU patients, titanium dioxide remains on the list of colours available for use in medicines (per the provisions of Regulation 2022/63, Article 16) and that TiO_2 is included in the new list of colours permitted for use in medicinal products, other than those included in the Union list of authorised food additives, per Article 27 in the 2023 draft of the general pharmaceutical legislation (Com (2023)192 final). In addition, based on the existing comprehensive safety package for titanium dioxide, in particular, as additional scientifically sound data has been made available, industry is of the opinion that a permitted daily exposure (PDE) for titanium dioxide can be calculated. This PDE will provide a safe exposure limit and will finally support the comparison of Safety Data of the alternatives and will ensures the use of titanium dioxide as an excipient in pharmaceuticals. Industry asked the EMA NcWP for scientific Advice on this topic.

Although it is unusual from a toxicological perspective to derive a PDE for a non-hazardous compound, a PDE calculation using scientifically robust data will increase confidence of patients in the safety of medicinal products containing TiO_2 and will allow the pharmaceutical industry to continue to provide patient access to life-saving medicines and to develop innovative high-quality medicines in the future.

Taking all currently available data (low bioavailability, negative in vivo mutagenicity and carcinogenicity) and calculations together, Industry is proposing an oral PDE of 2250 mg/day to support the risk-benefit assessment of E171 as an excipient in oral pharmaceutical products, despite the fact that no hazardous properties have been identified for this material. Establishing the PDE will reassure patients that TiO_2 use is actively monitored and controlled at safe levels. Request on Scientific Advice from EMA was submitted on January 31, 2024 by Sanofi.

Annex 1

General Considerations for Safety Assessment of Nanoparticles in Excipients

Nanoparticles were mentioned in the E171 EFSA opinion and also in the exchange of information between the EMA and Industry on the 16th October 2023, this is a topic that is not well understood and this summary will help to clarify the situation.

Classification on the status of a material as nano or non-nano have been and are still an area of ongoing discussion for academia, industry and policy makers leading to a variety of definitions, guidance, and legislation. Moreover, the ongoing development on the best applicable analytical techniques to provide evidence on the nano content adds uncertainty to the nano discussion.

The major intention of policy makers in defining nanomaterials is to focus on material which might merit additional safety evaluation for the purpose of protecting human health. The underlying rationale for this approach is that material in nano form might have a different physiological distribution and consequently a different risk/safety profile compared to the non-nano form. The risk assessment approach varies around the world with the EU (EFSA) taking a precautionary principle approach compared to other regions where a balanced risk assessment approach is favoured.

While currently there are no specific regulations for nanomaterials which may be contained in medicinal products and their components, crossover between industrial sectors is leading to related questions being asked of marketing authorisation holders and in turn to excipient manufacturers.

In 2022 the EC published a new "Recommendation on the definition of a nanomaterial" (2022/C229/EC) this is an update of the previous version published in 2011. This definition is intended to be incorporated into any new or revised EU or National Regulations by policy makers and regulators as they get written, but as of today this has not yet happened. The definition on the size of a nanoparticle is the same (<100nm), but the concentration of nanoparticles present to define a nanomaterial has been confirmed and this is >50%.

Almost all solid food ingredients, additives and excipients contain nanoparticles, particles of <100nm in size. Nanoparticles in food generally dissolve in the body's GIT. Many nanoparticles are created naturaly. For example, cow's milk naturally contains casein micelles, which are nanocapsules created by nature to deliver nutrients to newborn calves. Others are created by standard technologies commonly used during production for food additives or excipients such as drying, milling grinding etc These can be described as unintentional or incidental nanoparticles that are not essential for the function of the excipient, but they are simply generated by the manufacturing process. The vast majority of excipients will contain incidental nanoparticles and they will have always been present since they were first used in drug products many decades ago. Excipients would have been assessed for safety at the time of first use although it is unlikely that the presence of nanoparticles would have been known at the time as the ability to accurately measure particles of this size was not widespread and this is still the case today.

Engineered nanomaterials are intentionally created to perform a specific function which is dependent on their nanoscale properties. For example, iron hydroxide adipate tartrate is an engineered nanomaterial developed for use in food supplements as a source of bioavailable iron[21]. Its nano properties enable it to be more bioavailable and therefore easier for the body to absorb and use.

There are currently no pharmacopeial monographs or food additive specifications where there is a specification for the nano content. The only region where there is some guidance on the presence of

[21] Understanding Nanoparticles and Engineered Nanomaterials: Use and Labelling. EU Speciality Food Ingredients Factsheet. Dec 2022

nanoparticles in excipients is the United States where FDA guidance acknowledges nanoparticles can be present in excipients and that they are likely to have always been present. In their view if these excipients with a history of use in humans are used in the same way as they have been used historically with the same dose level and in drug products with the same route of administration then they are considered low risk. However, if an excipient is created, or modified, to give it the benefit of nanoscale properties then this needs to be fully characterized based on their functionality and intended use. Proper controls, including test methods and acceptance criteria, a description of material source, and grade should be defined in a premarket application, with justification for how those acceptance criteria enable the product to meet its desired quality target product profile[22].

In the European Union there is no such guidance for excipients used in medicines, which means that the guidance from other industries plays a role in the excipient selection process. Considering currently available information, the parameters to define nanomaterials are not applied consistently. This inconsistency is a drawback for manufacturers of engineered nanomaterials or excipients containing incidental nanoparticles that are used as pharmaceutical raw material (pharmaceutical excipient and active pharmaceutical ingredient), and for drug manufacturers in complying with multiple regulatory requirements.

EFSA (European Food Safety Authority) takes the role as risk assessor and widens the risk evaluation from nanomaterials only as defined by the relevant food regulation to material not covered by regulatory definition but keeping some parameters of nano as described above. The definition of nanomaterial in use by EFSA is not aligned with the new 2022 EC definition. To set the scene on required risk evaluation EFSA published guidance documents on the technical requirements to establish the presence of small particles (<500nm) including nanoparticles (<100nm)[23]. A second document on risk assessment of nanomaterials to be applied in the food and feed chain as also published[24].

To determine if the EFSA assessment should take into account nano-specific considerations it splits the criteria into three sections:

1. Addresses solubility and dissolution rate as key physicochemical properties to assess whether consumers will be exposed to particles.
2. Establishes the information requirements for assessing whether the conventional material contains a fraction or consists of small particles, and its characterisation.
3. Describes the information to be presented for existing safety studies to demonstrate that the fraction of small particles, including particles at the nanoscale, has been properly evaluated.

If the material in question is a nanomaterial then it will need to undergo full assessment by EFSA, it is interesting to note that in the case of titanium dioxide it does not fulfil the particle size criteria for a nanomaterial but was selected based on its perceived nanoscale properties (e.g. Specific Surface Area) which have been artificially generated using sonication in many studies and this is not an industrial process in either the food or pharmaceutical industries. Since the EFSA opinion was published in 2021 further evidence has come to light that demonstrates that the titanium dioxide samples used in the 1979 National Cancer Institute (NCI) NIH Carcinogenicity study are representative of the E171 grades used in Europe today. It could be argued that if titanium dioxide was submitted to EFSA today it would not necessarily be subject to the same nano assessment that was conducted in 2020. Reference to this NCI study, and its outcome that titanium dioxide is not carcinogenic by the oral route, is made in

[22] Drug Products, Including Biological Products, that Contain Nanomaterials. Guidance for Industry. FDA, April 2022 Pharmaceutical Quality/CMC

[23] EFSA Guidance on technical requirements for regulated food and feed product applications to establish the presence of small particles including nanoparticles, EFSA Journal 2021;19(8):6769

[24] EFSA Guidance on risk assessment of nanomaterials to be applied in the food and feed chain: human and animal health. EFSA Journal 2021;19(8):6768

both the Health Canada and FSANZ reports and allows them to conclude that consumption of titanium dioxide (E171) as a food additive is not a concern for human health.

Guidance from EMA on the assessment of incidental nanoparticles in excipients would be welcome.