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# Regulatory 101: Safety Of Titanium Dioxide

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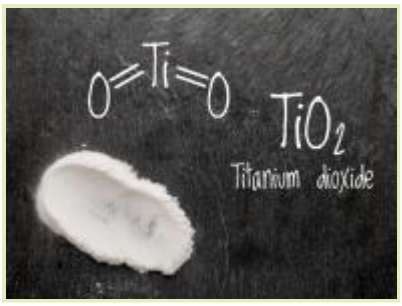


Regulatory 101 provides a forum for pharma professionals to share information about how they manage their respective quality and compliance responsibilities with regulatory considerations. Topics such as regulatory inspections, FDA-483s and Warning Letters, GMP manufacturing compliance topics, product technical management, and similar topics are planned for discussion -- all of which are supportive to the work of the quality and compliance function. Topics previously discussed in Regulatory 101 include the following:

1. Environmental Excursions and Drug Product Stability. JGXP V23, #5, Sept 2019
2. Drug Names – Categories, Approval Processes, and Problems in Use. JGXP V23, #6, Nov 2019.
3. Field Alert Reports, JGXP V 24, #2, March 2020.
4. Drug Name Modifiers – Definition, Categories, Generics, and CAPA. JGXP, V24, #3, May 2020.
5. New Drug Submissions in Major Markets. V24, #4. July 2020.
6. The Basics of Post Approval/Variation Submissions in the United States and European Union. JGXP V24, #6, Nov 2020.
7. Preservative Efficacy Test. JGXP, V25, #1, Jan 2021
8. Biologic Non-Proprietary Drug Names – Terminology and Format. JGXP, V25, #2, Mar 2021
9. Drug Names – Reader Q&A. JGXP, V25, #3, May 2021
10. What do the cGMP Regulations Say about Recalls? JGXP, V25, #4, July 2021.
11. Bulk Holding Time Requirements. JGXP, V25, #5, September 2021.
12. Animal-Derived Ingredients, FDA, and Regulations, JGXP, V25, #6, November 2021.

Regulatory 101 will be successful if our readers participate in its development. Suggestions for future discussion topics are invited. Readers are also invited to contribute manuscripts for publication – please share your successful approaches to quality and regulatory problem-solving. Please contact Coordinator Karen Zimm or Managing Editor Stacey Bruzzese through the Comments section below with questions, suggestions, or topics for discussion.

Titanium Dioxide ($TiO_2$) is a naturally occurring mineral utilized by the pharmaceutical and other industries including paint, cosmetics, and food. A current hot topic is Europe's potential safety concern over the use of $TiO_2$ in foods and the potential impact on the use of $TiO_2$ in medicines.

## HISTORY OF $TIO_2$

$TiO_2$ is used as a white colorant and an opacifying agent. The pharmaceutical industry has used $TiO_2$ safely for over 50 years. It is present in many pharmaceutical dosage forms in tablet coatings, capsule shells, and in packaging materials. $TiO_2$ is also referred to as E171 in Europe and referenced in this manner in published literature. $TiO_2$ is considered an inert substance having no impact on the active pharmaceutical ingredients or other formulation ingredients in the dosage form.

## $TiO_2$ FUNCTION

The colorant and opacifying properties of $TiO_2$/E171 contributes to a robust dosage form, protecting active ingredients, ensuring shelf-life stability, and thus securing the efficacy and stability of pharmaceuticals for longer time periods. $TiO_2$/E171 is an inert excipient meaning it has no pharmacological effect and therefore should not modify the active pharmaceutical ingredient. This is critical for the effectiveness of medicines when used by patients.

## STATUS OF $TIO_2$ IN EUROPE

On April 25, 2019, France banned the use of $TiO_2$/E171) effective January 1, 2020. The ban was to remain in effect until at least December 31, 2020 at which time it was renewed for another year. This ban prohibits any food product containing $TiO_2$ from being commercially marketed in France. The ban was applicable to foods only and did not impact the presence of $TiO_2$ in medicines, toothpastes, or cosmetics.

The ban is based on a precautionary stance that titanium dioxide nanoparticle additive is a potential carcinogen. It is important to note that "the lack of scientific data" is the conclusion based on an analysis of 25 studies by the French National Agency for Food Safety, Environment and Labor. They concluded that the studies were not sufficient to "confirm or deny the potential" carcinogenic effects of titanium dioxide when used as a food additive (1).

An initial European Food Safety Authority (EFSA) assessment in 2016 highlighted the need for more research. The rest of Europe patiently waited for an update by EFSA on its previous 2016 assessment of $TiO_2$. Ultimately Professor Maged Younes, Chair of EFSA's Expert Panel on Food Additives and Flavorings (FAF), said: "Taking into account all available scientific studies and data, the Panel concluded that titanium dioxide can no longer be considered safe as a food additive. A critical element in reaching this conclusion is that we could not exclude genotoxicity concerns after consumption of titanium dioxide particles. After oral ingestion, the absorption of titanium dioxide particles is low however they can accumulate in the body" (2).

Based on genotoxic assessment conducted by the FAF Expert panel, evidence for general toxic effects was not conclusive. Prof. Matthew Wright, chair of EFSA working group on E171 and a member of the FAF Panel, stated that concern for genotoxicity could not be ruled out and consequently a safe level for daily intake of the food additive could not be established.

While the EFSA role was to evaluate the risks linked to $TiO_2$ as a food additive, on October 7, 2021 the EU Member states approved the European Commission's proposal to ban the use of $TiO_2$/E171) as a food additive for 2022. The Commission's proposal is based on EFSA scientific opinion that concluded that $TiO_2$ could no longer be considered as safe when used as a food additive due to the concerns regarding genotoxicity cannot be ruled out. The next steps call for the Council and the European Parliament to give feedback on the draft Regulation. If there is no objection, the Regulation is expected to be adopted and published at the beginning of 2022 and applicable to the use of $TiO_2$ in food products.

The pharmaceutical industry was requested to provide feedback on the EFSA opinion by three European associations representing the human medicines manufacturers: Association of the European Self-Care Industry (AESGP), European Federation of Pharmaceutical Industries and Associations (EFPIA), and Medicines for Europe. This report is available online (3).

The Titanium Dioxide Manufacturers Association (TDMA) disagrees with European Commission's classification and has posted additional resources available on the TDMA website (4).

## GLOBAL IMPLICATIONS

Although the current opinion applies only to foodstuffs in Europe, there is concern regarding foreboding implications to the pharmaceutical industry and medicines not only in Europe but globally.

At this time, the pharmaceutical industry has this concern under evaluation and is looking at implications to their global product portfolio. Is this opinion and ban scientifically justified? Pharmaceutical companies are now trying to determine a strategy to deal with potential implications from the European ban. Will the opinion of other global health authorities follow Europe's lead?

Finding a functional alternative ingredient for $TiO_2$ is challenging. Making a post-approval change to a regulated pharmaceutical product requires a great deal of work and resources. Identification of a functional alternative, reformulation of products, stability studies, and global regulatory post-approval submissions are just a few of the challenges facing the pharmaceutical industry if $TiO_2$ is banned globally. It is also apparent that this effort will take years to complete.

Any sudden ban or restrictions on the use of $TiO_2$ could potentially cause drug shortages if enforced and have a major impact on patients. However, it will take time, many scientific studies, and a great deal of effort to address the concerns surrounding $TiO_2$. Unfortunately, it is not an easy fix.

## REFERENCES


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