KU LEUVEN

FACULTY OF PHARMACEUTICAL SCIENCES

MASTER OF DRUG DEVELOPMENT

The potential ban of titanium dioxide in the development and use of medicinal and self-care products:

A scoping review and semi-structured interviews

THESIS

submitted by

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List of abbreviations

AC	Academic
ADI	Acceptable Daily Intake
API	Active Pharmaceutical Ingredient
AESGP	Association of the European Self-Care Industry
ANSES	National agency for food safety and security
CJEU	Court of Justice of the European Union
COM	Committee On Mutagenicity
COT	Committee On Toxicity
DM	Decision Maker
EC	European Commission
EFSA	European Food Safety Authority
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EU	European Union
FAMHP	Federal Agency for Medicines and Health Products
FDA	Food And Drug Administration
FSANZ	Food Standards Australia New Zealand
GALT	Gut-Associated Lymphoid Tissue
GI	Gastrointestinal
HP	Healthcare Provider
ICF	Informed Consent Form
ID	Industry
JECFA	Joint Expert Committee on Food Additives
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
OSD	Oral Solid Dosage
PIS	Participant Information Sheet
PO	Patient Organisation
RAC	Committee for Risk Assessment Committee
SCCS	Scientific Committee on Consumer Safety
TDMA	Titanium Dioxide Manufacturers Association
UV	Ultra Violet

Summary

Background: Titanium dioxide (TiO_2) has been used for years as an additive in medicinal and self-care products. It was banned as a food additive in the European Union (EU) as of August 2022. The European Medicines Agency is considering whether to extend this ban to medicinal products, and the Scientific Committee on Consumer Safety is re-evaluating its use in cosmetics. Since 66 % of oral solid dosage forms in Europe contain TiO_2, a ban could have significant implications for all stakeholders involved in the development and use of TiO_2.

Objectives: This study aimed to examine the potential impacts, challenges, and needed actions associated with a ban on TiO_2. It pursued three sub-objectives: *(i)* to outline the background of TiO_2 and its toxicity and safety profile; *(ii)* to identify the medicinal and self-care products affected by a possible TiO_2 ban and the associated implications and challenges; and *(iii)* to understand stakeholder perceptions on the potential TiO_2 ban.

Methods: A scoping review was conducted using PubMed, Embase, WebOfScience, and Limo, as well as consultations of grey literature and key stakeholder websites. Afterwards, semi-structured interviews were conducted with stakeholders from five groups (developers, academia, decision makers, healthcare providers, patient organisations) using purposive and snowball sampling. Interviews were recorded, transcribed ad verbatim, and analyzed thematically.

Results: *(i)* The literature revealed that TiO_2 is widely used due to its exceptional properties, like its high refractive index. The European Food Safety Authority concluded that genotoxicity cannot be ruled out, while outside the EU, TiO_2 is generally considered safe. Oral toxicity is subject of ongoing debate, yet there is general agreement on its safety for dermal use, and inhalation hazards are widely acknowledged. *(ii)* This study revealed that TiO_2 is present in an estimated 91,000 medicinal products and many self-care products, such as creams. Reformulation would create a huge workload for companies and regulators, who would need to evaluate all changes. Potential alternatives of TiO_2 could alter product characteristics, which could affect adherence and product identification, potentially causing errors from production to consumption. *(iii)* The interviews showed agreement across all stakeholder groups that a ban on TiO_2 could affect the accessibility of medicinal products, but priorities varied. Industry and decision makers raised concerns about global differences, and industry emphasised the importance of clear communication from reliable sources. Decision makers stressed the importance of reasonable, but not excessive, timelines for decision-making and implementations related to TiO_2. Healthcare providers and patient organisations prioritised correct communication to themselves and patients, and risk mitigation strategies incorporating patient perspectives. Academics stressed the enormous workload associated with a potential TiO_2 ban, but believed that replacement of TiO_2 would be feasible.

Conclusion: The findings of this study indicate that oral toxicity of TiO_2 remains uncertain. However, TiO_2 is considered safe for dermal use, and toxic when inhaled. Many similarities and disparities were identified in the opinions of different stakeholders. Whether or not TiO_2 will be banned, clear communication about its safety and use from reliable sources will be important. In addition, patient perspectives should be considered in decision-making around TiO_2.

Samenvatting

Achtergrond: TiO_2 wordt reeds jaren gebruikt als additief in geneesmiddelen en zelfzorgproducten. Vanaf augustus 2022 is het in de EU verboden als voedingsmiddelenadditief. Het Europees geneesmiddelenagentschap overweegt of dit verbod moet worden uitgebreid tot geneesmiddelen, en het Wetenschappelijk Comité voor Consumentenveiligheid herevalueert het gebruik in cosmetica. Aangezien 66 % van de vaste doseervormen in Europa TiO_2 bevatten, zou een verbod aanzienlijke gevolgen kunnen hebben voor alle belanghebbenden betrokken bij de ontwikkeling en het gebruik van TiO_2.

Objectieven: Deze studie beoogde de mogelijke effecten, uitdagingen en noodzakelijke acties omtrent een verbod op TiO_2 te onderzoeken. Drie subdoelstellingen werden nagestreefd: *(i)* uitzetten van de achtergrond van TiO_2 en zijn toxiciteits- en veiligheidsprofiel; *(ii)* nagaan op welke geneesmiddelen en zelfzorgproducten een eventueel TiO_2 verbod betrekking zou hebben en de implicaties en uitdagingen daaraan verbonden; en *(iii)* percepties van belanghebbenden over een mogelijk TiO_2 verbod begrijpen.

Methodes: Er werd een scoping review uitgevoerd met behulp van PubMed, Embase, WebOfScience en Limo, alsook grijze literatuur en websites van belanghebbenden. Nadien werden semi-gestructureerde interviews uitgevoerd met belanghebbenden uit vijf groepen (ontwikkelaars, academici, beleidsmakers, zorgverleners, patiëntenorganisaties) met behulp van doelgerichte en sneeuwbalsteekproeven. De interviews werden opgenomen, woordelijk getranscribeerd en thematisch geanalyseerd.

Resultaten: *(i)* De literatuur wees uit dat TiO_2 veel wordt gebruikt vanwege zijn uitzonderlijke eigenschappen, zoals zijn hoge brekingsindex. De Europese voedselveiligheidsautoriteit concludeerde dat genotoxiciteit niet uit te sluiten is, terwijl TiO_2 buiten de EU over het algemeen als veilig wordt beschouwd. Orale toxiciteit is onderwerp van discussie, maar er is algemene consensus over de veiligheid voor dermaal gebruik, en het gevaar van inademing wordt algemeen erkend. *(ii)* Uit deze studie is gebleken dat TiO_2 aanwezig is in 91.000 geneesmiddelen en vele zelfzorgproducten, zoals crèmes. Herformulering zou een enorme werklast betekenen voor bedrijven en regelgevers, die alle wijzigingen zouden moeten evalueren. Mogelijke alternatieven van TiO_2 zouden de productkenmerken kunnen wijzigen, wat de therapietrouw en geneesmiddelenidentificatie zou kunnen beïnvloeden, en mogelijk fouten zou kunnen veroorzaken van productie tot consumptie. *(iii)* De interviews toonden aan dat alle belanghebbenden het eens zijn dat een verbod op TiO_2 de toegankelijkheid van geneesmiddelen zou kunnen beïnvloeden, maar prioriteiten varieerden. De industrie en de beleidsmakers uitten bezorgdheid over globale verschillen, en de industrie benadrukte het belang van duidelijke communicatie vanuit betrouwbare bronnen. Besluitvormers benadrukten het belang van redelijke, maar geen excessieve, termijnen voor besluitvorming en implementering omtrent TiO_2. Zorgverleners en patiëntenorganisaties gaven prioriteit aan correcte communicatie naar henzelf en patiënten en risicobeperkingsstrategieën met aandacht voor het patiëntenperspectief. Academici benadrukten de enorme werklast in verband met een mogelijk verbod op TiO_2, maar geloofden dat vervanging van TiO_2 haalbaar zou zijn.

Conlusie: De resultaten van deze studie duiden op een onzekere orale toxiciteit van TiO_2. TiO_2 wordt echter veilig geacht voor dermaal gebruik, en toxisch bij inademing. Er werden veel overeenkomsten en verschillen vastgesteld in de meningen van verschillende belanghebbenden. Ongeacht of TiO_2 al dan niet zal worden verboden, zal duidelijke communicatie over de veiligheid en het gebruik ervan vanuit betrouwbare bronnen belangrijk zijn. Bovendien moet bij de besluitvorming rond TiO_2 rekening worden gehouden met het patiëntenperspectief.

1. Introduction

This section covers: *(i)* the rationale for discussing a titanium dioxide (TiO_2) ban and the use and properties of TiO_2, including its safety and toxicity profile. *(ii)* the history of TiO_2 as an additive and the various regulatory aspects. *(iii)* the implications of a possible ban on TiO_2.

1.1 Titanium dioxide: how the discussion of a possible ban was triggered

In the last decade, there has been increased attention to the possible toxicity of TiO_2. In particular since 2016, the safety of TiO_2 has been a rising topic (1). Specifically, it has been claimed that TiO_2 could cause DNA and chromosomal damage through different routes of exposure (2). Several studies showed that TiO_2 may pose a threat to human health, by causing risks like ovarian and liver damage (2,3). Despite massive endeavours in recent years to clarify the toxicological profile of TiO_2, differences in approaches and controversial results make it difficult to determine its toxicological profile with certainty (2). As a result, opinions on the potential toxicity of TiO_2 are divided and repeatedly it emerges that there is insufficient data to make a conclusive statement. Various agencies have evaluated its safety and many organisations are still in the process of reviewing TiO_2. Meanwhile, TiO_2 has been banned in the European Union (EU) for use in food. Since in the EU any colourant in medicinal products must be authorized as a food additive, the use of TiO_2 in medicinal products is currently under review as well (4). Discussions regarding a TiO_2 ban evolve around questions like “How will this progress, and which stakeholders are involved?” “What are the perceptions of different stakeholders?” “And how can the use of TiO_2 be safely monitored in the future?” This kind of questions shaped the rationale behind this study.

1.2 Use of titanium dioxide in food, pharmaceuticals and self-care products

TiO_2 is a versatile substance with applications in various industries. In particular, TiO_2 is often used in cosmetics and sun products, since it ensures that the skin is protected from light (5). For this purpose, TiO_2 nanoparticles are commonly found in dermal products (6). Further, it is used as a pigment in food, medicinal products, toothpaste and other self-care products (7). Self-care products include food supplements, cosmetics, medical devices and over-the-counter medicinal products, i.e. medicinal products that are available without a prescription (8). Certain dermal and vaginal creams, as well as toothpastes, are classified as medical devices. As a result, TiO_2 is also present in this class of products (9,10). Furthermore, TiO_2 is found in paint and several other building materials (5).

1.2.1 Properties of titanium dioxide

TiO_2 is a natural oxide of titanium, which occurs in a range of crystalline and non-crystalline forms (11). The high refractive index provides TiO_2 with light-scattering properties (12). In fact, a high refractive index indicates that a large amount of light is reflected at the surface, which provides protection from light (13). In addition, it provides an opaque appearance and makes TiO_2 ideal for use as a white pigment (12). As a result, it acts as an opacity and colouring agent in oral solid dosage forms (OSDs) (3,14). To obtain the white pigment, particles of TiO_2 with a size range of 200 to 400 nm are preferable since these have the best light-scattering properties (3,15). Three different crystal structures of TiO_2 occur, being anatase,

rutile and brookite (16). Only the first two were authorised as food additives, used in e.g. dairy products, food supplements and chewing gum (16,17). It is shown that anatase and rutile can retain their unique properties at high temperatures (16).

1.2.2 Titanium dioxide as an additive

TiO_2 as a food additive is also known as E171, a synthesised powder grade of TiO_2 with a particle size of 60 nm to 300 nm (5). It is the anatase crystal form, approved as a colourant for use in food and medicinal products in many countries (11). E171 has very strict purity requirements and it is physically stable in pharmaceutical use (18). This food grade TiO_2 can be found in 66% of all OSDs in Europe. It owes its popularity to its protective function for medicinal products and to providing unique identification and batch-to-batch consistency. Unique identification of dosage forms is very important for patients. In this way, risks are reduced at different steps in the drug life cycle. For example, the chance of mixing up products during production and the risk of incorrect administration are significantly reduced (11).

1.3 Toxicity of titanium dioxide

1.3.1 Titanium dioxide as a nanomaterial

According to European Union (EU) Recommendation 2011/696/EU, a material is called a nanomaterial when 50 % of the particles are in the nano range, i.e. below 100 nm. The exact definition of the EC is the following: "*Nanomaterial means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm.*" (19). E171 is not a nanomaterial according to the criteria in this recommendation, since E171 comprises about 40 % TiO_2 nanoparticles and about 60 % TiO_2 particles larger than 100 nm (18,20). Nanomaterials have different toxicity profiles, as they have different properties in terms of chemistry and structure (21). They can cause damage on several levels, since they have the ability to induce free radicals, e.g. active forms of oxygen and nitrogen. Furthermore, they have a high penetration rate in organisms and can damage the cytoskeleton. Some nanomaterials would be able to penetrate the cell nucleus and conjugate with DNA (22). It is claimed that nanocrystals of TiO_2 can be absorbed, which could be harmful for the human body (23). Although the gastrointestinal (GI) absorption of TiO_2 particles is small, they could accumulate in the human body as they have a long half-life (12). In addition, TiO_2 nanoparticles have been found to induce DNA strand breaks and chromosomal damage, as well as genotoxic effects *in vivo* (3,14). Genotoxicity is characterised by the disruption of genetic material through mechanisms like DNA breaks, lesions, deletions, mis-segregation or non-disjunction, potentially leading to gene mutations (24).

1.3.2 Absorption pathways of titanium dioxide

Since TiO_2 is widely used in medicinal and self-care products, oral exposure to these particles is possible (25). TiO_2 nanoparticles seem to be able to penetrate through the skin, respiratory and GI tracts. In this way, the particles would spread into the body and pose a potential risk to consumers and patients. There are different types of TiO_2 as discussed above. Each of these has a specific action in the human body, as well as a distinct toxicity profile (15). E171 is believed to be distributed systemically via the blood

circulation or lymphatic system. Physicochemical properties may change under the influence of digestive enzymes and pH levels in the mouth and GI tract, which could affect *in vivo* absorption (3).

1.4 Safety of titanium dioxide

1.4.1 History of titanium dioxide as a food additive

TiO_2 has been used as a food additive for many years. Already in 1966, its use in food was approved by the Food and Drug Administration (FDA) if the level did not exceed 1 % of the food weight (23). Furthermore, TiO_2 was authorised by EU directive 94/36/EC, allowing E171 for use as a food additive until February 2022 (12). No maximum level was set, but it was allowed to be used in food at quantum satis (18). In the EU, TiO_2 was first assessed for its safety by the Scientific Committee on Food in 1975. It did not establish an acceptable daily intake (ADI) for TiO_2 at that time, and two years later it was listed in the category *"colours for which an ADI was not established but which could be used in food"* (12). An ADI is the maximum amount of a particular substance to which a person can be exposed daily over a long-term period, with no or minimal risk of adverse effects (26). Since 2009, the European Food Safety Authority (EFSA) has been re-evaluating all food additives approved before January 2009 as part of a routine re-evaluation program (12,27). In this context, TiO_2 was re-evaluated in 2016 (12). EFSA is an impartial EU agency to provide scientific advice on risks related to food (28). They concluded that its use as a food additive had no toxic effects (12). To determine an ADI, they had insufficient data at that time and TiO_2 was re-approved as a food additive in the EU in 2016 according to Regulation (EC) No 1333/2008 (12,29). In January 2017, Bettini et al. (23) found that nanoparticles were present in E171. These could result in colon micro-inflammation and initiated preneoplastic lesions in rats through absorption into the gut (23). In 2018, EFSA was requested by the EC to review four new publications, including the paper from Bettini et al. (23), since these raised concerns about the safety of E171. From this evaluation, EFSA's existing opinion did not change (30). Following the ban in France, the EC requested EFSA to conduct another safety assessment of E171 as a food additive in 2020. It was determined that the possibility of genotoxicity could not be excluded, and as a result, the safety of E171 as a food additive could no longer be guaranteed (12). This led the EC to amend Regulation 1333/2008, prohibiting TiO_2 for use in foods (14). In February 2022, legislation EC 2022/63 finally came into force, officially banning the use of E171 in food. From August 2022, no more products could be marketed in the EU that contained E171 (4). Only products legally marketed before August 7th 2022, meaning products that entered production before this date, were allowed to remain until the end of their shelf-life. Since this date, the additive is also no longer permitted in imported food in the EU (12).

France took the lead in banning TiO_2 in foods. Already on April 25, 2019, they decided to implement this ban and it took effect on January 1, 2020. The decision was based, on one hand, on the paper by Bettini et al. (23), and on the other hand, on the fact that no acceptable daily intake (ADI) could be established (12,23). The application of the precautionary principle was also considered in this decision. Further, following the EC ruling, several countries are re-evaluating the use of TiO_2 in food. Some countries are conducting their own research. In contrast, Switzerland, for example, is following the position of the EC.

The World Health Organisation and the Joint Expert Committee on Food Additives (JECFA) will re-evaluate TiO_2 by 2024 (12). JECFA is an international scientific committee consisting of experts in various relevant fields, jointly managed by the Food and Agriculture Organisation of the United Nations and the World Health Organisation (31). Canada and The United Kingdom (UK) are examples of countries that do not follow the EC and the EFSA conclusions. Canada claimed that there is no exclusive evidence that TiO_2 would pose a health risk (12). In addition, the US FDA has also ruled that TiO_2 is not toxic (32).

1.4.2 Previous and current developments and evaluations of titanium dioxide

Resulting from the EFSA safety assessment, TiO_2 was banned for use in food. Considering this ban and the fact that every colourant in medicinal products should be approved as a food additive, the European Medicines Agency (EMA) is currently reviewing the use of E171 in medicinal products (12,33). Possible alternatives as well as the safety, quality and availability of medicinal products are taken into account (14). In the EU, the EMA is responsible for the scientific evaluation, monitoring and safety assurance of medicinal products (34). A final decision will have to be made by 2025 (12). In the meantime, the EC is maintaining E171 on the list of colourants for approved use in medicinal products. They will re-evaluate this in 2024, when the assessment from EMA is available (14). The Scientific Committee on Consumer Safety (SCCS) is the committee of the EC that conducts evaluations of non-food consumer products, like cosmetic products and its ingredients, personal care products and toys. Based on their evaluations, the EU Cosmetic Regulation is being amended (35). The SCCS also did a safety evaluation of TiO_2 in cosmetic products in 2020. They found that TiO_2 was not safe for products capable of being inhaled (36). However, the safety of TiO_2 in cosmetic products is being re-evaluated following the EFSA opinion (37). In the United States (US), all these tasks fall under the responsibility of the FDA. They are responsible for protecting public health by regulating human medicinal and biological products, veterinary medicinal products, medical devices, food, cosmetics, as well as tobacco products and electronic products that emit radiation (38).

1.5 Implications of a potential ban of titanium dioxide in medicinal products

Since 66 % of available oral medicinal products in Europe contain TiO_2, a ban could have far-reaching consequences. This can result in several actions. Firstly, it can be decided to replace TiO_2 with another additive. The second option is to simply omit TiO_2 and the last option is to withdraw products that contain TiO_2 (14). Replacing or removing TiO_2 in medicinal products would lead to several possible variation procedures, depending on the impact on the finished product (39). This could create a huge workload for companies, the EMA and National Health Authorities. This could almost certainly lead to significant pharmaceutical shortages and withdrawals, what could have profound implications for patients. Further evaluation is needed to decide what will happen in the future regarding the use of TiO_2 as an excipient in medicinal products. EMA is currently unable to confirm whether or not it is feasible to replace TiO_2 (14).

1.6 Regulations affecting the use of titanium dioxide

Several regulatory aspects complicate the use of TiO_2. As stated before, in the EU, any excipient used as a colourant must be approved as a food additive. Consequently, the use of TiO_2 in medicinal products

would no longer be allowed. However, TiO_2 is provisionally maintained on the list of colourants for use in medicinal products (14). The new regulation EC 2022/63 states that EMA must reassess the toxicity of TiO_2 by April 2024, and the EC will have to make a decision by February 7, 2025. It is crucial that the pharmaceutical industry makes every effort to accelerate the research and development of alternatives to replace TiO_2 in medicinal products, and to submit the necessary amendments for the relevant Marketing Authorisations (MAs) (4). Not any substance can be used to replace TiO_2, and the toxicological data of a possible substitute must be significantly better (14). Additionally, TiO_2 is often characterized as being merely a colorant, while it serves multiple functions in medicinal and self-care products (12).

1.7 Problem statement: Insufficient evidence on the impacts, challenges and needed actions linked to a titanium dioxide ban, and insight into stakeholders' perceptions

Since TiO_2 is present in many oral medicinal products, the scope of products affected by a potential ban would be enormous. Therefore, more research is needed to map existing literature to better understand the range of products that would be affected, aiming to provide complementarity on current literature. Furthermore, there is a need to outline the impact a potential ban might have. To clarify this matter, more evidence-based insights from the literature are needed, as well as increased understanding into stakeholder views. While prior research has investigated whether or not TiO_2 is safe, no research has been conducted aiming to provide insights into the opinions of the various stakeholders and how they would be affected if a ban is to be implemented. Affected stakeholders are the pharmaceutical and self-care industry, academic researchers, trade organisations like the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the Association of the European Self-Care Industry (AESGP), patients and patient organisations, regulators, policy makers, governmental agencies, as well as doctors and pharmacists. These insights are needed, because all these stakeholders would be impacted by a potential TiO_2 ban. Accordingly, they may have different perspectives and priorities, resulting in different opinions.

2. Objectives

The overall objective of this study was to investigate the potential impact, challenges, and needed actions related to banning TiO_2 in the development and use of medicinal and self-care products. To achieve this goal, the following sub-objectives were pursued.

Objective 1: To understand the background of titanium dioxide and its toxicity and safety profile

1. To research the properties of TiO_2
2. To investigate the safety of TiO_2
3. To examine the different routes of exposure to TiO_2 and their implications
4. To explore how different countries are positioning towards the TiO_2 challenge

Objective 2: To map medicinal and self-care products affected by a possible titanium dioxide ban and to examine the implications and challenges associated with it

1. To identify medicinal and self-care products affected by a potential TiO_2 ban
2. To research the consequences related with replacement or ommitment of TiO_2
3. To research the challenges related with replacement or ommitment of TiO_2
4. To research the possibility of defining an Acceptable Daily Intake of TiO_2

Objective 3: To map stakeholders' perceptions on the impact of a potential titanium dioxide ban

1. To investigate the position of the different stakeholders toward a possible TiO_2 ban
2. To evaluate the impact of banning TiO_2 on different stakeholders
3. To identify challenges and opportunities associated with a potential TiO_2 ban
4. To examine needed actions from the various stakeholders if TiO_2 would be banned in medicinal and/or self-care products
5. To research the possibility of defining an Acceptable Daily Intake of TiO_2

3. Methods

3.1 Study design

This study was conducted as part of the master's thesis of the master in drug development at the KU Leuven. The first phase involved a scoping review to map the current landscape and to identify the consequences of a potential ban on TiO_2. In a second phase, the perspectives of various stakeholders were explored through semi-structured interviews. The study was subjected to an ethical evaluation procedure and the protocol was approved by the Ethics Committee Research of UZ / KU Leuven. The approved study has been assigned the study number S67296.

3.2 Phase 1: Scoping literature review

3.2.1 Search strategy

A scoping literature review was conducted between September 2022 and May 2023, using the databases PubMed, Embase and WebOfScience. Further, the search mechanism Limo was consulted. Given the complex, non-unambiguous topic (multiple stakeholder opinions, multidisciplinary, different countries and organisations considered), several search terms were developed applicable to the different databases. To this end, the search queries were developed to include three different concepts relating to the research objectives, namely 'pharmaceutical', 'titanium dioxide' and 'impact' *(Figure 1).* Many other search terms were used in the process, depending on the specific topic. For example, when looking for the status of TiO_2 in a particular country, this country was included in the search query as well. Articles from the last ten years were reviewed, meaning articles dating from 2012 to the present. Only sources in English, French and Dutch were included, in line with the researchers' native language, and the full text had to be freely available for KU Leuven students.

Grey literature was also included, like presentations from major conferences on TiO_2. For example, the presentations of the symposium "The future Role of Titanium dioxide as an excipient in Pharmaceuticals" of the International Pharmaceutical Excipient Council in Brussels on September 14-15, 2022 were assessed. Further, presentations from the Association of Industrial Galenic Pharmacy "Info Day TiO_2: Challenges & opportunities" in Paris on May 17, 2022 were consulted. Particular regulatory guidelines were reviewed as well. Finally, the websites of key stakeholders were researched. For example, websites of EFSA, the EC, the Titanium Dioxide Manufacturers Association (TDMA), the Belgian Association of Consumer Healthcare Industry and the Federal Agency for Medicines and Health Products (FAMHP) were examined.

Based on the scoping literature review, the background of TiO_2, as well as its safety and the routes of exposure were examined. In this way, an attempt was made to get a good understanding of what TiO_2 is and why it might pose a threat to human health. Subsequently, it was identified which products would be affected if TiO_2 were to be banned and the related consequences. Furthermore, the study looked at how different countries perceive the TiO_2 concern, and it explored the possibility of establishing an ADI.

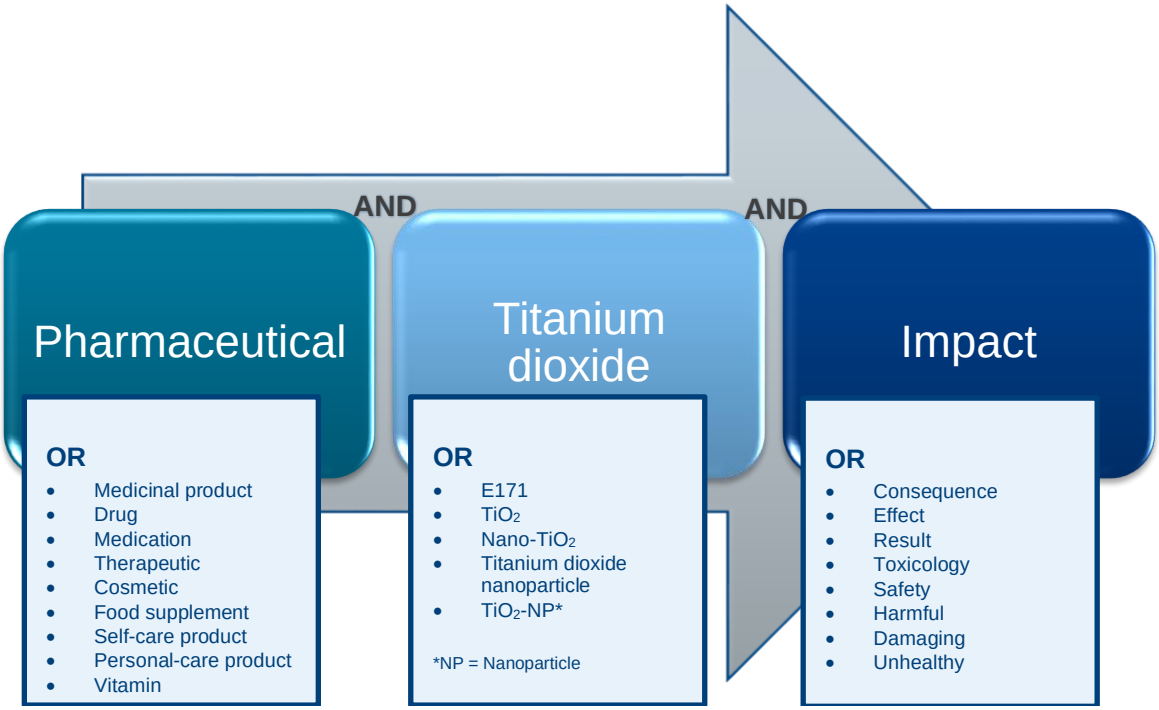


Figure 1: Sections of the search strategy.

3.2.2 Article selection

Articles were selected based on the title, abstract, language and date. If they met the criteria, the article was read through and if it raised interesting aspects it was used for the scoping review.

3.3 Phase 2: Semi-structured interviews

In the next step, the perceptions of the different stakeholders regarding a possible ban on TiO_2 were examined using semi-structured interviews. The consolidated criteria for reporting qualitative research (COREQ) were used to report the interview process *(Appendix 1)* (40). Interviews were conducted by master student Margot Suetens, and the first interview was facilitated by PhD researcher Alice Vanneste.

3.3.1 Interview guideline development

The outline of the qualitative study followed a predetermined semi-structured interview guideline with the questions that were asked to the participants *(Appendix 2)*. However, new questions could arise during the dialogue, depending on the participant's response (semi-structured).

3.3.2 Participant selection recruitment

Interviewees were invited via e-mail and an informed consent form (ICF) *(Appendix 3)* and Participant Information Sheet (PIS) *(Appendix 4)* were delivered to participants via e-mail as well. These were prepared in three languages, namely French, Dutch and English. In this way, efforts were made to provide the ICF and PIS to the potential participants in their native language to ensure that they fully understood what participation in the study entailed. The ICF had to be returned signed before the start of the interview. This ICF explained the objectives, method and implications of the study; the potential benefits, risks and disadvantages of participation; the handling of personal data, as well as the retention period and storage method of these data. In addition, it explicitly stated that audio recordings were made during the interview.

3.3.2.1 Inclusion and exclusion criteria

Participants needed to speak English or Dutch and were considered able to provide input with regard to the research aims (purposive sampling). Stakeholders who would be affected by a potential ban on TiO_2 in medicinal or self-care products were included. These had to meet the inclusion criteria of one of the five stakeholder groups outlined in *Table 1*.

Table 1: Inclusion criteria per stakeholder group.

Stakeholder group	Profiles	Specific inclusion criteria
Industry	Pharmaceutical industry > Formulation > Regulatory affairs > Production	At the time of the interview, participants were employed in and/or were representative in: • Individual pharmaceutical companies • Companies for self-care products • Consultancy companies like PharmaLex • Trade organisations (e.g. AESGP, TDMA, Medicines for Europe, EFPIA and Pharma.be)
	Self-care industry	
	Trade organisations	
Academia	Academics > Formulation > Regulatory affairs	At the time of the interview, participants were employed in/at • A university at a faculty in pharmacy, medicine or biomedical sciences And possibly additionally connected to • The pharmaceutical industry, e.g. by working in a consultancy company
Decision makers	Regulators	At the time of the interview, participants were working at/for: • Authoritarian bodies like EFSA and EMA, including committees located under them, like Pharmacovigilance Risk Assessment Committee (PRAC) • Governmental agencies like FAMHP • Policy authorities like the EC
	Government agencies	
	Policy makers	
Healthcare providers	Doctors and pharmacists	At the time of the interview, participants were employed as doctors or pharmacists in a hospital, a pharmacy, or involved within clinical trials.
Patient organisations	Patient organisations	At the time of the interview, participants were employed or volunteering in a patient organisation representing patients with diseases for which OSDs constitute the therapy.

Further, it was important that the participant was over 18 years old and had signed the ICF prior to participating in the study.

3.3.2.2 Recruitment

During the qualitative phase of the study, the aim was to investigate which stakeholders would be affected by a possible ban on TiO_2 and how these stakeholders approach the matter. For this purpose, there was estimated to be two to five interviewees within each stakeholder group, but the final number depended on the obtaining of data saturation. Data saturation is defined as the point where additional interviews no longer reveal significant new themes (41). If the data was not saturated after five interviewees within a given stakeholder group, efforts were made to schedule additional interviews until data saturation was obtained. In a first step, purposive sampling was used. This involved an active search for participants who met the inclusion criteria. In addition, snowball sampling was used for the recruitment of participants, meaning that new potential participants were contacted by suggestions from previous interviewees. Organisations and companies like TDMA, EFPIA and PharmaLex were contacted through general mail addresses on their websites. Same for authoritarian bodies like EFSA and EMA. Furthermore, academic staff was sought through the university website, e.g. www.kuleuven.be/wieiswie/nl/person/search. Contact details of doctors and pharmacists were found on the hospital website, i.e. via

www.uzleuven.be/nl/artsen-en-specialisten. Moreover, participants' email addresses were kept for the sole purpose of inviting the participants and were not retained after the end of the study.

3.3.3 Interview conduct

Before the interview began, participants were asked if they had questions about participation in the study and the objectives of the study, as described in the PIS. Furthermore, they were informed that the interview would last half an hour to one hour and could stop whenever they wanted, and that they could choose not to answer certain questions. The ICF was reviewed one last time together with the participant. Both in the ICF and at the start of the interview, it was clearly stated that the person was not obliged to participate. Both for participating and not participating, as well as for ending the study early, there were no negative consequences for the individual. Data, including audio clips and notes, of uncompleted interviews were not included in the data analysis and were destroyed. To ensure confidentiality, only researchers and the participant attended the interview. The interviewer started by introducing herself and briefly indicated again what the interview would cover. In addition, participants were informed that questions could always be asked during the interview, that there were no wrong answers and that clarification of questions could always be requested. Afterwards, participants were asked to briefly introduce themselves and share their expectations of the interview. At the beginning of the interview, the interviewer asked again if the participants were okay with the audio recording being started. Finally, the interview was started based on the questions prepared in the interview guideline.

3.3.4 Analysis

Collected data was analysed thematically using the framework method as described by Gale et al. (42). The interviews were transcribed ad verbatim into transcripts and afterwards transcripts were pseudonymized. Pseudonymisation is a de-identification process whereby all data allowing (in)direct identification of participants is removed, and each participant is given a unique, study-specific and arbitrary code (43). The key with the link between the name and the code was securely stored on OneDrive for Business of KU Leuven, protected with a password, to which only the researchers had access. Subsequently, the data was analysed through the thematic framework approach. The overall goal of framework analysis is to identify, describe and interpret important patterns and themes. The two major components are, first, creating an analytical framework and, second, applying this analytical framework. This was done using five steps, namely familiarizing with the data, identifying a thematic framework, then indexing all the research data against the framework and charting to summarize the indexed data. In the final steps, patterns were mapped and interpreted (44). For coding, complementary deductive (prepared from the guide) and inductive codes (created during the transcript analysis process) were used. The transcripts were coded by Margot Suetens using NVivo software and data extracted from the interviews was used in the master's thesis using themes and pseudonymous quotes. An overview of the codes, their frequency and the links between them are outlined in *Appendix 5 and Appendix 6.*

4. Results

4.1 Phase 1: a scoping literature review

4.1.1 Properties of titanium dioxide

TiO_2 has a molecular weight of 79.87 g/mol and is chemically stable, biocompatible and a strong oxidising material. At the same time, it is inexpensive and has low production costs (45). TiO_2 crystals occur in nature mainly in three polymorphs, namely brookite, rutile and anatase. In addition, there are some fewer common structures (14,45). Of the polymorphic ones, rutile is the most thermodynamically stable (45). Anatase and rutile are often used industrially. Due to the tetragonal structure, the refractive index is determined by orientation. Nevertheless, the particle material has a high refractive index in all dimensions, since the crystals are randomly oriented most of the time. In medicinal products, the anatase form is used. It is less hard, glossier and less abrasive and dense than rutile. In addition, it is able to disperse light very well, since it has a very high refractive index. This ability to spread light provides the bright white colour of TiO_2 (14). This enables TiO_2 to be a very good white pigment and opacifier (12). Additionally, TiO_2 can absorb UV light and protects against heat degradation (14,46). Other beneficial properties include being tasteless and odourless, chemically inert, insoluble in water and improving the smoothness of the finished product. Finally, because TiO_2 is inert, it does not adversely affect the bioavailability of the active pharmaceutical ingredient (API) (11,47). Most commonly, particles of TiO_2 ranging from 200 nm to 400 nm are used in cosmetic products (15). In medicinal products, TiO_2 particles of nanodimension as well as particles larger than 100 nm are found (18).

4.1.2 Use of titanium dioxide in food, cosmetics and medicinal products

4.1.2.1 Titanium dioxide in food products

Until August 2022, TiO_2 was used in a lot of food products in the EU. Food supplements are available in different OSDs, namely dragees, capsules and tablets. These first two contained respectively three and four times more TiO_2 than tablets, up to amounts of 0.018 g TiO_2 per capsule (20). Even concentrations up to 1.25 µg Ti/mg in form of TiO_2 were found in candies and chewing gum (12,17). The highest concentrations were present in chewing gum with white coatings and in general, candies and chewing gums with a hard outer shell contained higher concentrations. Furthermore, it was present as an anti-tacking agent in powder mixtures for food, such as in powder to make pudding. Even in various dairy products, such as milk and yoghurt, TiO_2 concentration ranged up to 0.26 µg/ml (17).

4.1.2.2 Titanium dioxide in cosmetics

In cosmetics, TiO_2 is used as a UV-filter or white pigment (15). TiO_2 is present in sunscreens, toothpaste as well as in various face creams. Furthermore, it can be present in deodorants, shaving cream, lip balm and shampoo. The concentration in toothpastes can go up to 5.6 µg/mg, or up to almost 0.5 % of the product's weight. Sunscreens can have very large amounts of TiO_2, as much as 14 to 90 µg/mg, functioning as UV-protector. White-coloured shampoos, deodorants and shaving creams contained lower levels of less than 0.01 µg/mg (17).

4.1.2.3 Titanium dioxide in medicinal products

In the EU, it is estimated that 91,000 medicinal products for human use contain TiO_2 (48). Hence, in each EU member state, there are several thousands of nationally authorized products and hundreds of centrally authorized products containing TiO_2 (49). TiO_2 serves as an opacifier and colourant in OSDs (14). Examples include capsules, powders or granules and tablets. Furthermore, it is present in a limited number of non-oral dosage forms, for uses like cutaneous, oromucosal, sublingual, transdermal and vaginal use. In addition, it can be found in packaging materials of medicinal products (46). TiO_2 is present in a lot of essential medicinal products such as antibiotics and antidiabetics, as it is a non-reactive ingredient which makes it well tolerated (46,49). A ban on TiO_2 could have serious consequences for patients, since TiO_2 is present in nearly all therapeutic classes of medicinal products (46). Although, the food and pharmaceutical industries represent only 1 % of the use of TiO_2, compared to 95 % industrial use (14). TiO_2 enhances whiteness and opacity and accentuates contrast with other colourants, making a large palette of colours available, which plays an important role in medicinal product recognition, allowing patients to distinguish different types of medicinal products. This is also directly related to patient compliance and safety (46,49). Furthermore, TiO_2 can ensure that light sensitive active ingredients are protected and that only a thin coating is needed to achieve the desired quality characteristics that do not compromise bioavailability (49,50). An overview of examples of medicinal products containing TiO_2 and their therapeutic classes are outlined in *Appendix 7* (51)**.** This is by no means an exhaustive list. It attempted to outline an understanding of how medicinal products of hugely diverse therapeutic classes contain TiO_2. TiO_2 is even present in often vital medicinal products like oral anti-cancer therapy.

For various medicinal products, TiO_2 content ranged from very low to a rather high concentration of up to 0.014 µg Ti/mg in form of TiO_2 *(Figure 2)* (17). In addition, the level of consumption of medicinal products is significantly lower than for food and cosmetics, and consumption is strictly controlled by the dose (48).

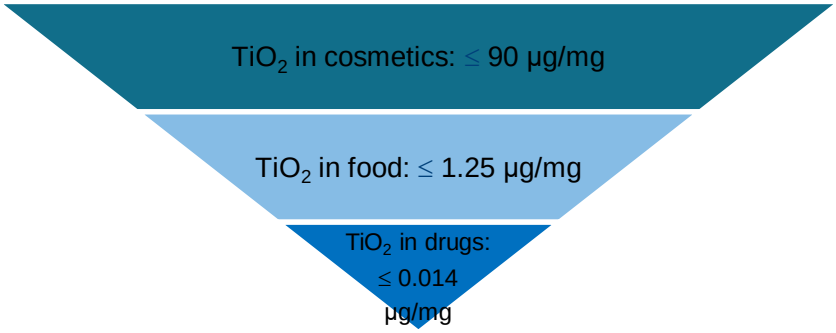


Figure 2: Overview of the amounts of TiO_2 in several types of products.

4.1.3 Uptake and toxicity of titanium dioxide

Nanoparticles of TiO_2 are believed to penetrate through the skin, through the respiratory tract or pass through the GI tract. Afterwards, they could spread throughout the body, posing a potential risk to consumers (15).

4.1.3.1 Oral intake

TiO_2 is present in many oral medicinal products and possible oral ingestion must also be considered, for example, when using a lip balm. The particles could enter the mouth and thereby the GI tract (3). Pele et al. (52) already showed in 2015 that part of orally ingested pharmaceutical and food-grade TiO_2 particles were directly absorbed in the blood stream of healthy volunteers. They distinguished an apparently early absorption and a later absorption peak, which would occur respectively in the proximal small intestine and in the distal small intestine (52). TiO_2 nanoparticles would interact rapidly with the mucus layer and penetrate the mucosa, and further enter the oral epithelium, with smaller particles penetrating deeper. As a result, they could affect the physiological homeostasis of buccal/sublingual cells in the mouth. While absorption of orally ingested TiO_2 through a healthy intestinal barrier appeared to be very low, several factors could facilitate absorption, e.g. impaired intestinal barrier function (3). It was also indicated that TiO_2 particles could accumulate in specific organs through repeated prolonged oral exposure (15). As such, kidney damage was demonstrated after oral administration of TiO_2 nanoparticles in rats. For example, oxidative stress, increased inflammatory markers and functional and histological damage due to tubular necrosis were found. Furthermore, pathomorphological changes in the lungs and kidneys and functional changes in the central nervous system were discovered. Finally, even brain damage was shown (53). A possible maternofoetal passage of TiO_2 was also revealed, highlighting the need to evaluate the potential risk of TiO_2 nanoparticles exposure during pregnancy (3). Gmoshinski et al. (54) assessed the risks of oral intake of TiO_2 nanoparticles by conducting a meta-analysis of 64 studies. The most frequently observed effects occurred in the liver, including damage to liver tissue, oxidative stress and changes in biochemical parameters of blood plasma. In addition, immunotoxicity was frequently observed. Finally, signs of neurotoxicity and reproductive toxicity emerged. The researchers also revealed that the nanoparticles could enhance the pathogenicity of opportunistic micro-pathogens of the gut microbiome. These disruptions of the intestinal microflora have a harmful effect on Gut Associated Lymphoid Tissue (GALT) and on the acid balance in the intestinal lumen, what may result in proliferation of inflammatory cells. This affects the production of pro- and inflammatory cytokines and the absorption of nutrients and metabolites in the microflora, which may explain the systemic effects of TiO_2 nanoparticles. The conclusion was reached that the risks could become intolerable when the percentage of nanoparticles of the total mass exceeded 10 % (54). In contrast, the study by Blevins et al. (55) revealed that E171 exhibited no significant effects on peripheral or GI tract immune homeostasis, inflammation or histopathological evaluations of small and large intestines, liver, spleen, lungs and testes. There was no difference found in the levels of inflammatory cytokines, even at higher doses of E171 than evaluated in other studies, for example the study by Bettini et al. (23). The study by Blevins et al. (55) also suggested that E171 does not induce colitis or tumourogenesis and no evidence of direct carcinogenesis was observed. The data indicated that even under pathological conditions in the gut, E171 was harmless via diet and no abnormalities were observed in the small or large intestine of E171-treated rats (55).

4.1.3.2 Dermal exposure

In healthy skin, after application of for example sunscreen containing TiO_2, the majority of the particles remain on the skin and only a small proportion would penetrate deeper into the stratum corneum, with smaller particles penetrating deeper (3,15). However, it was also suggested that the nanoparticles can penetrate into the granulosum of the stratum. In certain instances, it was demonstrated *in vivo* that the application of TiO_2 nanoparticles multiple times a day resulted in the penetration of particles through the stratum corneum and even into viable cells within the epidermis. Nevertheless, It was generally believed that TiO_2 does not penetrate beyond the surface layers in the skin to viable cells, and that it is unable to reach general circulation either in healthy or compromised skin. Hence, it was claimed that TiO_2 nanoparticles up to a concentration of 25 % as an UV filter in sunscreen are not harmful when applied to healthy, intact or sunburned skin (15).

4.1.3.3 Inhalation exposure

Inhalation of TiO_2 nanoparticles would form a safety concern, particularly when using sprayable products. TiO_2 nanoparticles were primarily found in the upper respiratory tract, namely in the mouth, pharynx, nose, larynx and trachea. Nevertheless, they are capable of penetrating the deeper lungs and alveoli. Coughing, mucociliary clearance and alveolar macrophages in the lungs eliminate the particles, but an estimated 10 % of the insoluble particles remain. These can penetrate through the pulmonary barrier and spread through the body (15). The study of Yu et al. (56) supported the possibility that inhalation of TiO_2 particles in normal lungs could lead to cell proliferation and increased inflammation. Various adverse effects were reported in mice exposed to TiO_2 using a whole-body exposure chamber, ranging from bronchial atelectasis with hyperplasia and even hyperaemia. Furthermore, it was shown that TiO_2 nanoparticles could enter the cells of mice, affecting the Endoplastic Reticulum (ER) and disrupting mitochondria, as well as causing ER stress in the lungs (56). In addition, an increase in various cytokines and cytotoxicity markers in the lungs were found in rats after inhalation of TiO_2 nanoparticles and a link was found between exposure to TiO_2 nanoparticles in the workplace and neurological symptoms (53).

4.1.4 Safety assessments and regulatory actions concerning titanium dioxide

TiO_2 is one of the most studied and evaluated substances worldwide. As a result, not all evaluations lay in line with each other (12). Therefore, several evaluations from different stakeholders were examined to gain insight into the safety of TiO_2. *Figure 3* plots a chronological overview of the various actions on TiO_2 in recent years and *Table 2* outlines the findings and conclusions of the various safety assessments and regulatory actions concerning TiO_2.

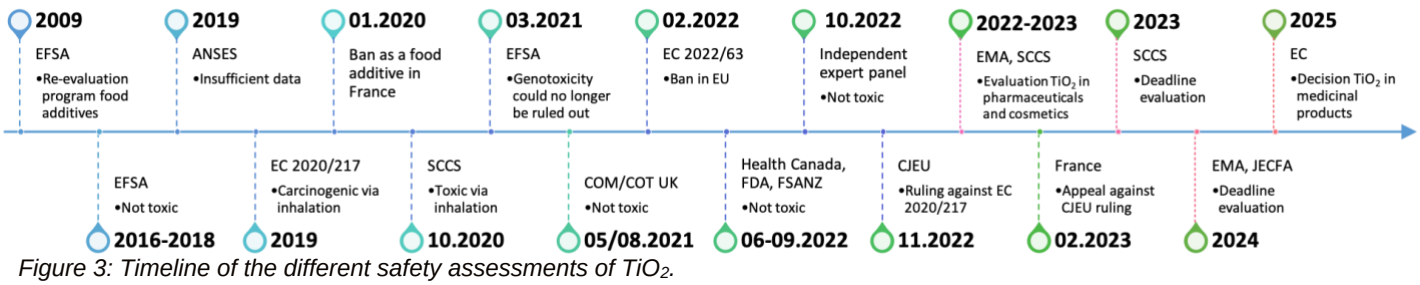


Figure 3: Timeline of the different safety assessments of TiO_2.

- EFSA = European Food Safety Authority
- ANSES = National agency for food safety and security
- EC = European Commission
- SCCS = Scientific Committee on Consumer Safety
- COM / COT = Committee on Mutagenicity / Toxicity
- FDA = Food and Drug Administration
- FSANZ = Food Standards Australia New Zealand
- CJEU = Court of Justice of the European Union
- EMA = European Medicines Agency
- JECFA = Joint Expert Committee on Food Additives

Table 2: Summary of the different committees and their findings on the safety of TiO_2 as a food additive.

Committee	Timing	Findings	Conclusion
ANSES	2019	Insufficient data to address uncertainties about toxicity, better characterization of E171 required (57).	Limiting exposure by promoting safe products (57).
EC (RAC)	2019	TiO_2 should be classified as carcinogenic via inhalation when ≥1 % particles ≤10 µm (58).	Hazard class carcinogen 2 (58).
SCCS	2020	TiO_2 in sprayable hair products safe ≤1.4 % for consumers, ≤1.1 % for hairdressers. Safe in loose powder facial makeup ≤25 % (36).	Carcinogenic via inhalation of sprayable products (36).
EFSA	2021	Accumulation TiO_2 in organs leading to genotoxicity. Concern for immunotoxicity, inflammation, neurotoxicity. Causation of DNA and chromosomal damage (37,59).	Genotoxicity could no longer be ruled out (37).
COM/COT UK	2021	EFSA conclusions based on very weak evidence. More reliable and robust data sets needed (60,61).	Insufficient robust evidence to draw a definitive conclusion (60).
FDA	2022	Safe under certain conditions, i.e. max 1 % of weight product and only with appropriate diluents (32,62).	Safe in cosmetics, food products and medicinal products (32).
FSANZ	2022	No evidence that TiO_2 poses a health risk to humans. Used in many foods for many years, no adverse effects have been reported (63).	No safety concerns related to the use of TiO_2 (63).
Health Canada	2022	Studies raising toxicity concerns did not use food-grade TiO_2 or broke it up into smaller particles: not representative for TiO_2 as a food additive (60,64).	No health risks identified, further research recommended (37).
Independent expert panel	2022	Difference in studies considered relevant compared to EFSA. Genotoxic effects secondary to physiological stress (60).	Existing evidence does not support a direct DNA damage mechanism (60).
CJEU	2022	Classification carcinogen 2 by EC incorrect. Wrong density value used by RAC and can only concern a substance with intrinsic ability to cause cancer, which is not the case (65).	Classification as possible carcinogenic is wrong (65).
France	2023	Appeal against decision CJEU (66).	Suspensive effect. Classification remains until end of procedure (66).

4.1.4.1 National agency for food safety and security (ANSES): opinion on the safety of titanium dioxide for use in food

As visible on the timeline in *Figure 3,* France was the first country to ban TiO_2 at the beginning of 2020 (67). This happened because, in February 2019, the French government asked ANSES to examine the most recent studies on the oral toxicity of TiO_2. Subsequently, ANSES issued an opinion on April 12, 2019 (68). They decided that there was insufficient data to address uncertainties about toxicity, and a better characterization of E171 was required. They recommended limiting exposure for workers, consumers and the environment by promoting safe products that are equivalent in function and efficacy and that are not, or do not contain, nanomaterials (57). As a result, the French government felt that there was too much uncertainty and on April 17, 2019, decided to prohibit the sale of foods containing TiO_2 for at least one year; namely, from January 1, 2020 to December 31, 2020. France based this safeguard measure on what is allowed under Article 52 of EU Regulation 178/2002 that states that procedures for the authorisation of certain substances have to be reviewed within one year (67,69). Subsequently, on December 21, 2020, the French government decided to extend the ban for one year, effective from January 1, 2021 (70). During this year, the EC made the decision to ban TiO_2 in the EU (12).

4.1.4.2 European Food Safety Authority evaluations

1) 2016: A re-evaluation of titanium dioxide as a food additive

Under the re-evaluation program for food additives initiated in 2009, TiO_2 underwent its first re-evaluation in 2016 *(Figure 3).* EFSA confirmed that it was safe for use as a food additive. Firstly, they concluded that the bioavailability of TiO_2 is low and independent of its particle size. As such, the vast majority of an oral dose of TiO_2 is excreted unchanged in the faeces, and only a small amount of up to 0.1 % is absorbed by the GALT. From here it is distributed to various organs, out of which elimination is variable. It was further concluded that with oral ingestion of TiO_2 micro- and nanoparticles, there is most likely no genotypic hazard *in vivo*. The panel could not reach a definitive conclusion on the potential adverse effects on the reproductive system. In fact, the studies that demonstrated this used materials that did not correspond with E171, and in the limited database on reproductive endpoints of E171, no evidence was found of such an effect. The panel was also unable to determine an ADI and it was concluded that definitive and reliable data were needed on the reproductive toxicity of E171 for the establishment of an ADI (71). So overall, TiO_2 was still considered safe by EFSA and its use as a food additive was not affected (37).

2) 2018: Evaluation of four new studies raising concerns about potential toxicity of titanium dioxide used as a food additive

Following EFSA's 2016 report, the EC made a call for data to enable a re-evaluation and close all data gaps. A subsequent evaluation of TiO_2 followed in 2018 *(Figure 3),* since several studies raised again concerns about the toxicity of TiO_2 (61). These studies concerned both *in vivo* rodent experiments as *in vitro* research, indicating toxicity at the colon, liver, and potentially the reproductive organs, as a result of exposure to TiO_2 nanoparticles (18,23,72,73). Overall, it was concluded that the studies did not justify reopening the existing EFSA opinion on the safety of TiO_2 in form of E171 as a food additive. EFSA cited reasons such as non-representative TiO_2 materials or administration methods, and uncertainties surrounding the study design, for the lack of sufficient evidence regarding the potential risks of E171. Since the four studies contained uncertainties about whether TiO_2 was toxic or not, they were not considered relevant to the risk assessment of food-grade TiO_2 (30). Therefore, it was decided that the results did not provide sufficient evidence to conduct a new carcinogenicity study (23,30). Nevertheless, this decision could be reconsidered in the light of new information. Further research on the potential effects observed in the studies could increase the applicability to the risk assessment of E171 by reducing the level of uncertainty (30).

3) 2021: Final safety assessment of titanium dioxide as a food additive

In 2021, in response to the uncertainty created in France, the EC requested EFSA to conduct a new safety assessment of TiO_2 as a food additive *(Figure 3)*. EFSA took into account all new data that had become available since the evaluation in 2016. These included data generated by a consortium of interested business operators in response to the data call launched by the EC, and new data extracted from the published literature. In addition, data from an extended one-generation reproductive toxicity study was reviewed. This led to the conclusion that a potential risk of genotoxicity could be associated

with TiO_2 particles in E171 (59). No cut-off value for TiO_2 particle size with respect to genotoxicity could be established, since available data were insufficient to determine threshold doses/concentrations of TiO_2 particles below which genotoxicity would not occur (37). The panel concluded that TiO_2 particles show low absorption (59). Although, TiO_2 in form of E171, as well as test nanomaterials, could accumulate in internal organs and tissues to levels that could cause genotoxicity. This would result from the long half-lives of elimination for TiO_2 particles in major internal organs (37). No evidence was found that E171 could result in general toxicity, organ toxicity and reproductive toxicity, but some findings in animals indicated concern for immunotoxicity, inflammation and neurotoxicity, due to the presence of several immune-related and inflammatory markers. Furthermore, the panel concluded that TiO_2 particles could result in DNA strand breaks and chromosomal damage, but do not cause gene mutations (59). Potential mechanisms for genotoxicity could be through generation of reactive oxygen species, chronic inflammation, or direct interaction with chromosomes (37). The panel considered studies with TiO_2 nanoparticles relevant for the safety assessment of TiO_2, as TiO_2 particles in pure E171 are likely to form agglomerates. If dispersion procedures are used in the formulation process, these agglomerates may deagglomerate, which can result in many free TiO_2 nanoparticles. Conditions in the GI tract may also influence this proportion of free nanoparticles. When particles were smaller than 30 nm, they were no longer considered relevant, since this particle size was not used in food (59). Criticism came from many directions following this EFSA conclusion, mainly from pharmaceutical companies and industry organisations, but also from other countries (12,74,75). The EFSA evaluation would have been based mainly on tests using test material not representative for E171, as well as exposure conditions not representative for how humans are exposed to TiO_2, like intraperitoneally. Furthermore, EFSA did not consider certain relevant studies, like the study of Blevins et al. (55), which showed that there is no genotoxicity of TiO_2. EFSA also mainly did a safety assessment of TiO_2 nanoparticles, while E171 is not a nanomaterial (37).

4.1.4.3 Findings by the Committee on Mutagenicity (COM) and Committee on Toxicity (COT) of The UK on the safety of TiO_2 as a food additive

Shortly after the publication of EFSA's report, the COM and COT conducted a safety review of TiO_2 and published their opinions in May and August 2021, respectively *(Figure 3)*. The findings were not in line with the EFSA opinion, and they challenged that TiO_2 could cause genotoxicity. The COM decided that there was insufficient robust evidence to draw a definitive conclusion. They felt that more reliable and robust data sets were needed to draw a conclusion about the mutagenicity of TiO_2 (60). The COT concurred with this conclusion and felt that EFSA's conclusions were based on very weak evidence and may cause unnecessary concern to the public (61).

4.1.4.4 Health Canada's evaluation of titanium dioxide as a food additive

In June 2022, Health Canada conducted an independent safety assessment of TiO_2 in response to the announced ban in the EU *(Figure 3)*. However, the findings of Health Canada did not correspond with those published by EFSA. Health Canada claimed that the studies raising toxicity concerns about TiO_2 did not use the same food-grade TiO_2, and the studies that actually did use food-grade TiO_2 broke it up

into smaller particles. Consequently, these were not representative for TiO_2 as a food additive (60). They found no evidence of cancer or other toxic effects in mice and rats exposed to high concentrations of TiO_2. Furthermore, no changes in DNA were found and no reproductive toxicity, immune toxicity, developmental toxicity, no damage in the GI system, nervous system or other adverse effects on the general health of the animals were observed. They concluded that there was not enough conclusive scientific evidence that could demonstrate toxicity of TiO_2 that may pose a problem to human health. However, they would continue to monitor scientific data and possibly re-evaluate their opinion as needed (64). Hence, no compelling health risks were identified by Health Canada, yet they did recommend further research. For example, studies using complex *in vitro* gut models that closely reflect the *in vivo* situation should be conducted. They felt that the EFSA publication could not present sufficient evidence and that they could cause unnecessary distress to the public by their conclusion (37).

4.1.4.5 FDA's opinion on the safety of TiO_2 for use in food

The FDA carried out an independent safety evaluation of TiO_2 as well during 2022 *(Figure 3)*. They evaluated the EFSA findings and concluded that TiO_2 does not raise health concerns. They also noted that some genotoxicity tests included materials unrepresentative for TiO_2 as a food additive, and other tests included non-representative routes of administration. Therefore, TiO_2 may still be used as a food additive. However, this is subject to some conditions, including that TiO_2 should not exceed 1 % of the weight of the product (62). A second requirement is that mixtures of food colourants made with TiO_2 may contain only appropriate diluents, namely silicon dioxide or aluminium oxide, as dispersants and not more than 2 % in total (76). Furthermore, they guaranteed that TiO_2 could be safely used in cosmetics, even cosmetics intended for use around the eye (32).

4.1.4.6 The actions of other countries regarding the safety of TiO_2 in food

While some countries choose not to adopt the EFSA opinion, others either conduct their own re-evaluation or adhere to the EFSA opinion after EU's food ban on TiO_2. Switzerland and Jordan are examples of countries following the EFSA opinion to ban TiO_2 in food (12,77). The Jordan Food and Drug Administration banned imports of TiO_2 and foods containing TiO_2. Furthermore, its use in food production processes was prohibited. Finally, the registration of foods for special uses and dietary supplements for athletes was suspended. These actions became effective on January 1, 2023 (78).

Food Standards Australia New Zealand (FSANZ) evaluated TiO_2 in 2016 and determined that there was no evidence to suggest any significant health risks related to its use as a food additive. In Japan, it was used in food without limitations, except in a few categories where it was prohibited. Finally, in India, TiO_2 was permitted in chewing gum up to a maximum of 1 % and in powdered concentrate mixtures for fruit drinks up to a concentration of 100 mg/kg. All these countries have recently evaluated or are currently re-evaluating the use of TiO_2 in response to the rising concerns about possible toxicity (79). FSANZ completed the safety assessment of TiO_2 in September 2022, based on the published scientific literature and various information received about the safety of TiO_2 *(Figure 3)*. As a result, they concluded that there was no evidence that dietary ingestion of TiO_2 does pose a health risk to humans. In this regard,

they shared that TiO_2 has been used in a wide range of foods for many years, and no adverse effects have been reported to date. Therefore, they decided that the use of TiO_2 poses no safety concerns (63). In the meantime, JECFA is also conducting an independent assessment on the safety of TiO_2. Following a call for data in November 2022, with a submission deadline of February 2023, they are currently conducting a comprehensive evaluation, which is expected to be completed by 2024 (80). *Figure 4* illustrates whether or not TiO_2 has been banned in different countries around the world.

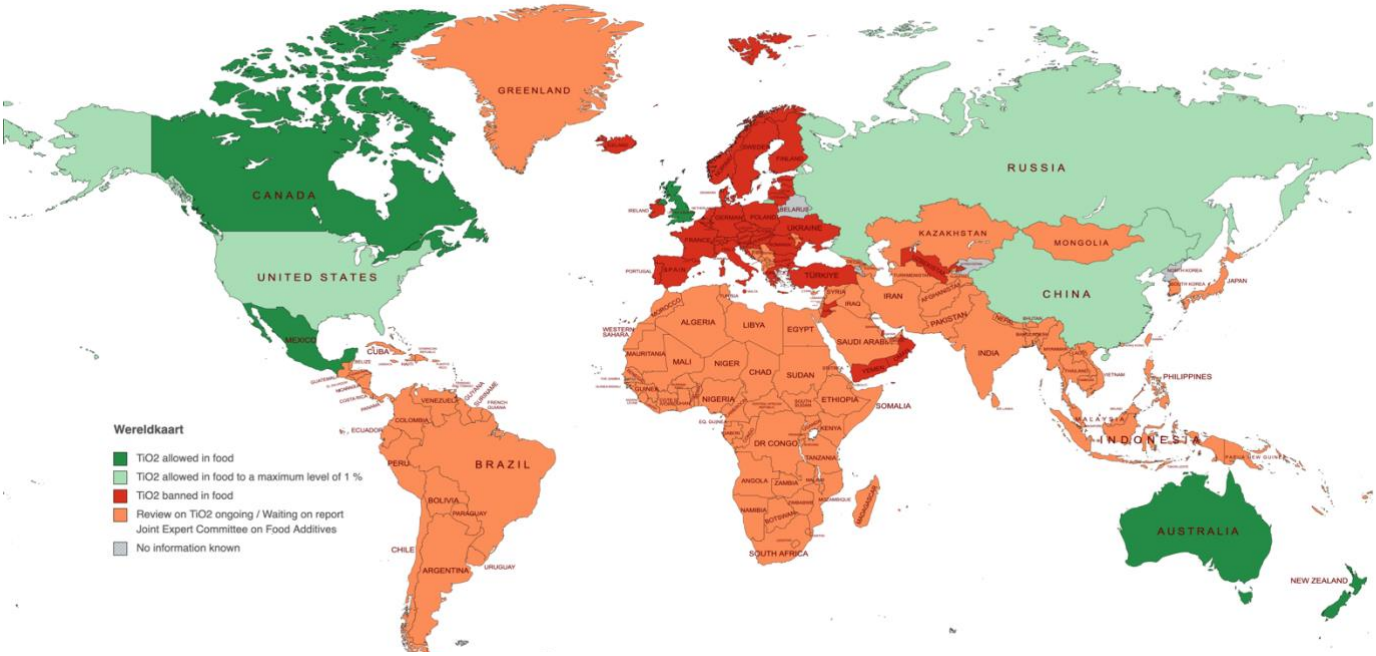


Figure 4: Illustration of the status whether or not TiO_2 has been banned in different countries in the world. (Retrieved from various sources, both writen as oral, under which the presentation of Kevin Hughes (12).)

4.1.4.7 Weight of Evidence assessment by an independent expert panel

In addition, the Titanium Dioxide Manufacturers Association, representing major European producers of TiO_2, asked an independent expert panel of toxicologists and other relevant experts to perform a weight of evidence evaluation of TiO_2 following the situation in the EU *(Figure 3)*. In October 2022, their analysis led to the conclusion that genotoxicity cannot be attributed to TiO_2, as none of the data examined suggested that TiO_2 is capable of inducing DNA damage. There appeared to be differences between the EFSA and expert panel assessments in terms of the types of studies and endpoints included or excluded, how reliability was scored and how the test design was assessed. Due to this different approach, EFSA considered more studies relevant compared to the expert panel. However, the expert panel included more *in vivo* studies, yet concluded that significantly fewer studies were positive in terms of toxicity (60). It was proven that genotoxicity was associated with factors like oxidative stress, inflammation, apoptotic cytotoxicity or necrosis, suggesting that it could be secondary to physiological stress. Furthermore, no *in vitro* and *in vivo* gene mutations were found, confirming this finding. However, a definitive conclusion was difficult to reach. For this, more robust *in vivo* gene mutation studies would be helpful. Furthermore, no relationship was found between particle size and possible genotoxicity. Neither nanoparticles, nor larger particles of TiO_2 had any correlation with a specific genotoxicity response (60). In summary, no direct evidence of a DNA breakage mechanism of TiO_2 was found (37).

4.1.4.8 Review of titanium dioxide via inhalation by the Risk Assessment Committee (RAC)

In October 2019, the EC amended regulation (EC) No 1272/2008 with regulation (EU) 2020/217 *(Figure 3)* (81). This meant that the EC reclassified TiO_2 as carcinogenic by inhalation, following a review of the RAC, a committee of the European Chemicals Agency (81,82). TiO_2 should be classified as hazard class carcinogen 2 and hazard statement H351, when the substance or mixture contains 1 % or more particles smaller than or equal to 10 µm. Furthermore, the label on mixtures containing TiO_2 must state that hazardous inhalable dust is generated during use, which may not be inhaled (EUH212). In addition, solid mixtures should be labelled with EUH212 if they contain at least 1 % TiO_2, regardless of the particle size. Liquid mixtures do not belong to the carcinogenicity 2 classification, but if they contain more than 1 % TiO_2 particles less than or equal to 10 µm, it should be listed on the label that dangerous inhalable droplets can be formed when atomized, which may not be inhaled (EUH211) (58,82).

In November 2022, the Court of Justice of the European Union (CJEU) ruled that the EC made an error in evaluating the credibility and suitability of the study that led to the reclassification of TiO_2 as a class 2 carcinogen *(Figure 3).* The RAC would have made the lung overload assessment based on a scientific study that used a density value of non-agglomerated particles of TiO_2. However, particles would tend to agglomerate, and these agglomerates would have a much lower density. In addition, such classification could only concern a substance with the intrinsic ability to cause cancer, which criterion was not met. As a result, the conclusion would not have been reliable according to the CJEU (65). This judgment resulted from three different lawsuits, including one brought by members of the TDMA (83). Subsequently, this decision was appealed by the French government on February 8, 2023 to overturn the classification of TiO_2 as carcinogenic, considering that the General Court crossed the limits of its judicial review by conducting its own assessment and interpretation of the scientific data. This appeal had a suspensive effect on the ruling and the class 2 carcinogenic classification will therefore remain until the end of the procedure (66).

4.1.4.9 Opinion of SCCS on titanium dioxide used in cosmetic products

In October 2020, the Scientific Committee on Consumer Safety published a safety assessment of TiO_2 in cosmetics *(Figure 3)*. They concluded that it is not safe in hair styling products in spray application, even below a concentration of 25 %, and poses a risk to consumers and hairdressers. It would be safe up to a maximum concentration of 1.4 % for consumers and up to 1.1 % for hairdressers. In contrast, SCCS concluded that pigmented TiO_2 is safe in loose powder makeup up to a maximum concentration of 25 %. These conclusions were based only on possible carcinogenicity via inhalation, i.e., from aerosol, spray or powder products (36). The SCCS considered nanomaterials of TiO_2 relevant, since pigmented forms of TiO_2 contain a significant proportion of nanoparticles. However, resulting from the EFSA opinion, the EC requested the SCCS in May 2022 to re-evaluate the safety of TiO_2 in cosmetic products, with a particular focus on genotoxicity via inhalation or oral exposure (37,84). Dermal exposure should not be reconsidered, as it was believed that TiO_2 is not absorbed through the skin. On June 22, 2022, the SCCS confirmed this request and they were granted a nine-month deadline to complete the assessment (84). Nevertheless, no update on this topic is published in the meantime.

4.1.5 Possible ban of titanium dioxide in medicinal products in the European Union resulting from the EFSA statement

4.1.5.1 Omission of titanium dioxide

When TiO_2 is present for merely aesthetic reasons, it might be acceptable to omit it with possibly minor adjustments in quantitative composition. If TiO_2 performs other functions, an alternative excipient would have to be found to replace it (85). However, since TiO_2 performs the function as opacifier in many medicinal products, omission might have many implications. For photolabile compounds, there may be a stability problem (11). In addition, there would be far fewer colours available, since TiO_2 would be applied to opacify coloured systems. A change in appearance of the tablets would make identification difficult at various steps, from production to intake of the medicinal products (14,86). Also clinical trials would be impacted, as the possibilities for masking medicinal products would be significantly reduced (11). Moreover, it is described in the literature that a large proportion of oral medicinal products would have to be reformulated when TiO_2 is omitted. The granulation, mixing and tabletting phases may change due to changes in the composition and properties of the pre-tablet material. This could change powder flowability and compression profile, which could impact tablet strength (46). Opacifiers like TiO_2 would protect the medicinal product from light. When this opacifier is omitted, it is claimed that the protective function must be replaced. Blundell et al. (14) suggested that a move to uni-dose packagings, for example non-transparent blisters, could be considered. Drawbacks of these would be not allowing other moisture or oxidation-inhibiting components. Moreover, when healthcare providers or patients remove medicinal products from their original packaging, for example to fill a pillbox, the stability of the medicinal product may no longer be assured as the medicinal product is no longer protected (14).

4.1.5.2 Replacement of titanium dioxide

1) Difficulty of replacing titanium dioxide

According to EMA, based on available data before September 2021, no material has been identified that offers the same unique combination of properties as TiO_2 (49). Due to its distinctive properties, limited alternatives are available to substitute food grade TiO_2. Currently there is only one white alternative on the list of food colourants, namely Calcium Carbonate ($CaCO_3$) or E170, which itself is being reviewed by EFSA (12,48). In addition, there would be a lot of challenges to get the same results as with E171. All materials identified as alternatives so far, for example rice starch, talc and dicalcium phosphate, do not achieve the same technical efficiency (12,46). These materials exhibit lower UV light protection, a lower refractive index, lower opacity and much more batch-to-batch variability. Furthermore, much higher concentrations of these alternative materials would be needed to achieve the same outcome. In addition, research on new alternatives would require much more time than current timelines allow. Even then, equivalence would not be achieved and several characteristics of the dosage forms would change (12). Moreover, almost all anti-counterfeiting, tablet identification and marking mechanisms would be significantly affected if TiO_2 needs to be replaced, and ink printing is also done with TiO_2. It is also reasoned that particle size and efficiency are intrinsically linked and that without nanodimensions,

materials are likely to be much less efficient. Therefore, some of the materials proposed as alternatives to TiO_2 may also be considered nanomaterials (11,14).

2) Alternatives to titanium dioxide: requirements and possibilities

The alternative material must have similar pharmaceutical properties such as stability, physicochemical properties and compatibility with the other excipients and the active ingredient of the medicinal products. Further, it should be a quality colourant and opacifier at sufficiently low doses (14). In addition, any alternative should have an acceptable safety profile (49). Replacing TiO_2 would have various profound implications (46). For example, the blocking of light is an important function of a coating that also provides longer shelf life and fewer storage restrictions. Not all products could provide this feature (49). As a result, it may be necessary to adjust the storage conditions or shorten the shelf life (85). An evaluation should be made to determine whether the change of excipients and as a result the composition of the product affects the quality and manufacturability. Therefore, reassessment of the production process and process validation would be required (85). Furthermore, when bioavailability is impacted, a bioequivalence study should be carried out (46). If light-sensitive drugs do not have protective packaging, photostability testing would need to be performed as well. Finally, it is also important that the changes do not affect taste acceptability in patients (85). In many cases, the colour and appearance of products will no longer be the same which could already greatly enhance patients' non-compliance (11). It has been shown that patients who have to switch between medicinal products with different appearances showed lower adherence (86). In fact, changing the colour of a product increased non-compliance to 34 %, and for a change in the shape of a tablet this increased to 66 % (11). Because TiO_2 would provide homogeneity of colour and appearance which clarifies batch-to-batch differences, patient confidence is promoted (14). In addition, the colour of the product is critical in distinguishing different medicinal strengths (49).

For coatings and capsules, the most apparent options appeared to be various forms of $CaCO_3$. Other materials that have been identified, which met some of the required material properties, included phosphates and carbonates, starch, isomalt, talc, zinc oxide and cellulose derivatives (14,87). With talc, caution must be taken for the related silicate asbestos in talc, and the difficulty in distinguishing the two silicates. Combinations of the identified alternatives may be required to meet the necessary attributes. In addition, certain alternatives would require additional compatibility studies, mainly the carbonates and phosphates, as they can change the pH of the dosage form (14).

3) Regulatory requirements of alternatives

For now, the use of TiO_2 is still allowed in medicinal products. Nevertheless, the pharmaceutical industry is expected to make every possible effort to search for alternatives and to control their use (88). In the Note for Guidance on development pharmaceutics (CPMP/QWP/155/96), the necessary data for replacing an excipient can be found. When it is a new excipient, used for the first time or for the first time through this route of administration, all information regarding manufacturing, characterization and relevant safety data should be provided (85). Since TiO_2 is present in different dosage forms and performs different functions, it would be very difficult to find one overall substitution (49). The scientific data that

are required to support replacement or elimination of TiO_2 in various pharmaceutical forms would depend on the function of TiO_2 in the individual medicinal product (85). Each medicinal product would therefore have to go through its own evaluation process. As a result, the different alternatives, formulation forms, stability data, clinical data and so on will all have to be evaluated and examined individually (14,49). It may take several years to reformulate each individual product, depending on the level of reformulation and the necessary studies that would need to be conducted. As a colourant, TiO_2 could be replaced by other colourants (49). These should be included in the Food Additives positive list in Regulation 1333/2008 and comply with Commission Regulation (EU) Nr 231/2012 on colourants for use in food (29,49,85,89). Further, it would be uncertain whether the possible alternatives would be positively assessed by EU regulators. Many would have outdated toxicological information and less real-world evidence for their use as colouring and opacifying agents (14).

4.1.5.3 Impact of banning titanium dioxide in pharmaceutical coatings

Medicinal products would require thicker coats with alternative materials. Exposure to adverse conditions may be greater as alternative materials would provide less protection and potential effects on the physical properties of the coatings and protection from moisture and light must be considered (11). However, formulations without TiO_2 are already under development, with for example $CaCO_3$ (87). There would be little information on how suitable they are for general use, given their limited use and therefore insufficient data (49). If TiO_2 must be replaced in coatings, the coating process itself would be affected as well (87). There would be a change in the time required to efficiently coat the tablets, since the film coating process depends on the viscosity of the spray solution, which is determined by its composition. Any alternative that impacts the viscosity would require the coating process to be re-optimized (14). Although, even if the viscosity and spray rate would remain the same, a higher weight increase in the coating would require a longer process time. This would be the case if identified alternatives exhibit lower opacity than TiO_2, as a larger amount of the product may be required to obtain the same coverage (87). If a longer coating cycle is required, additional research on the stability of the API in the hot, humid environment of the coating pan may also be necessary (14). In addition, increased weight gain could affect the medicinal product's release profile, as well as its bioavailability and the dimensions of tablets, which could affect packaging and stability (11,14). The alternative should also have a luster equivalent to that of TiO_2 (14). Furthermore, the replacement of TiO_2 would greatly reduce the colour palette. Pastel colours in particular would be very difficult to obtain, and the stability of coloured coatings would often be much lower and will fade after only a few hours of daylight (87). TiO_2 would also play an important role in a number of ways of identifying a tablet and/or introducing anti-counterfeiting measures into a tablet (50). The first is tablet debossing. If thicker coatings must be applied, the number, uniqueness and complexity of features that can be included in this debossing technique would be reduced. Furthermore, pharmaceutical print inks contain TiO_2 and would need an opaque layer for definition. Any deviation in the appearance of medicinal products could lead to misidentification and subsequently result in incorrect medicinal product intake or dosing. Moreover, TiO_2 would have the ability to be irradiated by an UV laser that changes the colour from white to grey without affecting the surface properties of the coated tablets, and since some anticounterfeiting

techniques for medicinal products are based on this capability, it would be favourable if possible alternatives have this capability as well (14). Finally, it would be common for alternative coatings to perform very well at lab scale, but to fail at industrial scale due to minor differences in equipment (87).

4.1.5.4 Impact of banning titanium dioxide in capsules

TiO_2 could affect the quality and performance of hard- and soft-shell capsules. It would provide complete masking of the capsules and would protect ingredients susceptible to light degradation (90). Aside from the fact that colour diversity would be reduced if TiO_2 will be banned, colour stability over time may also be adversely affected. To ensure that capsules are filled correct with API and that capsule shells does not break during this process, certain attributes, like weight uniformity and brittleness, must be met. Each of these properties could be affected by the replacement of TiO_2 (14). Capsules without TiO_2 are already introduced into the market as well (49). A researched option is iron dioxide. These would give the ability to obtain a wide range of colours. When TiO_2 is replaced by, for example, $CaCO_3$, the capsules would be only semi-opaque, leaving the content visible (90). Furthermore, $CaCO_3$ would not be compatible with gelatine, and is therefore incapable of being used in gelatine-containing capsules (14). Protection from UV light would be greatly reduced as well. However, the general characteristics of the capsule could be preserved with $CaCO_3$. Tetra sodium pyrophosphate and trisodium phosphate are solutions proposed by Lonza. Good results could be obtained with them, but these are not authorized as colourants following regulation 2009/35/EC (33,90). Other options are being further explored, but also in terms of capsules, there would not be a one-size-fits-all approach and a possible solution would differ between different medicinal forms (90).

4.1.5.5 Variation procedures resulting from banning titanium dioxide

After reformulation, variation procedures are required to approve the changes before the product can be reintroduced into the market. These procedures can be time and cost intensive for different stakeholders, e.g. authorities and Marketing Authorisation Holders (MAHs), which could lead to significant pharmaceutical shortages or withdrawals. Shortages may arise either from the prioritisation of certain products or from the inability of the different stakeholders to handle the sudden rise in demand. Post-approval variation procedures could be time-consuming, dependent on the nature and type of the variation (49). An overview of the possible variations can be found in *Appendix 8*. Variation procedures for excipient composition or colour replacement could be completed and approved as early as 30 days (49). In fact, addition, removal or replacement of the colouring system is a Type IA_{IN} variation. In this case, TiO_2 performs merely the function as colourant and the functional characteristics may not be altered by the change, the stability profile should remain similar, the change should not affect differentiation between strengths, should not adversely affect taste acceptability for paediatric formulations or should not raise potential safety concerns (91). A modification of an excipient that has other functions on top could take up to three months (49). Changes in a test procedure, including replacement or addition, that may be a consequence of replacing or removing TiO_2 would be a Type IB variation. Also, changing the type of container, which could be necessary when the UV filtering function of TiO_2 is lost, should usually be submitted as a Type IB variation. Moreover, for a change in the physicochemical properties of the

excipient that may affect the quality of the final product, even a Type II variation could be required (91). In practice, these changes would almost never be uncomplicated and regulatory procedures could take up to one year. With major changes in composition of, for example, a functional coating, this timeframe could even extend to more than one year. Research showed that a change in excipient is rarely filed as a low-risk Type IA variation. Variation procedures for the replacement of TiO_2 with another excipient are expected to be part of a grouped change application, with the associated complexity of submission and review. Due to the large numbers of variation requests that would result from a TiO_2 ban, and the reformulation of the many medicinal products, there may be capacity issues within the regulatory network (49). Workload distribution and cooperation between MAHs and National Competent Authorities should be strongly considered (85). Prioritisation would be very important and must take into account several factors, such as expected benefit, challenges and threats (49).

4.1.5.6 Differences in titanium dioxide use between markets

It would be possible that in certain countries and certain markets, existing products or products soon to be marketed may not require a modification or a modified product would not even be accepted. Some markets value product appearance more than others, and some simply do not have the resources to start researching and implementing changes for such a large proportion of their OSDs. This may result in some pharmaceutical companies introducing different product lines for different markets. If two products are produced in the same production facilities with the same quality regime, but with different analytical methods and final specifications, they may still have different ultimate quality. Furthermore, differences in shelf life are also possible and there may be differences in appearance between batches. The possibility of problems with quality also exist, and these problems may be different between the two products. Moreover, preventive measures against counterfeiting may differ (11).

4.2 Phase 2: Semi-structured interviews

4.2.1 Included participants

22 participants were enrolled from five different stakeholder groups *(Table 3).* Participants from the US, France, UK, Denmark, the Netherlands, Germany, Switzerland and Belgium were included.

Table 3: Participants enrolled in each stakeholder group.

Stakeholder group	Profile	Number of participants
Industry	Individuals solely active in the pharmaceutical industry, consultancy companies in life sciences and/or pharmaceutical industry associations.	10
Academia	Academics employed at a university at a faculty in pharmacy, medicine or biomedical sciences, and sometimes additionally connected to the pharmaceutical industry, e.g. by working at consultancy firms.	3
Decision makers	Individuals employed at regulatory bodies, government agencies and policy makers in the EU.	4
Healthcare providers	Pharmacists employed in a pharmacy or involved in clinical trials.	2

Patient organisations	Individuals working or volunteering in a patient organisation.	3

Results from the interviews were first described thematically and afterwards presented by stakeholder group to clearly outline their priorities. Discussed themes include the origin of the TiO_2 discussion, challenges and concerns about the TiO_2 situation, the global situation of TiO_2, feelings and attitudes about the TiO_2 discussion and the potential next steps.

4.2.2 Origin of the discussion on titanium dioxide

According to some stakeholders within the industry group, the discussion on TiO_2 started with the introduction of the concept of nanoform ingredients about ten years ago, when the food legislation was revised. Mainly France would have been very strong on the nanotechnologies from a risk assessment standpoint. TiO_2 was *"the flagship nano ingredient that started to concentrate a lot of political discussion already 10 years ago in food.",* Industry 2 (ID2). As a result, feelings were divided in the industry when the EFSA ruling followed in 2021. About half of the industry stakeholders saw it coming, as this issue had been discussed for a few years, mainly in the context of food regulation, and had therefore been working on it. Others were very surprised and did not expect EFSA to go ahead with the ban. The industry stakeholders realised that food regulation was linked to medicinal products, so any action there had an impact on their industry. Therefore, a lot of stakeholders within the industry indicated that they had been following this issue for quite some time. Also, the EFSA opinion has been called a *"non-opinion"* (ID3), given that they could not make a concrete statement, but just could not rule out the possibility of genotoxicity. This left the industry with many uncertainties, addressed in the following sections. Decision makers and academics were also aware of the problems associated with TiO_2 and did see it emerging more, while healthcare providers and patient organisations lacked awareness of the situation and had limited knowledge of the history, which made them unable to provide an informed opinion on whether or not they saw a ban coming.

4.2.3 Faced challenges in the current situation of titanium dioxide

4.2.3.1 Differences between food and medicinal products

Stakeholders from all stakeholder groups raised many differences between the use of TiO_2 in food versus in medicinal products. Firstly, the concentration in medicinal products would be much lower and TiO_2 would be of a different, higher quality. Furthermore, the fact that the use of medicinal products is restricted was considered important at this point, compared to food where persons can consume unlimited amounts. On the other hand, replacing TiO_2 in food would not be the same as a replacement in medicinal products according to the industry and academics group. In food and food supplements, there would be much more flexibility and less restrictive regulatory procedures involved. The postponement of the decision until 2025 and the continued allowance of TiO_2 in medicinal products was attributed to this reason. However, some stakeholders among the decision makers group argued that if the food industry could reformulate, the pharmaceutical industry should also be capable of doing so. Decision Maker 1 (DM1) stated the following: *"In the food sector, the industry had to adapt. If you compare the food industry and the pharma industry, I don't think the pharma industry has less resources."* Industry stakeholders and

some academics strongly disagreed, given the huge differences between food and medicinal products. Quoted by Academic 2 (AC2): "*When I hear politicians and others in Europe say, well, the food industry changed, we banned it and they've changed. There's no reason the pharmaceuticals can't do that too: wrong! That's simply not true. Changes are completely different when you try to apply it to pharmaceuticals."*. The other included decision makers aligned themselves more with the views of industry stakeholders and indicated that a ban in medicinal products would be much more invasive and intensive. A few academic stakeholders' visions were more in line with those of healthcare providers. They indicated that reformulation in food and drugs is completely different, but if it were really necessary, it would work out. Finally, participated patient organisations indicated that patients are probably less aware of this, and that they would believe that the pharmaceutical industry should be able to reformulate. Overall, the opinions of different stakeholders were not aligned, as some very much emphasised the differences between food and medicinal products and others considered them much less important.

4.2.3.2 Risk benefit analysis

Most stakeholders agreed that when a particular risk is identified in food, this risk should be avoided. Although the majority of industry stakeholders did not approve of the ban on TiO_2 in food, stakeholders within the patient organisations, decision makers and healthcare providers shared the above view, since TiO_2 would have no important function in food, but would be present for aesthetic reasons. On top of this, all risks would be determined based on total exposure of everything a person consumes. This would be different in medicinal products, where a benefit risk analysis of one finished product would be in place. Although there were disagreements between and within stakeholder groups as to whether excipients were part of the benefit risk. Industry groups and some academics strongly believed that TiO_2 should be part of the benefit risk given the positive and unique properties that it provides to the medicinal product. Healthcare providers agreed and felt that excipients can also perform a very important function within a medicinal product. However, they did understand that not everyone shared this opinion. Within the patient organisation groups, there was discordance at this point. Some felt that if there is a risk associated with an excipient, this excipient should be avoided. Others believed that the positive attributes of an excipient should definitely be considered. Within the decision makers group, a similar pattern was observed. In the current situation, there would be the risk of the potential toxicity of TiO_2 on the one hand, but also the risk of unavailability to the medicinal product and the associated threats. On the other hand, there would be the therapeutic benefit of being able to receive the therapy. At the product level, TiO_2 would also have many positive properties which should be considered according to the stakeholders.

4.2.3.3 Regulations on titanium dioxide

The EC would be obliged by the commission regulation to decide on the use of TiO_2 in medicinal products by 2025. The pharmaceutical legislation is currently under review, but implementation may not happen in time, so the current legal system would still apply. Within the decision makers group, three options were considered. Maintain the status quo, cut the link between medicinal products and food completely, or find an intermediate solution. Some stakeholders within the industry group indicated that a leaked

version of the draft of the new pharma legislation had already surfaced. This version included an additional set of colours that may not be used in food, but which are allowed in medicinal products. TiO_2 would be explicitly mentioned as one of the candidates. The industry stakeholders and some academics mentioned that they would love the food and pharma regulations to be separated, since they considered it controversial how current regulations are structured is leading to a domino effect. Regulators would be encouraged to review the use of TiO_2 in cosmetics and medicinal products, because of the decision in food. These were considered far-reaching implications, and industry stakeholders believed that a system is needed where different outcomes for the same substance or molecule in different classes of products would be possible. Without stating that they agreed, healthcare providers found the link between medicinal products and food very rational. *"The bottom line then is that if it's not considered safe to eat, you don't want to put it in your medicinal product either."*, Healthcare Provider 2 (HP2). Additionally, in the EU there would be guidance on the identification of medicinal products and the avoidance of medication errors. As quoted by ID3: *"Kind of catch 22 is that in Europe there are guidelines for identifying and avoiding medication errors in medications. So pharmaceutical companies have to comply with those guidelines, but on the other hand, politicians remove colours and the ability to colour medications."*

Furthermore, the annulation of the regulation of the classification of TiO_2 as a carcinogen would have been the result of the CJEU considering the classification being based on poor studies, which was found unacceptable, as stated by the industry group. Industry participants felt that the same happened with the ban in food. It was believed that a very strong legal case could be made against the food ruling, especially if it would be extended to medicinal products. Moreover, France would currently be appealing the CJEU ruling on the classification of TiO_2. Within the industry group, this was considered very disappointing, as this would drag on for years, retaining its classification as a carcinogen class 2.

Healthcare providers and patient organisations did not address the regulatory aspects.

4.2.3.4 Political aspect of the titanium dioxide discussion

On top of the obvious scientific aspect, the political aspect of the current TiO_2 challenge came up regularly. Stakeholders of the industry and academics group, as well as those in patient organisations and healthcare providers groups, and even some decision makers, expressed concern that decisions are being influenced by political perceptions rather than scientific evidence. Hence, the decision for a ban in food would have been taken rather because regulators got distressed after the ban in France and were under pressure from advocacy and consumer groups, than for its toxicological profile, as EFSA would never have said TiO_2 is unsafe. According to ID3: *"Any decision on banning something is a big decision, right? Especially in pharmaceuticals. Something as big as this has to be done really carefully and should only be done based on the science. We can't allow politics, we can't allow the media, we can't allow desired outcome syndrome to interfere with the science."* The industry participants hoped that science and final reports would be listened to, but were concerned that the decision on TiO_2 in medicinal products would also become a political one. They believed that the industry needs to feed all channels with valid and scientific information to prevent moving towards that direction.

4.2.3.5 Establishment of an acceptable daily intake of titanium dioxide

All stakeholder groups came to a consensus that setting an ADI could serve as an argument against banning TiO_2, as it could ensure its safe use. Although in practice this did not appear to be feasible. On the one hand, it was argued by both participants from the industry as decision makers if genotoxicity is present, the ADI would be zero. On the other hand, it would be very difficult to follow the daily intake up in reality. Participants from the industry, academics and decision makers indicated that healthcare providers and primarily pharmacists would have to monitor whether a patient's total intake of TiO_2 from all the medicinal products he takes stays below the established maximum dose. With prescription medicinal products, this was believed feasible, but OTC medicinal products can be obtained by patients unrestricted, without close follow-up. Despite there also being a maximum intake per day of OTC medicinal products, these would be difficult to monitor, especially in countries where these are obtainable outside pharmacies. Healthcare providers consider this a challenge, hence do feel that the necessary technology is required here to support them. HP1 shared: *"It is a very big challenge to include that in the medication review. There should be enough sources where you can consult it or possibly have it added to the pharmacy software where you get a pop-up of ADI exceeded. So, I do think it's a possibility, but there has to be the right technology behind it and the right person, because people need to be motivated to monitor it."* In any case, patient organisations did think an ADI could reassure patients.

4.2.3.6 Challenges related to replacement of titanium dioxide

All included stakeholders mentioned that replacing TiO_2 would be accompanied by several challenges.

1) Finding alternatives of titanium dioxide

First, finding alternatives would not be evident according to the industry stakeholders and some academics. However, other academic stakeholders were slightly more positive about the situation and were convinced that alternatives could be found. Opposed to industry stakeholders, who saw it less brightly. According to them, apart from potentially $CaCO_3$, there would be no viable alternative available. Others either do not have an E-number, meaning that they are not allowed for use in food and medicinal products, or would not be suitable to replace TiO_2. Healthcare providers expressed optimism about the potential for finding alternatives, as they believed there are numerous possibilities and they could not imagine that none of them could replace TiO_2. Within the decision makers group, opinions were divided, with some indicating the difficulties of finding an alternative, while others agreed with the academics stakeholders' and healthcare providers participants' views. Patient organisations showed less awareness of potential alternatives, but they stated that patients would expect alternative options to be available.

2) Use of other substances

Some stakeholders in the decision makers, industry and academics group expressed concern that a lot of other additives are closely being looked at, and possibly will be reviewed by EFSA in the coming years. In particular potential alternatives like iron oxides and $CaCO_3$. Quoted by DM2: *"It would be completely ridiculous if we pick something further down the list and then in three years' time, EFSA comes back and*

reaches the same conclusion and then we are back to square." This concern was not raised by the stakeholders within the patient organisations and healthcare providers group.

3) Properties of titanium dioxide

Furthermore, the industry stakeholders and some academics brought up the argument that TiO_2 would not possess one single function as a colourant, but is also an opacifier that protects against light and UV and reduces the amount of oxygen and moisture that can reach the medicinal product. Moreover, it is inert and would therefore be compatible with many ingredients. Its tremendously high refractive index would be enormously difficult to achieve with any alternative. As a result, pharmaceutical appearance would change. As alternatives would be unlikely to match these properties, they would impact the long-term stability and impurity profile of medicinal products. Consequently, the need for modification of the existing packaging materials may arise. Achieving a one-to-one exchange would be a challenging task as identifying an alternative that can perform all, or at least the essential functions, would be difficult according to the industry. Patient organisations included in the interviews cited the positive features of TiO_2 themselves and were concerned about the smoothness and size of tablets related to swallowability, as well as appearance and stability. Decision makers were aware that TiO_2 carries unique properties and understood the difficulty of a replacement. While some of them were optimistic about the possibility of finding alternatives, the others had more doubts about it. Included academics held divided opinions, as some saw TiO_2 as purely aesthetic and not essential to the medicinal product's therapeutic effectiveness. Healthcare providers participants did not address the properties of TiO_2.

4) Improvement in both excipient as finished product

Industry participants shared the opinion that if TiO_2 is replaced, it should be substituted with a superior excipient that would enhance the overall medicinal product. They were concerned that compromises would have to be made in terms of quality. Almost all industry stakeholders and a few academics believed that no alternative could lead to an equivalent product and only second-class products would result from replacing TiO_2. They also believed that TiO_2 free medicinal products brought to the market should have at least the same safety behind them. Included healthcare providers agreed. Within the group of decision makers, it was agreed that any alternative additive should be equivalent, leading to an equivalent finished product. Although disagreement existed as to whether the alternative should be superior. One decision maker argued that if TiO_2 were to be replaced, the alternative should yield improved outcomes rather than just equivalence, as investing all those resources in something that is not even an improvement would not be beneficial. The others believed that equivalence should be achieved. Patient organisations felt that medicinal products should remain similarly favourable to patients.

5) Formulation aspect of replacing titanium dioxide

Industry participants suggested that replacing TiO_2 would require a significant amount of effort and time, and that the reformulation process would be more complicated than it appears. The coating process would have to be adjusted, specifically air flow, pan speed, pan load, spray speed and exhaust air temperatures should potentially be adapted. During the film coating process, the ingredients would be exposed to heat, spraying and incoming coating air streams. From that point of view, API stability would

have to be considered. They also mentioned different holding times, bark stability and differences in process controls. With each of the alternatives out there, the product would have to be coated with a significantly higher weight gain of two to three times the weight increase with TiO_2, to get an acceptable level of opacity that would not even be the same as with TiO_2. This could impact dissolution, bioavailability and stability of the finished product. Afterwards, the new analytical method would have to be validated for the new formula. Ultimately, compatibility and stability studies would have to be performed again. One stakeholder from the industry quoted as such: *"Film coating with TiO_2 takes no more than two or three hours. If this suddenly takes five hours, it affects the processability of film coating tablets in the factories. We have less production and the product becomes more expensive, which definitely has an impact.",* ID5. Academics agreed that reformulation would be an enormous amount of work. However, some were positive towards the situation and believed it would be a feasible process despite the enormous workload. The other stakeholder groups had less knowledge and insights on this aspect.

6) Regulatory procedures resulting from replacement of titanium dioxide

Stakeholders from the industry, academics and decision makers groups believed the likelihood of a Type IA variation resulting from replacement of TiO_2 being reasonably low. In many cases, it would even involve Type II variations. These would be expensive, would take a long time and would require individual comprehensive evaluation. However, each formulation change would have its own variation package. The number of variation dossiers would be enormous and the decision makers, academics and industry participants mentioned the huge workload for regulators and pharmaceutical industry. However, one stakeholder from the decision makers indicated to believe that it would be feasible. Patient organisations, healthcare providers and some academic stakeholders believed that if needed, it would be achievable, but they expressed less understanding of variation procedures.

4.2.4 Concerns related to the current situation of titanium dioxide

4.2.4.1 Impact of replacing titanium dioxide on patients, patient adherence and appearance of tablets

A common perspective existed between decision makers and industry stakeholders to ensure that patients do not suffer from either a toxic substance or lack of their therapy, and that patients should be protected in any case. Participated healthcare providers, academics and patient organisations strongly agreed on this. Ultimately, the overarching priority was accessibility for patients, patients' lives and the quality of their lives. Industry stakeholders and part of the academics mentioned that the appearance of medicinal products would most likely change if TiO_2 is replaced with an alternative. Together with the participated patient organisations, they believed this would affect patient compliance. The majority of the decision makers stakeholders also feared that adherence could suffer, but the other questioned to what extent this is actually true in reality. Healthcare providers stated that current availability problems were already causing frequent switches to substitutes. As a result, some patients became already accustomed to change. Nevertheless, they mentioned that appearance of medicinal products is often the identification feature, especially in older patients or with polypharmacy, and a change in the appearance would be a challenge in terms of adherence. This was strongly emphasised by interviewed patient organisations.

They stated: *"Many people recognize their medication by the shape and colour of the pills as an indication, if all the pills are small white and round, then you have a problem.*", Patient Organisation 1 (PO1). Furthermore, it was highlighted by the majority of the industry stakeholders and academics, some decision makers and all healthcare providers and patient organisations stakeholders that if patients get to know about the current problematic and the ban of TiO_2 in food, their compliance could again suffer.

4.2.4.2 The importance of proper communication and the fear of a communication crisis

Communication was mentioned by all stakeholders to be of enormous importance and miscommunication should be avoided in any case. Especially among industry participants, healthcare providers and patient organisations, there was a high level of concern regarding incorrect communication about TiO_2 that could cause unnecessary panic. One of them phrased it as follows *"The biggest concern I have is possible communication crisis all the time. If there is a crisis of communication where patients or consumers start to freak out and suddenly do not consume because of the presence of TiO_2, we have massive disruption and that will have a much bigger health impact than TiO_2 itself."*, ID2. It would be very difficult to explain to the general public that TiO_2 is banned in food, but is still present in their medicinal products. Within the group of decision makers, there were inconsistencies as to what extent patients would already be aware and concerned. Some argued that after the ban in food, they already received regular enquiries about the use of TiO_2 in medicinal products. Others claimed to have heard very little about it and stated that patients were not aware of the situation. Nonetheless, there was agreement within and among all stakeholder groups that it is hugely important to communicate correct information through the right communication channels, being via the decision makers themselves or via official and reliable communication channels. Healthcare providers were aware to be often the primary point of contact and were therefore mentioned by all stakeholders to play an important role in this transmission of information. On top of this, patient organisations indicated that they would inform patients when the time is right. However, pharmacists and patient organisations highlighted that they should be informed in time, since they currently have very little notice of the situation. This should take place via national health authorities to overarching pharmacist associations and patient organisations. They felt correct and accurate messaging to patients to be important, since it was often already very difficult to get patients to take their medication, which could be further complicated due to miscommunication.

4.2.4.3 Impact of replacing titanium dioxide on resources and innovation

It was claimed by almost all industry stakeholders and some decision makers and academics that if all companies need to change the formulas of medicinal products containing TiO_2, it would massively exhaust their resources. This would not only be a huge investment in money, but also in terms of time and workforce. All of these resources invested in replacing TiO_2 and looking for alternatives, could not be used to develop innovative therapies. Although it was cited by a few industry participants that innovation could also be associated with replacement of TiO_2. However, the reformulation would bind resources that otherwise could be used for innovative processes. Consequently, all industry stakeholders feared that the number of new medicinal products coming into the market during subsequent years would be limited.

Beyond the pressure on companies' resources, regulatory bodies mentioned that they would be under enormous pressure as well. To review all the new data from reformulated medicinal products, industry stakeholders stated that regulators would need a huge amount of additional staff for which they would not have the capacity. Although for half of the decision makers stakeholders, this did not appear to be a concern. Further, industry stakeholders and some decision makers emphasised that if all the work force would be dedicated to this, new product development would again be pushed aside. This topic was not discussed by participants in the patient organisations and healthcare providers group.

4.2.4.4 Impact of a potential titanium dioxide ban on access and supply of medicinal products.

The number one concern of all stakeholders was the availability of and access to medicinal products. ID7 stated as such: "*My biggest concern is, no matter what decision is taken, we don't have a problem with access and supply of medicinal products to patients in Europe. That remains the standard concern and I think that's what we need to be looking at from now on to make sure that any steps as we move forward won't lead to that."* On the one hand, reformulating all 91,000 medicinal products containing TiO_2 would require an enormous amount of time and efforts for both industry and regulators. In addition, industry and some academics stakeholders revealed that not all companies are willing or have the ability to make this huge investment, for example small niche products that do not generate sufficient revenue or generic companies that do not have the set-up to conduct all these studies. This could cause life-saving medicinal products to be withdrawn from the EU market. There was concern within the healthcare providers group and included patient organisations about who would bear the cost of the reformulations. For the companies that do make the investments, these enormous costs were stated to be most likely borne by the patient, with a possibility of becoming too expensive for some patients to afford their therapy. The regulators were also concerned about the pressure on their capacities as cited above. This could again result in shortages if they are unable to keep up.

4.2.5 Global situation of titanium dioxide

4.2.5.1 Differences between countries and continents

Globally there was stated by all stakeholders to be no uniformity about the safety of TiO_2. These global inconsistencies caused considerable concern among stakeholders, since pharma is a global industry. If TiO_2 is banned only in the EU, a different formula would need to be commercialised here, while pharmaceutical companies highly prefer a global formula. These global differences, where a market authorisation is different in the EU than in the rest of the world, would cause a lot of pressure on production, distribution and supply, as well as huge pressure on the regulatory framework. The industry stakeholders and some academics stated that in case TiO_2 will be banned in the EU, there would be a specific production for the EU, medicinal products would have to change globally, or medicinal products would be withdrawn from the EU market. In the first case, the distribution chain was claimed to become more vulnerable to shortages. If problems would occur on the production line for the EU market, it would not be able to be taken care of by another production line for the US market, for example, since these medicinal products might contain TiO_2. This would also result in an increased risk of shortages and would

create a trade barrier. In addition, there would be the possibility that new pharmaceutical developments would only reach the market outside the EU, which could negatively impact the accessibility of medicinal products. Also, in terms of communication, it was emphasised by the patient organisations and healthcare providers that it might be very difficult to explain that different countries came to different conclusions on the safety of a substance. The majority of the decision makers stakeholders also expressed considerable concern about the global differences of this widely used excipient and its impact on medicinal product availability and innovation in the EU in the event of a TiO_2 ban.

4.2.5.2 JECFA

In the industry group, the included stakeholders were very curious about the JECFA report, which they believed will be very influential. There would be countries that follow the EU, countries that follow the US, and finally many countries that follow JECFA. They believed that this assessment may be an important signal, influencing other regulators in their final assessments and conclusions. Therefore, stakeholders in the industry group were counting for a rational outcome from JECFA during 2024. Although industry participants were hopeful for a conclusion in favour of TiO_2, their priority was that the conclusion should be based on well-established studies. They strongly believed that JECFA would ensure that the decision-making process is grounded on reliable scientific evidence. The other stakeholders had little or no contribution on this topic.

4.2.6 Attitudes and feelings toward the current titanium dioxide situation

Industry participants and some academics considered current developments regarding TiO_2 highly controversial. Usually, when there is a gap in data, as was the case in the 2021 EFSA assessment, a request for additional data is made. However, this request was not carried out, and the industry participants expressed regret that they were not given the chance to provide the missing data. They believed the EU's approach being rather conservative, too precautionary and risk averse and they argued that not much room had been allowed for other approaches. As such, ID10 stated: *"As in candies that can be consumed by children in uncontrolled amounts, that this could pose a risk and that there would be restrictions, for example, or in terms of a maximum amount would be more to understand. But the EC decided not to opt for use restrictions, but for a complete ban."* Even the healthcare providers stakeholders not fully agreed with the approach taken. They considered regulations that seek to protect people from every possible risk questionable, especially in this situation, since TiO_2 has not been proven to be toxic. Furthermore, what would be very controversial according to the industry stakeholders is when people would die because of not taking medicinal products due to the TiO_2 problem. They found it unfortunate to have to look at a very small amount of TiO_2, while other diseases would need this attention much more. Meanwhile, the majority of industry participants expressed optimism that a viable solution would be found allowing continued use of TiO_2. Nonetheless, they were already proactively working on alternatives and in case it would be necessary, these could be further developed. Decision makers were mainly concerned that if toxicity is observed, they would be forced to ban TiO_2. They indicated to be well aware of the difficulties that a ban may entail and hoped that the situation will evolve towards a positive

outcome for all stakeholders, but mainly towards safe use of medicinal products for patients. Patient organisations agreed, and hoped that the impact on patients could remain limited.

4.2.7 Next steps in the titanium dioxide challenge

4.2.7.1 Pros and cons of a potential titanium dioxide ban in medicinal products

Stakeholders within the industry group and some academics raised several arguments why a ban on TiO_2 would not be appropriate. The first was its safe use in the past. TiO_2 would have been used as an additive in medicinal products for many years without safety problems. Within the patient organisations and healthcare providers groups, and even within the decision makers group, most stakeholders agreed. Furthermore, the concentration in medicinal products would be much lower than in food, and according to some in the industry group, the concentration necessary to cause toxicity would be vastly higher than the concentration present in medicinal products and even in food. Additionally, the use of medicinal products would be restricted compared to the unlimited use of food. Even in chronic patients or polypharmacy, consumption would still be constrained and exposure to TiO_2 would be limited. On top of this, industry stakeholders mentioned that many of the studies showing potential toxicity of TiO_2 would have been conducted with unrepresentative materials for TiO_2 in food and medicinal products. As a result, industry and industry associations did develop a consortium to study the alternatives of TiO_2 and its safety. By generating evidence that could be used by the EMA, further evaluation of the feasibility of removing TiO_2 from the list of colourants for use in medicinal products could be supported. The majority of decision makers participants concurred with these arguments opposing the ban on TiO_2. However, they believed that if genotoxicity were demonstrated, this would constitute a strong basis for a ban. Healthcare providers, patient organisations and academic stakeholders were in strong agreement and believed that toxicity should be avoided at all costs. Industry stakeholders also agreed, but believed toxicity to be so minimal that medicinal use would not pose a risk to patients.

4.2.7.2 How to approach a potential titanium dioxide ban in medicinal products

If a ban were to be imposed nonetheless, stakeholders agreed that this would require appropriate timelines. What these timelines should be was a bit of a disagreement. According to the industry participants, it would take at least 10 to 15 years to implement the changes. Academia acknowledged that considerable timelines would be needed to complete all the necessary work and confirmed this timeframe. Within the group of decision makers, there was no unanimity on this period. Some of them felt the industry was playing with time. However, they were aware that in order to find alternatives and to demonstrate their safety, a particular timeline would be required. Although, many stakeholders within the industry group trusted the approach of the decision makers. They opined to know that they cannot enforce what they have done with food products, but for medicinal products, it could take many years. The decision makers also indicated themselves that they were looking to find a pragmatic approach to move forward carefully. In turn, industry stakeholders stressed to be working diligently to find data and alternatives to support the EMA by reaching a scientifically sound outcome. Furthermore, some believed that exceptions should be made for certain small-scale medicinal products, where the industry could

clearly demonstrate that it really does not make sense to reformulate. Some decision makers indicated that if a good justification is provided, making exceptions could be possible. In contrast, some of the industry and decision makers stakeholders mentioned this not being feasible in practice. One of them highlighted as follows: "*On what basis do you justify discrimination for a small volume versus a large volume product? I think that's tricky from a legal point of view."*, ID6. Within the group of healthcare providers, a possible solution at this point appeared banning TiO_2 in new developments, but remaining it in existing products. AC2 hoped as follows: "*So hopefully we can change the course in Europe, but if we can't, we got to make sure that we keep the rest of the world from catching the virus that apparently has existed in Europe."*

4.2.8 Patient perspective

Participants of patient organisations and healthcare providers described it being difficult to consider patients as one uniform group, as there would be many differences between individual patients. On the one hand there would be patients that are really engaged with their disease and their therapy, while others would always look for excuses not to take their medicinal products. For both groups it would be important that information about TiO_2 is brought in a proper and correct way. Patient organisations and healthcare providers indicated that they play an important role here. Patient organisations emphasised that with certain serious diseases, patients heavily rely on their therapy and if they should balance the risk of unavailability against a possible safety risk, patients would opt for an undetermined safety risk for the sake of the benefit of the therapy. It would not always be easy to find a therapy that a patient is really good with. If this suddenly changes, this would cause anxiety for the patient. Especially with chronic diseases, changes or unavailability of the patient's familiar therapy could cause problems. With more preventive medicinal products or medicinal products for less serious diseases, this would be often less the case and patients may be slightly more cautious if a potential risk is involved. In contrast, some included patient organisations indicated that *"Patients want to be 100 % sure that it's safe. If there's a hint of insecurity, people often aren't really going to nuance that.",* PO2. Especially if it does not concern an active substance, the patient would have little understanding of why TiO_2 cannot simply be replaced.

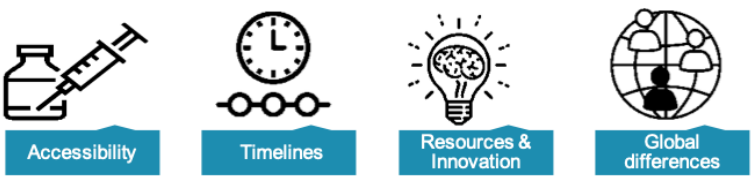
4.3 Main findings per stakeholder group

Table 4: Shared and specific priorities for each stakeholder group.

	Priorities for each stakeholdergroup
Shared priorities	**All stakeholders:** • Avoidance of patients suffering: accessibility for patients and the quality of their lives **Developers, academics and decision makers:** • Global differences in perspectives and regulations on TiO_2 • Impact of the TiO_2 situation on resources and innovation • Appropriate timelines for current research on alternatives and for the implementation of a potential ban **Developers and academics:** • Differences between food and medicinal products and benefit risk analysis **Developers, healthcare providers and patient organisations:** • Importance of clear and correct communication towards all stakeholders **Healthcare providers and patient organisations:** • Medicinal product appearance • Impact of the TiO_2 situation on the costs of medicinal products • Impact of the TiO_2 situation on patient adherence
Specific priorities	**Developers:** • Avoidance of political influences into the scientific discussion of TiO_2 • Difficulties related to replacement of TiO_2

4.3.1 Main findings within the industry group

Industry stakeholders regularly stressed that many medicinal products would be withdrawn from the EU market if TiO_2 is to be banned. This together with the enormous workload that replacement of TiO_2 would entail, could tremendously compromise the accessibility of medicinal products, resulting in far-reaching effects on patients who would no longer have access to lifesaving medicinal products. In addition, they emphasised that huge timelines would be needed in case of a TiO_2 ban. New pharmaceutical development would also be compromised. On the one hand, the enormous workload for regulatory authorities would devote their capacities to assessing these reformulations, delaying assessment of new medicinal products. On the other hand, industry stakeholders highlighted that new medicinal products containing TiO_2 may only be marketed outside the EU, leaving patients in the EU with potentially very serious diseases for which no therapies may be available. Furthermore, the differences between food and medicinal products were highly emphasised and in line herewith, it was indicated that a benefit risk analysis should be applied in the case of medicinal products. Industry stakeholders also feared that replacing TiO_2 would be accompanied by second-class products that are not as good as they could be. This would be a shame for patients to be denied the best products, when there is no demonstrated safety risk. One of the biggest concerns that emerged by the industry stakeholders was that decisions were no longer made based on well-founded science, but rather based on politic influences. In addition, they were afraid of a communication crisis where patients no longer want to take their therapy containing TiO_2, as this could again have a huge impact on public health *(Table 4)* *(Figure 5)*.



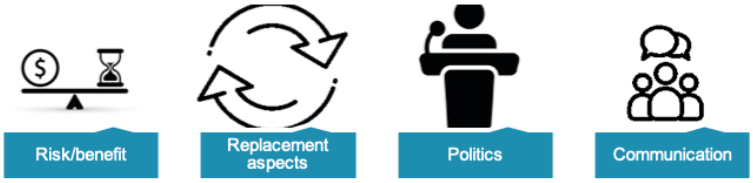


Figure 5: Main interests of the industry.

4.3.2 Main findings within the academics group

In general, most academics viewed the TiO_2 situation more positively. They believed TiO_2 was primarily used for aesthetic purposes and could be replaced with alternatives. However, all of them acknowledged the importance of conducting a benefit-risk analysis and the significant differences between food and medicinal products. The academics also agreed that a ban would require significant efforts from both companies and regulators and a huge amount of resources and costs, and that appropriate timelines must be provided. They emphasised the global impact and stated that formulas might need to be adjusted globally, given the pharmaceutical industry's global organisation. Ultimately, their foremost concern was ensuring the availability of safe medicinal products for patients *(Table 4)* *(Figure 6)*.

Figure 6: Main interests of academics.

4.3.3 Main findings within the healthcare providers group

Healthcare providers were aware that they are a primary point of contact for patients, and therefore play an important role in communicating appropriate information. To this end, they believed that they also need to be properly informed about the situation. Their biggest concern was the accessibility of medicinal products. They indicated that there were already a lot of availability problems and that this affects every day healthcare practice tremendously. When this would become worse, they feared that a lot of patients would no longer have access to their therapy, which could have major consequences. Pharmacists also indicated that pharmaceutical appearance does have an impact on patient compliance and prevention of medication errors, but again due to current shortages, switching to other medicinal products is already common. Lastly, they feared that medicinal products would become more expensive, which could also impact compliance and affordability of therapy for patients *(Table 4)* *(Figure 7)*.

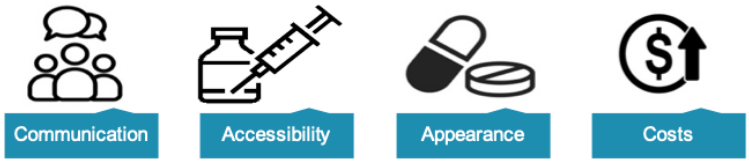


Figure 7: Main interests of health care providers.

4.3.4 *Main findings within the patient organisation group*

The interests of patient organisations were mainly in the availability of medicinal products. Alternatives are not always available, and when they are, not all patients are comfortable with them. In this regard, it was believed that with certain chronic or severe diseases like asthma, patients are already more likely to accept a possible risk because they really need their therapy to remain stable and the idea of unavailability causes a lot of distress. Opinions were divided on whether a ban on TiO_2 is necessary. Important here was the fact that TiO_2 is theoretically just a colourant. Some patient organisations indicated awareness that TiO_2 is more than just a colourant. Others indicated that it is not only about reality, but also about perception. If patients would hear that TiO_2 is just a colourant, there would be a real chance that they prefer to eliminate the risk. In any case, communication would be of enormous importance to inform patients, as well as patient organisations, in a correct and uniform way. They feared that the media would jump on, causing a lot of unnecessary panic. To avoid this, it was important for patient organisations to be informed in time, in order to be able to reassure patients. Furthermore, they expressed concern that patients would have to bear the costs associated with a possible reformulation. As a last priority, they indicated that appearance of medicinal products is of enormous importance, since patients often distinguish medicinal products by shape and colour, rather than by its name. Patient organisations reported that patients already frequently struggle to adhere to their therapy properly, and any incorrect communication, increased costs, or differences in appearance could further undermine adherence *(Table 4)* *(Figure 8)*.

Figure 8: Main interests of patient organisations.

4.3.5 *Main findings within the decision makers group*

In the decision makers' group, everyone agreed that availability of medicinal products for patients and, as a result, the quality of patients' lives should be at the basis of this discussion. Therefore, they considered it extremely important to provide the right timelines to ensure this, although not excessively long ones. The majority of included decision makers stressed the enormous workload for regulatory bodies that a ban would entail. This together with the workload for pharmaceutical companies should be considered when defining the timelines. A few stakeholders also feared that there would be a major impact on innovation. Another huge concern for most of the decision makers stakeholders were the global discrepancies that would be caused if TiO_2 is banned in medicinal products in the EU, bearing in mind that the pharmaceutical industry is a global industry, and this could again have an impact on availability as well as innovation of medicinal products in the EU *(Table 4)* *(Figure 9)*.

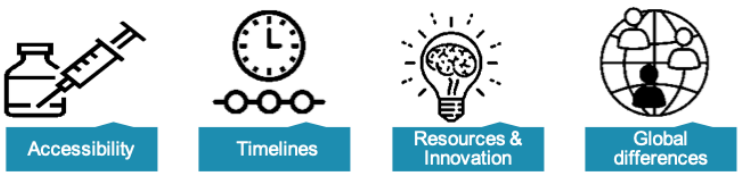


Figure 9: Main interests of decision makers.

5. Discussion

5.1 Insights from the literature

Based on the literature, it became clear that TiO_2 is an exceptional excipient that can offer particular properties to medicinal products and cosmetics, that until now, could not be perceived with other additives. The high refractive index provides the brilliant white colour and it has the ability to absorb UV light, representing a good application both as a sunscreen as to protect a light-sensitive API. In addition, its inertness makes it compatible with all types of ingredients in pharmaceutical formulation (11,14,45,46,92). Furthermore, the quantity of TiO_2 in medicinal products is much lower compared to food or cosmetics, and the use of medicinal products is restricted (17,20,48,92). This demonstrates that exposure to TiO_2 via medicinal products may be very limited. In addition, a toxicologist made a simulation of the number of tablets that would have to be consumed to reach a potentially genotoxic dose. Burgoon (93) revealed that 681 tablets should be taken every six hours during eight and a half years (93,94). This suggests that even a patient who must chronically take multiple medicinal products would remain well below the limit of genotoxicity, although it seems important for these results to be confirmed by further research.

The literature revealed the striking pattern of varying outcomes in safety assessments of TiO_2 across different countries and continents. EFSA concluded that they had insufficient data to claim any longer that the use of TiO_2 was safe, and that genotoxicity could no longer be ruled out (59). Important to note that it could not be confirmed that toxicity is present. Following the subsequent ban of TiO_2 in food in the EU, safety assessments were conducted by several other countries. From these, Health Canada, the FDA, COM/COT UK and FSANZ claimed that the studies on which EFSA based its conclusions were not representative for the use of TiO_2 in food. They believe that EFSA unnecessarily caused concern among the public and they did not identify any safety risks (60–64,77). The only countries outside the EU that did introduce a ban were those that did not conduct a safety assessment themselves, but blindly followed the EU, like Switzerland (77). On top of this, a group of independent experts did a review of the EFSA statement. Even they concluded that studies with unrepresentative materials were included, and other *in vivo* studies that were conducted with correct materials were not. They also concluded that there is no direct health risk associated with the use of TiO_2 (60). These inconsistent results seem to indicate that something may have gone off in the EFSA evaluation of TiO_2. It is important to fill the data gaps in EFSA's review and conduct a thorough evaluation to reach a conclusive outcome on the safety of TiO_2.

Although data from the literature on oral intake of TiO_2 also indicated toxicity, a threshold was difficult to calculate (15,52,53). However, the question can be raised whether it is necessary to replace TiO_2 if a safe maximum dose can be guaranteed. According to one study, the risk is no longer acceptable if the proportion of TiO_2 nanoparticles to the total mass exceeds 10 % (54). Blevins et al. (55) even demonstrated absence of oral toxicity. These outcomes indicate that toxicity may be limited after all. Nevertheless, if any toxicity is present, it is of enormous importance to clear this out based on the existing data and possible additional data to provide confidence in the safe use of TiO_2. It was also shown that

toxicity via dermal application poses no threat and inhalation of TiO_2 would be harmful (15,36,53,56). All these results appear to suggest that cosmetics and medical devices that do not come into contact with the mouth do not pose a safety concern. In contrast, inhalation poses a major risk, and TiO_2 in sprayable cosmetics and medical devices should definitely be avoided.

Banning TiO_2 in medicinal products would bring many challenges that should be carefully considered before taking regulatory actions. The consequences of a ban should be mapped out along with the benefits and risks that both banning and not banning TiO_2 would entail. Challenges include the significant difficulties in reformulation and finding an alternative that is sufficiently opacifying, provides the API with the same protective properties, is compatible with other ingredients, and does not affect the bioavailability of the API (11,14,49,92). There are also the potential implications for patient compliance and medicinal product identification if appearance were to be affected (14,86). However, if appearance would change significantly, it seems essential that healthcare providers communicate promptly and clearly with patients to ensure that they are aware of the changes, in order to minimise the impact on adherence. An increased risk of falsification should also be taken into account, as anti-counterfeiting measures often involve TiO_2 (11,14). In addition, it should be noted that not every proposed alternative is authorised according to the list of food additives in Regulation 1333/2008, and complies with Commission Regulation (EU) No 231/2012 on colours for use in foods (29,89). Moreover, reformulation efforts would entail the need for variation dossiers, as well as large investments in research and development (49). Nevertheless, innovation may also arise from this research. In fact, searching for alternatives can be considered a positive challenge for the pharmaceutical industry, who should look for innovative, safe alternatives that result in at least as good finished products, while also meeting patient needs. Nevertheless, it is important to find a suitable alternative that meets all these criteria, and until this is the case, the continued use of TiO_2 is recommended.

5.2 Patterns of similarities and disagreements in stakeholders' perceptions

It was notable that despite not all stakeholders feeling this way, there was a clear overarching objective across stakeholder groups, being patient wellbeing *(Table 4).* Although the perception of how this should be achieved was not the same for each individual. It was striking how the interests of patient organisations aligned with those of the healthcare providers. They prioritised the interests of patients above everything else, considering it to be of the utmost importance. Decision makers and industry stakeholders cared about patients' interests as well. Although they were also more concerned with each other. It could be noticed that some stakeholders within the decision makers group were concerned about how the industry is acting on the situation. On the other hand, the industry was concerned about how some within the decision makers provided political influences and made less scientifically grounded decisions. The perceptions of some stakeholders within the decision makers group, academics group and industry stakeholders showed notable conflicts. For example, part of the decision makers believed that if the food industry could adjust, the pharmaceutical industry should also be capable of doing so if required. However, the industry stakeholders strongly opposed this idea, citing significant differences with medicinal products such as the strict regulations that allow less flexibility. In line with this, there were

disagreements in opinions on the feasibility of finding an alternative. While the industry stakeholders and some decision makers highlighted the difficulties and the fact that no suitable alternative had been found so far, the academic stakeholders and the other decision makers, along with the healthcare providers, were more positive towards possibilities for alternatives. They believed that a huge number of possibilities exists and could not imagine that not a single one could provide the same properties to medicinal products as TiO_2. Patient organisations were divided on this. Most indicated that they were not very aware of what TiO_2 was, but some highlighted its positive properties and were concerned about alternatives. There was also no consensus between the stakeholder groups on benefit risk analysis and whether or not to consider excipients in this respect. The majority of stakeholders felt that TiO_2 should be part of the benefit risk analysis, given the important properties that it can confer to a medicinal product. For instance, the majority of the stakeholders within the patient organisation group indicated that in more severe diseases with life-saving medicinal products, the risk might be more acceptable than with less severe diseases, referring to the greater benefit the medicinal product might provide in the first case, and the more serious consequences associated with not being able to access therapy. Although within the decision makers and patient organisations, some stakeholders indicated that when a safety risk is associated with an excipient, it should be avoided, as opposed to an API where there should be a trade-off with the benefits. In this respect, it should be pointed out that not everyone showed equal understanding of the importance of excipients in medicinal products. TiO_2 could be of great importance and not only have aesthetic implications, but also impact shelf life, stability and bioavailability, amongst others. Nevertheless, alternatives should be explored, addressing these critical properties to ensure the quality of the medicinal product. There was frequent disagreement within the decision makers group, particularly regarding the impact of a medicinal product's appearance on patient adherence. While some were convinced of this, others expressed doubts. In any case, it seems important to provide proper information to patients in case of changes in appearance of their therapy. Lastly, some included decision makers were confident that the industry is making every effort to deliver as much data as possible to the EMA by November. This was opposed to those who believed the industry is playing with time. Similarly, they did think the industry is working to find alternatives, but found it frustrating that they always needed more time and that they complained about resources. Creating uniformity in views on the TiO_2 situation is important, and this should be based on evidence rather than speculation. In fact, the existence of heterogeneous opinions around this topic showed an argument for transparently communicating the advantages and disadvantages of TiO_2 and the associated uncertainties. In addition, every effort should be made to clarify the toxicological profile and safety impact of TiO_2. In the end, the patients should be able to make their own informed decision. Accordingly, the opinions of all stakeholders were in line that any suffering by patients should be avoided in any sense. Which means, if TiO_2 is found to be toxic, patients should be protected and TiO_2 use should be avoided. However, patients should also be protected from unavailability of their therapy. Whatever the outcome, the patient could be the victim of the situation, which must be avoided at all costs. Therefore, it is of enormous importance to make thoughtful decisions about both banning TiO_2, and if banned, about the necessary timelines. The postponement of the decision in

medicinal products until 2025 seems a good first step to allow for more research to get a complete understanding of the problematic before making impactful decisions. Although the industry has just until November to collect and generate data, which does seem like a very short period for the enormous amount of studies involved in researching alternatives. It is desirable that EMA will acquire adequate data to develop an informed opinion on the use of TiO_2 in medicinal products, as well as the feasibility of replacing it. However, if EMA lacks sufficient data to arrive at a conclusive opinion, it may be necessary to prolong the assessment period and to request more data from the industry. As long as no alternatives have been found, it does not seem appropriate to ban TiO_2.

5.3 Patterns between the literature and stakeholder perceptions

The most important similarities and differences in findings through the literature and interviews are plotted in *Table 5.*

Table 5: Found specificities in the interviews and literature were plotted. The literature highlighted the background of TiO_2 and specific features, and the interviews stressed the importance of a risk-benefit analysis and patient perspectives, among others. Similarities between literature and interviews highlighted the importance of certain topics.

	Specificities		Similarities	
Literature	Anti-counterfeiting	Concentration	Unique properties	Global differences
	Toxicology		Appearance	Timelines
Stakeholder perceptions	Political influence	Improvement	ADI	Accessibility
	Resources & innovation	Risk/benefit	Replacement aspects	Scope of products
	Patient perspective	Communi-cation	Costs	Regulatory

In the literature, much information was obtained about TiO_2 toxicity and its mechanisms. Furthermore, detailed information was retrieved on the amount of TiO_2 in different product classes, like cosmetics, medical devices, food and medicinal products, which gave an idea of TiO_2 exposure. The importance of TiO_2 in anti-counterfeiting measures was also frequently mentioned. The interviews offered complementarity in this regard by coming up with a number of new topics. Among other things, stakeholders cited their concern about political influences in decision making and the importance of correct communication and a proper communication flow. It also came up that if TiO_2 were to be banned, some stakeholders feared that second class products would enter the market that are not as good as they were or could be. Stakeholders worrying that innovation would be delayed as a result of a TiO_2 ban was also a new topic. Furthermore, the importance of benefit risk analysis in medicinal products was discussed and, in this regard, the major difference with food. Finally, the interviews were an opportunity to include patients' perspectives as much as possible within the boundaries of the study. Ultimately,

numerous similar topics were raised in both the literature and among stakeholders, which emphasises the importance of these topics, for example global differences. It is truly impressive how a decision within the EU can have such far-reaching consequences, causing regulators worldwide to allocate resources to assess a non-excludable toxic excipient. In fact, this study clearly illustrated a case of how, based on the same data and uncertainties, different agencies can come to different conclusions, thus having different impacts on patients depending on where they live. It seems hugely important to encourage global cooperation between regulators to uniformly carry out benefit-risk assessments of medicinal and self-care product ingredients. In this way, the evaluation can become more efficient and unambiguous across the world. Based on the uniform outcomes, each regulator could still attach its individual implications based on its own priorities. Although it is also recommended that there is uniformity in the availability of additives and thus finished products in the different countries. Additionally, both parts of the study addressed the scope of products that could be impacted by a ban on TiO_2. The literature revealed that TiO_2 is a component of over 91,000 human-use medicinal products and is widely present in self-care products such as toothpastes and creams. Despite the absence of an exclusionary list, the industry, academics and decision makers stakeholders did have a good understanding of the products that would be impacted. However, patient organisations and healthcare providers were less aware of this. As a result, future research should aim to precisely map these products to ensure all stakeholders are fully informed. Furthermore, regulatory aspects were also covered in both the interviews as the literature. For instance, some stakeholders in the industry group revealed that a leaked version of the draft of the new pharmaceutical legislation had surfaced and that it contained the option to include an additional set of colourants that are not allowed for use in food, yet authorised in medicinal products. In the meantime, this draft version became public and it stated that colours may be used in medicinal products when they are included in the list of authorised food additives according to Regulation (EC) No 1333/2008. In addition, a colouring agent might be placed on an additional list established by the EC after thorough evaluation, if the colour has been removed from the Union list of authorised food additives on the basis of a scientific opinion from EFSA (95). Although, it must be noted that this is only a draft version subject to potential changes, and the implementation of this new pharmaceutical legislation is not expected by 2025. Therefore, the decision regarding the ban on TiO_2 would need to be made earlier. However, it is not unlikely that this decision will be postponed in order to align with the new legislation. A final important similarity were costs and economic impact of a possible ban. It is important to bear in mind that any economic consequences could also affect patients. On the one hand, a ban on TiO_2 could result in certain medicinal products becoming unavailable, potentially causing patients to switch to more expensive drugs, if alternatives are available at all. On the other hand, pharmaceutical companies that decide to reformulate drugs could increase prices to cover the huge investments. For already more expensive or non-reimbursed medicinal products, or for patients with difficulties financing their therapy, this could have a huge impact. Therefore, it is extremely important to consider the situation from the different stakeholders' points of view. Economic considerations should not prevail, but as soon as the patient's

wellbeing would also be compromised by the economic prospects, these should definitely be taken into account to make an informed decision.

5.4 Strengths and limitations

This research conducted a literature review and a qualitative study complementarily, trying to ensure completeness. A good basic background understanding was retrieved from the literature and clearly outlined in the first part of the thesis. In the second part of the thesis, this knowledge was built upon by information obtained from interviews with various stakeholders. Stakeholders from very diverse organisations and areas of expertise were interviewed. This along with the large number of interviews ensured broad insights being gained within the different stakeholder groups. It is remarkable that there was a greater number of stakeholders included in the industry group. The variation in domains and aspects among stakeholders was the reason for this. New interesting topics still regularly emerged and data saturation was only obtained after eight interviews. However, data saturation was obtained within four out of five stakeholder groups and for all codes, as outlined in the data saturation table in *Appendix 6.* A significant proportion of included stakeholders were industry participants. It should therefore be taken into account that industry insights could be more strongly present in the results of this master's thesis. In addition, it is worth noting that the healthcare providers group only consisted of pharmacists. The contacted doctors expressed inadequate knowledge about the TiO_2 situation and thus did not consider themselves capable of making a valuable contribution to the study. Since the opinions of both pharmacists were quite aligned and no exceptional new insights were gained from the second interview, it is assumed that data saturation was obtained at this point. Nevertheless, it may be recommended to question the opinions and perceptions of doctors in future research as well, and again the opinions of pharmacists when they are better informed about current developments. Similarly, profound understandings were acquired within the academic perspective and data saturation was reached in the academic group after the second interview. Furthermore, wide insights were gained into the group of decision makers by being able to interview policy makers, regulators and governmental agencies. This does have the consequence that data saturation was not obtained within this stakeholder group, as views and opinions were not aligned, and even the last interview revealed interesting new themes. Within the patient organisations group, it was possible to include three patient organisations. Although their opinions were not always fully aligned, the same themes emerged and data saturation was obtained after the second interview.

This study unfortunately did not manage to capture the cosmetics viewpoint. The members of the SCCS indicated to have an obligation of silence as long as the TiO_2 topic is on the agenda, and therefore it was not possible to include them in the interviews. Other cosmetics associations also did not consider participating during this delicate period. They reported to be awaiting the outcome of the SCCS decision and did not intend to openly discuss the issue in the meantime. The same was applicable to EFSA's perspective. They indicated to have a duty of silence as well and would not be allowed to have public

discussions about this topic. Since their comprehensive safety assessments and information on their website already provided a great deal of information, this was felt to be less of an obstacle.

The study sought to include the patient perspective as much as possible through interviews with patient organisations that represent patients with diseases eligible for OSDs. Nevertheless, the patients themselves were not included, since this was not feasible within the boundaries of this master's thesis.

Lastly, it was not only a delicate subject for the cosmetics industry, but also for the pharmaceutical industry and academics, as well as for decision makers. It was not always possible for everyone to respond openly to questions because of current developments. Employment at organisations with active developments with TiO_2, and the fact that some information was not yet publicly known, would sometimes have limited the ability of pharmaceutical companies or industry associations to answer certain questions in-depth. The current uncertainty about the future of TiO_2 may also have complicated decision makers' ability to answer questions at times. This may have acted as a limitation in the acquisition of information, although this was partly mitigated by the pseudonymity of the data. Subsequently, patient organisations and healthcare providers were sometimes insufficiently aware of the situation to answer particular questions, such as "Can you tell me how you experience this matter from your professional point of view?". Nevertheless, their insights were very valuable.

5.5 Recommendations for future research

Considering the highly challenging topic with numerous ongoing and upcoming developments, it is encouraged to closely monitor these developments in the future. In light of TiO_2's safety and toxicity concerns, it is of utmost importance to gather more clinical evidence, including interventional studies and real-world data, to substantiate these concerns and reach a unified and clear conclusion. In addition, a report of SCCS's review of cosmetics will be available soon. This will be hugely impactful in the cosmetics field. Therefore, it appears a worthwhile suggestion to follow this up and conduct a qualitative study within the cosmetics and self-care industry as soon as this report is available. Furthermore, it seems important to include patients' own perspectives as well when the timing is appropriate. Currently, there are still many uncertainties and it is important to create uniformity in opinions regarding the safety and use of TiO_2. Afterwards, patients can be informed carefully and their perceptions can be considered. Incorporating patient experience data is essential to understand patients' priorities with respect to their medicinal products regimen, and to identify potential trade-offs they are willing to make. After all, the question is if they are willing to give up their trusted therapy in exchange for avoiding uncertainty around genotoxicity. This balance is preference-sensitive and this question should be able to be answered by patients themselves. Therefore, ensuring that patients' voices also receive attention is of enormous importance. At the end of the day, it is the patients who have to face the consequences of a possible ban on TiO_2. As a result, including patients in subsequent studies is recommended. Lastly, as already cited, it is of enormous importance to establish an exhaustive list of the medicinal and self-care products that would be affected by a TiO_2 ban in order to adequately inform all stakeholders.

6. Conclusion

This study captured the complex and dynamic developments of TiO_2. It was revealed how TiO_2's unique properties contribute to the current estimate of 91,000 registered medicinal products containing TiO_2 in the EU. It can be concluded that the safety of TiO_2 can be guaranteed when applied dermally, while it exhibits toxic properties when inhaled. Oral toxicity cannot be excluded based on the literature and an ADI has not yet been able to be established, although some studies claim that oral toxicity would be quite minimal or even non-existent. Outside the EU, many countries, like Canada and the US, have concluded that TiO_2 does not pose a health concern. Both decision makers and industry stakeholders indicated that a ban on TiO_2 will certainly lead to shortages or even unavailabilities, as many companies would choose to withdraw certain products from the EU market and a huge workload would be created for both companies that will have to reformulate, as for regulatory bodies evaluating the changes. Therefore, efforts should seek to develop a strategy for managing the enormous workload for both regulators and companies. Included industry stakeholders stressed the differences between food and medicinal products, and in that regard the importance of a thorough benefit risk analysis that includes the benefits of TiO_2. In this respect, it is important to clearly chart all risks, challenges and benefits related to a TiO_2 ban in order to be able to make an informed decision. Additionally, the various stakeholder groups agreed that proper communication from reliable sources is of enormous importance to avoid unnecessary distress. Ultimately, the overarching priority of all stakeholders was patient accessibility, patient lives and quality of their lives. Patients, patient organisations and healthcare providers must be properly informed about the situation and about possible changes in medicinal products to ensure patient compliance and medicinal product identification do not to suffer. Moving forward, it will be important to ensure open, transparent and pragmatic discussions with all stakeholders that prioritise patient safety and availability of their therapy. This will allow the creation of uniformity in the opinions of the different stakeholders and enable decisions to be made that are supported by all stakeholders. Finally, it will be important to understand and include patients' perspectives on potential different strategies, given the impact of a potential TiO_2 ban on patients.

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8. Appendices

8.1 Appendix 1: COREQ Check-list

No	Item	Guide questions/ description	Explanation	Page
Domain 1: Research team and reflexivity				
Personal Characteristics				
1.	Interviewer/ facilitator	Which author/s conducted the interview or focus group?	All interviews were conducted by Margot Suetens, and one interview was facilitated by Alice Vanneste.	P. 8
2.	Credentials	What were the researcher's credentials? *E.g. PhD, MD*	M.S.	P. 8
3.	Occupation	What was their occupation at the time of the study?	Master Student PhD Researcher	P. 8
4.	Gender	Was the researcher male or female?	Female	/
5.	Experience and training	What experience or training did the researcher have?	None	/
Relationship with participants				
6.	Relationship established	Was a relationship established prior to study commencement?	The researcher did her best to establish a connection by sending a clear and open invitation e-mail to the potential participants.	P. 8
7.	Participant knowledge of the interviewer	What did the participants know about the researcher? e*.g. personal goals, reasons for doing the research*	Explanations had been provided to potential participants about the background of the researchers as well as the objectives and rationale behind the study.	P. 58-60
8.	Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. *Bias, assumptions, reasons and interests in the research topic*	Education-related characteristics such as study discipline, internship and the fact that the study is conducted as part of Margot's master's thesis.	P. 58-60
Domain 2: study design				
Theoretical framework				
9.	Methodological orientation and Theory	What methodological orientation was stated to underpin the study? *e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis*	Collected data from the interviews was analyzed thematically using the framework method as described by Gale et al. (42).	P. 10
Participant selection				

10.	Sampling	How were participants selected? *e.g. purposive, convenience, consecutive, snowball*	Combination of purposive and snowball sampling.	P. 9
11.	Method of approach	How were participants approached? e.*g. face-to-face, telephone, mail, email*	email	P. 8
12.	Sample size	How many participants were in the study?	22	P. 25
13.	Non-participation	How many people refused to participate or dropped out? Reasons?	18 individuals who were contacted did not want to participate due to the fact that they either did not consider themselves suitable for participating in the study, or they did not want or were not allowed to speak publicly about the delicate subject at this time. Another 21 did not respond to the invitation email.	P. 45
Setting				
14.	Setting of data collection	Where was the data collected? e.*g. home, clinic, workplace*	Home	/
15.	Presence of non-participants	Was anyone else present besides the participants and researchers?	No	P. 10
16.	Description of sample	What are the important characteristics of the sample? *e.g. demographic data, date*	Stakeholder group, number of participants per stakeholder group and country of origin.	P. 25
Data collection				
17.	Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	A pre-prepared semi-structured interview guideline was available and one pilot interview was conducted.	P. 8 P. 54-55
18.	Repeat interviews	Were repeat interviews carried out? If yes, how many?	No	/
19.	Audio/visual recording	Did the research use audio or visual recording to collect the data?	Audio recordings were collected.	P. 10
20.	Field notes	Were field notes made during and/or after the interview or focus group?	Field notes were created to already indicate the main themes derived from the interview in order to facilitate the processing of the data afterwards.	P. 10
21.	Duration	What was the duration of the interviews or focus group?	Each interview lasted 30 minutes to 1 hour.	P. 10

22.	Data saturation	Was data saturation discussed?	Yes. Data saturation was obtained for four out of five stakeholder groups. In the stakeholder groups of the healthcare providers, academics and patient organisations, this was achieved after 2 interviews. With the industry, this required 8 interviews. Within the decision makers group no data saturation was achieved.	P. 45
23.	Transcripts returned	Were transcripts returned to participants for comment and/or correction?	No, just one interviewee requested his transcript and had no comments.	/
Domain 3: analysis and findings				
Data analysis				
24.	Number of data coders	How many data coders coded the data?	One	P. 10
25.	Description of the coding tree	Did authors provide a description of the coding tree?	Yes	P. 62
26.	Derivation of themes	Were themes identified in advance or derived from the data?	Both	P. 10
27.	Software	What software, if applicable, was used to manage the data?	NVivo	P. 10
28.	Participant checking	Did participants provide feedback on the findings?	A few requested to review the data before publication. Therefore, if publication will take place, a review by eight participants will have to be carried out first.	/
Reporting				
29.	Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.*g. participant number*	Yes	Result section 4.2 P. 25 - 39
30.	Data and findings consistent	Was there consistency between the data presented and the findings?	Yes	Result section 4.2 P. 25 - 39
31.	Clarity of major themes	Were major themes clearly presented in the findings?	Yes	Result section 4.2 P. 25 - 39
32.	Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Yes	Result section 4.2 P. 25 - 39

8.2 Appendix 2: Topic guide

Introduction

- *First, allow me to present myself. My name is Margot Suetens and I am a senior master student in pharmaceutical drug development at the KU Leuven. I am currently doing a 9-month internship at Bayer. Furthermore, I am writing my thesis on the potential ban of titanium dioxide under the supervision of Dr. Rosanne Janssens, Alice Vanneste.*
- *I would like to thank you already for taking the time to participate in this interview. Your views, opinions and experiences are very important to our research.*
- Explain **shortly the purpose** of the interview:

o With this interview we want to identify the consequences that are associated with banning titanium dioxide and in what way you as a stakeholder will be affected. Furthermore, I would like to check what your perspectives are in this matter and how you see it progressing in the future. The interview will take about 30 minutes to 1 hour.
o Results will be implemented in my master's thesis.

• Put the interviewee **at ease**:

o *I want to emphasise that there are no right or wrong answers, and that it is no problem if you might not know the answer. In that case, it would be great if you could recommend us the name of a contact person who could clarify this aspect.*

o *This interview will be digitally recorded. This makes it easier for us to process all information that is provided in the interviews. Anything you say today will be completely confidential, and will be processed pseudonymously, meaning we will not use your name or any personal/company details, unless agreed otherwise. The data collected today will be stored securely and viewed only by approved researchers on this project. Participation is completely voluntary, you can withdraw at any point (no explanation needed). You do not have to answer any questions during the interview if you do not feel comfortable answering them.*

- *Before starting the interview, we will go over the informed consent form together. If there are any uncertainties or questions, please feel free to ask. The ICF must be signed before we can move on to the questions.*
- *Do you have any **questions** before we start the interview?*
- *We will start with some warming-up questions. Subsequently, we will turn on the recording function and focus more on the research questions about the topic of titanium dioxide.*

Questions

I. Introductory questions

➢ *Could you please start with introducing yourself?*

➢ *Can you tell us a bit more about your current position and how long have you been working in your current position?*

- *What are your expectations of this interview?*

• *Let's start with the research questions now. Do I have your permission to turn on the recording function?*

II. Questions about the theme titanium dioxide

(A) Current landscape of medicinal products and self-care products containing titanium dioxide
  - Can you briefly tell me what you know about the current situation of titanium dioxide?
  - Can you tell me how you experience this matter from your professional point of view?

(B) Implications and challenges related to banning titanium dioxide
  - In what fields do you think there would be consequences if titanium dioxide is banned in medicinal products and further possibly in self-care products?
    - What consequences do you think will be faced?
    - How, if at all, would you be affected by a ban?
  - What, if anything, do you think needs to change about how the use of titanium dioxide is currently being managed?
  - Why, if applicable, would you think, titanium dioxide should be banned in medicinal products and self-care products?
  - Do you think a possible ban on titanium dioxide would be justified?
  - What challenges are related to banning titanium dioxide?

(C) Action point needed if titanium dioxide would be banned in medicinal products and self-care products
  - How do you think the banning of titanium dioxide can be addressed?
  - Do you have any suggestions or solutions on how we can address this matter in the future?
  - What is needed, if titanium dioxide would be banned?
  - How should a ban on titanium dioxide be handled?

V. Round-up questions

These were all the questions I had for you. ***Thank you*** *very much for participating.*

- *Do you want to* ***add*** *anything else?*
- *Do you want to* ***emphasise*** *something?*
- *Do you think we* ***forgot*** *something?*

- *Do you think we've* ***overlooked*** *some relevant questions?*
- *Do you have any* ***questions for me****?*
- *Do you have a suggestion for* ***other interesting interviewees concerning this topic****?*

• *I will turn off the recording now.*

Conclusion

Thank you *for your participation.*
If you have any other questions, comments, or want to get in touch with me, please do not hesitate to ***contact me or my promotor.***

8.3 Appendix 3: Consent form

Consent form – Version 20/12/2022

Stakeholders' perception on banning titanium dioxide in the development and use of pharmaceuticals and self-care products: a scoping review and semi-structured interviews.

Head of research:	Dr. Rosanne Janssens Department of Pharmaceutical and Pharmacological Sciences Onderwijs en Navorsing 2, Herestraat 49 box 521 3000 Leuven tel. +32 16 37 29 47
Contact person:	Margot Suetens – Master Student Department of Pharmaceutical and Pharmacological Sciences Onderwijs en Navorsing 2, Herestraat 49 box 521 3000 Leuven cell phone +32 494 15 79 75
Research team:	Margot Suetens Alice Vanneste Rosanne Janssens Caroline Vanduffel

To be completed by the PARTICIPANT

Please read the terms below. If you agree to the terms, please tick the box at the bottom of this form to confirm your participation.
Terms:

- I have read the information sheet, Version 20/12/2022, regarding this study and I have had an opportunity to ask questions or discuss any concerns about it;
- I was given sufficient time to decide whether I am willing to participate in this study;
- I am aware that participating in this study is completely voluntary;
- I am aware that I can stop participating in this study at any time, without having to give a reason;
- I give permission for my personal information to be stored for 10 years and I am aware that I can request this to be deleted within 30 days after confirmation of receipt of my request; I'm aware that such a request may not be fulfilled in case that the information is already processed, deletion renders or seriously impairs the study objectives, or that regulations and laws that apply to this research require my personal data to be retained;
- I give permission that my coded data will be used in de master's thesis of Margot Suetens following the standards established by the European General Data Protection Regulation (GDPR), national and local laws;
- I give permission that the coded study results can later be used for publications as well as educational purposes;
- I'm aware that I can review my collected personal data and have any inaccuracies corrected;
- I have received the information sheet and I hereby confirm my voluntary participation in the study.

If you agree to the terms, please tick the box below to confirm your participation:

☐ I agree with all terms listed above and hereby confirm my participation in this project

Participant's name Signature Date

To be completed by the RESEARCHER

I have discussed the content of the invitation letter and informed consent form with the above-mentioned participant. I asked for any additional questions and I have answered these.

Researcher's name Signature Date

8.4 Appendix 4: Participant information sheet

KU LEUVEN

Information Sheet – Version 20/12/2022

Stakeholders' perception on banning titanium dioxide in the development and use of pharmaceuticals and self-care products: a scoping review and semi-structured interviews.

Head of research:	Dr. Rosanne Janssens Department of Pharmaceutical and Pharmacological Sciences Onderwijs en Navorsing 2, Herestraat 49 box 521 3000 Leuven tel. +32 16 37 29 47
Contact person:	Margot Suetens – Master Student Department of Pharmaceutical and Pharmacological Sciences Onderwijs en Navorsing 2, Herestraat 49 box 521 3000 Leuven cell phone +32 494 15 79 75
Research team:	Margot Suetens Alice Vanneste Dr. Rosanne Janssens Caroline Vanduffel

Dear Mr./Ms.,

You were invited to voluntarily participate in a study on the potential consequences of banning titanium dioxide. Your opinion on this topic will be asked, since we would like to map the perspectives of different stakeholders. Before you confirm your participation in this study, we ask you to read this information sheet carefully. For any questions regarding this study, please contact the contact person mentioned at the top of this form.

What is the purpose of the study?

Since August 2022, titanium dioxide has been banned as a food additive due to the fact that, according to the EFSA, genotoxicity cannot be excluded. The EMA is currently investigating whether or not this ban should be extended to pharmaceuticals and will report on this by 2024. Furthermore, the SCCS is conducting a re-evaluation of the safety

of titanium dioxide in cosmetics. This study will identify the potential impact of a ban on titanium dioxide in medicinal products and further in self-care products. Different stakeholders will be affected and they all have different views on how to deal with this matter. For instance, regulators like EMA will face a huge increase in workload if this ban were to be implemented. Drug development and use will also experience enormous consequences. To clarify this matter, a scoping literature review and a qualitative study will be conducted. For this purpose, the topic will be examined from the perspective of various stakeholders

Who is conducting the study?

The study is conducted by researchers at the University of Leuven in collaboration with Bayer SA-NV. Since Margot Suetens is doing her internship at Bayer SA-NV, the internship supervisor will co-supervise her during the master thesis. However, the supervisor will not get in contact with the collected data, but will only be reviewing the processed data in the thesis.

Is this study scientifically and ethically justified?

The Ethics Committee Research UZ / KU Leuven approved the study. Ethics committees verify if the rights of participants are respected by researchers during a study, if the balance between risks and benefits is beneficial for the participants and if the study is scientifically and ethically justified.

Do I have to participate?

Your participation is completely voluntary. You can refuse to participate. There is no cost associated with participating in this interview and you will not receive any compensation to take part.

What is asked of me?

The interview will take about 30 minutes to 1 hour and will be conducted at a place and time of your choice, or remotely via Skype or Microsoft Teams. Data will be gathered through the conduct of an interview where the interviewers will ask you questions about your perspective on the potential ban on titanium dioxide. The interview will be audio-recorded and afterwards written out (transcribed). Audio recordings will be destroyed from the moment they are transcribed.

How will my personal data be kept confidential?

The data collected during this study will be stored in the secured database OneDrive for Business of KU Leuven. The study will adhere to the national and local data protection laws. Your identity and that of other participants will be kept strictly confidential. Only researchers from the University of Leuven will have access to the recordings and personal information. In the secured database where the information of all participants is kept and analysed, information that could lead to your identification (e.g. name, address) are removed by researchers from the University of Leuven and replaced by a number when the interview is written out (transcription). This process is called coding and from the coded (pseudonymized) data you cannot be identified; so no reporting of your personal identifying information in reports or publications can happen. Only coded data will be shared with other researchers.

How will my coded (pseudonymized) data be used?

Your coded data will be used to learn more about the vision of different stakeholders that could be affected by a ban on titanium dioxide. The results will be analysed by Margot Suetens and will be processed in her master's thesis.

How long will my personal data be stored?

Records containing your personal data and your coded data will be retained at the study site (University of Leuven) for a period of 10 years from the end of the study. After completion of the study all non-identifiable coded data will be transferred to Margot Suetens' supervisors Dr. Rosanne Janssens and Alice Vanneste. They will store the data in KU Leuven's central repository called SharePoint, a cloud-based data repository to store and exchange data in a secure and protective environment. Only Dr. Rosanne Janssens and Alice Vanneste will have the password to access the data.

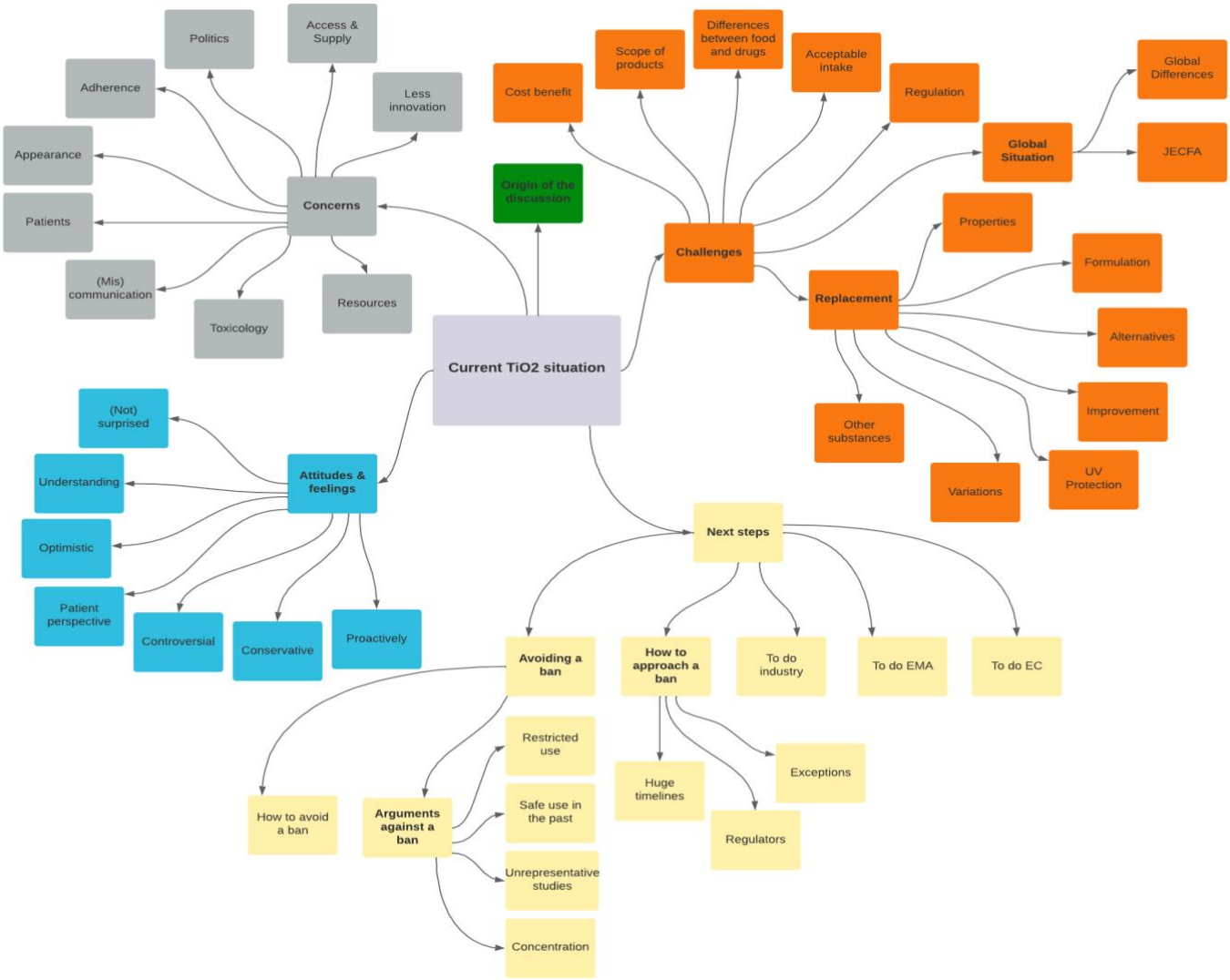
What rights do I have concerning my personal data?

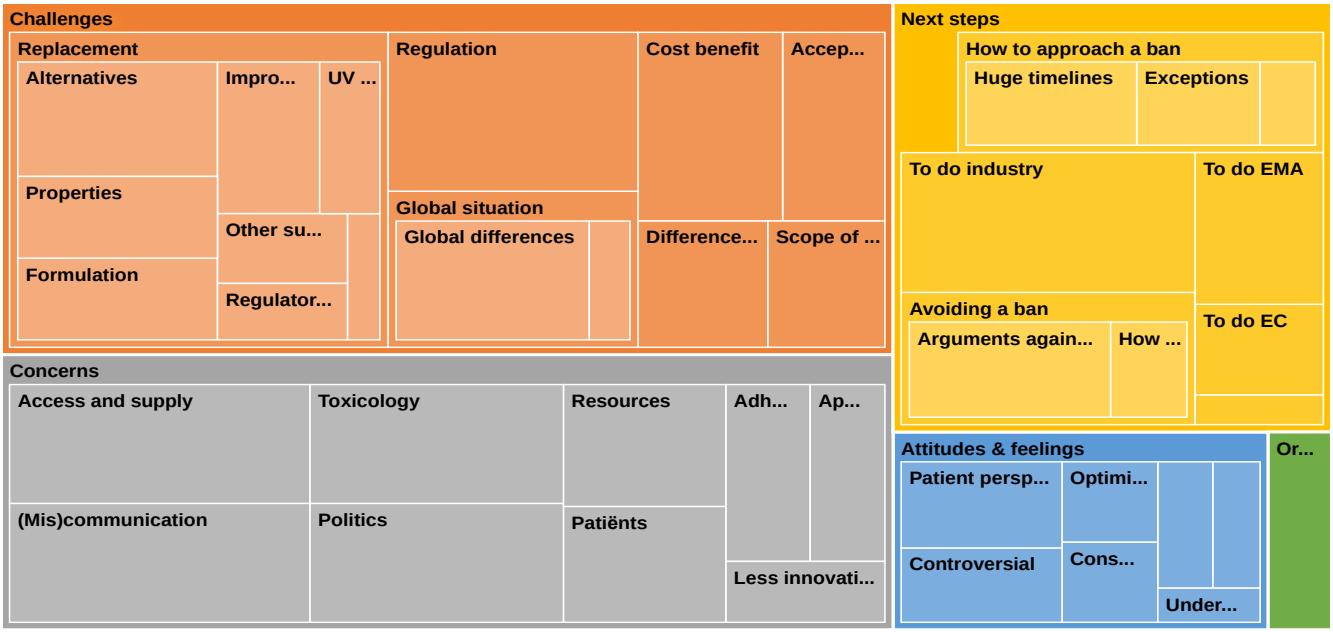
If you would like to review, correct, update, restrict, object to the processing or delete personal data, or if you would like to receive an electronic copy of the personal data you have provided, you should contact one of the persons mentioned at the top of this form. Your request for data deletion will be addressed within 30 days after your request have been confirmed. Such request may not be fulfilled in case that deletion renders or seriously impairs the study objectives, or in the case that regulations and laws that apply to this research require this data to be retained. Please note that you may not be able to review some of the data until after the end of the study. You can request the contact persons mentioned at the top of this form to forward any questions, concerns or complaints you may have to the data protection officer of the University of Leuven. You also have the right to lodge a complaint to the data protection authority in Belgium via e-mail: contact@apd-gba.be or phone: +32 (0)2 274 48 00.

Please contact the contact person mentioned at the top of this form for any questions regarding this study or to confirm your participation.

Thank you for your interest and participation!

8.5 Appendix 5: Code tree





8.6 Appendix 6: Data saturation table

Name	Description	Example	Files	References
Attitudes & feelings			0	0
(Not) surprised	Some saw a ban in food coming, while others were very surprised.	“Let’s say from our side we were quite surprised with the outcome of the EFSA opinion.”	5	8
Conservative	Conservative approach of the EU concerning titanium dioxide.	“So, I'm not saying it's wrong, I'm no one to say it's wrong. But I think it's a very conservative approach that needs to be revisited.”	5	9
Controversial	How things proceeded in the TiO2 situation is considered very controversial by some.	“I mean it only takes a handful of people to die from a disease because they didn't get the medicinal product because of the issue with TiO2, it'll be a major controversy.”	5	14
Optimistic	Some people are positive about the outcome of the discussion.	“So, I think that there can be good answers. I'm actually cautiously optimistic that it can be concluded in a good manner.”	7	10
Patient perspective	How would patients look at the situation and how should they or should they not be included in this discussion?	“As long as they feel, it's a far from my bed show, no problem. But if they find that it's about their medicinal product then some very critical people are going to react on this.”	7	16
Proactively	On the one hand, proactively looking at other excipients that might be debatable in the future and, on the other, exploring alternatives even before the ban.	“So, idea is not to wait until ’25 to start but doing kind of proactive work just now and in case it is needed that we just finalise it what’s needed registration etc but we needed to build on this proof of concept work that we are doing today.”	3	7
Understanding	Understanding why certain decisions were made.	“I understand very well that they say, titanium dioxide rather not in chewing gum and so on anymore because you can eat that every day and several a day.”	3	4
Challenges			0	0
Acceptable intake	To what extent is it possible in practice to establish an acceptable daily intake?	“They may be able to set an ADI. I'm hoping that they will have enough data to set an ADI.”	14	22

Name	Description	Example	Files	References
Cost benefit	With pharmaceuticals there is a cost benefit analysis, but with food one will take action as soon as there is a risk, because here we do not have a clear benefit.	“So, I think there will continue to be some cost benefit to medicinal products in terms of the quality of the medicinal products that you produce. And the safety of it versus the quality and safety of using titanium dioxide in the future.”	14	30
Differences between food and drugs	There are a lot of differences in, amongst others, the use and regulation of food and drugs.	“Which is unfortunate because while you can fairly easily remove titanium dioxide from foods, it's very much harder to remove it from pharmaceuticals and coatings.”	10	18
Global situation	What does the global situation look like, what is its importance and what is the impact of possible differences?		0	0
Global differences	Differences between marketing authorisations in different countries (including differences in production lines etc)	“And any other food safety authorities, they decided that it's safe.”	14	35
JECFA	JECFA is currently doing an evaluation of TiO2 by 2024.	“I think the JECFA assessment will be some kind of an important sign that will potentially also influence other regulators in their final assessment.”	5	9
Regulation	Different legislations and regulatory guidelines complicate the titanium dioxide matter.	“But for us, the big controversy is now that the food legislation is intrinsically linked to other pieces of legislation. It has a sort of domino effect.”	13	44
Replacement			0	0
Alternatives	Alternatives to titanium dioxide are being sought.	“Unfortunately, calcium carbonate is so far the most practical and the only viable solution that is out other phosphates and so on. Others do either not have an E number labelling or they are not suitable.”	13	30
Clinical trials	Clinical studies use titanium dioxide for drug blinding so that placebo oral dosage forms look exactly the same as its active counterparts.	“They have to redo all the clinical studies or at least a large part of the clinical studies with the drugs that are on the market, because of the changed composition of your product.”	3	5
Formulation	Reformulation has several implications	“What could be very much affected is the amount of film coating for example that you have to spray onto tablets.”	9	22

Name	Description	Example	Files	References
Improvement	It is important that by replacing titanium dioxide, a better product is made and not a product of inferior or the same quality.	“We know that that coating holds a potential risk, but a bad coating also holds a potential risk, so this is a situation where that you have to start weighing all those things against each other.”	11	20
Other substances	It is not just titanium dioxide, but other substances that are being looked at or may be looked at in coming years.	“So, you could also envisage that there is a scenario that some potential alternatives to titanium dioxide is established and then suddenly EFSA bans another colour.”	8	11
Properties	The unique properties of titanium dioxide make it difficult to be replaced.	“As a colour, but also as an opacifier. This is the complexity of the matter as well. It doesn't have only one function.”	13	21
Regulatory Procedures	Replacing titanium dioxide will require a huge workload of variation dossiers.	“And also, you know we speak about variation. So, if there is an alternative the company could say now I want to change it. And I submit an application for a variation.”	8	11
UV Protection	Will possibly be less because titanium dioxide with its high reflective index is a good protector against UV. Can be compensated by protective packaging, for example.	“Titanium dioxide is excellent at preventing UV damage. I mean, that's why it's in many sunscreens. It does protect APIs. So yeah, there's nothing like that.”	9	14
Scope of products	The scope of products that would be affected by a ban on titanium dioxide would be enormous.	“Basically, you're talking over 91,000 drug products that would have to be reformulated in Europe alone.”	12	15
Concerns			0	0
(Mis)communication	Miscommunication can cause unnecessary panic which can pose a danger to patients' health (if they stop taking medication, for example). There should be honest and clear communication so that there are certainly no misunderstandings.	“The problem they have now is how do you divide the message “we have banned it foot so it’s bad”, how do you explain to the general public to ban it in food but don't ban it in pharma.”	20	40
Access and supply	Important to ensure access to medicinal products at all times and to avoid supply problems.	“And for certain classes of drugs, they may not supply it to Europe. So, things like orphan, paediatric medicinal	22	39

Name	Description	Example	Files	References
		products could be threatened. Orphan disease state drugs could be trapped.”		
Adherence	Patient adherence could be impacted as a result of the changed appearance of the drugs when titanium dioxide is replaced or just as a result from them hearing about the banning in food.	“So, compliance of patients to their medicinal products in the future could be a bit of an issue.”	14	17
Appearance	The appearance of the drugs could change drastically if titanium dioxide is replaced with all the consequences.	“It's like, what does the actual finished tablet look like with the replacement technology?”	13	15
Less innovation	There is a lot of investment in research into alternatives etc which puts innovation aside.	“You know you are like putting all your resources in reformulating and then new drug products coming to the market will be really slow over the next 10 years.”	12	15
Patients	Patients could be impacted a lot by the situation.	“So, there's all kinds of downsides for the patient and the consumer if pharmaceuticals went down this path.”	15	23
Politics	It is not only a scientific subject but also the political aspect is very present.	“And so, I think if you look at how EFSA made their decision, it appears to me that it was made more from a political and media perspective than it was on a scientific basis.”	15	33
Resources	Huge amount of money, time and effort needs to be invested.	“If titanium dioxide would be banned and there would be a legal obligation to reformulate all products. Then the companies would have to make very huge investments.”	12	22
Toxicology	How safe or not safe is titanium dioxide really?	“Currently I do not want to make a judgment here, but I guess titanium dioxide that it is safe.”	14	34
Next steps	What are the next steps, what is needed from the various stakeholders and what decisions need to be made by them?	“So, there's quite a lot of still up in the air, a lot of debate. If it goes all the way through, then it will not be very easy. Either for the pharma industry or for the for the regulators in Europe.”	8	10
Avoiding a ban			0	0
Arguments against a ban	Several reasons are addressed for why a ban should be avoided.		0	0

Name	Description	Example	Files	References
Concentration	Very low concentrations of titanium dioxide in pharmaceuticals in comparison with food.	“In tablets that will be something like 1% or even much less. It's much less compared to food. So, it’s very little, because it's used in coatings mostly, so that's already very little as well, That's really not much.”	9	11
Representativeness	Many studies do not use the right particle size or the right titanium dioxide, which makes them considered unrepresentative.	“As opposed to looking at material that doesn't even represent the product that we use and saying that there's some uncertainties about studies that to be honest looked at in EFSA were very questionable studies in the 1st place.”	8	10
Restricted use	In food it is possible to consume i.e. a whole bag of skittles, but you do not consume a whole box of dafalgan. The use of pharmaceuticals is restricted.	“You have a controlled intake, you have a dose that you take one tablet, two tablets, three tablets a day. The amount of coating on there is minimal. The amount of titanium dioxide again is controlled, so the exposure and the risk are low.“	7	8
Safe use	Titanium dioxide has been safely used for many years.	“Especially for medicinal products that we’ve seen have been used for many many many years and have worked safely and efficiently.”	10	12
How to avoid a ban	How can a ban on titanium dioxide in medicinal products be avoided?	“The titanium dioxide industry is putting together existing studies and developing new studies to demonstrate that it is safe.”	8	12
How to approach a ban	A ban cannot be implemented overnight and should be handled carefully to avoid shortages etc.		0	0
Exceptions	For example, for niche products etc, exceptions should be potentially allowed.	“There should be exceptions allowed for things that for example aren't used much anymore, so that's where they still have to invest, redo all the studies and so on that's going to cost more than it's going to yield actually.”	10	16
Huge timelines	To do all the necessary studies, reformulate the drugs and submit the necessary variation files requires huge timelines.	“Again, industry has predicted that changing all the products would take more than 10 years.”	14	22
Regulators	How should regulators approach a ban?	“The regulators now need to provide us with some guidance we need to follow.”	5	9

Name	Description	Example	Files	References
Postponement	Postponing the decision on whether or not to ban TiO2 because the industry has insufficient time to collect all the necessary data.	“So that's why in 2025 we need to just postpone.“	6	7
To do EC	Next steps for the EC	“the Commission gets like here to make a decision. I think what the Commission will take into account is what is the situation so they’ll see what industry is identified.”	7	12
To do EMA	Next steps for the EMA	“EMA has to provide an updated study.”	9	21
To do industry	Next steps for the industry	“You know with a lot of the things that are coming out now and some of the additional data and what we'll all be providing to the EMA by this fall to help convince them what to do.”	13	43
Origin of the discussion	Where and why did the discussion about the safety of TiO2 started?	“Finally, the decision was taken February 7 and the effective date in August with the six months of grace period on that we had to remove them basically all the titanium dioxide from our food supplements in the EU markets.”	12	14

8.7 Appendix 7: Example list of medicinal products containing TiO_2 (51)

Brand name	Product name	Therapeutic class
Clarinase	Pseudoephedrine, Loratadine	Antihistamine
Estivan	Ebastine	Antihistamine
Ceterizine (all brands)	Cetirizine hydrochloride	Antihistamine
Moxonidine (all brands)	Moxonidine	Centrally acting antihypertensive drug
Cobisoprolol (all brands)	Bisoprolol, Hydrochlorothiazide	Beta-blocker, diuretic
Bisoprolol (all brands)	Bisoprolol	Beta-blocker
Propranolol, Inderal	Propranolol hydrochloride	Beta-blocker
Metformine HCl Teva, Sandoz	Metformin hydrochloride	Antidiabetics
Trajenta	Linagliptine	Antidiabetics
Onglyza	Saxagliptine	Antidiabetics
Sitagliptine (all brands)	Sitagliptin phosphate monohydrate	Antidiabetics
Jardiance	Empagliflozin	Antidiabetics
Xtandi	Enzalutamide	Oral chemotherapy (Prostate cancer)
Verzenios	Abemaciclib	Oral chemotherapy (Breast Cancer)
Zeposia	Ozanimod	S1P receptor modulator (MS)
Ropinirol (all brands)	Ropinorol	Dopamine agonist (Parkinson's disease)
Nubeqa	Darolutamide	Oral chemotherapy (Prostate cancer)

8.8 Appendix 8: Overview of the possible variations (39)

Variation type	Description
Type IA **Type IAIN**	Minimal or no impact on the Quality, Efficacy or Safety. Do and Tell: minor variations that do not require any prior approval. Notification by MAH within 1 year. Do and tell immediately: certain minor variations of Type IA require immediate notification after implementation, in order to ensure continuous supervision of the medicinal product.
Type IB	Minimal or no impact on the Quality, Efficacy or Safety. Tell, Wait and Do: Minor variations that must be notified before implementation. The MAH must wait a period of 30 days to ensure that the notification is deemed acceptable by the relevant authorities before implementing the change.
Type II	Major variations with a possible significant impact on Quality, Efficacy or Safety, that require approval of the relevant competent authority before implementation. A change that is not an extension and may have a significant effect on the quality, safety or efficacy of the medicinal product concerned.
Extensions	These applications will be evaluated in accordance with the same procedure as for the granting of the initial MA to which it relates. Extension can be granted as a new MA or included in the initial MA to which it relates. Example: changes to the active substance and changes to the strength, pharmaceutical form and route of administration.
Grouping	Several variations for 1 MA: different types of variations possible. Handled according to the 'highest' variation type in the group.
	One Type IA variation for several MA's: These Type IA variations should be identical for all concerned MA's.
	Grouping for Type IB or Type II variations only possible for national MA's with the same MAH and when authority agrees to this procedure.
Worksharings	Same change (Type IB, II, Group) affects several MA's of the same MAH in one application. The change requires no or limited need for assessment of a potential product-specific impact. Reference authority is chosen to avoid duplication of work in evaluating the dossier.

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