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Final feedback from European Medicine Agency (EMA) to the EU Commission request to evaluate the impact of the removal of titanium dioxide from the list of authorised food additives on medicinal products

Executive Summary

- Titanium dioxide (TiO_2) is extensively used as an opacifier and colourant in medicines due to its multiple functionalities[1].
- TiO2 is used very frequently in oral solid dosage forms (e.g. tablets, soft capsules, hard capsules, granules/powders for oral solution and oral suspensions), in oral semi-solid dosage forms (e.g. oral paste, oral gel). It is present in many essential medicines for human including antidiabetics, antibiotics and others and several veterinary medicinal products. TiO2 is also present in dosage forms administered via routes other than oral, e.g., products for cutaneous, inhalation (capsule shells), oromucosal, sublingual, transdermal and vaginal use.
- To date, no single material has been identified that provides the same combination of properties that are unique to TiO_2 (e.g. opacity, enhancing contrast, inertness, protection from UV light and the finish/smoothness of the resulting product). Separating out the different functionalities of TiO_2 for those medicinal products in which it serves more than one function is difficult or might not be possible at all.
- Possible alternatives identified so far include calcium carbonate, talc and starch. A number of disadvantages have been identified with these alternatives (e.g. inability to obtain sufficiently thin films, supply chain issues, mined materials with associated elemental impurity risk).
- The feasibility of replacing TiO_2 cannot be confirmed at this stage. Each affected medicinal product will need an individual review and assessment, which will require investigation of alternatives, product reformulation, generation of new data related to manufacture, dissolution and stability etc. and potentially new clinical data (e.g. generation of

[1] Approximately 91,000 human medicinal products and 800 veterinary medicinal products contain TiO_2 in the EU according to EU Trade Associations (see Annex I and II)

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bioequivalence studies), which subsequently will all have to be assessed by the national competent authorities and EMA.

- The direct and indirect impacts on medicines for human and veterinary use are expected to be aggravated in the scenario, where Europe would be the only region globally to ban TiO2 as excipient in medicines, which would require industry to develop new formulations for the majority of oral solid dose products potentially for the EU only, with titanium dioxide continuing to be used in the majority of medicines globally.
- An acceptable transition period for phasing-out TiO2 in all or specific uses in medicines covered by the scope of colouring matters is currently difficult to envisage or estimate. The time needed to reformulate each individual product could be several years depending on the level of formulation and studies required, to be followed by the necessary regulatory procedures for assessment and approval.
- Considering the scale of the use of this excipient, the time and costs involved in the reformulation and the volume of products impacted, it is considered that any requirement to replace TiO2 in medicines will almost certainly cause significant medicines shortages and discontinuations/withdrawals of medicines from the EU/EEA market with major implications for patients and animals. Particular concerns arise in relation to certain vulnerable classes/types of products such as paediatric medicines, orphan medicines, low sales volume products, bee products, etc.).

Background

On 6 May 2021, the European Food Safety Authority (EFSA) published its opinion on the safety of food additive Titanium dioxide (TiO_2), recommending that on the basis of all currently available evidence along with all uncertainties, in particular the fact that genotoxicity could not be ruled out, TiO_2 can no longer be considered as safe when used as a food additive.

On 17 May 2021, the European Commission (EC) requested the European Medicines Agency (EMA) to provide an analysis with the aim to define the technical purpose of titanium dioxide in medicinal products; feasibility of alternatives to replace it without negative impacting the quality, safety and efficacy of medicines; and if confirmed, considerations to be taken into account to define a transition period for phasing out this excipient.

To support the analysis, the Agency was asked to seek the input from industry stakeholders. For this purpose, a list of questions was drafted to be addressed by Human (AESPG, EFPIA, Medicine for Europa) and Veterinary (AnimalhealthEurope, EGGVP) industry trade associations. Responses to these questions are provided in Annex I and Annex II.

A group composed of Quality Working Party (QWP) experts and relevant EMA departments and Committees have prepared the following responses to the EC request. This report was endorsed/adopted by CHMP, CVMP, CMDh, CMDv and QWP.

Question 1: Define the technical purpose of TiO_2 in medicinal products, the scope, and the functions of TiO_2.

Titanium dioxide is listed in Ph. Eur. as a white or almost white powder; it is practically insoluble in water and does not dissolve in dilute mineral acids. It is a simple chemical substance and is widely available.

Due to its opacity, whiteness, chemical inertness, and the protection it provides from UV light, titanium dioxide is a widely used excipient in pharmaceuticals. TiO_2 is odourless and tasteless, and as such has no negative impact on palatability.

It is used frequently in oral solid dosage forms (e.g., tablets, soft capsules, hard capsules, granules/powders for oral solution and oral suspensions). In veterinary medicinal products, it is also used in oral semi-solid dosage forms (e.g., oral paste, oral gel). It is present in a number of essential medicines for human including antidiabetics, antibiotics and others and several veterinary medicinal products, e.g. for bees. TiO_2 is present in a limited number of dosage forms administered via routes other than oral, e.g., products for cutaneous, inhalation (capsule shells), oromucosal, sublingual, transdermal and vaginal use.

Titanium dioxide is mainly used as an opacifier and colourant in pharmaceuticals, which implies:

- Enhancing whiteness and opacity, and accentuation of contrast against other colourants, thereby enhancing distinguishing features of oral solid dosage forms. Product colour is important for distinguishing different strengths of medicinal products and for patient acceptability.

- Protection of photosensitive active substances from degradation due to exposure to UV/visible light. Reducing light permeability of the coating layer contributes to longer shelf-lives and less storage restrictions, which allows easier handling and storage.

Historically, there is a legislative link allowing the use of colourants listed in Annex II to Regulation (EC) No 1333/2008 in human and veterinary medicinal products without further justification. This has effectively resulted in the function of TiO2 being typically described as a 'colourant' in marketing application dossiers although TiO2 exhibits multiple (highly advantageous) functionalities from a pharmaceutics perspective. Indeed, its multiple functionality is one reason for the widespread use of TiO2.Separating out the different functionalities of TiO2 for those products in which it serves more than one function is difficult or might not be possible at all. A typical example often seen in MA dossiers would be film-coated tablets of multiple strengths, which contain (in the coating) TiO2 at a single concentration across all tablet strengths and additionally, colourants like iron oxide yellow and iron oxide red which are present in the different tablet strengths at different concentrations to produce different coloured tablets. While TiO2 in such a case, is contributing to overall appearance of the tablets (including colour) it does so indirectly by increasing opacity. The intended specific colour (needed to distinguish the different strengths) is actually provided directly by the additional colourants. In case of light sensitive active substances, opacity of tablets would also be relevant for protection from light. Taking the above example into account, it can be concluded that the primary role of TiO2 in medicinal products might be other than as a colourant. For example, increasing opacity is typically more important than providing white colour. Ultimately, it would be the responsibility of the applicant / MAH to justify the functionalities of TiO2 relevant for a specific medicinal product, which would need to be assessed on a case by case basis. In this context, it has to be noted that such a justification is typically not already presented in MA dossiers due to the food additive status of TiO2 and its longstanding and widespread use.

TiO2 is monographed in the European Pharmacopoeia and is considered to be suitable for use in the medicinal products as an excipient.

Due to its unique combination of physicochemical properties, TiO2 imparts several highly desirable properties to medicinal products. It is widely used in tablet coatings where it can act to prevent light transmission, moisture absorption and improve opacity. Whilst other excipients can also be used for the same purposes in tablet coatings, where due to its physicochemical properties, TiO2 enables the application of a thinner, less brittle coat compared to other excipients, thereby imparting all of these desired quality attributes whilst still allowing rapid bioavailability of the actives once the product is ingested.

Reports from National Competent Authority databases and EU's Art 57 database indicate that there are several thousand nationally authorised products per member state containing TiO2. There are also hundreds of centrally authorised products containing TiO2. Human and Veterinary Industry associations have provided data on the number of medicinal products containing TiO2 in relation to the pharmaceutical form (see Annex I and Annex II).

Question 2: Feasibility of alternatives to replace TiO_2 if at all possible, without impacting negatively the quality, safety and efficacy of medicines.

Based on the currently available data, no single material has been identified that provides the same combination of properties that are unique to titanium dioxide (e.g. opacity, enhancing contrast, inertness, protection from UV light and the finish/smoothness of the resulting product).

A suitable alternative would have to:

- Have similar pharmaceutical properties (e.g., opacification, stability, degradation protection).
- Be a simple chemical substance that has similar physicochemical properties (e.g. chemically inert).
- Be compatible with the other components of the pharmaceutical product.
- Have an acceptable safety profile.

Possible alternatives identified so far include calcium carbonate, talc and starch. However, a number of disadvantages have been identified with these alternatives (e.g., inability to obtain sufficiently thin films, supply chain issues, mined materials with associated elemental impurity risk).

Data available in the public domain indicates that many excipient manufacturers are working to develop TiO_2 free formulations for use in:

- Tablet coatings
  Coating suppliers have developed titanium dioxide free coating range. However, these are not currently widely used and there is therefore limited information available regarding their general suitability for use.

- Capsule shells
  Titanium dioxide free capsule alternatives are available.

Most tablet coatings and capsule shells are manufactured as ready-to-use excipients and reformulation of the medicinal product contained within the tablet/capsule may not be required. However, compatibility studies and comparative studies (such as dissolution and/or bioequivalence and stability studies) would be required before these replacement excipients could be introduced for each of the formulations/presentations of authorised medicines.

TiO_2 could be replaced by other pigments, such as iron oxides. However, this will result in different colour and require formulation development work, and may also impact other factors, such as patient acceptability/compliance. Alternative colorants would need to be either already included, or added to, the Food Additives positive list in Regulation 1333/2008.

From a technical point of view, it should be possible to find alternatives to TiO_2 containing coatings (at least for the majority of products); however, feasibility to do so is another issue. Given the widespread use of TiO_2 in different dosage forms, a single replacement excipient cannot be identified. Each medicinal product will need an individual review and assessment, which will require investigation of alternatives, reformulation, generation of new data related to manufacture, dissolution and stability etc. and potentially new clinical data (e.g. generation of bioequivalence studies).

Following this, subsequent approval by way of variation would be required before the reformulated product could be brought to the market. All of these development and regulatory activities take time (See question 3 below) and there is a real risk, particularly for niche products or products with limited market share that the time and costs involved in the reformulation could result in significant medicine shortages or for medicines to be discontinued and withdrawn from the market. This risk is amplified by the fact that the revised formulations would likely only be required for the EU/EEA markets.

With respect to the potential impact of the removal of TiO_2 would have on the quality, safety and efficacy of medicines the following potential direct impacts have been identified:

- Quality:
  Technical reformulation and manufacturing challenges, potential new analytical methodologies, potential incompatibilities, shorter shelf life at least temporarily until all stability studies are performed.

- Safety and efficacy:
  Potential bioequivalence issues due to changes in formulations (thicker coatings etc.).
  Unanticipated changes to benefit-risk determinations arising from use of alternatives.

- Safety:
  Any new alternative colourants 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 regard to residues of veterinary medicinal products in foodstuffs or animal origin or be classified as being out of-scope of the regulation.

Indirect impacts to be considered include:

- One-by-one reformulation necessary for the European market which may impact global manufacturing chain – all products cannot be reformulated at the same time (see Annex I and Annex II for number of medicinal products affected).

- Shortages caused either by prioritization of certain products for reformulation or inability of supply chains to support the shift in demand.

Changes in the composition of medicines will require new formulations to be developed for the majority of oral solid dose products potentially for the EU only, with titanium dioxide continuing to be used in the majority of medicines globally. Globally, in the scenario where Europe remains the only large region to consider that TiO_2 should no longer be used in medicines, it can be expected that such changes would have a significant impact on the manufacturing and supply chains of a significantly large number of medicinal products.

Potential supply disruption for medicines can be expected where no alternative is possible / known, or if extended development manufacturing trials are required. It is not possible to quantify the impact on individual products or product ranges. However, considering the scale of the use of this excipient and volume of products impacted, it is considered that a requirement to replace TiO_2 will almost certainly cause significant medicines shortages on the EU market.

Conclusion

Taking into account the potential direct and indirect impact on the quality of medicines as described above as well as major supply disruption expected, it is not considered feasible that replacement of TiO_2 can be achieved without a negative impact on the quality and availability of medicines in EU/EEA. Given the volume of products potentially impacted by a decision to require removal of TiO_2 in medicinal

products, it is considered highly likely that many products may be discontinued and particular concerns arise in relation to certain classes/types of products (e.g. paediatric, orphan, low sales volume, bee products, etc.).

In conclusion, the impact of a potential requirement for replacement of TiO_2 in every medicinal product on global harmonisation, product development, availability and access to medicines should be carefully considered.

Question 3: If the feasibility is confirmed, consideration to be taken into account 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.

The feasibility of replacing TiO_2 cannot be confirmed at this stage.

A transition period timeframe recommendation is currently difficult to estimate and the time needed to reformulate each individual product could be several years depending on the level of formulation and studies required (development, manufacturing of representative batches, process validation, stability data, bioequivalence, etc..). In this respect, cross reference is made to the Industry submissions (see Annex I and Annex II) where further details of the potential timeframes are included and the total time for implementation in all products of 7 to 12 years is estimated.

Another issue is the time needed for post-approval variation procedure, which depends on the nature of a change and the type of variation. For example, if a change is classified as type IAIN no B.II.a.3 (Changes in the composition (excipients) of the finished product- deletion or replacement of colouring system), it can be approved in 30 days. Where the excipient fulfils other functions, the change can be applied as type IB no B.II.a.3 b) 6 and the procedure may take about 3 months. However, experience demonstrates that these changes are rarely straightforward, and the regulatory procedures may take up to 1 year (see analysis for Centralised variations below). If significant changes in composition (e.g. functional coating) have to be made the time period for the required type II variation could be in excess of one year.

In order to substantiate the feasibility/complexity that can be expected when replacing an excipient, reference is made to the Note for Guidance on development pharmaceutics (CPMP/QWP/155/96), and the Note for Guidance on Development pharmaceutics for veterinary medicinal products (EMEA/CVMP/315/98), and the data requirements described therein. The guidelines state that the choice and characteristics of excipients should be justified for the intended purpose and that the quality of the excipient should be guided by its role in the formulation and the proposed manufacturing process. In cases where a novel excipient is used (i.e. an excipient used for the first time in the finished product, or via a new route of administration in the EU), full details of the manufacture, characterisation, and controls with cross reference to supporting safety data should be provided[2].

Development steps required to replace an excipient:

To replace an excipient in a finished product formulation the following steps are necessary:

- Alternative excipients with similar function(s) must be identified and an evaluation conducted of their physicochemical properties and how these may influence the product

[2] Section 4.6. of the guideline on excipients in the dossier for application for marketing authorisation of a medicinal product, EMEA/CHMP/QWP/396951/2006

manufacturability, stability[3] and clinical performance (e.g. bioavailability). A compatibility study to demonstrate the compatibility of the new excipient with the active substance(s) and any other excipients in the formulation must be conducted[4].

- Once compatibility is demonstrated, prototype formulations need to be prepared and an evaluation made of whether the change(s) has any impact on the finished product quality and manufacturability. The results from these investigations are taken into consideration to select the prototype(s) formulations for further development and the need for further changes evaluated (e.g. optimization of the quantity of the excipients, or replacement by other excipients).

- Evaluation of performance (dissolution, bioavailability) of the selected prototype(s); for some products bioequivalence studies need to be performed (see below discussion on type of variation).

- Manufacturing process re-evaluation vis-à-vis the introduced formulation changes and the necessary technology transfer (scale up), including process validation are the next steps.

- The analytical methods (QC methods, in-process controls) will have to be adjusted or replaced and validated in order to ensure their suitability for use with the new composition.

- Finally, stability studies of the new formulation need to be conducted to support the changes to the product composition (and possibly to the manufacturing process) and to establish the appropriate shelf life for the new formulation.

The development steps outlined above may go beyond a simple change and constitute a product/process re-development to a greater or lesser extent. It is also important to note that these product development steps are product specific.

Regulatory procedures to register replacements in excipients:

From the regulatory point of view, the EC variation classification guideline includes a classification for such a change (B.II.a.3)[5]. The conditions and documentation to be supplied differ depending of the type of change, type of product, role of the excipient in the formulation and the potential impact of the proposed change to the quality/safety/efficacy of the product.

Exemplary documentation required to be submitted by the applicant as part of the variation application requesting the replacement of the excipient is:

- Results of stability studies carried out under ICH/VICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of 3 months, and assurance that these studies will be finalised covering the approved shelf-life, and

[3] Section 4.8. of the guideline on excipients in the dossier for application for marketing authorisation of a medicinal product, EMEA/CHMP/QWP/396951/2006
[4] Section 4.2. Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product, , EMEA/CHMP/QWP/396951/2006 and Note for Guidance on Development pharmaceutics for veterinary medicinal products - EMEA/CVMP/315/98
[5] B.II.a.3. Change in the composition (excipients) of the finished product of the Guideline on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures .

that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action)

- Data to demonstrate that the new excipient does not interfere with the finished product specification test methods.
- Any new proposed excipient must comply with Regulation (EC) No 1333/2008 [6] and Commission Regulation (EU) No 231/2012 [7] for colours for use in foodstuffs.
- A justification for the change/choice of excipients etc. must be given by appropriate pharmaceutical development.
- For solid dosage forms (tablets, capsules, etc.), comparative dissolution profile data should be provided.
- Some excipient changes might affect bioavailability and in these cases a bioequivalence study comparing the old and the new formulation.
- For veterinary medicines intended for use in food producing animal species, proof that the excipient is classified according to Article 14(2)(c) of Regulation (EC) No 470/2009 or that it is considered as not falling within the scope of Regulation (EC) No 470/2009.

This information should be submitted by the applicant as part of the variation application requesting the replacement of the excipient.

In addition to the main variation change required, i.e. B.II.a.3. change in the composition (excipients) of the finished product, for coated tablets and capsules, it is likely that variation B.II.a.4 "Change in coating weight of oral dosage forms or change in weight of capsule shells" may also be required. This change may be a type IA, IB or II, depending on the type of product and fulfilment of the guideline conditions.

Furthermore, following on from the necessary development activities discussed above, it can also be envisaged that other variations may be warranted for individual products 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 analytical methods for the finished product (B.II.d.2), changes in the finished product specification (B.II.d.1), processes (B.II.b.3) and in-process controls (B.II.b.5), changes in the packaging of the finished product (B.II.e.1), changes in product shelf life and storage conditions (B.II.f.1).

As a specific example, if the newly introduced excipient has different physicochemical properties than the replaced excipient (e.g. flow density) and this is relevant for the manufacturing process performance, an adjustment of the manufacturing process may be required. Depending of the changes made, process validation may also be necessary. As indicated above, the impact of the change on the finished product performance and stability must also be evaluated.

Expected variation category for excipient changes:

[6] Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives.
[7] Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council

In order to understand the type of variations that would likely be needed to remove TiO_2 and to help estimate the volume of work that would be required, an analysis of finalised variation procedures to change/remove excipients was conducted. The analysis was carried out for Centralised applications for human medicines over the 3-year period 2018-2020 and details are provided below.

Analysis results:

Of a total of 7223 variations detailed on the human database on 29 July 2021, there were 30 variation procedures which contained a variation under scope "B.II.a." change in description or composition.

In only four variation procedures the change in description/composition was the only change applied for at the same time (4 x Type IB).

In all other procedures the change in composition was part of a larger grouped variation submission which included multiple additional changes consequential to, or related to, the change in composition (26 procedures; 10 x Type II, 12 x Type IB, 4 x Type IA).

This clearly demonstrates that a change in excipient is rarely submitted as a low risk Type IA variation and variations to implement a replacement of TiO_2 as an excipient in the finished product are more likely to be submitted as part of grouped variation submissions, with consequential complexity in the submission and assessment.

Even in relation to the above referenced standalone Type IB variations, the documentation requirements are relatively extensive as illustrated by the below example taken from one such submission:

- 3.2.P.1 (description and composition of the finished product)
- 3.2.P.3.2. (batch formula)
- 3.2.P.3.3 (description of the manufacturing process of the finished product)
- 3.2.P.4.1 (specifications of the excipients)
- 3.2.P.4.2 (analytical procedure of the excipients)
- 3.2.P.4.4 (justification of the specifications of the excipients)
- 3.2.P.4.5 (excipients of human or animal origin)
- 3.2.P.5.1 (specifications of the finished product)
- 3.2.P.5.4 (batch analysis of the finished product)
- 3.2.P.5.6 (justification of specifications of the finished product)
- 3.2.A.2 (adventitious agents safety evaluation)
- Stability studies under ICH conditions for 3 commercial batches of product manufactured with the new excipient to cover the full registered shelf-life.
- Justification for the absence of bioequivalence studies
- Justification for the change/choice of excipients
- Comparative dissolution profile data of at least two pilot scale batches of the finished product in the new and old composition

The time required for NCAs to conclude on the assessment of a change of excipient will depend on the Type of variation submitted, the quality of the data, and the time to respond to the request of supplementary information by MAHs. It is estimated that this could from 3 months up to 1 year.

Bottlenecks can be expected in Industry's process of reformulation/redevelopment, in supply chains and potentially at the level of the EMA/NCAs in relation to processing and approving post approval changes. Submission of large numbers of variation applications may lead to capacity issues within the EU regulatory network in view of the estimated number of human and veterinary medicinal products affected. 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 (e.g. nitrosamines and COVID-19 pandemic), challenges or threats at the time.

Conclusion

Given the large number of products impacted, it will not be possible to carry out the work for all products simultaneously and prioritization of product reformulation will be necessary. This will increase the overall time needed for implementation. Prioritization by the Pharmaceutical industry is likely to be focused on high volume products, and not necessarily on products for medical need and there is currently no mechanism available to regulators to dictate the priority of products to be reformulated. Industry estimates for reformulation of individual products vary from 3 to 5 years and regulatory estimates to approve individual changes are 3 months to 1 year. Taking these timeframes and the volume of products involved into account, the industry estimates of 7-12 years are not considered unreasonable. QWP conclude that a transition period of 10 years or even longer would be required for the phasing out of TiO_2 in medicines.