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on the use of titanium dioxide in medicinal products

1. CONTEXT

Titanium dioxide has been used for decades as a whitening agent in food, a pigment in medicinal products and a UV protectant in cosmetics. Due to its high opacity and brightness, titanium dioxide is used in a very large number of medicinal products (91 000 human medicinal products and 1 600 veterinary medicinal products) as a pigment (to add whiteness or accentuate the boldness of other colours) and opacifier (to ensure that tablets have a uniform colour when manufactured). It also helps maintain the colour during the product's shelf life and can serve as a protective coating to preserve the active pharmaceutical ingredient.

Since 2009([1]) the use of colours in human and veterinary medicinal products has been restricted to those authorised as food additives under Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives ([2]), subject to compliance with the relevant purity criteria ([3]). The use of excipients other than colours in medicinal products is subject to EU rules on medicinal products and is evaluated as part of the overall benefit-risk profile of a medicinal product.

On 6 May 2021, the European Food Safety Authority (EFSA) published a scientific opinion on the safety assessment of titanium dioxide as a food additive ([4]). In its opinion, the EFSA said that, on the basis of all the evidence available, a concern about genotoxicity could not be ruled out, and given the many uncertainties, it concluded that titanium dioxide could no longer be considered safe when used as a food additive.

To understand whether it would also be appropriate to ban titanium dioxide in medicinal products, the Commission asked the European Medicines Agency (EMA) to provide a scientific analysis of the technical purpose of the use of titanium dioxide in medicinal products, the feasibility of replacing it and possible time frames for finding alternatives. This analysis was provided on 8 September 2021 ([5]).

In its conclusions, the EMA said that titanium dioxide is frequently used in several essential medicinal products in oral solid and semi-solid dosage forms. The EMA explained that, from a technical point of view, it should be possible to find alternatives to replace coatings that contain titanium dioxide as a colour or for other purposes. However, it stressed that the feasibility of the alternatives had not yet been confirmed at that stage, as replacing titanium dioxide would negatively impact the quality, safety and efficacy of the medicinal products in question.

([1]) Directive 2009/35/EC of the European Parliament and of the Council of 23 April 2009 on the colouring matters which may be added to medicinal products (OJ L 109, 30.4.2009, p. 10).

([2]) Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives (OJ L 354, 31.12.2008, p. 16).

([3]) 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 (OJ L 83, 22.3.2012, p. 1).

([4]) EFSA Journal 2021;19(5):6585.

([5]) See: 2021-09-08-Report on pharmaceutical aspects on impact of removal of TiO2 on medicines + Executive summary - Final (word version)

Finally, considering the scale of the use of this excipient, the large number of products affected and the global nature of the supply chains, the EMA underlined that a requirement to replace titanium dioxide would almost certainly cause significant shortages of medicines on the EU market.

Based on both the EFSA's assessment and the EMA's analysis, the EU banned titanium dioxide as a food additive in 2022 but maintained its use as a colour in medicinal products by virtue of Commission Regulation (EU) 2022/63 ([6]). That Regulation stipulates that the Commission must review the situation regarding medicinal products three years after its entry into force on the basis of an updated analysis by the EMA of the feasibility of alternatives to replace titanium dioxide ([7]).

Against this background, on 3 August 2023 the Commission asked the EMA to conduct an updated analysis of the feasibility of alternatives to replace titanium dioxide without negatively impacting the quality, safety and efficacy of medicines or their availability. To support the requested analysis, the EMA was asked to seek the input from industry stakeholders. It sent the outcome of the updated analysis to the Commission on 1 April 2024.

2. THE EMA'S FINDINGS OF APRIL 2024

The EMA's updated analysis of the feasibility of replacing titanium dioxide is based on the pharmaceutical industry's input on a set of questions prepared by the EMA's scientific experts. The EMA evaluated the responses regarding currently commercially available titanium-free alternatives and prepared its updated analysis accordingly.

On the basis of the conclusions of the EMA's September 2021 analysis, the industry established a set of key performance indicators (KPIs) to understand how the alternatives perform and how they compare to titanium dioxide. The KPIs include elements such as uniformity of colour and appearance, opacity, available colour palette, *in vitro* performance and photostability of the active substance after coating with the alternative. They correspond to well established critical quality attributes associated with oral solid dosage forms and are routinely tested as part of finished product testing (e.g. photostability and opacity, appearance and colour, and dissolution/disintegration).

Some of the main findings of the EMA's updated analysis are summarised below.

- Uniformity of colour and appearance in medicinal products can be significantly impacted by replacing titanium dioxide, which traditionally imparts an opacity that helps achieve a uniform colour across tablet coatings. When using alternative film coatings, the inherent colour of the tablet core can affect the coverage and colour uniformity, potentially limiting success in coating certain tablet formulations. Consequently, alternative coatings often

([6]) Commission Regulation (EU) 2022/63 of 14 January 2022 amending Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council as regards the food additive titanium dioxide (E 171) (OJ L 11, 18.1.2022, p. 1).

([7]) Under Article 3 of Regulation (EU) 2022/63, 'The Commission shall, following consultation on the European Medicines Agency, review the necessity to maintain titanium dioxide (E 171) or to delete it from the Union list of food additives for the exclusive use as colour in medicinal products in Part B of Annex II to Regulation (EC) No 1333/2008 within three years after the date of entering into force of this Regulation.' Recital 18 of the same Regulation provides as follows: '…This review should be based on an updated assessment of the EMA to be performed before 1 April 2024. It should take into account the progress made during this period to develop alternatives to titanium dioxide (E 171) in medicinal products both for new products and for replacing it in authorised products, and possible impacts on quality, safety and efficacy, as well as on the availability of medicinal products. Where replacement of titanium dioxide (E 171) in medicinal products has not taken place or been initiated within this period, only objective verifiable reasons related to the lack of feasibility of its replacement should be taken into account.'

require more intense colours to achieve uniform coverage. Reformulating tablets to replace titanium dioxide could lead to issues with patient compliance due to changes in the visual appearance of the medicinal products.

- Opacity is another key aspect affected by replacing titanium dioxide. Titanium dioxide provides effective opacity even in minimal quantities, but alternative coatings often require a much higher percentage by weight to achieve similar opacification, leading to increased processing times and costs. The variable opacity of the alternatives poses challenges, making the reformulation of various products complex.
- The available colour palette for medicinal products is reduced when using titanium dioxide-free coatings. Many alternative coatings fail to achieve the same surface coverage and opacification as titanium dioxide for the same weight gain, thereby limiting their use in product identification and anti-counterfeiting measures. This difference in colour matching can create barriers to adopting titanium dioxide alternatives, as it becomes more difficult to make a visual distinction between products and strengths, potentially affecting patient adherence and safety.
- The *in vitro* performance of the current alternative capsule shells and coatings shows no significant changes in disintegration and dissolution when compared with titanium dioxide-based counterparts. However, the long-term stability of their performance is still under investigation. There are concerns that the thicker coatings required by alternative materials might affect the stability and shelf life of medicinal products. Successful small-scale studies of the alternatives at early testing phases do not guarantee similar outcomes on a commercial manufacturing scale, which means that additional process development work is needed to ensure reproducibility.
- Regarding photostability, alternative capsule systems that do not contain titanium dioxide generally offer less protection against light. This increases the risk of degradation for photolabile medicines, potentially requiring more protective packaging. Overall, switching from titanium dioxide presents complications in terms of maintaining product appearance and stability under light exposure. These photostability issues are also relevant for tablets.

On the basis of these findings, the EMA concluded that all the alternatives tested were inferior to titanium dioxide when assessed against the entire set of KPIs. Some alternatives performed well on certain KPIs but not others.

The EMA considered that, for some medicines, the use of titanium dioxide as an excipient can be critical for their safety and efficacy. For example, this is important when it serves as an opacifier to protect medicines from light and prevent degradation, or to ensure that a minimal amount of coating is used to enable tablet dissolution.

According to the EMA, the same technical challenges are expected to apply to products currently under development. Given the widespread use and acceptability of titanium dioxide, it is the material of choice for coating materials, capsules, etc. This means that it is included very early on in the development of products and formulations and at the clinical study stage of investigational medicines.

The EMA believes that the technical challenges identified are a realistic representation of the situation. Attempts to replace titanium dioxide will present significant logistical challenges for industry for both authorised products and products currently under development.

If a satisfactory alternative for titanium dioxide was to be identified, the EMA agrees with industry estimates that the timelines for reformulating individual products would vary from four to six years, depending on the complexity and risks of reformulation and bearing in mind regulatory procedures. This implies that a typical pharmaceutical company would need at least between seven and 12

years to reformulate their portfolio, given the average volume of medicines affected in such companies and the fact that these reformulations would need to be staggered. The submission of post-approval variations of marketing authorisations for so many products would also further prolong the time needed, due to capacity constraints in the EU regulatory network.

According to the EMA, these multifaceted challenges are highly likely to result in medicines being withdrawn, medicines being unavailable while being reformulated, new medicines taking longer to bring to market, and potential shortages.

Any requirement to make titanium dioxide-free medicines available would apply only in the EU/EEA and not globally. Companies would therefore have to create supply chains, processes and product dossiers specifically for the EU/EEA market. This could increase the likelihood of shortages or discontinuations of medicines because of the cost and complexity of maintaining them on the EU/EEA market. It might also affect the competitiveness of the pharmaceutical industry in the EU.

The updated analysis submitted to the European Commission by the EMA in April 2024 confirms the findings of its first analysis of September 2021. The EMA concludes that removing titanium dioxide is likely to be feasible for less than 5% of authorised medicines, as no simple one-to-one replacement exists, and that the same technical challenges are expected to apply to medicines currently under development. The EMA also believes that, in the hypothetical scenario that viable alternatives to titanium dioxide were identified, a transition period of more than 12 years would be required to phase out titanium dioxide in medicines, given the time needed to reformulate the portfolios of medicines of the companies concerned and for the regulatory post-approval process.

Independently of the feasibility analysis undertaken by the EMA and summarised above, an industry consortium submitted a request to the EMA in January 2024 for scientific advice regarding the safety of titanium dioxide in medicinal products. A general safety review falls outside the scope of scientific advice, but the EMA conducted its own assessment of the data submitted outside of a formal procedure, adhering to its standard practice of evaluating any newly submitted safety information on authorised substances. In March 2025, the EMA shared its findings with the Commission. They had been reviewed by both the European Chemicals Agency (ECHA) and the EFSA and endorsed by the EMA's Committee for Medicinal Products for Human Use.

Based on these data, the EMA considered any carcinogenicity risk resulting from exposure to titanium dioxide in medicines to be negligible, given the combination of the small quantities involved and the pharmaceutical-grade quality used. This conclusion is based on the limited set of data submitted by the industry consortium and not on a comprehensive review by the EMA of all available data.

3. CONCLUSION

The Commission has carefully assessed the EMA's findings in its updated analysis of April 2024 on the feasibility of replacing titanium dioxide with alternatives. The EMA's report highlights the following issues: (i) the importance of titanium dioxide for the safety, quality and efficacy of medicinal products; (ii) the lack of feasible alternatives at this stage; and (iii) the risk of shortages, which could be detrimental to patients, considering the very large number of medicinal products affected.

In view of the EMA's findings, the Commission takes the view that the use of titanium dioxide as a colour in medicinal products, as provided for in Regulation (EU) 2022/63 amending Regulation (EC) No 1333/2008, should be maintained.

Nevertheless, the pharmaceutical industry plays a vital role in monitoring and adapting to scientific progress. Companies should therefore remain actively engaged with new scientific developments

regarding excipients, particularly when developing new products. This approach is in line with modern scientific practice and ensures that marketing authorisation applications for new medicines provide sound justifications for their choice of excipients, including the use of titanium dioxide.