

USE OF TITANIUM DIOXIDE AS EXCIPIENT IN HUMAN MEDICINES

INDUSTRY FEEDBACK TO QWP EXPERTS/EMA QUESTIONS



Contents

Introduction.....	2
A - information (quantitative and qualitative) of TiO ₂ presence in medicinal products EU/EEA	4
1. Please indicate the estimated proportion of <veterinary / human medicinal products> (quantitative data or percentage, where possible) which currently contain TiO ₂ as excipient. It would be helpful if the quantitative information could be broken down in terms of the dosage forms impacted e.g tablets, capsules, pastes etc. A breakdown in innovators, generics, OTC, IMPs of products containing TiO ₂ would also be appreciated. For quantitative information, please include the methodology used.	4
1. Member Survey	4
2. Article 57 database analysis done by the associations	8
3. IQVIA database analysis done by the associations	11
4. Data comparison explanations.....	12
2. Please indicate the function of TiO ₂ in these products (i.e. colorant, coating agent etc.)	13
1. Background	13
2. Uses in detail.....	13
3. Other identified properties and functions (data taken from the member survey):.....	14
B - TiO ₂ possible alternatives and timelines	15
3. Please indicate if alternative excipients to TiO ₂ are available and elaborate on the technical feasibility to replace TiO ₂ with these alternative excipient (for subset of products/which ones/are there different issues for different products/types of products?). Please consider to liaise with suppliers of the alternative excipients, as needed. If no alternative excipient is found, and TiO ₂ has to be removed, can you elaborate, what negative influence on finished product quality it can have?.....	15
1. Overview	16
2. Possible alternatives identified are:	16
3. Company R&D investment in alternatives	18
4. Feasibility to continue product supply	18
5. Points to be considered for alternatives.....	18
6. Technical feasibility assessment would need to include:.....	19
7. Safety assessment/aspects	19
4. In case an alternative for TiO ₂ is available, please indicate approximate timelines to prepare and file for such a change.	20
Global aspect.....	21
C - Industry impact assessment of the situation on the pharmaceutical sector.....	22
5. Please indicate if the requirement to exchange TiO ₂ for another excipient would in your view impact availability of certain medicines in the market. Please be specific. If issues are anticipated for individual products/groups of products, these should be highlighted.....	22
New products and those in development	25
6. What would be, in your view, the economic impact of the requirement to exchange TiO ₂ for another excipient?.....	26

Introduction

This document is submitted on behalf of the three European associations representing the human medicines manufacturers (AESGP, EFPIA, Medicines for Europe) as feedback to the QWP experts/EMA in relation to the opinion of European Food Safety Agency (EFSA) on Titanium Dioxide (TiO₂) as food additive (E171) and its impact on human and veterinary medicinal products. It aims at providing written answers to the group of QWP experts on the following list of questions received on 4 June 2021 by the set deadline of 30 June 2021

A - information (quantitative and qualitative) of TiO₂ presence in medicinal products EU/EEA

1. *Please indicate the estimated proportion of <veterinary / human medicinal products> (quantitative data or percentage, where possible) which currently contain TiO₂ as excipient. It would be helpful if the quantitative information could be broken down in terms of the dosage forms impacted e.g tablets, capsules, pastes etc. A breakdown in innovators, generics, OTC, IMPs of products containing TiO₂ would also be appreciated. For quantitative information, please include the methodology used.*
2. *Please indicate the function of TiO₂ in these products (i.e. colorant, coating agent etc.).*

B - TiO₂ possible alternatives and timelines

3. *Please indicate if alternative excipients to TiO₂ are available and elaborate on the technical feasibility to replace TiO₂ with these alternative excipient (for subset of products/which ones/are there different issues for different products/types of products?). Please consider to liaise with suppliers of the alternative excipients, as needed. If no alternative excipient is found, and TiO₂ has to be removed, can you elaborate, what negative influence on finished product quality it can have?*
4. *In case an alternative for TiO₂ is available, please indicate approximate timelines to prepare and file for such a change.*

C - Industry impact assessment of the situation on the pharmaceutical sector

5. *Please indicate if the requirement to exchange TiO₂ for another excipient would, in your view, impact availability of certain medicines in the market. Please be specific. If issues are anticipated for individual products/groups of products, these should be highlighted.*
6. *What would be, in your view, the economic impact of the requirement to exchange TiO₂ for another excipient?*

Please note that the present document has been issued based on the following:

- The 3 associations submitting do not represent the totality of the Marketing Authorisation Holders for titanium dioxide containing human medicines currently marketed in the EEA.
- The data that the three associations have been requested to collect and process in this exercise are commercially sensitive. In putting together this written feedback, associations' secretariats have been complying with competition law and their internal related guidelines.
- With those legal constraints, putting together this document has been and remains resource intensive while not providing an exhaustive picture of the situation.
- This written feedback cannot substitute for a bigger data collection/assessment exercise (through e.g. public calls for data or database assessment) handled by the regulators.
- This document takes into account the results from the survey which ran between June 15th and June 28th 2021 and was open to direct and indirect members of the 3 associations.
 - For confidentiality reasons, the survey was not open to non-member companies. Many member companies were not in a position to share certain commercially sensitive information with the associations' secretariats.
 - Due to the tight data collection timeline, not all member companies were in a position to provide the requested feedback on time.
 - This document only presents a preliminary analysis of the survey results, as more time would be needed to have a more exhaustive assessment of the data collected.
- Further to a request from the 3 associations to EMA for information available from Article 57 related to marketing authorisations containing titanium dioxide in EEA, EMA provided the associations on 23 June 2021 with a line listing of the medicinal products for human use containing TiO₂ as excipients based on data held in the Article 57 database as of 16th June 2021.

- Further to an additional request from the 3 associations to EMA, EMA provided on 29 June to the associations with the following, based on data held in the Article 57 database as of 16th June 2021:
 - The total number of EV codes for EEA medicinal products that currently have a valid marketing authorisation in the Art. 57 database
 - The total number of EV codes for EEA medicinal products that currently have a valid marketing authorisation in the Art. 57 database and are used orally (based on the field "Route of Administration" being 'Oral' or 'Oral use')
- EMA provided on 30 June to the associations, the following, based on data held in the Article 57 database as of 16th June 2021: an Excel table that summarises the information per category provided on 29 June.

General Considerations It is the industry's priority to keep the market supplied with authorized medicinal products, including some containing TiO₂.

As elaborated in this document, any restrictions on the use of TiO₂ in medicines would have an immediate and significant impact on access to many pharmaceuticals, such as prescription and over-the-counter tablets, hard and soft capsule shells, tablets, liquids, suspensions, ointments, creams. TiO₂ is used in practically all therapeutic classes of medicines and as such could have serious consequences to patients if medicines become unavailable.

The EMA should apply a pragmatic approach in their evaluation on the use of TiO₂ in human medicines in the EU/EEA to ensure product availability and patient supplies.

Considering the industry case and foreseeable issues concerning alternatives to replace TiO₂ - a robust benefit-risk analysis of a ban of TiO₂ carefully in order is recommended to avoid the high likelihood of shortages for significant time or even the termination of licenses due to economic decisions or impossibility to reformulate.

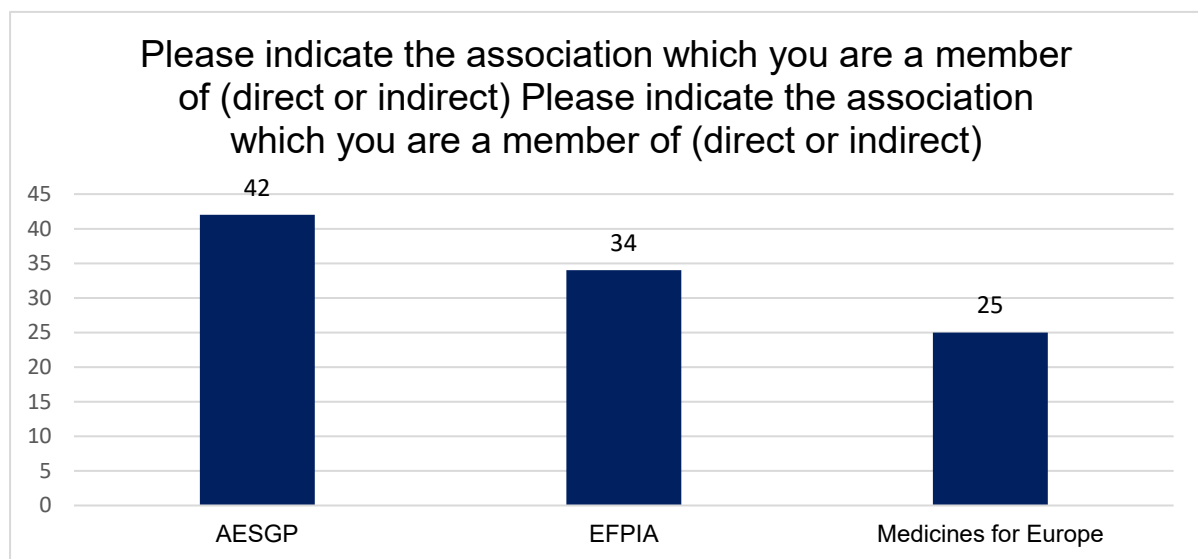
A - information (quantitative and qualitative) of TiO₂ presence in medicinal products EU/EEA

1. Please indicate the estimated proportion of <veterinary / human medicinal products> (quantitative data or percentage, where possible) which currently contain TiO₂ as excipient. It would be helpful if the quantitative information could be broken down in terms of the dosage forms impacted e.g tablets, capsules, pastes etc. A breakdown in innovators, generics, OTC, IMPs of products containing TiO₂ would also be appreciated. For quantitative information, please include the methodology used.

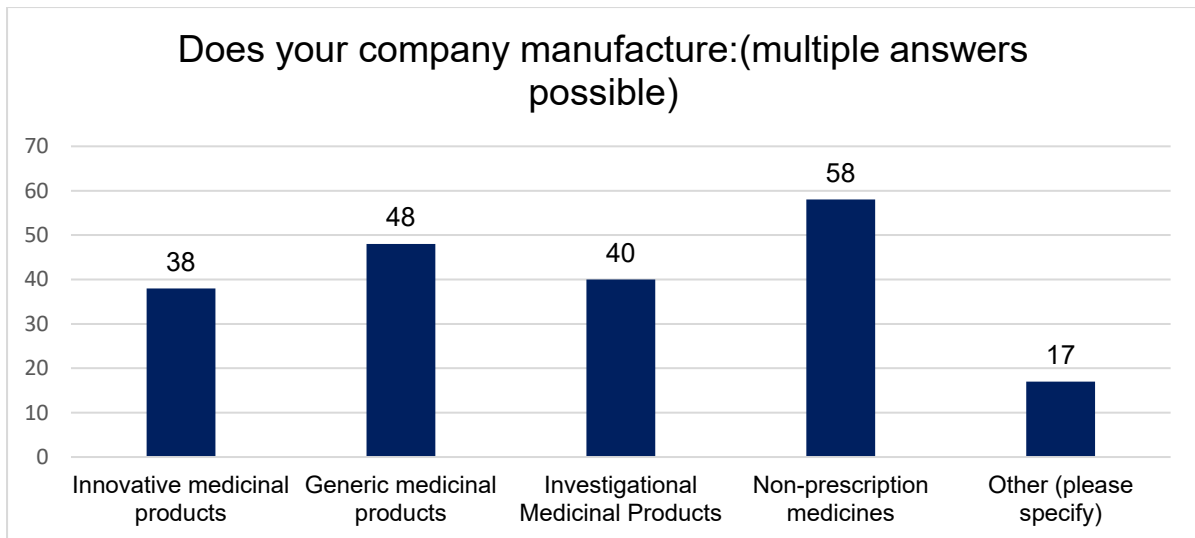
In order to answer this question, the three associations (AESGP, EFPIA and Medicines for Europe) ran a survey among their members and investigated both the Article 57 database and IQVIA database in order to collect the necessary data on human medicinal products.

1. Member Survey

The survey ran between June 15th and June 28th and we have collected a total of 88 answers from all three associations. Due to the short amount of available time, we were unable to cover the whole membership of our associations. However, it gives a clear picture of the impact and struggles to come should a decision be taken to completely remove TiO₂ from human medicinal products.



Since some respondents are members of more than one association, the total number observed in the graph above exceeds 88. We were able to cover a broad range of companies from global to small ones, that manufacture a variety of medicinal product types.

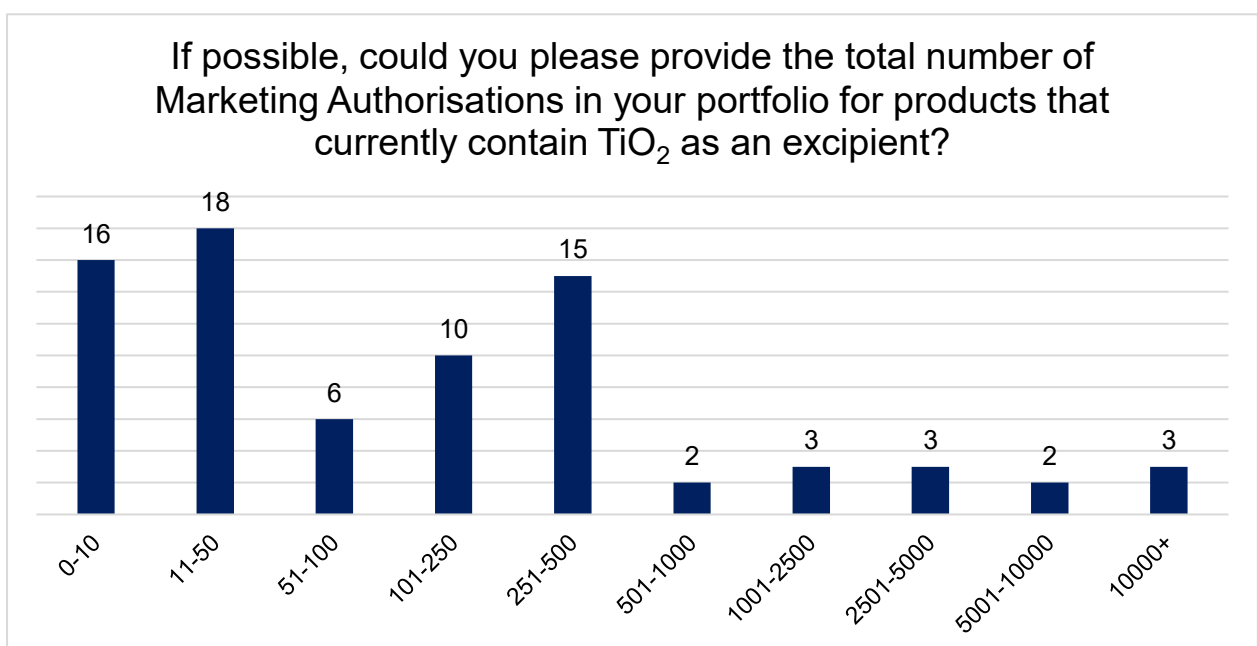


In order to further understand the respondents' portfolio types, companies were asked what their portfolios consists of, and in the graph above we have summarized their answers. This answer does not explain the breakdown of products on the market, it provides an overview on what type of companies responded to the survey. This further consolidates the fact that our respondents cover all the requested categories of human medicinal products.

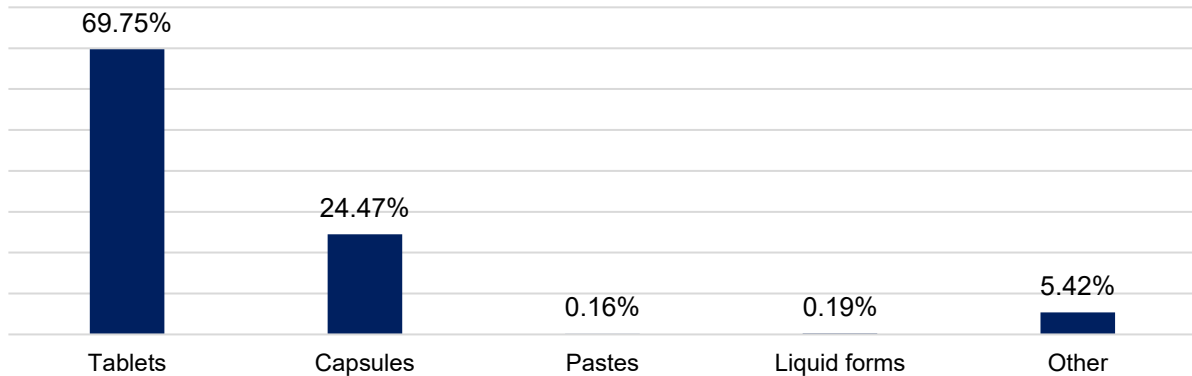
The breakdown of "other" is not relevant for the scope of this survey since it goes even beyond human medicinal products. However, all the next answers will only contain data on human medicinal products meant to be ingested.

In terms of quantitative and quantitative data, we have tried to assess both, unfortunately some of our members were unable to gather the required data in the limited available time. We believe that this shortcoming can be partly tackled by analysing both IQVIA data and the Art. 57 database. However, for transparency reasons, we will include all data we managed to collect.

When asking our companies "how many Marketing Authorisations in their portfolios contain TiO_2 as an excipient", we have collected a total of 88.763 MAs. 78 companies answered to this question. Below we have split the MAs by respondent to highlight the variety in size of affected portfolios (number of MAs on the y-axis vs number of companies on the x-axis):

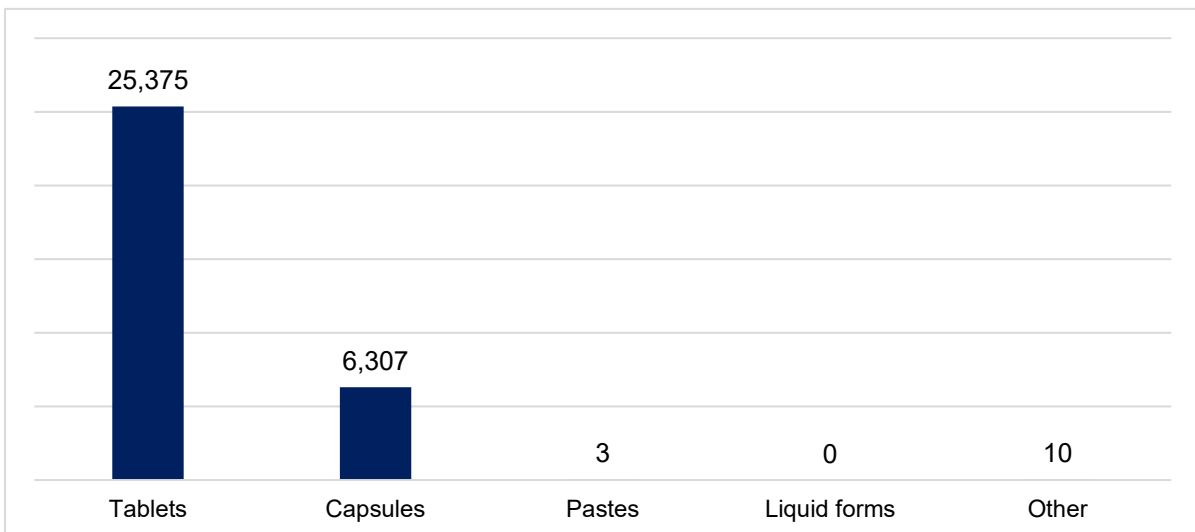


Please estimate the percentage of your products that contain TiO₂ formulated as:



In order to provide more quantitative data and to show the impact these products have on the market we asked our members to provide us with sales data. Unfortunately, the response rate to these two questions was lower because some members did not have enough time to gather all the required information or chose not to share such sensitive data with the Trade Associations. Nevertheless, we have received 68 answers to the question: "How many unit packs/year of products that contain TiO₂ does your company sell in the EU/EEA?". The total number amounts to 2.986.334.061.

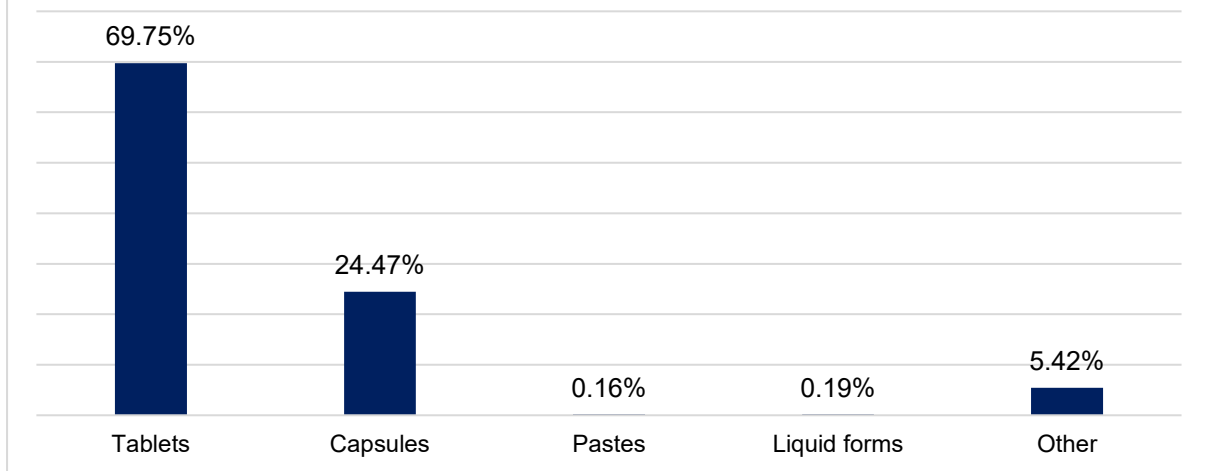
Also, we have asked our members to split the sales numbers per pharmaceutical form categories. On this question we have received 51 answers, that are distributed below. Numbers are expressed as millions of €.



It is understood that all the qualitative and quantitative data was obtained by our members from their own internal repositories, by analysing their internal data and then summarizing it for us in the format requested.

Next, we have investigated the percentage of products that contain TiO₂ split by the categories requested: tablets, capsules, pastes, liquid forms and other). 85 companies have provided data for this question.

Please estimate the percentage of your products that contain TiO₂ formulated as:



We have also asked each respondent to provide a percentage of products that contain TiO₂ as an excipient. The average of all 86 answers received is **44.46%**. Due to the limitations of the survey coverage in comparison to the Art. 57 database, and after receiving more data from EMA (Wed. 30.06.2021 19:32) we decided to use the Art. 57 database analysis results in all further calculations and estimations.

2. Article 57 database analysis done by the associations

Following our request to have the Art. 57 database analysed, we have received from the EMA an extract from the Art. 57 database which contains all products with a valid Marketing Authorisation that contained TiO₂ at the date of 16 June 2021. On 30th of June we have received further data from EMA consisting in extracts on total numbers on all categories requested. Therefore, we were able to finalise our analysis and show with a very high degree of precision the number of individual products that contain TiO₂ as an excipient. The only uncertainty we could identify with the Art. 57 database is the repetition of certain entries due to duplication, or multiple submissions for multiple Routes of Administrations/Pharmaceutical Forms, as also identified by the EMA. Nevertheless, by observing the duplication numbers in the data provided by the EMA, we believe these errors to add to no more than 1%. This is, at the moment, the most reliable indicator of the presence of TiO₂ in the pharmaceutical sector.

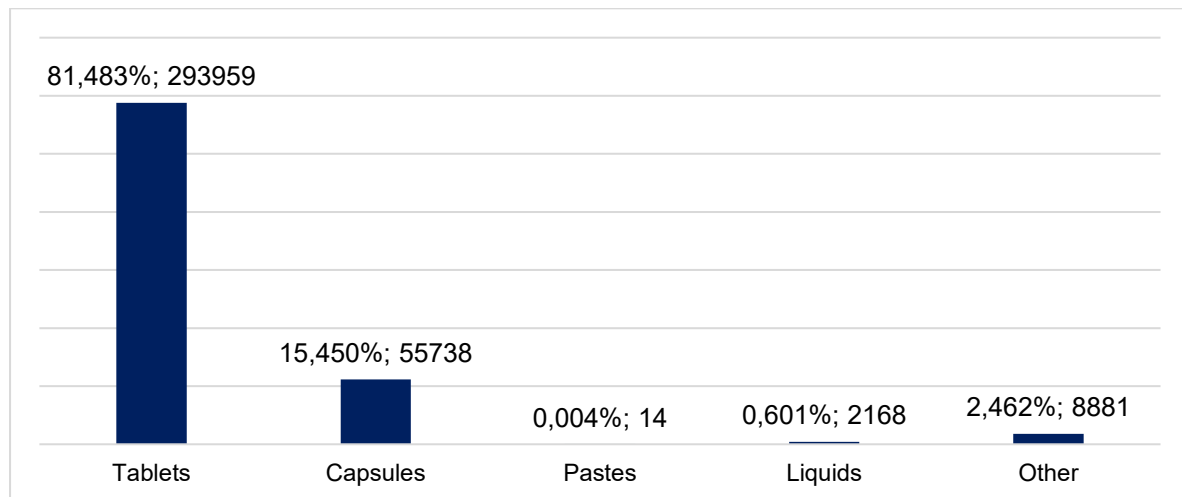
We have a total of 534.657 unique EV Codes in the Art. 57 database.

Out of these, we have a total of 360.760 unique EV Codes for ingested products.

By analysing the data we concluded that:

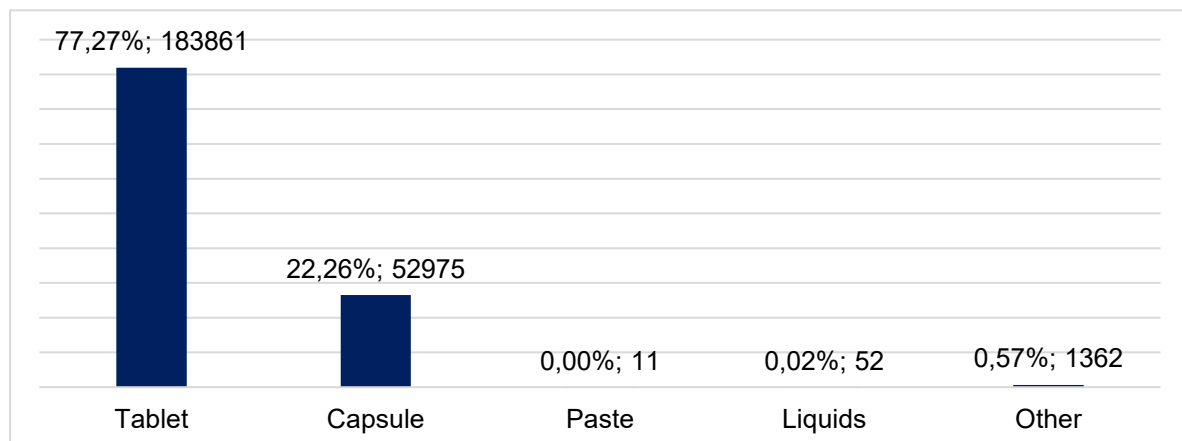
- 44.50% of all EV Codes found in the Art. 57 database contain TiO₂
- 65.95% of all EV Codes **representing ingested pharmaceutical forms** contain TiO₂.

The EV Codes for ingested products are split in categories as following:

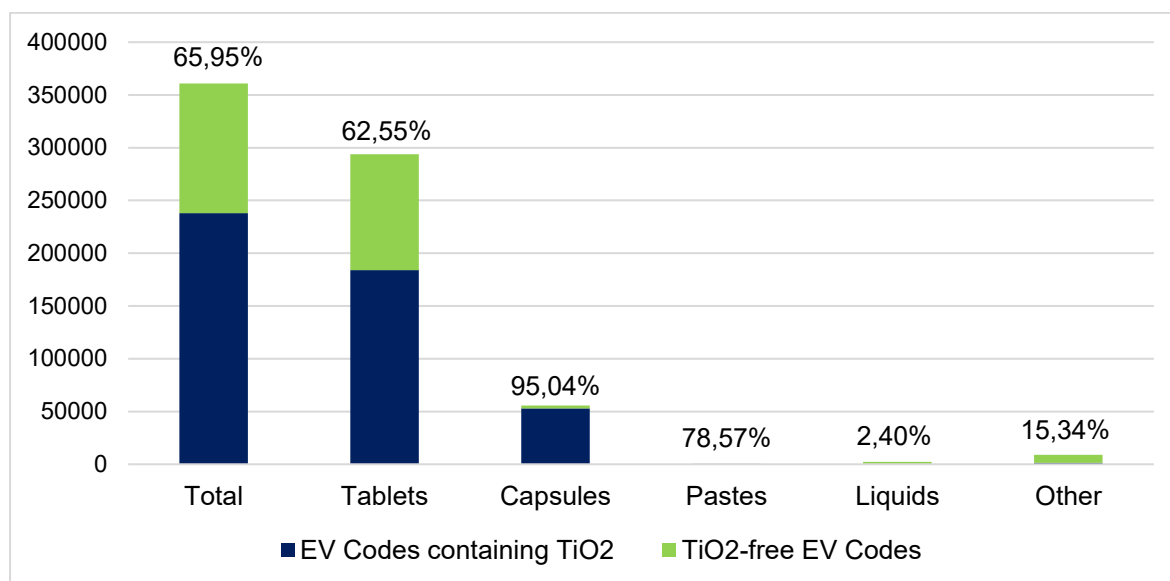


We have a total of 237.934 unique EV Codes representing ingested pharmaceutical forms **that contain TiO₂**.

They are split in categories as in the following graph:



In the graph below the total height of the columns represents the total amount of EV codes split by category. In blue we have marked all TiO₂ containing EV Codes, in green we have marked the difference between the total amount of EV Codes and the EV Codes containing TiO₂. **The data labels on the graph represent the percentage of EV Codes in each category that contain TiO₂.**



In order to obtain these numbers, we have filtered the data received from EMA by “Product EV Code”; “Route of Administration”; “Substance Names”; “Ingredient Role” and “Authorised Pharmaceutical Form”.

We have chosen Product EV Code as it is a unique identifier in the Art. 57 database.

For “Route of Administration”, we have filtered all the entries that are either one of:

BUCCAL USE
GASTROENTERAL USE
ORAL
ORAL USE
SUBLINGUAL USE

For “Substance Names” we have filtered all the entries that are either one of:

TITANIUM DIOXIDE
TITANIUM DIOXIDE BP
TITANIUM DIOXIDE PH EUR
TITANIUM DIOXIDE USP

For “Ingredient Role” we have filtered all the entries that are:

Excipient

And for “Authorised Pharmaceutical Form” we have filtered all the entries and split them by category as following:

-tablets: BUCCAL TABLET
CHEWABLE TABLET
COATED TABLET
COMPRESSED LOZENGE
DISPERSIBLE TABLET
EFFERVESCENT TABLET
FILM COATED TABLET
FILM COATED TABLETS
FILM-COATED TABLET
FILMTABLETTEN

GASTRO-RESISTANT COATED TABLET
GASTRO-RESISTANT TABLET
LOZENGE
MODIFIED RELEASE TABLET
MODIFIED-RELEASE TABLET
MODIFIED-RELEASE TABLETS
ORODISPERSIBLE TABLET
PROLONGED RELEASE FILM-COATED TABLETS
PROLONGED RELEASE TABLETS
PROLONGED-RELEASE FILM-COATED TABLET
PROLONGED-RELEASE TABLET
SCORED FILM COATED TABLET
SUBLINGUAL TABLET
SUGAR-COATED TABLET
TABLET
TABLETS
TABLETS FOR ORAL SUSPENSION
TABLETTEN

-capsules: CAPSULE
CAPSULE FOR ORAL USE
CAPSULE, HARD
CAPSULE, SOFT
CAPSULE, PROLONGED RELEASE, HARD
CAPSULES
CAPSULES CONTAINING PROLONGED-RELEASE MICROGRANULES.
CHEWABLE CAPSULE, SOFT
GASTRO-RESISTANT CAPSULE
GASTRO-RESISTANT CAPSULE, HARD
GASTRO-RESISTANT CAPSULE, SOFT
GASTRO RESISTANT CAPSULES, HARD
GRANULES IN CAPSULES FOR OPENING
HARD CAPSULES
HARD GELATIN CAPSULE
MODIFIED-RELEASE CAPSULE, HARD
MODIFIED-RELEASE CAPSULE, SOFT
PROLONGED-RELEASE CAPSULE
PROLONGED-RELEASE CAPSULE, HARD
PROLONGED-RELEASE CAPSULE, SOFT
SOFT CAPSULE

-pastes: TOOTHPASTE
DENTAL PASTE

-liquids: ORAL SUSPENSION

-other: BUCCAL FILM
ORODISPERSIBLE FILM
COATED GRANULES
COATED GRANULES IN SACHET
EFFERVESCENT GRANULES
GASTRO-RESISTANT GRANULES
GRANULES
GRANULES FOR ORAL SOLUTION
GRANULES FOR ORAL SOLUTION IN SACHET
GRANULES FOR ORAL SUSPENSION
GRANULES FOR ORAL SUSPENSION IN SACHET
GRANULES IN CAPSULES FOR OPENING
GRANULES IN SACHET
GRANULES IN SINGLE-DOSE CONTAINER

MEDICATED CHEWING-GUM
 PROLONGED-RELEASE GRANULES
 PROLONGED-RELEASE GRANULES FOR ORAL SUSPENSION
 ORAL POWDER IN SINGLE-DOSE CONTAINER
 POWDER AND SOLVENT FOR ORAL SUSPENSION
 POWDER FOR ORAL SOLUTION
 POWDER FOR ORAL SOLUTION IN SACHET
 POWDER FOR ORAL SUSPENSION
 PROLONGED-RELEASE GRANULES

For the total number of products containing TiO₂ we have used the data directly supplied by the EMA, filtered under the same condition as we did, per our request.

3. IQVIA database analysis done by the associations

Formulations – IQVIA database – Absolute volumes

The IQVIA SMART - Global MIDAS Edition database was accessed on 14.06.2021 and 18.06.2021. First, volume data for all oral formulations was extracted and then, volume data for all other formulations was obtained to be able to compare with the total volume of medicinal products. 'Non-human use and unknown formulation' were excluded from the calculations. The volume measures that were used are:

- Standard units = 'dose units' (tablets, syringes)
- Units = Total projected number of shipping packs sold
- International product = Products are linked to an international product if two out of the three following characteristics match: Local product name - Active ingredient - Marketing corporation
- Molecule list

Category	2020 Units	2020 International Product	2020 Molecule list
Oral Solid Ordinary	18884522048	35684	7262
Oral Solid Retard or Long-acting	1376594415	2445	278
Oral Liquid Ordinary	2746029304	13663	5544
Oral Liquid Retard or Long-acting	65295	3	3
Parenteral Ordinary	4722855023	11771	2440
Parenteral Retard or Long-acting	135667402	332	121
Rectal systemic	93234227	538	218
Nasal systemic	21925747	75	38
All other systemic	134038904	367	74
Oral Topical	640962959	1328	976
Topical, Dermatological, Haemorrhoidal, External	6143584559	8395	3589
Ophthalmic	1049547078	2353	622
Otic	39443387	217	139
Nasal Topical	782607551	959	360
Lung Administration	547238983	615	105
Vaginal/Intra-Uterine	124745963	656	286
Grand total oral medicines	23007211062	46625	11160

Grand total all other products (including injectables)	14435851783	26137	7899
Grand total all other products (excluding injectables)	9577329358	14762	5794
Share Oral solid + liquid (including injectables)	61,45%	64,08%	58,56%
Share Oral solid + liquid (excluding injectables)	70,61%	75,95%	65,83%

Share of products that contain TiO₂

Based on the conclusions drawn from the Art. 57 database analysis that 65,95% of all EV Codes contain TiO₂, we calculated the absolute and relative values for products containing TiO₂.

- Absolute volume: number of standard units, units, international products and molecules that contain TiO₂ (2020 data).
- Relative volume: percentage of all medicinal products that contain TiO₂. We have done one calculation where we include the injectables and one where we have excluded them (2020 data).

	Units	International Product	Molecule list
Share products that contain TiO₂ (including injectables)	40,52%	42,26%	38,62%
Share products that contain TiO₂ (excluding injectables)	46,57%	50,09%	43,41%
Absolute volume	15.173.255.695	30.749	7.360

4. Data comparison explanations

Depending on the source of information used, the “product” concept will be different. Assuming that products are **at least defined** by their **Active Ingredient/Composition, Dosage form** and **Route of Administration**, the following concepts exist, from the finest to the most coarse level of granularity:

1. **Art. 57 DB “full”**: Every product EV code refers to an “authorised” product, for a unique combination of **market**, (sometimes) **language**, **strength** and packaging **presentation**. The definition of market differs based on the procedure type (Centralised, MRP/DCP, National). For a given packaging presentation, this means that CAPs typically have 3 EV-codes, one for EU, plus two for the non-EU EEA countries (Iceland and Norway), as for non-CAPs these will have up to 29 EV codes (or even more for some multi-lingual countries like Belgium). That number then needs to be multiplied by the different presentations, however in the case of non-CAPs not necessarily all presentations are authorised in all member states. As stated earlier, there are roughly 360.000 EV codes representing ingestible products (roughly 67% of total). Note that “authorised” does not necessarily mean marketed or available in the supply chain.
2. **Marketing Authorisations**: in the majority of markets these are granted at the level of the **market & strength**, NOT at the language or presentation level (except for a few member states).
3. **Stock Keeping Units**: in many cases there will be almost a 1-1 correspondence between EV-codes and SKUs. However, there are two exceptions: **multi-market packs** which would lead to a situation where multiple EV-codes are combined into 1 SKU, and conversely for the CAPs, the **EU region will be covered by multiple SKUs** to avoid having to include multi-lingual

labelling covering 25 languages. If an SKU exists it also means that the product is marketed or even available in the supply chain.

4. **Art. 57 DB “Public Data”**: The publicly available data is an aggregate report of authorised products **by market**. The language, strength and presentation details are filtered out, which means that we have only 91.000 ingestible products listed here (roughly 58% of total).
5. **Company concept of “product”**: this could refer to an entire product family sharing the same active ingredient.

It's unclear which definition the survey respondents used when answering the question on the percentage of products using TiO₂. To illustrate the differences between levels (1) and (5), one company reported 64.1% (281) of all product EV codes corresponding to 52% (13) of all company products.

Generally, there is a tendency that the EV-code level more heavily skews the non-CAPs, more often older small-molecule type products. Therefore, the percentage of EV codes containing TiO₂ will be higher than the percentage of company products.

2. Please indicate the function of TiO₂ in these products (i.e. colorant, coating agent etc.).

1. Background

Titanium dioxide, or TiO₂ (E171), is a naturally occurring mineral that is used in many industries (e.g. food, cosmetics, paint etc.) as a white colourant and opacifying agent (opacification is important to avoid degradation of medicine components induced by radiation or heat).

The pharmaceutical industry has been using TiO₂ safely for more than 50 years. TiO₂ is present in the majority of pharmaceuticals, in the coating of tablets, films of capsule shells or packaging materials. Its ubiquitous use is due to critical functions resulting from the following properties:

- INERT SUBSTANCE

TiO₂ is of particular benefit because it does not impact the properties of the active ingredient(s) of a medicine nor with other essential non-active components of a medicine (excipients). Being an unreactive ingredient, it is a common substance in medicines because it is well tolerated.

- CONSISTENT HOMOGENOUS COLOURING

TiO₂ enables a large colour scheme and plays an important role as opacifier. Consistent colouring of medicines plays a significant role in the recognition of a medicine to allow for differentiation for the patient, who needs to be able to readily distinguish between multiple medicine types, ultimately with direct impact on therapeutic adherence and patient safety. It is also a key indication for healthcare professionals and emergency centres in case of intoxication. In addition, colour variations may give false indication to the user that the product has degraded or is not efficacious.

- RADIATION PROTECTION

Beyond its optical properties, TiO₂ also ensures stability of pharmaceuticals since it absorbs visible and UV light and, hence, protecting photosensitive ingredients from degradation and extending shelf life.

Overall, TiO₂ contributes to a robust dosage form, protecting active ingredients, ensuring shelf-life stability and, thus, securing the safety and efficacy of pharmaceuticals for longer periods.

2. Uses in detail

Titanium dioxide has a unique combination of properties important to product quality.

TiO₂ has at least 2 key functions:

1) *Colouring agent* – It has a high refractive index which means it has the ability to scatter light. This gives it an ultra-white appearance. It is used as a colorant as a whitening, pigmenting agent which may

also act to accentuate other colours to help differentiate different dosage strengths. It also ensures adequate reproducibility of colours from batch to batch.

2) *Opacifying agent* – as part of thin film coating of tablets, pellets and hard capsule shells; assure batch-to-batch conformity and helps protect the active ingredients against UV/light and heat degradation. It is an essential component of the protective layer which aids in preserving the safety, efficacy, and quality of the product over its' shelf life by supporting the physical integrity of the product or is a stabilizer for photosensitive formulations by protecting other UV sensitive ingredients from degradation on exposure to visible light

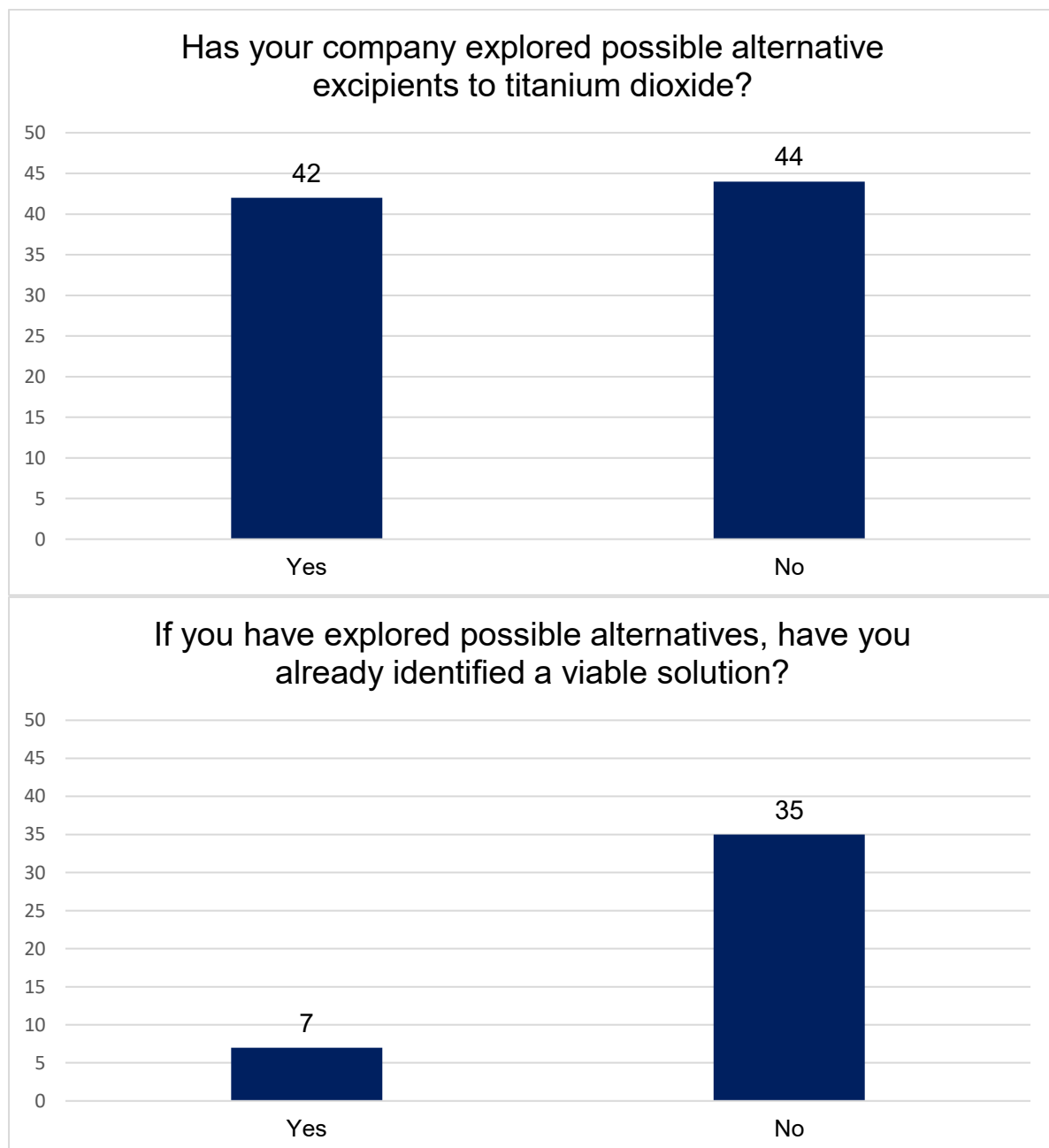
3. Other identified properties and functions (data taken from the member survey):

- Masking agent for taste and smell
- Masking agent of unattractive appearance of the ingredients
- Improve product appearance by ensuring that the tablet coating is smooth (and uniform) and therefore easy to swallow. This is important for the consumer perception of the tablet, since blotchy coatings may give the perception that something may be 'wrong' with the tablet.
- It also provides a unique visual identity to each medicine. These properties of the film coating contribute to patient dosing compliance, especially for those patients taking multiple medications concurrently.
- It also supports imprinting/marketing on Capsule shell or tablet marking (using UV laser).
- Refiner in coating allowing thin non-brittle coatings, avoids sliding of coatings
- Colour (different dosage strengths) is important for patients with limited eyesight.
- Prevents water absorption into the tablet. Some (e.g. herbal) preparations are highly hygroscopic and therefore it is essential that the film coating is a barrier against humidity.
- Colorant to support blinding in clinical studies
- It provides a strong anticounterfeiting measure for a drug due to unique look of the tablets and capsules
- Low weight gain of coating to tablet core
- Often added to primary packaging materials (e.g. blister packs) where it can play an important role in maintaining the shelf-life of the blister pack and preventing premature degradation of the packaging from light.

B - TiO₂ possible alternatives and timelines

3. Please indicate if alternative excipients to TiO₂ are available and elaborate on the technical feasibility to replace TiO₂ with these alternative excipient (for subset of products/which ones/are there different issues for different products/types of products?). Please consider to liaise with suppliers of the alternative excipients, as needed. If no alternative excipient is found, and TiO₂ has to be removed, can you elaborate, what negative influence on finished product quality it can have?

Indicative results of the survey previously quoted identify that research is underway by pharmaceutical companies to identify alternatives however with minimal viable solutions identified, please see figures below:



The graphs above show the number of responses to each question. The answers taken into account for the second question were only from companies that answered “Yes” to “Has your company explored possible alternative excipients to titanium dioxide?”.

1. Overview

The survey of leading pharmaceutical manufacturers showed that no globally recognized suitable alternative to TiO₂ is available that does not significantly impact changing the appearance of the dosage form. Any known alternatives would not perform as effectively as TiO₂ or pose a reduced risk to human health.

Investigations into alternatives have not identified any excipient with comparable properties in regards to whiteness, refractive index, water-solubility and particle size available which leads to the same uniform film quality as TiO₂. Therefore, it is expected that each medicinal product will require a case-by-case approach when designing a TiO₂ free formulation since no other excipient can directly replace it and all its properties. The alternative excipient must be safe for the patient in all aspects and compatible with the medicinal products.

Finding alternatives to replace TiO₂ is made even more difficult because of the limitations and regulations to which pharmaceuticals must abide. TiO₂ is not part of the active ingredient but helps to deliver the so-called ‘finished dosage form’. Suitable alternatives would need to have similar functional properties as TiO₂ (e.g. opacity, stability, protection from degradation), and at the same time complying with criteria such as compatibility and absence of reactivity with the other components of the pharmaceutical product i.e., both active ingredients and (other) excipients.

It is also important to point out that TiO₂ is an inert substance and only a small amount of TiO₂ is needed to achieve the desirable properties. Alternative materials with the necessary functional properties would likely have to be added in larger amounts while still not delivering the same appearance of the dosage form that TiO₂ affords,

In company medicines' portfolios, the replacement of TiO₂ presents a significant, multifactorial challenge. It must be demonstrated that the replacement will have the same or sufficiently similar performance as an opacifier and pigment. It must be possible to obtain the material in sufficient volume/scale from suppliers who can provide it in line with the required quality standards for pharmaceuticals. For use as a pigment or opacifier, any alternative material must have a superior benefit-risk ratio than TiO₂ and comply with the relevant regulations. It must be capable of being processed on existing production lines.

It must be compatible with the other ingredients in the formulation without having an impact upon the existing product critical quality attributes associated with the rest of the formulation. It must itself be stable and not interact with the formulation in any way as to compromise stability, including stability of product appearance. It must not adversely impact product cost of goods in order that the final patient is able to procure their preferred products at the same price as they have done previously.

From the above, it will be understood that for any given product the identification of an alternative to titanium dioxide will be a significant multi-year undertaking. It will also be understood that each formulation requiring titanium dioxide replacement will be associated with a multi-year development program leading to a CMC package that can be submitted to the relevant health authorities.

2. Possible alternatives identified are:

- Carbonates
 - Magnesium carbonate
 - Calcium carbonate
 - Calcium carbonate + isomalt
- Phosphates
 - Dicalcium phosphate
- Starches
 - Rice starch

- Talc
- Removal of TiO₂ from the composition with no replacement

In the survey with members from the 3 associations, those who responded that alternatives have been identified, refer to those listed above. While there are a number of possibilities, as previously mentioned, none have all the properties as TiO₂. Furthermore, there are many remaining concerns of their application in medicines.

There are legitimate concerns that alternatives being explored may also potentially be identified as having potential safety concerns in future. Given that it will take time to take up alternatives, it is critical for patient safety that there is sufficient confidence in the safety of the alternatives.

Possible alternatives to TiO₂ need to be considered for a number of properties:

- superior benefit-risk ratio than TiO₂
- compatibility with APIs
- patient tolerability
- need still to be established for pharmaceutical use
- technical trials done for drug products
- impact on appearance/aspect
- coat/capsule thickness with change in weight expected and impact of a thicker coat/capsule on dissolution
- drug product performance (e.g. dissolution and bioavailability)
- impact on stability
- impact on packaging
- light protection efficiency
- bio-equivalence
- taste may be different
- visual appearance (including overtime during storage)
- packaging changes

Calcium carbonate and talc are similar products of mineral origin, however there are more reactive than TiO₂ and do not provide the same degree of light protection (opacity). Talc and calcium carbonate may also be less sustainable materials and may be difficult to purify due to their mineral origin. Talc also has the potential for asbestos contamination.

Organic substitutes (such as corn starch or isomalt) have not been studied extensively as opacifiers/colorants and a significant amount of R&D would be needed to evaluate their suitability as TiO₂ alternatives. Ensuring that GMO-free sources are available would also be a challenge.

Carbonates, phosphates and starches all have less opacifying performance, are not as white, and are not inert. The safety profile of the alternatives still requires verification.

Current knowledge indicates that more coating material is required to obtain acceptable appearance. Influence on properties such as dissolution and stability are yet unknown.

These alternatives are influencing in a negative way the viscosity of the coating solution, process performance, process time, spraying rate, etc.

Carbonates as excipients need to be included at a higher concentration and have the negative impact on the film coatings of reducing film strength which can lead to coating defects and a matt/rough tablet surface that could impact packing efficiency. It also does not provide the similar opacity and therefore needs a higher coating weight gain which will impact the coating process efficiency. For light sensitive drugs the reduced opacity may also cause a higher rate of degradation.

Carbonate and Talc are mined material which will have on top a significant negative environmental impact if being used.

Corn starch as theoretical alternative is not able to produce any thin films and as such not suitable for tablet coating and we have not seen it anywhere being offered.

3. Company R&D investment in alternatives

A number of companies indicated they have initiated research into alternatives, technical feasibility studies and various pilot projects. However, it is clear from all responses that there is no simple one-for-one replacement for TiO₂ which covers all properties, performance and functions required. Some selected examples outlining activities below:

Company 1 example: In the past 18 months, one company evaluated 17 unique tablet coating formulations for one strength of one product with 5 different opacifiers. All but one exhibited unacceptable colour variability even at higher weight gain of 6%. The one formulation with acceptable colour uniformity exhibited significant colour change on stability. Alternate coating formulations may not exhibit the same strength and bulk and packaged shipping studies would need to be performed. The colour of the commercial product was not able to be matched with any formulation evaluated without using TiO₂.

Company 2 example: has explored alternatives in 2020 and 2021: Replacement tests with different calcium carbonates, calcium oxides, calcium phosphates and starch have been performed resulting in insufficient coverage (tablets with spots, inhomogeneous, no real batch-to-batch conformity), sliding coats due to much higher amounts needed, "dirty" colours (missing whiteness) or breaking coats during stability. Better coverage has been achieved with iron oxides but the tablet would need to change and the colour spectrum is limited.

Company 3 example: Pink, Yellow and white as Titanium-Dioxide Free (TF) variant was tested and compared to the usual TiO₂-coatings. Summary of comparability:

- Manufacturability is similar
- TF coating need to be applied in higher coating levels (w/w%) to achieve sufficient coverage
- All TF colours did not match the original colour --> different colour codes
- After light stability, TF coating tended to turn darker (TiO₂ turn lighter or stay the same).

4. Feasibility to continue product supply

There is no guarantee that a replacement for TiO₂ can be found for every product, and a ban on TiO₂ would result in withdrawal of some products from the market and loss of patient access to that medicine. Each product will have to be evaluated on its merits and extensive studies will need to be conducted to understand the feasibility of removing or replacing the TiO₂ for each product.

Any required changes to production lines as a result of an ingredient change could add significant monetary and time investment and delay in product availability on the market or at the worst case could result in product de-list if the alternative ingredient severely impacts product manufacturability.

5. Points to be considered for alternatives

There are uncertainties regarding the importance of TiO₂ particle size, including nanoparticle content, on the effects observed in studies evaluated by EFSA. The importance of such physicochemical characteristics of TiO₂ is unclear in part because the characterization of TiO₂ is not straightforward. It is therefore important to take into account the physicochemical characteristics of any alternative material when considering its suitability as a replacement for TiO₂.

From a pharmacology and toxicology perspective, technical feasibility would be assessed by the type of activities necessary (e.g., determining acceptable intake/missible levels of candidate substitutes from existing literature). Additional toxicity or pharmacology studies might be needed if an excipient has the potential to modify the dissolution/release or bioavailability of the active ingredient or if the new component is absorbed and interferes with the endocrine system. Alternatively, new impurities may emerge (during stability testing) that require qualification either via existing literature or an additional toxicology study. If the quantities are low and within acceptable levels, clinical bioequivalence trials might be needed to evaluate substitutability with the original formulation in addition to dissolution studies. New excipients may alter the size of existing tablets/capsules, which would have a significant

negative effect on the intake (too big to be swallowed). All of these additional activities would add significant time and cost to reformulation initiatives.

6. Technical feasibility assessment would need to include:

- Reformulation and technology transfer required (development to scale up), including process validation and stability trials.
- Key unit operations (KOs) may become impacted. For example, granulation, blending and tableting stages may change due to characteristics of pre-tablet material through change. Powder flowability and compression profile may alter.
- Design space to be mapped and assess impact to process capability.
- Bioequivalence and organoleptic trials may be required.
Forced degradation studies may be required (TiO₂ may suppress degradation modes/new replacement may increase them or change deg profile).

7. Safety assessment/aspects

The magnitude of the potential effort needed to remove TiO₂ from medicines, together with the potential to negatively and seriously impact public health as a result, asks for a robust and thorough benefit/risk assessment by EU competent authorities responsible for medicinal products. This benefit-risk assessment is key to properly inform decision-making associated with a potential ban of the use of TiO₂ in EU medicines.

Failure to undertake such a benefit-risk assessment would also adversely affect the perception of Europe's competitiveness as a location to develop and manufacture medicines.

There is a need for a separated risk/benefit analysis for medicines to be conducted, as the quantities in use and exposure levels are significantly less than that used in foods.

- When compared to consumption in foods, the intake of TiO₂ from most oral medicines is expected to be highly controlled and very low (typically less than 10mg per day).
- The EFSA scientific opinion leaves a number of open questions that need to be addressed to inform a benefit/risk assessment of continued use of TiO₂ in medicines. Genotoxic effects observed in studies seem not to result in gene mutations and carcinogenicity.
- A decision to restrict TiO₂ in medicines should not be made out of the presumption that TiO₂ has carcinogenic effects.

4. In case an alternative for TiO₂ is available, please indicate approximate timelines to prepare and file for such a change.

In our previous surveys and analysis (2020), we had identified average timelines per product.

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

Our latest survey requested companies to estimate the timelines for the entire portfolio of products containing TiO₂. The results showed a diversity of responses and some companies were not able to provide a timeline at this stage. We do not know precisely what cost factors companies considered to identify these costs. We intend to seek further information from some contributors to clarify. To simplify the analysis, we have broken down the responses into ranges: less than 5 years, 5-10 years and 10-20 years. Due to the tight deadlines in gathering then analysing the data, we have not had the opportunity to gather more insight from companies on the methodologies they to determine this data.

- 8 respondents identified less than 5 years required – some of these responses seem to indicate the time/product rather than the whole portfolio so further clarification may be required.
- 21 respondents identified 5 to 10 years for the full portfolio.
- 10 respondents identify 12 to 20 years frames for their full portfolio.
- Many respondents were unable to calculate a timeframe for their portfolios.

Some issues complicating these timelines include

- Reformulating the whole portfolio cannot be done in parallel.
- Some reformulations will be more complex or require more complex regulatory steps.
- Many products are marketed internationally – so parallel regulatory processes would be needed globally (extending time commitments).
- Multiple regulatory processes could overwhelm the resources of the regulatory network and create delays
- The necessity to work with contract manufacturers.

This quote captures the input: Due to the high number of products affected, this will not be feasible for all products at the same time but a staggered approach will need to be taken. Total time estimated for implementation in all products: 7 – 12 years. An overloading of health authorities for approving the changes can be expected which might extend the timelines further and, particularly in case of type II variations bring an additional challenge to the supply of the products.

Global aspect

Titanium dioxide is one of the only globally approved substances for use in pharmaceuticals as a white colourant. TiO₂ is preferred for use in medicines globally, since it meets the most stringent of requirements governing the safety of medicines, including those set by the pharmacopoeias in Europe, Japan and the US, and is estimated to be used as an excipient in the majority of tablets and capsules or oral pharmaceutical solid dose forms currently supplied in the EU.

While appreciating that the EMA jurisdiction is specific to EU, the EMA should recognize the influence it has over regulatory decisions. Europe is regarded as a key reference market and regulatory decision by European regulators have undoubtedly an impact on other markets – therefore it is requested that this broader impact is also considered during the evaluation.

We expect issues with regard to regulatory processes for global products as most companies provide products to both EU and non-Eu markets. If reformulation will be forced by EU then maintaining parallel handling of products with/without titanium dioxide for different markets will be required (EU version without TiO₂ and non-EU version with TiO₂) and this is not always justifiable for companies from the patient, technical and economical perspective.

Supply chains are global and so any proposed restriction or ban would lead to a challenge for companies manufacturing and supplying products for the EU. There would need to be considerations on how to monitor non-EU countries and also consideration of supply issues.

Furthermore, it would affect world-wide supply for affected products and may lead to drug shortages for existing products as well as delay of new innovative drugs.

This will impact other (non-EU) markets which rely on EU approved medicines

C - Industry impact assessment of the situation on the pharmaceutical sector

5. Please indicate if the requirement to exchange TiO₂ for another excipient would in your view impact availability of certain medicines in the market. Please be specific. If issues are anticipated for individual products/groups of products, these should be highlighted.

The survey results consistently warn of availability risks related to a requirement to reformulate to replace TiO₂ with an alternative excipient. In the descriptive responses, companies indicated 7 types of challenges. Each identified challenge is complemented with a direct quote from the respondents.

1. Bottlenecks with suppliers of alternative excipients: Some respondents indicate challenges accessing suppliers of alternative excipients:

For example, *“There are already supply chain problems around excipients for TiO₂-free formulations following the food ban in France. A ban in medicines will most certainly cause a shortage.”*

For example, *“It is anticipated that the entire industry will be working with the same suppliers for Titanium dioxide alternatives. Given that the industry is only now adapting to this potential challenge it can be anticipated that shortages of the alternative materials will result in significant supply chain constraints.”*

For example, *“Replacement options candidates (talc, calcium carbonate): mined materials have supply chain risks (limited sources of GMP quality, environmental considerations)”*

2. Impact on Medicines Agencies’ resources is also cited multiple times:

For example, *“In addition, there might be an impact on health authority resources to review all the submissions, also the potential impact to human investigation if needed due to change in formulation.”*

3. The unwillingness of contract manufacturers to undertake the reformulation is also cited:

For example, *“TiO₂ Is present in a large part of our products and most of them are subcontracted. We cannot assure that our subcontractors will be supportive for such important changes (long, require human and material resources and costs a lot).”*

4. Technical unfeasibility or complexity to replace TiO₂ with an alternative is also cited as a risk:

For example, *“For some products reformulation may not be technically feasible, or economically viable. These products would simply be withdrawn from the EU market.”*

For example, *“Reformulation work may take multiple years for drug products with a complex compatibility & stability profile.”*

5. Potential negative impact of a reformulation on shelf-life or stability could also be a factor:

For example, *“If due to a worse stability (missing opacity of TiO₂) only a shorter shelf life of 2 years or even below can be achieved, this does not fit the pharmaceutical market and might result in product withdrawals.”*

For example, *“Only in the context of long-term ICH stability studies will the possibility of a replacement become apparent. Prerequisite: Compliance with the product specification/quality! If this is not guaranteed, long-term reformulations would follow or, in the worst case, marketing of the product would be discontinued.”*

6. Globally produced products could face challenges between EU production (not containing TiO₂) vs global production (containing TiO₂)

For example, “The additional complexity of managing dual supply chains for products with and without TiO₂ for EU and global markets (which have not expressed concerns about the use of TiO₂ in medicines) is another factor that could impact product availability.”

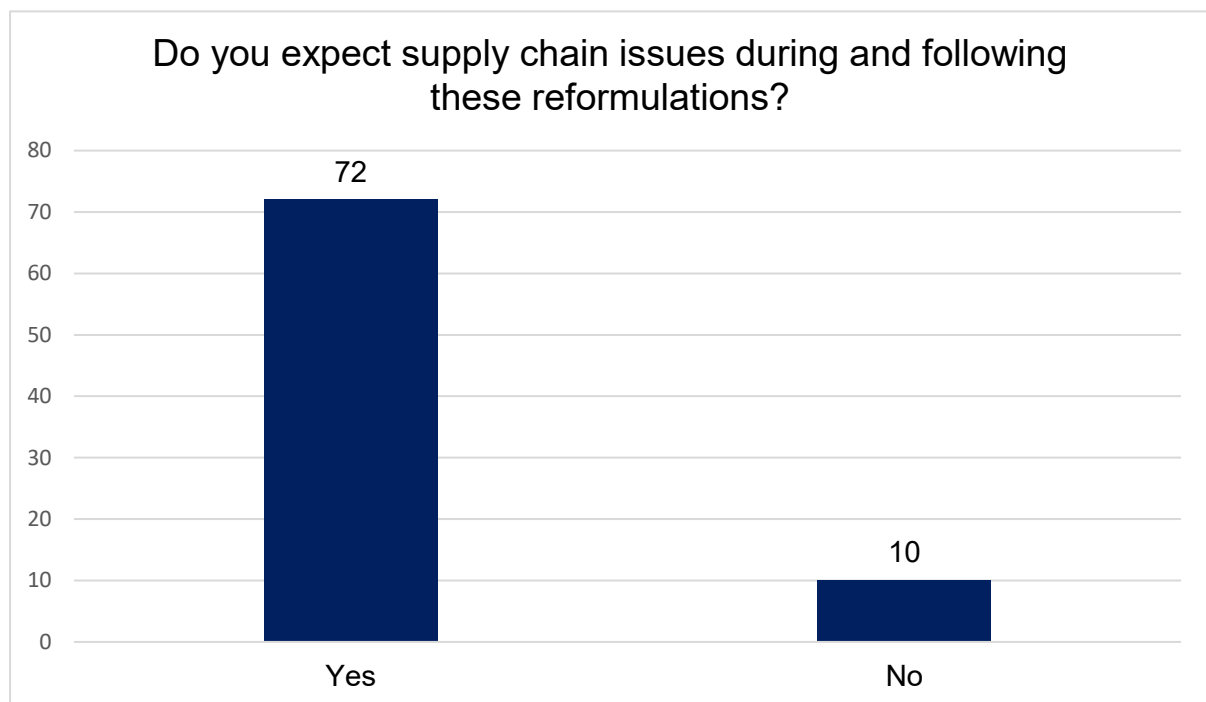
7. Negative impact on Research and Development: Funding identified for R&D will be redirected to cover reformulation costs and fees.

8. Economic/commercial viability: Additional costs related to the reformulation efforts will have to be absorbed by manufacturers. Many respondents have indicated that some products will lack the commercial viability to introduce such a reformulation.

For example, “In addition to the concerns noted above, some products could face the threat of discontinuation as a result of market dynamics. Given the substantial resource/time implications associated with reformulation, low(er) margin products are especially vulnerable.”

For example, “Shortages caused either by prioritization of certain products for reformulation or inability of supply chains to support the shift in demand. Reformulations will not be worthwhile for products with small sales quantities.”

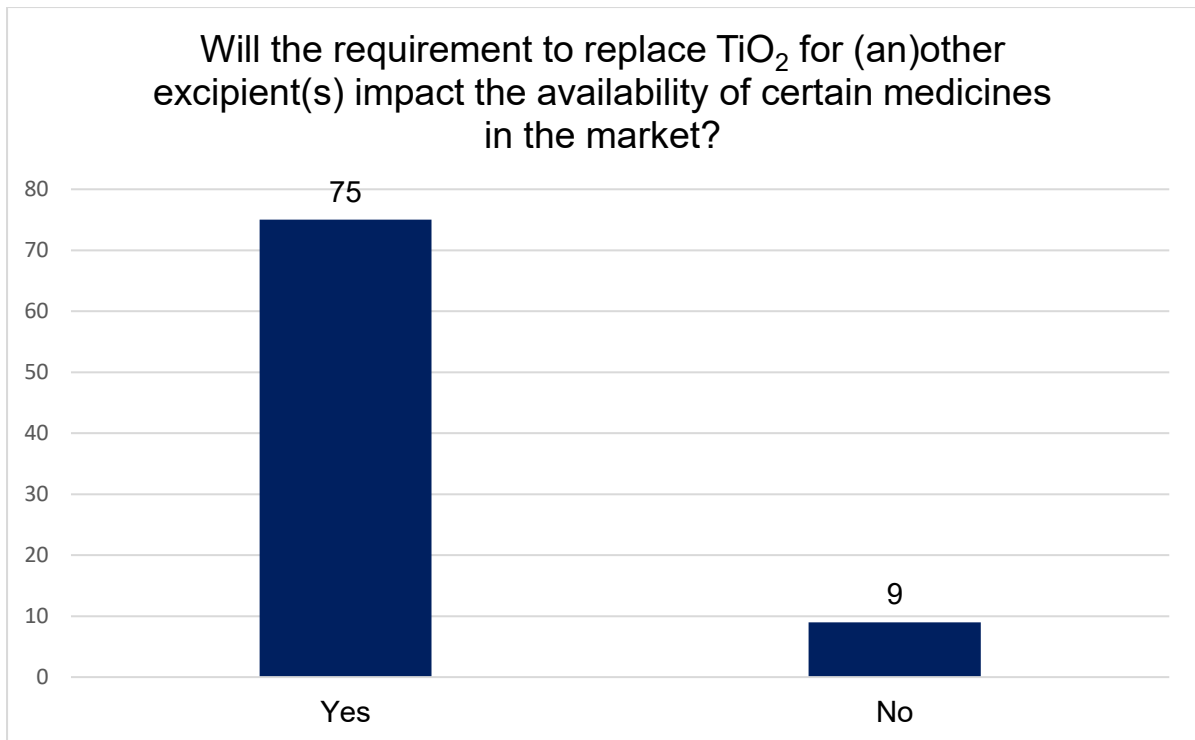
The quantitative results of the survey are broken down into supply chain, availability and withdrawal risks.



72 out of 82 of respondents expect **supply chain issues related to reformulations**.

This is because of the technical complexities associated with the reformulation and challenges related to alignment with contract manufacturers, among other challenges.

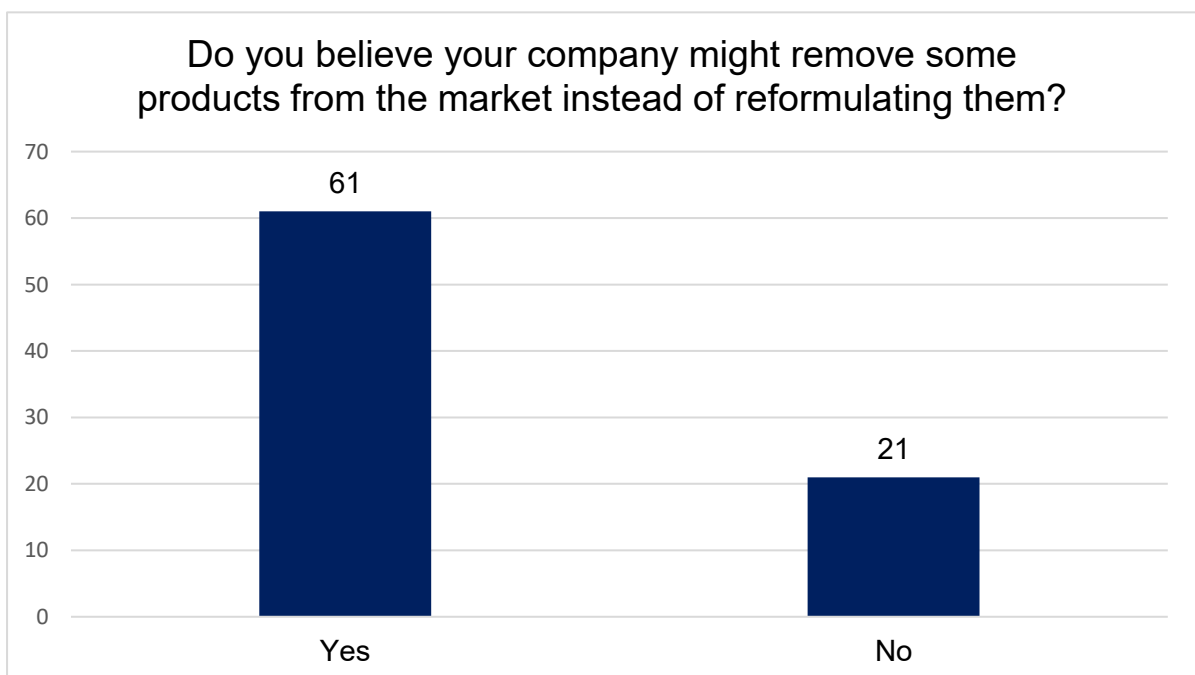
Companies also anticipate that suppliers of alternatives would need to be validated and there would be bottlenecks due to strong demand for such alternatives.



75 out of 84 respondents anticipate that a reformulation would impact the availability of medicines.

This could be related to:

- The lack of alternatives
- Commercial viability issues
- Challenges in the reformulation process
- Delays in the process (technical/regulatory)



61 out of 82 of respondents foresee market withdrawals as a major risk. The cost and feasibility of reformulation may affect the commercial viability of some products. The complexity of alignment with

suppliers or CMOs may be another factor. For some products, there may not be viable alternative excipients.

1. Resources

Considering the large number of affected products as well as the time required for the execution of the different stages, many companies have minimal human and material resources available to address all required changes in parallel and in addition to other work priorities.

2. Product discontinuation and shortages

Due to the very high development costs and regulatory fees, many companies would discontinue certain products.

A ban may lead to supplying issues in some territories.

It is likely many products will be phase out of the EU market, which will greatly impact patients' access to their medicines

Having to put in place an EU customized formulation will impact the viability of certain products and weaken our supply chain flexibility to (only) meet EU demand (pharma strategy and structured dialogue provide additional rationale);

Depending on the cost/benefit for each individual product, very likely some of our products will be removed from market.

3. New products and those in development

The questions of the Association survey focused on existing products. However, there are products in companies pipelines that will also be impacted by decision to replace/ remove TiO₂. As well as established marketed products, investigational products in the pipeline that are already at an advanced stage of development will also be impacted by any ban or replacement of TiO₂, this will delay clinical trials and therefore delay the launch of new products to patients.

IMPs (Investigational medicinal products) should not be excluded in the discussion on potential impact. In some companies, a large amount of the IMPs currently contain TiO₂, which means a significant impact on clinical trials and patients in the EU.

6. What would be, in your view, the economic impact of the requirement to exchange TiO₂ for another excipient?

There are a wide range of cost estimates provided by companies in the survey. Similar to the way “product” can be interpreted in various ways by different companies, also the various steps and setbacks in the reformulation process could have been taken into account differently by companies, especially given the fact that a similar scenario did not exist in the past. When creating the survey, we have not considered this option, and only realized it after the initial data analysis. Therefore, we are planning to reach out to some of the respondents again, especially to the ones that submitted answers in the high and low spectrum of possible cost to understand the logic behind their calculations, with the expectation to uniformize all the received data.

We believe that some of the different estimates of cost are linked to the complexity of a reformulation process or the risk of requiring additional manufacturing capacity notably in relation to:

Reformulation risks

- Light degradation risks
- Stability risks
- Risks to strength (hardness) possibly requiring packaged shipping studies
- Possible impacts on safety/efficacy (if replacement excipient affects API) that might require a clinical study
- For complex products: Gastro-resistant coatings (some alternative excipients would have a negative impact here). Controlled release or amorphous solid dispersions could be affected by the change in film coating

Manufacturing risk

- Risk of additional manufacturing costs if European production would need to be decoupled from global production (new CMO or manufacturing capacity)

As the cost analyses were submitted in descriptive terms, we have broken them down into 3 categories with a low estimate below €100,000, a medium cost estimate of €100,000-500,000 and a high estimate of above €500,000. The costs are estimated per product. According to the survey:

- 24% of companies identified costs below €100,000/product
- 31% identified costs ranging from €100,000-500,000/product
- 32% of companies identified a cost above €500,000/product

Example of a low cost (€90000)

Average ~ €90,000 (€15,000 – €150,000 for the reformulation work dependant on API cost and complexity of release profile + pan EU RMS with 1 strength product: €16,000 + €9,000 per additional strength for regulatory fees).

Example of a low/medium cost (€175,000)

Reformulation: €25,000;
Production Run: €100,000;
Stability: €15,000;
Dossier Preparation: €25,000;
Variation process: €10,000;

Example of a high cost:

Per product: €500.000 for easy Caps/tablet coating exchange - €1.500.000 if coating is functional (gastroresistance) – without registration fees per MA: 51.000 for easy Caps/tablet coating exchange – 154.000 if coating is functional (gastroresistance) – including registration fees. The range will be anything from 1 to 25+ Member States depending on the product, so the costs will vary significantly across the portfolio. coating is functional (gastroresistance) – including registration fees. The range will be anything from 1 to 25+ Member States depending on the product, so the costs will vary significantly across the portfolio.

The survey enabled a collection of estimated costs of reformulation per product. It is challenging to apply this data to an impact on the actual price of pharmaceuticals in European markets. We would underline, however, that these costs would most likely need to be absorbed by manufacturers given that medicines pricing is often regulated (with fixed prices) from a reimbursement perspective in Europe. Even in free pricing pharmaceutical market settings, there may be measures that limit the possibility to increase prices (i.e., maximum price caps/minimum rebate levels in procurement or other civil contractual arrangements having a similar effect).