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European Medicines Agency

Feedback from European Medicine Agency (EMA) to the EU Commission request to evaluate the feasibility of alternatives to replace titanium dioxide (TiO_2) in medicinal products and its possible impact on medicines' availability

Executive Summary

- TiO_2 is present in approximately 91000 Human medicinal products and 1600 Veterinary medicinal products on the EU market.
- In many medicines the use of TiO_2 as an excipient is critical to safety and efficacy (e.g. as an opacifier to protect from light and prevent degradation of the active substance, or to enable tablet dissolution).
- Removal of TiO_2 is likely to be feasible for less than 5% of the medicines.
- Extensive studies have been done by the pharmaceutical industry to investigate possible alternatives involving 20 possible excipients. All of the 20 alternatives were inferior to TiO_2 based on the entire set of KPIs. Significant challenges around manufacturability and photostability were observed.
- The investigations performed by the pharmaceutical industry thus far have confirmed EMA's interim conclusion in 2021 that it is not technically feasible to replace TiO_2 in all medicines, without negatively impacting the quality, safety and efficacy of the vast majority of those medicines.
- The same technical challenges are expected to apply to new products under development. Given the widespread use and acceptability of TiO_2, it is the material of choice in coating materials, capsules, etc. This means that it is included very early on in product and formulation development and clinical studies on these investigational medicines. Its removal from medicines under development is expected to raise the same technical challenges as for authorised medicines.
- The technical challenges identified by industry are considered to be a realistic representation of the situation.
- Attempts to replace TiO_2 will present significant logistical challenges for industry for both authorised products and products under development. Capacity issues for industry and

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

regulators will also arise. These multifaceted challenges are considered highly likely to result in withdrawal of products, unavailability of products while changes are undertaken and increased time in bringing new medicines to market. Severe shortages for European patients and animals can be anticipated.

- It should be highlighted that any requirement to make available TiO_2 free medicines would only be proposed in the EU/EEA and not globally. Accordingly, companies would have to create EU/EEA only supply chains, processes and dossiers. This will add to the potential that products may be subject to shortages or discontinued because of the cost and complexity of maintaining them on the EU/EEA market.
- In the hypothetical scenario that an alternative for TiO_2 is identified, Industry estimates that timelines for reformulation of individual products would vary from 4 to 6 years depending on complexity and risks associated with reformulation and considering regulatory filings. This would mean that a typical pharmaceutical company would spend at least between 7 to 12 years for reformulation of their portfolio, given the large volume of products affected. Submission of post-approval variation procedures for so many products would further prolong the time needed due to capacity constraints within the EU regulatory network.
- EU Regulatory experts have concluded based on the investigations reviewed that, in the hypothetical scenario that an alternative for TiO_2 could be identified, a transition period of more than 12 years would be required for the phasing out of TiO_2 in medicines.

Background

On the basis of the analysis by the European Medicines Agency (EMA) on titanium dioxide (TiO_2) provided to DG SANTE on 8 September 2021, the Commission proposed that TiO_2 remains provisionally on the list of authorised additives to allow its use in medicinal products as a colour. EMA's report (2021-09-08-Report on pharmaceutical aspects on impact of removal of TiO2 on medicines + Executive summary - Final (word version) (europa.eu) concluded that it was not possible at that stage to replace TiO_2 without impacting on the quality, safety and efficacy of medicinal products and thus also the availability of medicines in the EU. Therefore, the decision was made primarily to avoid shortages of medicinal products that could impact public health.

These measures were formalised in Regulation (EU) 2022/631 (the Regulation), adopted on 14 January 2022. Under Article 3 of the Regulation, a review clause is foreseen to allow the Commission to re-evaluate the situation within 3 years after the date of entering into force of the Regulation, i.e. by 7 February 2025, on the basis of an updated assessment by the EMA in April 2024. The Regulation also gives a clear sign that the pharmaceutical industry should make any possible efforts to accelerate the research and development of alternatives to replace TiO_2 in both new and already authorised products, and to submit the necessary changes to the terms of the marketing authorisations concerned.

On 5 August 2023, the European Commission (EC) requested the European Medicines Agency (EMA) to provide an updated analysis with the aim to understand the feasibility of alternatives to replace TiO_2, without negatively impacting the quality, safety and efficacy of medicines; and if the feasibility is confirmed, the impact on the availability of medicinal products, taking into account the number of medicinal products in which TiO_2 is used. EMA should also take into account considerations to help define a reasonable transition period for the phasing out of TiO_2 in all or specific uses in medicines covered by the scope of colouring matters.

To support the analysis, the Agency was asked to seek the input from industry stakeholders. For this purpose, the EMA organized a joint meeting with QWP, CMDh/CMDv, EC and Interested Parties (EU trade industry associations) on 16 October 2023 with the aim to learn of Industry's latest developments concerning replacing/removing TiO_2 in medicinal products. A list of questions was prepared and addressed by AESPG, EFPIA, Medicines for Europa, TiO_2 Alternatives Consortium, IPEC Europe, EUCOP, AnimalhealthEurope, and AccessVetmed industry trade associations. Responses to these questions are provided in Annex I.

An expert group composed of Quality Working Party (QWP) experts and relevant EMA experts and Committee members have prepared the following responses to the EC request. The report has been endorsed/adopted by CHMP, CVMP, CMDh, CMDv and QWP in March 2024.

Question 1: The feasibility of alternatives to replace TiO_2, without negatively impacting the quality, safety and efficacy of medicines.

Based on the research conducted by industry consisting in development of alternative coating and capsules and screening of potential alternatives against predefine quality and safety assessment, to date no excipient/combination of excipients has been identified to be equivalent to TiO_2, which has unique properties, such as providing light protection to many active ingredients and formulations and to ensure uniform appearance when used in minimal quantities. Several TiO_2 free coatings and capsules are commercially available, but their UV protection is lower, the resultant colour of the finished product is not as consistent and the alternatives present additional challenges during dosage form manufacture. These formulations also require a higher number of excipients rendering the

reformulation of the finished product and the resulting marketing authorisation variation more complex.

The excipients industry has created a number of options for TiO_2 free coatings and capsules which are currently being evaluated by medicinal product manufacturers. Film coating and capsule companies started by screening potential materials to assess their performance as an opacifier. The next step was to see how any material performed in film coating or capsule shell formulations compared to TiO_2. Once a viable material was identified the next step was to optimise that formulation and this may involve removing or adding additional excipients to counteract the lack of performance versus TiO_2 in one aspect or another. In all cases there are still compromises that need to be balanced against performance and quality of the coating or capsule, these will then be evaluated more closely and made into commercially available products if they are acceptable from a regulatory compliance standpoint. It is only at this stage that these optimised coatings and capsules can be fully evaluated (opacity, stability, process parameters, scale, availability, safety and quality) in finished products, and which needs to be repeated for each dosage type and active substance. The optimised coating or capsule shell formulations are the result of over 2000 different combinations of excipients being evaluated by excipient companies.

Taking into account all the aspects, there are only very few cases where a simple 1:1 substitution of TiO_2 with another excipient would be possible. The work has clearly shown that in almost every case a more extensive change in the formulation composition and concomitant manufacturing process changes would be required, even for the simplest reformulations. This could impact on the reliability of stable supplies to the market and potentially lead to medicine shortages and this could also impact on product performance. For example, changes will often be needed to the film forming polymer, plasticizers, extenders, and the final film thickness in addition to replacing the opacifier or pigment. Similarly processing conditions (such as coating solution spray rate) will also need to be modified in many cases.

Potential Replacement of TiO_2

As required by Regulation (EU) 2022/63, the pharmaceutical industry has conducted research into alternatives to TiO_2.

The activities focused on the identification of alternatives to TiO_2 for use in film coated tablets and hard capsule shells, as these two dosage forms represent the majority of products impacted by a potential ban for TiO_2.

The alternatives tested have been selected based on their commercial availability and their compliance with (at least) requirements for use in food. Several alternatives have been evaluated so far and some of the combinations tested are detailed in Annex 2 and Annex 3 of the Final Industry Report.

Key performance indicators (KPIs) were developed by industry in order to assess the suitability of the alternatives. Results for these KPIs for the tested excipients are provided for film coating systems and for hard capsule systems.

The work conducted to date demonstrates that in most cases a more extensive change than 1:1 replacement in the formulation and concomitant manufacturing process changes would be required, even for the simplest of formulations. For coatings and hard capsules there are several standard TiO_2 free formulations available, and selection depends on the film-forming polymer, structural additives (plasticizers, gelling agents), colorants and opacifiers and sometimes process aids.

For coatings the main alternatives identified by industry are hypromellose (HPMC) versus polyvinylalcohol (PVA) polymers combined with different plasticizers. For capsules the main alternatives are hypromellose (HPMC) versus gelatin with or without gelling agents. In addition to replacing TiO_2, changes will often be needed to the film forming polymer, plasticizers, extenders, and the final film thickness. Similarly processing conditions such as coating solution spray rate will also need to be modified in many cases.

All of the 20 TiO_2-free coatings studied in detail were inferior to the TiO_2 reference coats based on the entire set of KPIs. Some performed well when assessed against certain criteria but not others. Many did not achieve surface coverage and opacification at a 6% weight gain and those, which did, required a significantly higher coating level than the TiO_2 reference coats which may affect to in vivo performance of medicinal products. In general, the performance of the coloured TiO_2-free coatings was poorer than the white TiO2-free coatings.

In conclusion, none of the TiO_2-free coatings could match the properties of TiO_2. Their use will result in longer, more expensive and potentially less robust coating processes and may also impact on the stability and shelf-life of products. Colour matching between marketed products and TiO_2-free coatings will be extremely difficult and the colour palette available for product identification and anticounterfeiting measures will be reduced due to the poor performance of the coloured coatings.

There is also a risk to patient adherence due to the colour changes seen in some TiO_2-free coatings and to patient safety as a result of the limited colour palette available to distinguish between different products/strengths.

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

Based on the results of the systems evaluated, there are a number of general challenges in using the alternatives compared to TiO_2-based systems, as summarised below.

Film Coating

Manufacturability: To achieve uniform colour and appearance, typically the amount of coating material required is significantly increased:

TiO_2 coatings 3 -4% w/w, Alternatives: 6 – 8% w/w. This will increase coating times per batch and increase the cost of the products. Significant capital investment will be required to increase manufacturing coating capacity. Typically, a higher number of components in combination are required in the alternative coating materials to achieve manufacturability and/or acceptable appearance. This also increases the risk of excipient(s) incompatibility with the active substance.

Appearance: The colour of the tablet core impacts the ability of the alternative film coats to achieve coverage and colour uniformity, potentially restricting which tablet core formulations can be successfully coated. While TiO_2 imparted an opacity on top of which uniform colour could be readily achieved, for some of the alternative coating materials this is not the case and significantly intense colours are required to achieve uniform coverage.

Colour Palette: Significant additional development work will be required to select the most appropriate alternative coating system for each product and the colour palette is estimated to vary in the process. Therefore, many currently approved products will very likely have to change their appearance, creating potential patient compliance issues.

In-vitro performance: No significant impact on dissolution has been observed for any of the alternative systems evaluated to date. The impact of long-term stability on dissolution performance is still to be assessed.

Photostability: Use of alternatives could have a negative impact on photolabile products. Colour fading/change on exposure to UV light could result in product not meeting its appearance specification which is typically a finished product critical quality attribute. Light exposure could also potentially cause degradation or changes in the properties of the film coating, which can in turn affect the thickness of the coating.

Hard Capsule Shells

Studies conducted to date have been carried out using empty capsules and capsules containing model components. These would need to be repeated on a product-by-product basis before definitive conclusions can be drawn.

Mechanical Integrity: Both gelatin and HPMC based alternative opacifiers result in mechanical inferiority across a wide range of relative humidities. The following issues have been noted:

Appearance: Capsule shells where calcium carbonate is employed as an opacifier are typically transparent to semi-opaque

- Blinding of capsules content will be difficult to impossible in clinical trials.
- Increased risk for instability of photolabile medicines.
- Gelatin capsules with sodium phosphate systems offer acceptable opacity at relative humidities <40% but lose opacity at relative humidities >50%. Significant opacity loss occurs at 30°C/75% RH ((V)ICH Zone IVb).
- Potential patient compliance issues (due to the change of colour).
- Only available in white (additional colours currently not available for testing).

High Fe_2O_3 based systems appear to offer equivalent opacity to TiO_2.

- High Fe_2O_3 capsules are not globally acceptable due to regional restrictions on the amount consumed (NMT 5 mg/day under CFR Title 21).

Photostability (studies have been conducted using empty capsule shells):

- Calcium carbonate capsules tend to get whiter/lighter in appearance when exposed to ICH Photostability conditions.
    - May require more protective packaging.
- Sodium Phosphates capsules appear to be light stable.
- High Fe_2O_3 based systems appear to be light stabile.

Photostability (filled capsules): Industry experience shows that alternative capsule systems are not as protective compared to TiO_2 and Fe_2O_3 capsules under (V)ICH photostability conditions for model compounds of different light sensitivity.

In-Vitro Performance: Capsule shells evaluated to date are not showing any signals of changes in disintegration and dissolution performance when compared to their TiO_2 counterpart. The impact of long-term stability on dissolution still needs to be assessed.

It should be noted that success with alternative systems at the small scale of studies to-date may not be replicated at the commercial scale. More process development work will be required to achieve reproducibility batch to batch and more restrictive process parameters may be required.

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

The safety of alternatives needs also to be taken into account. Industry states in their responses that the safety of TiO_2 has been evaluated by many groups and regulatory authorities as presenting no concern, while many alternative materials on coating and capsules do not yet have the same cumulative evidence of safety as TiO_2. Additional data would need to be generated to ensure the safety of alternatives when used in medicinal and veterinary medicinal products. Any new alternative colourant would need to be added to the Food Additives positive list in Regulation 1333/2008. Additionally, for veterinary medicinal products authorised for use in food producing species, any alternative excipient would also need to comply with regulation (EC) No 470/2009, with regards to residues of veterinary medicinal products in foodstuffs or animal origin or be classified as being out of-scope of the regulation.

Investigations conducted by industry focused on immediate release tablets or hard capsule, where only minor changes to the formulation and manufacturing process are envisaged. Replacement of TiO_2 in more complex formulations or dosage forms such as oral suspensions, soft capsules or modified release formulations would present additional challenges relating to more complex changes to the formulation, manufacturing complexity and demonstration of similar in-vivo functioning performance. Reformulation of these type of products would require evaluation on a case-by-case basis.

Removal

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

Currently available TiO_2 -free coatings and capsule shells do not provide a sufficiently high level of protection from light. Removal of TiO_2 would therefore impact the type of packaging selected and may lead to shorter-shelf-life periods or restrictions in storage conditions.

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

Reduction

Based on the initial guidance of the EMA and the European Commission, reduction in TiO_2 levels in European medicines is not generally being considered for any product. However, this is a potential

approach that could minimize patient exposure to TiO_2 whilst maintaining product performance and minimizing product shortages. A similar approach to that used for preservatives might be feasible, with manufacturers being required to demonstrate the need for a certain level of TiO_2 to provide the necessary functionality (light protection, etc). To enable this approach, a permitted daily exposure (PDE) would need to be established based on toxicological data.

Conclusion

TiO_2 is an inert material that gives film coatings and capsules an effective opacity and protection from UV light. It allows the rapid development of consistent product colour regardless of the core colour and condition of the formulation, and regardless of the manufacturing process parameters used or the scale of production. One of its advantages is that it makes the coating process and resulting product very consistent and predictable.

In order to identify a suitable replacement, the material or combinations of materials must meet as many of these characteristics as possible, otherwise the quality of the resulting finished medicinal product is likely to be negatively impacted.

The evidence confirms that for some medicines, the use of TiO_2 as an excipient can be critical to safety and efficacy (e.g. as an opacifier to protect from light and prevent degradation, or to ensure that the minimal amount to coating is used to enable tablet dissolution).

The investigations performed by the pharmaceutical industry thus far have confirmed the view reflected in the EMA response in 2021 that it is not considered technically feasible to replace TiO_2 across the board in all medicines, without negatively impacting the quality, safety and efficacy of some, or all, of those medicines and thus their availability. With respect to new products currently under development, the same technical challenges are expected to apply. Given its widespread use and acceptability TiO_2, will have been the material of choice in coating materials, capsules, etc and is likely to have been included very early in product development and in early formulation development and clinical studies. Therefore, its removal from medicines under development is expected to raise the same technical challenges as for authorised medicines.

The technical challenges identified by industry are acknowledged and accepted as being a realistic representation of the situation. In addition, replacement of TiO_2 will present significant logistical challenges for industry for both authorised products and products under development. Capacity issues for industry and regulators will also arise. These multifaceted challenges are considered highly likely to result in withdrawal of products, unavailability of products while changes are undertaken and increased time in bringing new medicines to market.

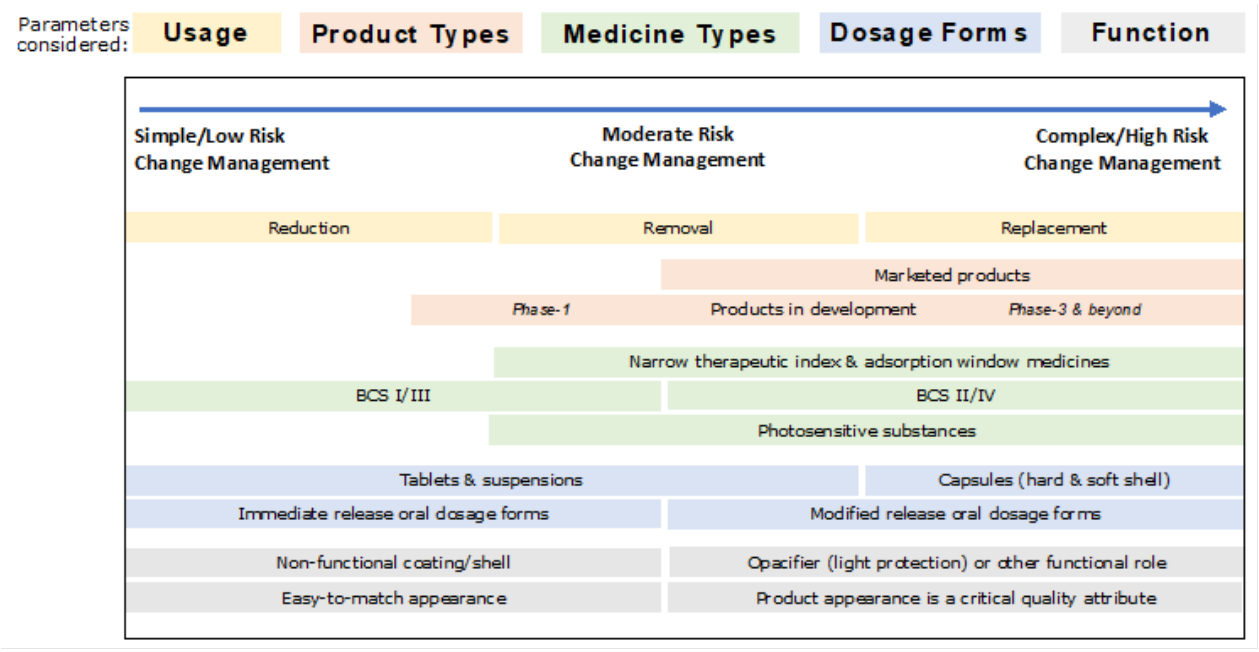
Question 2: If the feasibility is confirmed, the impact on the availability of medicinal products, taking into account the number of medicinal products in which titanium dioxide is used. EMA should also take into account considerations to help define a reasonable transition period for the phasing out of TiO_2 in all or specific uses in medicines covered by the scope of colouring matters.

Despite extensive efforts by the pharmaceutical industry, the feasibility of replacing TiO_2 cannot be confirmed.

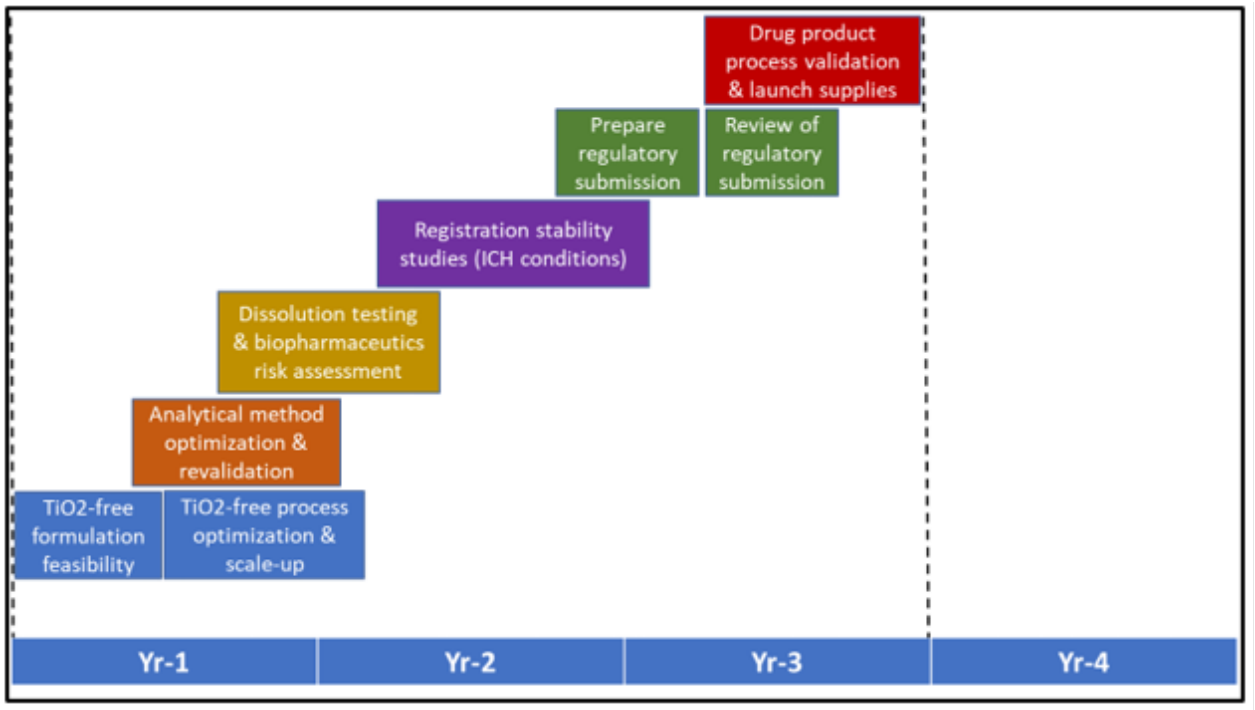
Industry investigations regarding reduction, removal or replacement of TiO_2 in film-coated tablets and capsules have shown that removal of TiO_2 is only likely to be feasible for a very small percentage of existing products (estimated to be estimated to be <<5%) and that there is no simple 1:1 replacement for TiO_2. In almost every case a more extensive change in the formulation composition and concomitant manufacturing process changes would be required, even for the simplest formulations. For each product the impact of these composition and process changes on the performance (potentially including bioequivalence) and stability of the medicines as well as any downstream impact on analytical methods (such as specificity) and packaging configurations (such as tablet size and thickness) would need to be evaluated. For details of the investigations performed, see the response to Question 1.

The feasibility of replacing TiO_2 in specialised dosage forms (e.g., prolonged release oral formulations) which are more complex than film-coated tablets or hard capsules, have not yet been investigated at all.

For a single product the complexity and risks associated with a reformulation depend on the product type, dosage form, usage and function (this information was provided by Industry, see Annex I:

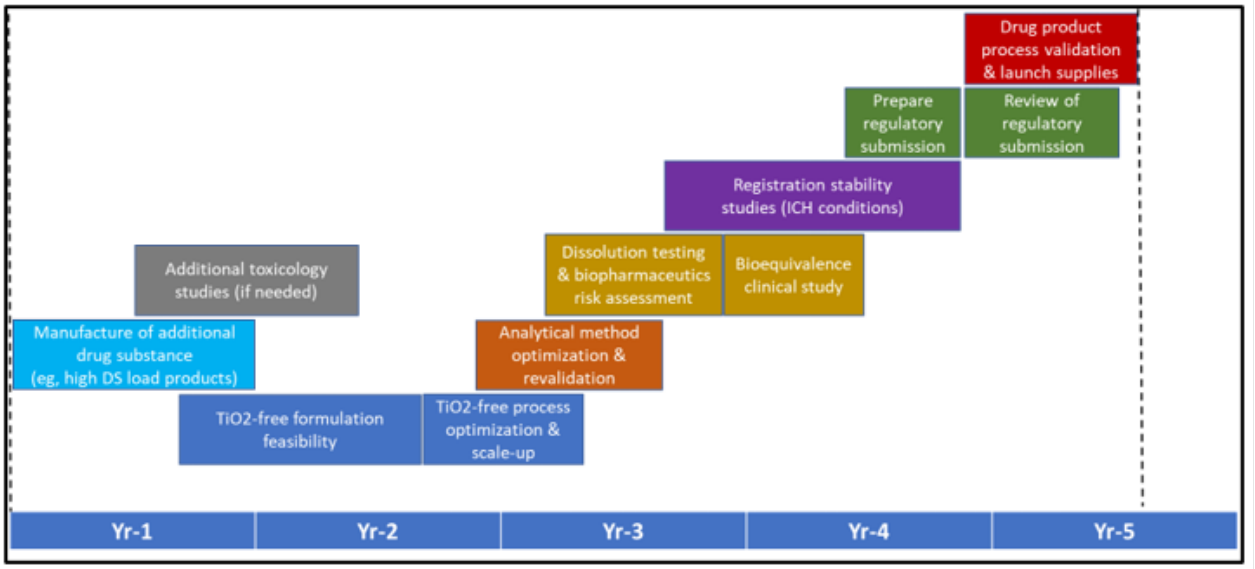


For a low-risk (simple) reformulation a timeline of 3 years is estimated:



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

For a high-risk (complex) reformulation a timeline of 5 years is estimated:



This scenario would apply e.g. for products where the active substance needs to be protected from light, the film coating controls drug release (modified release dosage forms), additional toxicology data needs to be collected on the alterative material(s) in the formulation or supplies of the active drug

substance are limited. Significant formulation or process changes and/or resulting impact on the product appearance, stability or performance (including bioequivalence) could all increase the time needed to develop a TiO_2-free medicine.

However, there are approximately 91 000 human medicinal products and 1600 veterinary medicinal products in the EU/EEA contain TiO_2 (> 50% of them being high-risk / complex formulations). Reformulation of so many products would be an unprecedented exercise and could not be done in parallel but would need to be staged.

To define a respective transition period is still difficult, because there are several uncertainties that could potentially have an impact on the time needed:

- Limited research & development capacities
- Availability of commercial quantities of TiO_2 -free film coatings and capsule shells
- Limited manufacturing capacity for reformulation activities
- Potentially impaired manufacturing process robustness of TiO_2-free medicines
- Potentially reduced long-term stability of TiO_2-free medicines
- Limited capacity for analytical testing
- Limited capacity for bioequivalence studies
- Competing resources consuming regulatory requirements e.g., nitrosamine remediation, EG/DEG testing, potential ban of per-and polyfluoroalkyl substances (PFAS)
- Measures needed to ensure patient compliance e.g., due to changes in product appearance, size and taste

Additionally, it should be noted that reformulation efforts to achieve TiO_2-free products would compete regarding above mentioned resources like raw materials, capacities for research & development, manufacturing and testing as well as bioequivalence studies with continuation of supply of existing products and development of new products to address unmet medical need.

In conclusion, it is conservatively estimated that it would take between 7 and 12 years for a typical company to reformulate their entire portfolio of new and existing medicines. For some large companies, it could take even longer.

Another issue is the time needed for related post-approval variation procedures, which depends on the nature of a change and the type of variation. The above summarized industry investigations have shown that in almost every case a more extensive change in the formulation composition (i.e., TiO_2 cannot be simply removed and there is no 1:1 replacement) and concomitant manufacturing process changes would be required, even for the simplest formulations. It has also been shown that thickness of tablet coating or capsule shells in most cases would be increased. For most products it is thus likely that a Type II variation (B.II.a.3 b) 2) would be required to address the respective change in formulation. Moreover, it can also be envisaged that other variations may be warranted as a direct consequence of implementing the excipient change. For example, these may be related to changes in

the shape or dimensions of the pharmaceutical form (B.II.a.2), changes in coating weight of oral dosage forms or change in weight of capsule shells (B.II.a.4), changes in analytical methods for the finished product (B.II.d.2), changes in the finished product specification (B.II.d.1), changes in the manufacturing processes of the finished product (B.II.b.3) and in-process controls (B.II.b.5), changes in the packaging of the finished product (B.II.e.1) or changes in product shelf life and storage conditions (B.II.f.1).[1]

The time needed for the post-approval variation procedures related to the replacement of TiO_2 for a single product could be in excess of one year. However, in view of the estimated number of human and veterinary medicinal products affected it is important to highlight that submission of large numbers of variation applications may lead to capacity issues within the EU regulatory network. In addition, an increase in pre-submission interactions between regulators and MAHs on regulatory/procedural aspects in view of the anticipated variations is likely, and the related workload in this regard should be taken into consideration. It can also be anticipated that potential requests for scientific advice associated with reformulation/redevelopment activities will increase at both centralised (EMA) and national (NCA) levels, with a consequential impact on workload for regulators. Resource prioritisation should be carefully considered taking into account the regulatory environment and balancing the anticipated benefit with other concurrent issues, challenges or threats at the time.

A considerable negative impact of this unprecedented reformulation exercise on medicines shortages - but also on development of new medicines addressing unmet medical need – would be inevitable, taking the following into account:

- For some products it will likely not be possible technically to remove TiO_2 from their formulation
- A requirement to produce TiO_2-free medicines is only proposed in the EU/EEA. Accordingly, companies would have to create EU/EEA only supply chains, processes and dossiers thereby adding technical, commercial, and regulatory complexity
- Reformulation of such a vast number of TiO_2 containing medicines would massively consume the very same resources (e.g., raw materials, capacities for research & development, manufacturing and testing as well as bioequivalence studies) that would be needed to continue supply of existing medicines, but also development of new medicines addressing unmet medical need
- Reformulation activities as well as having separate supply chains, processes and dossiers for different regions are costly, and it is unsure whether these costs can be recouped by companies
- A negative impact on shelf-life of existing medicines is expected
- A lack of a long enough transition period would additionally increase withdrawals of marketing authorizations and/or medicines shortages.

Conclusion

[1] [1]The corresponding variations for veterinary products are VRA-S F.II.a.3b)1, F.II.a 2, F.II.a.4, F.II.d.2, F.II.b.3, F.II.b.5, F.II.e.1 and F.II.f.1 respectively

Despite extensive efforts by the pharmaceutical industry to investigate a number of alternative formulations the feasibility of replacing TiO_2 cannot be confirmed without negatively impacting the quality, safety and efficacy of medicines.

Industry investigations to date have shown that removal of TiO_2 is only likely to be feasible for a very small percentage of existing products (<<5% human and veterinary medicinal products) and that there is no simple 1:1 replacement for TiO2.

TiO_2 is present in approximately 91000 human medicinal products and 1600 veterinary medicinal products.

For those products, where removal of TiO_2 is feasible, and given the large number of products impacted by the presence of TiO_2, it is estimated prioritization of product reformulation would be necessary. This would increase the overall time needed for implementation. Prioritization by the pharmaceutical industry would likely focus on high volume products, and not necessarily on products for high unmet medical need. There is currently no mechanism available to regulators to influence the priority of products to be reformulated.

In this context, it is highlighted that the requirement to make available TiO_2 free medicines would only be proposed in the EU/EEA and not globally. Accordingly, companies would have to create EU/EEA only supply chains, processes and dossiers. This would increase the likelihood of shortages or discontinuation because of the cost and complexity of maintaining them on the market.

Industry estimates that reformulation of individual products, where technically feasible, may vary from 3 to 5 years depending on the complexity and risks associated with a reformulation. Regulatory Bodies estimate the approval of individual changes of more than 1 year. Taking these timeframes and the volume of products involved into account, the industry estimations of 7 to12 years for a typical company, and even longer for large companies, are not considered unreasonable. Submission of post-approval variation procedures for a large number of products in parallel is likely and could prolong the time needed to approve all the changes due to capacity issues within the EU regulatory network.

QWP concludes that a transition period of more than 12 years would be required for the phasing out of TiO_2 in medicines in the hypothetical scenario that an alternative for TiO_2 would be found.

Even with such a transition period, a considerable negative impact on availability of medicines due to withdrawal of products and medicines shortages is inevitable. The resultant capacity and supply chain issues as highlighted above are also considered likely to hinder the development of new medicines addressing unmet medical need.