PQRI Workshop:
*TiO2 Use in Pharmaceuticals*
*Global Regulatory and Technical Challenges*
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# *Update on the History and Current Status of $TiO_2$ (E171) in Europe (Foods and Pharmaceuticals) and Concerns Related to Excipients Containing Nanoparticles*


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# Agenda

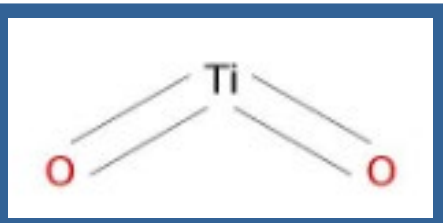
- Regulatory framework
- Timeline of events
- EFSA Opinion
- EMA Report
- Impact of food ban on pharmaceutical industry
- What's next?

*EFSA: European Food Safety Authority*
*EMA: European Medicines Agency*

# What is Titanium Dioxide

A commonly used white pigment and opacifier

- Oxide of titanium, one of the most common metals on earth
- Inorganic compound that occurs naturally under different crystalline forms (rutile & anatase being the most common ones)
- Due to its high refractive index, $TiO_2$ has light scattering properties making it excellent for use as a white pigment and opacifier.
- Commercially, pure $TiO_2$ is obtained from the mineral ilmenite (a titanium-iron oxide mineral) by a sulphate or chloride extraction process.
  - Pigment-grade $TiO_2$: µm-size particles, brilliant white appearance, mainly used for coloring purpose
  - Nano-grade $TiO_2$: particles sized less than 100nm, transparent, improved UV scattering and absorbing properties
- It is commonly used in a variety of product that people see and use on a daily base, e.g. paints, catalytic coatings, plastics, paper, cosmetics, and food.




| | |
|---|---|
| Molecular formula | $TiO_2$ |
| EC Number | 236-675-5 |
| EC Name | Titanium dioxide |
| CAS number | 13463-67-7 |
| E-number | E171 |
| INCI Name | C.I. 77891 |

*EC: European Community*
*CAS: Chemical Abstract Service*
*INCI: International Nomenclature Cosmetic Ingredient*

# The European Union (EU)

## How does it work?

**The EU is composed of 27 sovereign, independent Members States that have pooled some of their 'sovereignity' to gain strenght and the benifit of size.**

- → Some of the decision-making powers are delated to shared institutions
- → EU sits in between the fully federal system of the US and the loose, intergovernmental cooperation system of the United Nations.

| Who takes decisions? | What type of binding legislation? |
|---|---|
| • **European Parliament**, which represents the EU's citizens and is directly elected by them;<br>• the **Council**, which represents the governments of the EU Member States;<br>• the **European Commission (EC)**, which represents the interests of the EU as a whole.<br><br>→ EC **proposes** new laws<br>→ European Parliament and Council **adopt**<br>→ The Member States & the EC **implement** | A **regulation** is a law that is applicable and binding in all Member States directly.<br><br>A **directive** is a law that binds the Member States, or a group of Member States, to achieve a particular objective. Usually, directives must be transposed into national law to become effective.<br><br>A **decision** can be addressed to Member States, groups of people, or even individuals. It is binding in its entirety. Decisions are used, for example, to rule on proposed mergers between companies. |

A number of specialized EU agencies offer information or advice to the EU institutions, the Member States and citizens.

→ **European Food Safety Authority (EFSA):** provides the scientific basis for regulations protecting EU consumers from food-related risks.

# EU Regulatory framework

Various regulations depending on intended use

**CHEMICAL**
**European Chemicals Agency (ECHA)**

Reg **(EC) 1907/2006 -** Registration, Evaluation, Authorisation and Restriction of Chemicals (**REACH**)

- $TiO_2$ is registered in all forms, no authorization requirements or restrictions.
  → substances used in medicinal products and foodstuffs are exempted from the Registration Title of REACH

Reg **(EC) No 1272/2008 -** Classification, Labelling and Packaging (**CLP**)

- Certain powder forms of $TiO_2$ are classified as '*suspected carcinogen (category 2) by inhalation*'.
  → Pigmentary grade $TiO_2$ does typically not meet the conditions to qualify as category 2 material, as no method was specified this is down to interpretation.

**COSMETICS**
**Scientific Committee on Consumer Safety (SCCS)**

Reg **(EC) 1223/2009** - Cosmetic products

- approved for use as UV filter in e.g. sunscreens
- approved colorant (reference to food legislation for E171 purity criteria)

**FOOD**
**European Food Safety Agency (EFSA)**

Reg **(EU) 1333/2008** - Food Additives (food colorant: E171)
Reg **(EU) 231/2012** – Purity criteria

→ **BAN IMPLEMENTED: Reg (EU) 2022/63**

**PHARMA**
**European Medicines Agency (EMA)**

Directive **2009/35/EC** - Colouring matters which may be added to medicinal products

*Cross references food legislation*

# History of Titanium Dioxide Reviews

**Titanium dioxide has been the subject of multiple safety evaluations over the years**

USA

- FDA first approved in 1966, quantity limited to 1% by weight in foods. Approved for use in medicines and cosmetics (incl sunscreens)
- FDA utilized a 1979 NTP/NIH Study - *Bioassay Of Titanium Dioxide For Possible Carcinogenicity* to assist in their safety evaluations of TiO2 over the years

Global

- By the Joint FAO/WHO Expert Committee of Food Additives (JECFA) in 1969.
  - In 1969, JECFA allocated an acceptable daily intake (ADI) 'not limited except for good manufacturing practice'

Europe

- By the Scientific Committee on Food (SCF) in 1975 and 1977.
  - In 1975, the SCF did not establish an ADI for titanium dioxide, whereas in 1977, the SCF included titanium dioxide in the category 'colours for which an ADI was not established but which could be used in food'.
  - In 2016, a re-evaluation of titanium dioxide (E 171) as a food additive was conducted by the European Food Safety Authority (EFSA) as part of the routine re-evaluation program for food additives authorized for use in the EU prior to 20 January 2009.

# $TiO_2$ Safety Review Timeline

JUN 2016

- **EFSA opinion of the ANS Expert Panel of toxicologists is adopted.**
  - Concluded that the use of titanium dioxide as a food additive **does not** raise a genotoxic concern.
  - To be able to set an ADI EFSA issues a call for further data

JAN 2017

- **Bettini/INRA (French National Agronomic Institute) paper published**
  - Identifies that E171 titanium dioxide contains nano-particles
  - Claims E171 nanoparticles are absorbed in the gut and may cause pre-cancerous lesions in rats.

APR 2017

- **French Agency for Food, Environmental and Occupational Health & Safety (ANSES) publishes opinion on Bettini paper**
  - Although found previously unidentified effects, not enough data to challenge the 2016 EFSA opinion.
  - Calls for longer term studies to investigate promoter effect of E171 in colon

MAR 2018

- **At request of Member State (MS) , European Commission (EC) requests EFSA to review 4 new publications that raise concerns of E171 safety. (Including Bettini paper)**

# $TiO_2$ Safety Review Timeline

APR 2018

- **A MS requests Europe wide ban on E171 citing precautionary principle**
  - EFSA presented evidence to the SCOPAFF (Standing Committee on Plants Animals Food and Feed), no other MS supports this proposal – rejected.

JUN 2018

- **EFSA published Opinion on the 4 new papers**
  - Panel concluded that the outcome of the four studies did not merit re-opening the existing EFSA opinion related to the safety of TiO2(E 171) as a food additive.
  - EFSA did request that the industry toxicology programme was expanded to investigate the issues highlighted in the Bettini paper.

OCT 2018

- **EGALIM law published in France**
  - Public and political will is building against titanium dioxide
  - Clauses in this legislation provide the framework that would allow titanium dioxide E171 to be banned in France, with an implementation date foreseen on January 1st, 2019.

JAN 2019

- **FRENCH SUSPENSION DELAYED**
  - Further evidence supporting an 'urgent safety measure' needed from ANSES.

# EGALIM law

- "**Etats Généraux de l'Alimentation**" (EGALIM)
  - Project launched by President Macron
  - "Time for shared reflection and collective construction of new solutions"
  - Large public consultation on agriculture practices and food

- **"EGALIM-law"** 2018-938 for "balanced trade relationships in the agriculture and food sector and for a healthy, sustainable diet that is accessible for all"

- Main **objectives**:
  1. Fair revenue for farmers with a better split of the value throughout the value chain
  2. Improve the sanitary and environmental conditions of production
  3. Improve animal welfare
  4. Promote a healthy, sustainable diet, accessible for all
  5. Reduce use of plastics in food

$TiO_2$ suspension: one of the measures under 2.



Ban on the use of $TiO_2$ in foodstuffs

# $TiO_2$ Safety Review Timeline

APR 2019

➢ **ANSES publish further review of E171 on April 15th**

- ➢ Concludes that there is not enough data to prove that E171 is safe.

APR 2019

➢ **On April 25th, France publishes implementing order banning use of E171 in foods**

- ➢ Applies as from January 1st, 2020
- ➢ Decision is based on the Bettini paper, the lack of an ADI from the EFSA report and the precautionary principle.

MAY 2019

➢ **SCOPAFF committee discuss the ban in France**

- ➢ EFSA presented a summary of all the titanium dioxide E171 reviews of the last few years.
- ➢ The majority of the Members States prefers a harmonized approach relying on EFSA as the risk management body for the EU. No formal decision has been made on possible European actions.

JUN 2019

➢ **EFSA publishes Opinion on specifications for E171**

- ➢ Data supplied by industry as part of EFSA call for data.
- ➢ Proposes new E171 spec for particle size and particle size distribution to control nano content and asks for a reduction in some heavy metals limits

# The ANSES opinion

Literature review identified **25 new studies relative to the toxicity of oral intake of $TiO_2$** since 2017.

- Elements relevant to $TiO_2$ safety include impact on the regulation of histones, developmental abnormalities in vertebrates and *in vitro* genotoxic effects by oxidative stress.
- Those effects are identified for the different forms of $TiO_2$ nanoparticles, including $TiO_2$ as food additive.
- None of these new studies allows confirmation of the potential of $TiO_2$ as a promotor for carcinogenicity (cfr. INRA study)

As there are insufficient data to alleviate doubts about the safety of $TiO_2$, ANSES reiterated their 2017 recommendation:

- Need for precise **physico-chemical characterisation** of $TiO_2$
- Need for **better characterisation of the potential danger** of $TiO_2$
  → Given the wide use of E171 (in 51 food categories and at *quantum satis*),
  data must be provided by producers.
- Consider **justification for the use of $TiO_2$** as a food additive, based on well-defined benefits for the consumer (technological need, lack of alternatives, usefulness for consumers and society).



ANSES also reiterated its general conclusions on nanomaterials:

- **Limit the exposure** of workers, consumers and the environment
- **Favorise non-nanomaterial containing products** that are equivalent in terms of function and efficacy.

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# $TiO_2$ Safety Review Timeline

SEP 2019

➢ **Repeat call to ban E171 across the EU is requested by MS**

- ➢ Again reviewed at the SCOPAFF meeting and consensus is to wait for the EFSA review to be completed.
- ➢ MS reiterate their strong preference to have an EU-wide approach to food additives.

JAN 2020

➢ **E171 ban in foods comes into effect in France**

- ➢ EFSA presented a summary of all the titanium dioxide E171 reviews of the last few years. MS back the EFSA opinion and the need for a unified approach to food additives.

APR 2020

➢ **European Commission (EC) proposes to amend E171 specifications**

- ➢ Proposal based on EFSA recommendations and includes both limiting nano content and reducing permitted levels of heavy metals.
- ➢ Endorsed by MS and submitted to European Parliament in August.

SEP 2020

➢ **Some members of the European Parliament (MEPs) table resolution objecting to the new specification**

- ➢ MEPs argued strongly for a complete ban of E171 in the EU as a precautionary measure
- ➢ Resolution passes and EC withdraws the new specification (old specification remains in force)

# $TiO_2$ Safety Review Timeline

SEP 2020

➢ **Industry submits additional tox data on E171 to EFSA for review**

- ➢ All data requested in the 2016 EFSA call for data and the subsequent additions to answer the concerns raised by the Bettini paper.

MAY 2020

➢ **Final EFSA Opinion on E171 published**

- ➢ EFSA Concludes that "E171 can no longer be considered as safe when used as a food additive"
- ➢ Strong political will to ban E171

SEP 2021

➢ **EMA submits impact assessment on pharmaceutical use to European Commission**

OCT 2021

➢ **Legislation banning use of E171 in foods in the EU approved by MS and European Parliament**

# The EFSA Scientific Opinion

'E171 no longer considered safe when used as a food additive'

Taking into account the latest nanoparticles risk assessment approach and applying a precautionary approach, the Panel concluded that **E171 can no longer be considered safe as a food additive.**

- On the basis of the new data and strengthened methods, **genotoxicity concerns** after oral consumption of E171 cannot be excluded. Consequently **no safe level for daily intake** could be established.
- The amount of nanoparticles in E171 is generally low and are likely to form agglomerates. However, when dispersion procedures are applied, these agglomerates may deagglomerate, resulting in increased numbers of **'free' nanoparticles**.
- Although the gastrointestinal absorption of titanium dioxide particles is low, they may **accumulate in the body** due to their long half-life.
- Some findings regarding **immunotoxicity and inflammation** with E 171 as well as neurotoxicity with $TiO_2$ nanoparticles may be indicative of adverse effects.
- Combining the available lines of evidence on genotoxicity, $TiO_2$ particles have the potential to induce DNA strand breaks and chromosomal damage, but not gene mutations.

Nevertheless, EFSA did not identify any immediate safety concern!

*EC: European Commission*

# EFSA opinion and medicinal products?

Pharma legislation only allows authorized food colorants

EFSA opinion does not directly relate to medicinal products. However, EU pharmaceutical legislation on colourants cross references the food legislation.

| **Directive 2009/35/EC** on the colouring matters which may be added to medicinal products | | |
|---|---|---|
| Art 1: Only colors for use in foodstuffs are authorized | | |
| **Directive 94/36/EC**<br>List of food colours | → Outdated → | **Regulation (EU) 2008/1333**<br>List of food colors (Annex II – Part B).<br>+ list of other food additives |
| Art 2: Coloring matters must meet the specific purity criteria laid down for colors in foodstuffs | | |
| **Directive 95/45/EC** | → Outdated → | **Regulation (EU) 231/2012** |

- Removing E171 from the list of authorised food colours would effectively ban the use of $TiO_2$ as a colourant in medicinal products.
- EC asked EMA to investigate the use of E171, potential replacements and likely disruption of having to replace it.

# The EMA report

## Currently not possible to replace $TiO_2$

EMA/504010/2021 report published on 8 September 2021

Does not evaluate the safety of $TiO_2$ but assesses the impact of its removal from the list of food colorants.

- $TiO_2$ **is present in many medicines** (91,000 human medicinal products and 800 veterinary medicinal products):
  - (Semi-)solid oral dosage forms (e.g tablets, capsules, pastes, gels)
  - Also: cutaneous, inhalation (capsule shells), transdermal, …
- It is used as a **colorant and opacifier**:
  - Protection of API from light degradation, allowing for longer shelf life
  - Visual identity allowing to discriminate between various strengths & improving patient acceptability
- **Lack of alternatives** offering the same combination of properties that are unique to $TiO_2$
- The feasibility of replacing $TiO_2$ cannot be confirmed at this stage and requires **further investigation**
- Concerns on **unharmonized global situation**, where new products are to be developed for potentially Europe only.
- There is a "real risk" that the time and costs for the replacement of $TiO_2$ would result in "significant **medicine shortages**" or withdrawals from the market, with particular concerns for pediatric and orphan medicinal products.

**CONCLUSION**: replacement of $TiO_2$ in medicines can currently not be achieved without a negative impact on the quality and quantity of medicines in the EU.

# $TiO_2$ Future Timeline

FEB 2022

- **Legislation EC 2022/63 comes into force.**
  - Banning use of E171 in foods.

AUG 2022

- **It is now illegal to place food products containing E171 onto the EU market**
  - Products legally marketed before Aug 7th may remain on the market until end of shelf-life.

APR 2024

- **EMA to complete further review of the use of E171 in medicines**
  - Taking into account the safety of potential replacements, the safety and quality of medicines.
  - In addition the impact of availability of medicines in the EU.

FEB 2025

- **EC will make a final decision on the use of E171 in medicines**
  - 3 years after legislation (2022/63) came into force.

# Regulation (EU) 2022/63

Pharma companies are urged to look for alternatives

**Use of E171 is prohibited in all food categories, but E171 is maintained on the list of authorized food colorants to allow continued use in medical products. However, …**

Whereas 17

- *"It is of critical importance that the pharmaceutical industry makes any possible efforts to accelerate the research and development of alternatives that would be used as a replacement for titanium dioxide (E 171) in medicinal products, and to submit the necessary variation to the terms of the marketing authorisations concerned. In the absence of such efforts, competent authorities may request the concerned stakeholders to submit objective and verifiable reason explaining the non-feasibility of the replacement."*

Whereas 18

- Final EC decision will be based on the EMA review and….
- *"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."*

# Considerations

## Limited options to replace $TiO_2$

**Availability of alternatives?**

The current list of food colorants has only one white alternative (calcium carbonate – E170), and it presents challenges (e.g. inability to obtain sufficiently thin films, supply chain issues, mined materials with associated elemental impurity risk)

Titanium dioxide free coatings and capsules are already available, but:

- Do they provide the same level of whiteness and/or opacity?
- Do they offer the same product quality?
- Do they meet the current regulatory framework?

Revision of the current Directive on colouring matters which may be added to medicinal products would be desirable:

- Extension to all food additives from Reg 2008/1333?
- Use of substances other than food additives,  provided they are safe?

# What does industry need to know?

## Further guidance is needed

**What if $TiO_2$ cannot be replaced in a product?**

Regulation 2022/63 allows continued use of E171 to be justified, by “objective and verifiable reasons”, what does this mean in practice?

- Case studies or examples

**How to handle the replacement of $TiO_2$?**

- Clarification on what is permitted from the current legal framework.
  - Are substances that are not food colours also acceptable?
  - Are opacifying agents also classed as colours?
- What is the variation process for removing or replacing E171 in existing products?
- What is the timeline for this replacement assessment, many of these changes will be fairly complex?
  - Submit at renewal?
  - Can EMA handle the expected number of variations?

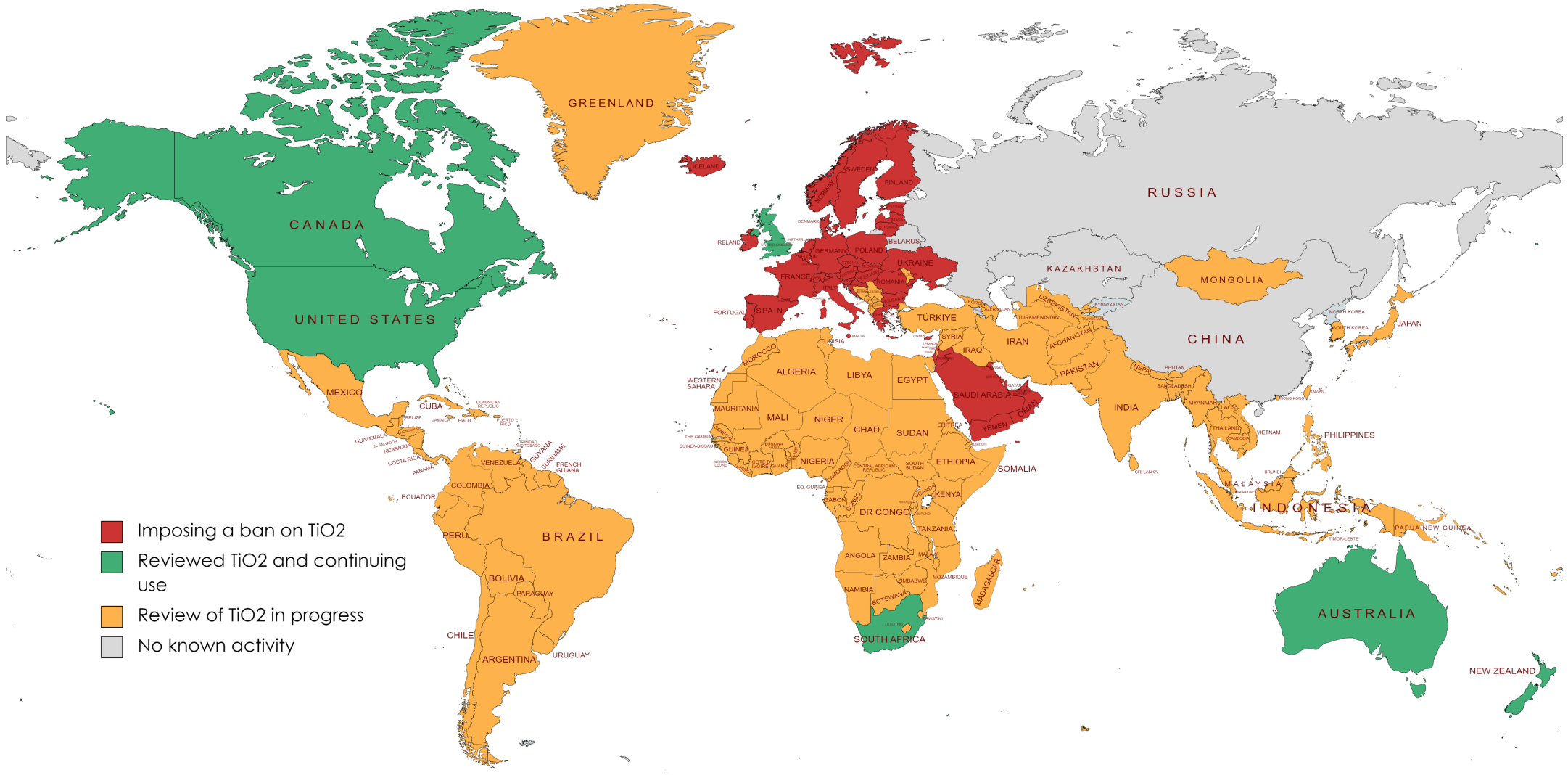
# EMA QWP Q&A Document – 1st July 2022

Quality of medicines questions and answers: Part 2 | European Medicines Agency (europa.eu)

- Outlines the variation route to be followed – still no guidance on how to justify continued use of titanium dioxide.
- New MAA Applicant – If close to submission and development work started proposed composition can contain titanium dioxide. However if applicants decide to remove $TiO_2$, this should be done before applying, or via a variation after authorisation granted, do not change during the MA procedure.
- MAH's of existing MAs – Make every effort to accelerate R&D into replacing $TiO_2$,
- Potential replacement materials need to meet the regulatory requirements, generation of new quality data on finished product (e.g. manufacture, dissolution, compatibility, stability) and potentially new bioequivalence studies.
  - Replacement colourants do need to meet 1333/2008 and 231/2012 regulations.

Direction of travel is for the removal of $TiO_2$ from Medicines

# Status of $TiO_2$ for use in Food




*Created using mapchart.net*

Information collated from various sources, January 2023

# Titanium Dioxide – CLP

- In 2019 EC declared that titanium dioxide needed to be labelled as a carcinogenic substance by inhalation in certain powder forms, and Regulation 2020/217 amending 1272/2008 was adopted.

- However the European Court of Justice ruled on 23rd November 2022 that:

  *"First, 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."*

- The General Court annuls the Commission Delegated Regulation of 2019 2020/217

France and the EC have appealed against the ruling 8th Feb 2023 – It is expected to take 18-24 months for the review process.

Until the appeal process is resolved the existing regulations remain in force.

# Revision of EU Pharmaceutical Regulations

- Biggest change to EU pharma regulations in 20 years, over a 1000pages to review.
- But one section does stand out, and it is on color:

(104) The use of colours in human and veterinary medicinal products is currently regulated by Directive 2009/35/EC of the European Parliament and of the Council[23], and restricted to those authorised in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives[24], for which specifications are laid down in Commission Regulation (EU) No 231/2012[25]. Uses of excipients other than colours in medicinal products are subject to the Union rules on medicinal products and are evaluated as part of the overall benefit risk profile of a medicinal product.

(105) Experience has shown the need to maintain to a certain extent the principle of the use in medicinal products of those colours authorised as food additives. However, it is also appropriate to foresee a specific assessment for the use of the colour in medicines when a food additive is removed from Union list of food additives. Therefore, in this specific case, EMA should carry out its own assessment for the use of the colour in medicines, taking into account the EFSA opinion and its underlying scientific evidence, as well as any additional scientific evidence and giving particular consideration to the use in medicines. EMA should also be responsible for following any scientific evidence for the colours retained for specific medicine use only. Directive 2009/35/EC should therefore be repealed.

# Nanoparticles

The concerns around titanium dioxide seem to derive from the fact that it contains particles in the nanoscale (<100nm), these are identified as a hazard in many food additives but rarely is any risk assessment conducted.

- **US - FDA** has a policy on nanoparticles/nanomaterials in medicines – risk assessment needs to be conducted if a new material, however if an existing excipient contains nanoparticles and has always done so and is used in the same manner (route of administration, dosage form, function and use level) this is considered low risk.
- **Europe - EMA** Has no policy. Concern driven by foods and France. EFSA now has a nano assessment guideline that is applied to food additives undergoing review.
  1. Characterise nano content,
  2. Prove the nano is content soluble
  3. Prove nano particles have always been present and were considered in previous safety reviews
- **France (ANSES)** – Report on "engineered nanomaterials" in foods – anything manufactured. Use special analytical techniques to identify and sets a zero tolerance level. Identifies 37 food additives or ingredients that contain or are suspected to contain nanoparticles.
  - They have not conducted any risk assessment, just the highlighting the hazard

# ANSES Assessment Criteria

**Within the framework of this expert appraisal, the Agency relied on its own classification of the term "engineered nanomaterial":**

- an engineered nanomaterial is a material of an organic, inorganic or composite nature, produced by humans for application purposes and comprised wholly or partly of constituent particles with at least one dimension between 1 and 100 nm (nanoscale);
- the dimensions of the constituent particles may be greater than 100 nm if these particles have a large specific surface area or nanoscale properties;
- constituent particles can be found in the form of aggregates or agglomerates whose dimensions can be much larger than the nanoscale;
- materials for which the nanoscale fraction was not intentionally produced during the manufacturing process are included in the scope of this classification.

# ANSES – Nano hazard list

- Substances proven to contain nanoparticles:
  - **Calcium carbonate**, **titanium dioxide**, **iron oxides and hydroxides**, calcium silicate, tricalcium phosphates, synthetic amorphous silicas, organic and composite compounds.
- Substances suspected of containing nanoparticles:
  - Aluminium; silver; gold; calcium and magnesium phosphates; ferric ammonium citrate; mannitol; microcrystalline cellulose; sodium, potassium and calcium salts of fatty acids; magnesium stearate; magnesium carbonate; sodium carbonate; aluminium sulfate; aluminium potassium sulfate; magnesium oxide; iron tartrate; ferrocyanides; magnesium silicate; talc; sodium, potassium and calcium aluminium silicates; zinc silicate, zinc acetate; isomalt.

ANSES published this ***Hazard*** list in May 2020 and pledged to assess the risk in the future. But this has still not been done, we get questions asking if excipients contain nano. So you see materials being excluded based on this document ***without*** adequate ***risk assessment***.

# Nanoparticle Problem Statement

- Differences in definition – ANSES, EC and EFSA
- EMA has no policy on incidental nanoparticles so there is a guidance vacuum in Europe.
- Most noise coming from ANSES and EFSA re food additive content.
- Only colours covered by food legislation, all others excipients can refer to Ph Eur.
- No pharmacopeial or food additive monograph requires any measurement of nano content – in fact only materials undergoing EFSA review need to do this.
- But still we get pharma customers asking us if our coatings contain “nano”
- Are decisions being made to exclude these materials based on incidental nano content? Not a real hazard, but rather the perception that there may be a future issue (social/political not necessarily scientific)

# Conclusions

## Titanium Dioxide

- EFSA has determined that E171 is no longer safe as a food additive.
  - Although a hazard has been identified, **no formal risk assessment has been conducted for use in pharmaceuticals**.
  - Removing E171 from all medicines in Europe is estimated to cost the pharmaceutical industry **€32bn to change 91,000 medicines**.
  - Even if they double their variation review capacity, it will take EMA **12 years to review** this number of variations.

- Regulation urges pharmaceutical companies to look for alternatives. However, due to its unique properties and restrictive regulations, E171 is not easy to replace.
  - Leading to increasingly **complex solutions** and therefore **complex variations**.
  - **Unclear impact** will be on the pharmaceutical industry, the EMA and the approval of new marketing authorizations in the EU.

- Currently the EU seems to be out of step with other regulatory regions, which could lead to the loss of global pharmaceutical products.

## Nanoparticles

- Excipients containing nanoparticles are seen as carrying a higher risk than ones that do not, this is a risk of adverse publicity, public perception and inadequate or zero risk assessment rather than any real threat to health. But unfortunately, excipient selection decisions seem to be being made on this basis.

# Questions?