Why would the EU want to ban titanium dioxide in pharmaceutical products? What would be the potential impact on patients?

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Editorial

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Titanium Dioxide (also known as E171) has recently been banned for use in foods and dietary supplements in Europe and there is a potential that E171 could also be banned in pharmaceuticals in Europe as early as 2025.

In May 2021, the European Food Safety Authority (EFSA) published an Opinion that titanium dioxide (TiO2) (E171) could "*no longer be considered safe when used as a food additive*" (1), and a ban on its use in foods was quickly proposed by the European Commission.

There is no credible scientific data demonstrating there are any safety concerns with continued use of TiO2. There were a few data gaps identified by EFSA regarding the presence of nanoparticles in the overall particle size distribution of titanium dioxide which have always been present in the pigment grade TiO2 that has been used in foods and pharmaceutical products for many decades without any evidence of adverse effects. Unfortunately, the EU Commission decided to take an overly cautious approach and invoke the precautionary principle, based on some unsubstantiated data, and ban TiO2 for all food uses rather than recommend additional safety data be generated to understand the actual risks of continued use of TiO2, if any. Asking for additional safety data is the normal process undertaken by EFSA when a data gap exists. However, surprisingly, EFSA did not give industry the opportunity to provide additional data to address any uncertainties in this case.

Potential impact to medicinal products – reformulation challenges

Time has been granted for the European Medicines Agency (EMA) and the pharmaceutical industry to assess the feasibility of various TiO2 alternatives and the impact a potential ban of TiO2 would have in pharmaceutical products.

It is important to stress there is no direct alternative that exists today for the replacement of TiO2(E171). All the benefits that TiO2 brings to a drug product; inertness, opacity, light protection, and so on, do not exist today in any alternative material which could be easily substituted into a ready-made color mixture or hard capsule shell for use in the pharmaceutical products. Several TiO2 free coating products and

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capsule shells are available on the market which may work in some applications but there will typically be real challenges with using these systems, especially where a drug substance is light sensitive or where the color of the tablet core or capsule shell fill material is not white.

Any EU ban on TiO2 for pharmaceutical uses would cause significant impact to patients' access to critically needed drug products in Europe. Currently there are more than 91,000 approved human drug products and approximately 800 veterinary medicines containing TiO2 on the market in the EU which would need to be reformulated if TiO2 were to be banned in pharmaceutical products.

Reformulation of these existing drug products is not simply a case of removing titanium dioxide or substituting it for the next white pigment. Each drug product needs to be assessed individually; titanium dioxide has some unique properties that cannot be easily replicated. To get anywhere close to the same level of opacity, multiple different excipients/food additives need to be used in combination. Each one needs to be assessed for compatibility, regulatory compliance, safety, availability, quality, and in the final product manufacturability, stability would also need to be determined. A recent paper was published by members of the IQ Consortium that explains the difficulties in reformulation very well (2).

Although there is variation from company to company, the overall estimated cost to the pharmaceutical industry is around €32bn. Many companies indicate that for low-volume products, or products with old dossiers that are too complicated to change, they will simply withdraw the drug products from the European Market (3). This would leave millions of European patients without the drugs they desperately need for their health.

Does this make any sense when there is no actual safety concern that has been demonstrated with the use of TiO2 in foods or drugs? In this author's opinion, the answer to this question is NO WAY!! If there actually was a safety concern that had been demonstrated, this would be an entirely different conversation. However, this is not the case! EFSA and the EU Commission have utilized poor quality studies on Nano TiO2 grades, that have little to do with the grades of TiO2(E171) that are actually used in food and pharmaceuticals, to come to an extremely cautious decision that is not justified in the eyes of many scientists around the world.

What does the scientific community have to say about the safety of TiO2?

"*A new Weight of Evidence review has recently been published from a panel of independent world-class toxicology experts that determined that existing evidence does not support a direct DNA damaging mechanism for titanium dioxide (nano or other forms). Part of this review highlighted that the 1979 carcinogenicity study in mice and rats conducted by NIH and other National Toxicology Program studies from the 80's and 90's used a grade of titanium dioxide called Unitane 220, which following an FDA request, has been characterized using retained samples to determine that Unitane 220 is representative of the E171 grades available on the market now. This information was not available to EFSA at the time of their analysis, but it now provides evidence that a significant number of additional genotoxicity studies were conducted with relevant samples and should be taken into account*" (3).

An independent toxicologist, Dr. Lyle Burgoon, was concerned about the approach being taken by EFSA and the EU Commission. He wrote a blog on this topic in response to a lawsuit raised against the manufacturer of Skittles in August 2022 and he has determined that an individual would need to consume 4,080 skittles per day every day for 9 years to get to the genotoxic dose of concern perceived by EFSA (which does not seem to exist from reliable data)(4). This lawsuit has since been withdrawn by the plaintiff with no explanation.
In response to another similar lawsuit, this time against the makers of Tylenol, Dr. Burgoon conducted the same calculation exercise and determined that an individual would need to take 681 tablets every 6 hours every day for 8.5 years before reaching EFSA's perceived genotoxic dose of concern (5).

Clearly any risk-benefit review conducted would quickly be able to demonstrate the real level of risk posed by

consumption of titanium dioxide from medicines, so why are pharmaceutical companies having to expend valuable resources on reformulating medicines when the data shows there is no need? This is a really good question!

The Court of Justice of the European Union speaks on TiO2 REACH Classification – reliable studies must be used for decisions

In a recent major court case against the EU Commission concerning the Reach Classification of TiO2, the EU General Court ruled to annul the Commission Delegated Regulation of 2019 in so far as it concerns the harmonized classification and labelling of titanium dioxide as a carcinogenic substance by inhalation in certain powder forms. This was a major decision against the EU Commission and stated that "*the Commission made a manifest error in its assessment of the reliability and acceptability of the study on which the classification was based and, second, it infringed the criterion according to which that classification can relate only to a substance that has the intrinsic property to cause cancer*" (6). TiO2 has not been shown to have this intrinsic property by any credible study, even for inhalation.

This ruling makes it clear that the EU Commission decisions should be based on high quality studies which are reliable, and this is not what the EU Commission has done regarding the ban of TiO2 for food uses. The EU Commission should be challenged to reassess their decision on the TiO2 food ban, given this recent Court Ruling on the REACH Classification. Certainly, they should not extend this unjustified food ban of TiO2 to pharmaceutical applications, given the outcome of this court case! However, this court case doesn't have any direct impact on the ban of TiO2 in food or pharmaceuticals since it was focused on the REACH Classification of TiO2. That said, there are indirect implications from this court ruling that can be leveraged, requiring that reliable and acceptable studies be the basis for regulatory decisions.

What do global regulators think?

Many regulatory agencies around the world are now also having to re-assess the safety of TiO2 due to the actions taken by Europe. It is important that these agencies use good science to assess the safety of TiO2 and not just default to a precautionary approach as has been taken in Europe. Therefore, it will be critical that the broad industry (food, dietary supplement and pharmaceutical) work together globally, to bring the facts to the regulators and answer their questions so that we do not see a spread of what has happened in Europe with TiO2 to other countries.

Regulators in the Canada, United Kingdom, Australia/New Zealand and the United States, have already re-evaluated the data for TiO2 (including the NIH and NTP studies referenced above) and have concluded that TiO2 is safe, and they clearly stated that they disagree with the precautionary actions taken in Europe.

For example, Health Canada published a State of the Science report in June 2022 where they concluded there is "*no conclusive scientific evidence that the food additive TiO2 is a concern for human health.*" They stressed the need to focus on data from the grades of TiO2 that are representative of what humans would be exposed to from actual food uses (not nano grades) and that sample preparation procedures used in toxicology studies should be relevant for the types of processes which TiO2 would be exposed to in food manufacturing. (7)
In September 2022, FSANZ, in Australia/New Zealand, published their review of the safety of titanium dioxide (TiO2) as a food additive. Their review found "*there is currently no evidence to suggest dietary exposure to food-grade titanium dioxide is a concern for human health*" (8).

The UK Food Standards Authority (FSA) has also done an initial assessment and come to a similar conclusion in January 2022. Their full review report is expected in Q1 2023 (9).

The US FDA has evaluated TiO2 safety and has recently stated that they do not see any safety concerns with TiO2 that changes their current position to allow the use of TiO2 in foods and drugs. In response to a recent request from the Titanium Dioxide Manufacturer's Association (TDMA), the FDA provided the following

response:

The FDA reviewed the findings of EFSA's 2021 Opinion on titanium dioxide. The FDA notes that EFSA's 2021 Opinion continued to confirm no general and organ toxicity, as well as no effects on reproductive and developmental toxicity. In its 2021 Opinion, EFSA noted that it could not rule out genotoxicity and included genotoxicity tests on titanium dioxide nanomaterials. Some of the genotoxicity tests included test materials not representative of the color additive, and some tests included administration routes not relevant to human dietary exposure. The available safety studies do not demonstrate safety concerns connected to the use of titanium dioxide as a color additive. The FDA continues to allow for the safe use of titanium dioxide as a color additive in foods generally according to the specifications and conditions, including that the quantity of titanium dioxide does not exceed 1% by weight of the food, found in FDA regulations at 21 CFR 73.575 (10).

Food Navigator magazine recently published a similar response from the FDA to one of their requests for comments on TiO2 safety. The FDA said that the available safety studies do not demonstrate safety concerns connected to the use of titanium dioxide as a color additive (11).

What is the pharmaceutical industry doing to address this issue?

The International Pharmaceutical Excipients Council (IPEC) is working with the IQ Consortium and other global industry groups in a collaborative way to share information throughout the industry and develop plans for collecting and providing information to EMA and other global regulatory agencies related to the challenges of trying to reformulate to a TiO2-free product due to the technical limitations of the alternatives. TDMA has developed a new science program to perform additional studies which should answer any questions related to TiO2 safety that regulators might have.

The goal of all these efforts is to provide the EMA (before they have to provide their report to the EU Commission in April 2024) with significant information to support the actual safety of the grades of TiO2 used in pharmaceuticals and outline the significant risks to patient availability of key drug products that would most definitely occur if the EU Commission were to go forward with a ban of TiO2 for pharmaceutical applications.

Will the EMA and the EU Commission listen to good science related to actual pharmaceutical risks, as opposed to the overly precautionary thinking which has led them to an unnecessary ban of TiO2 for food uses in the EU?

We can only hope that good science will prevail. However, there is no assurance that this will be the reality. Therefore, everyone in the pharmaceutical industry needs to speak out loudly, through whatever channels you may have, to request that good science be the basis of any EU decisions on TiO2 for pharmaceutical uses.

Let's hope we can avoid the chaos that would be caused if TiO2 were to be banned for use in pharmaceuticals in the EU, for no good reason, down the road!

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