

Enabling a Healthier World

PQRI Workshop:
TiO₂ Use in Pharmaceuticals
Global Regulatory and Technical Challenges
June 13-14, 2023

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Capsules & Health
Ingredients

Replacing titanium dioxide (TiO₂)

Challenges and opportunities from a capsule shell producer point of view

Bram Baert | PQRI | June 14, 2023



Content

- Hard capsules and TiO_2 – what we need to keep in mind
- What are the options without TiO_2
- TiO_2 alternatives – challenges and solutions



Capsules are very versatile dosage forms

The perfect fit

Capsules offer a wide range of customization possibilities

Visualization

- Different color formulas
- Imprinting



Functionality

- Immediate release
- Enteric capsule
- Inhalation capsules
- Sprinkle capsules
- Specialized clinical capsules
- Enrobing Gelcap technology



Hard capsule design is highly (pre)defined

Versatility comes with considerations

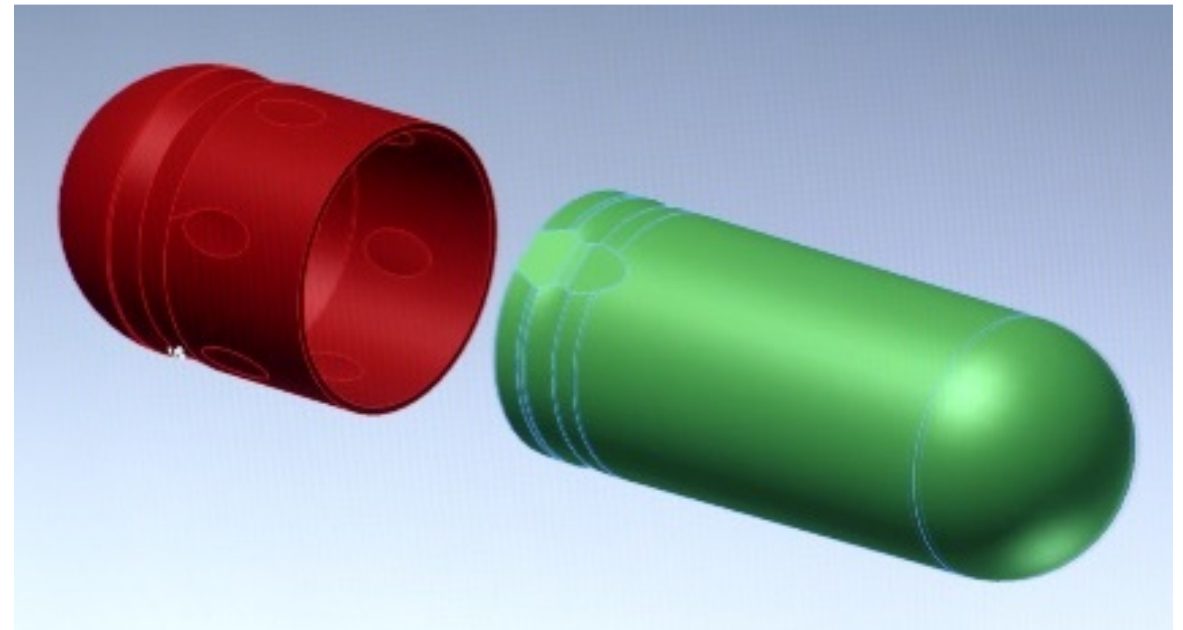
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Hard capsules design restricts possibilities for customization or functionality addition

- Free standing, thin polymeric film
- Shaped into targeted form
- With predefined dimensions
- Features tailored for the application

Capsula Lat. – small container

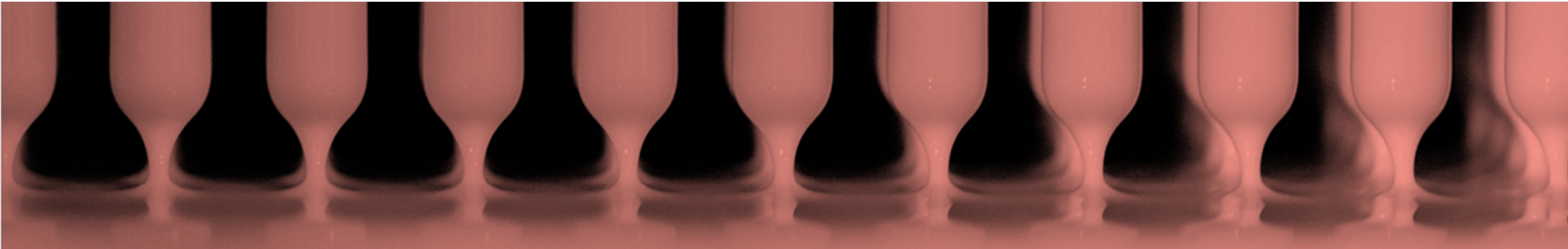


TiO₂ in hard capsules

What are the key functions?

TiO₂ is more than just another colorant

- **Like any other colorant** – it helps create a **visual identity** unique to the product
- **Unlike any other colorant** – it ensures **full masking** of the capsules fill and **protects the ingredients** susceptible to light degradation



Why is TiO₂ so well suited for use in hard capsules?

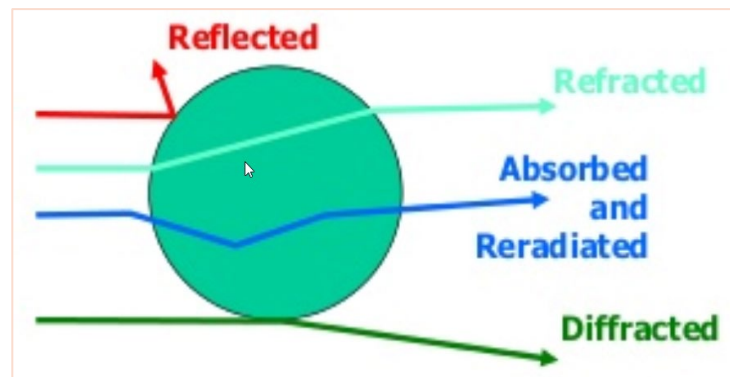
Unique properties

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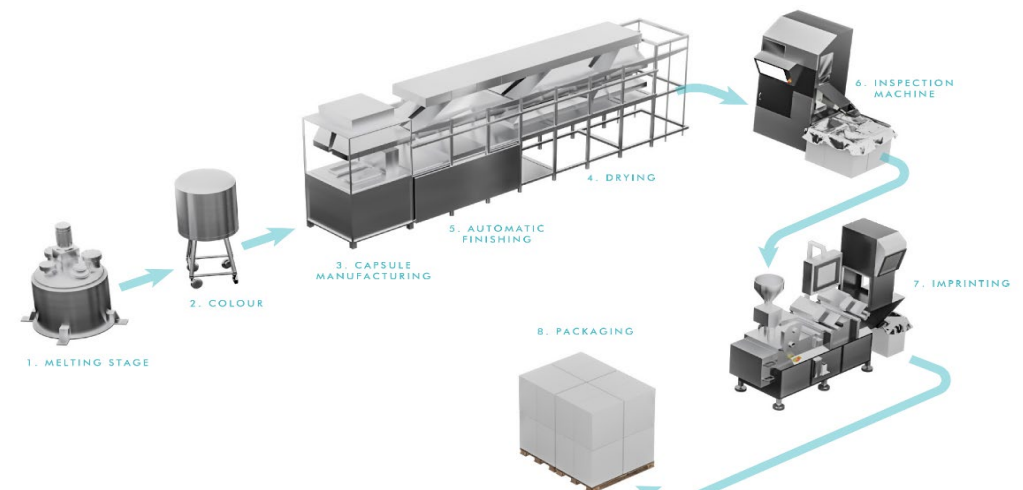
Distinctive TiO₂ properties

- Chemically **inert** and insoluble in water
- Unmatched **refractive index**
- **Highly stable** to heat, light and any ambient conditions
- Long and extensive history of **regulatory acceptance**



Impact on hard capsules

- **Manufacturing**
 - Stability
 - Reproducibility
 - Quality
 - Efficiency
- **Product**
 - Robustness
 - Machinability
 - Dissolution/Disintegration
 - Stability
 - Global reach



TiO₂-free capsules What are the options?

While significantly reduced, there are still many options for visual customization in TiO₂-free capsules.



Transparent (colored)
capsules



Iron oxides instead
of TiO₂



Alternative opacifying
technology

TiO₂-free portfolio solutions

Eliminate TiO₂

Keep existing color composition, but remove TiO₂



Transparent (colored)
capsules

- A broad offering that will aid in product identification.
- Loss of masking & light protection of original capsule.



Iron oxides instead
of TiO₂



Alternative opacifying
technology

TiO₂-free portfolio solutions

Iron oxides as alternative to TiO₂

Replace TiO₂ by iron oxides



Transparent (colored)
capsules



Iron oxides instead
of TiO₂

- Iron oxides as semi- or full-opacifier with wide shade options, alone or in combination with other colorants.
- Identification and compound masking is preserved in addition to some light protection.



Alternative opacifying
technology

Use of iron oxides as an alternative for your products

Considerations

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What are iron oxides?

- **Non-Artificial* colorants** for Pharmaceutical including OTC applications with broad regulatory acceptance
- Available in semi-opaque and opaque appearance
- Offer **some protection** against UV and visible light

Advantages

- Iron oxides are suitable for use with both gelatin and HPMC based capsules
- Wide color palette can be obtained

* : NATCOL classifies iron oxides as "N3" food colours : "colour identical with a colouring principle that occurs in nature, and which is produced by chemical synthesis. Non-artificial colour - Nature-identical colour"



REGULATORY INFORMATION & DOCUMENTS

Coni-Snap® hard gelatin capsules
Color Formulation Support
for Pharmaceutical Products
EU / US / JP

Colors formulated without titanium dioxide



REGULATORY INFORMATION & DOCUMENTS

Vcaps® Plus capsules
Color Formulation Support
for Pharmaceutical Products
EU / US / JP

Colors formulated without titanium dioxide



TiO₂-free portfolio solutions

Alternative white and opacifying solutions

Do solutions equivalent or identical to TiO₂ exist?



Transparent (colored)
capsules



Iron oxides instead
of TiO₂



Alternative opacifying
technology

What is possible?

What would be suitable TiO_2
alternative(s) for hard
capsules?



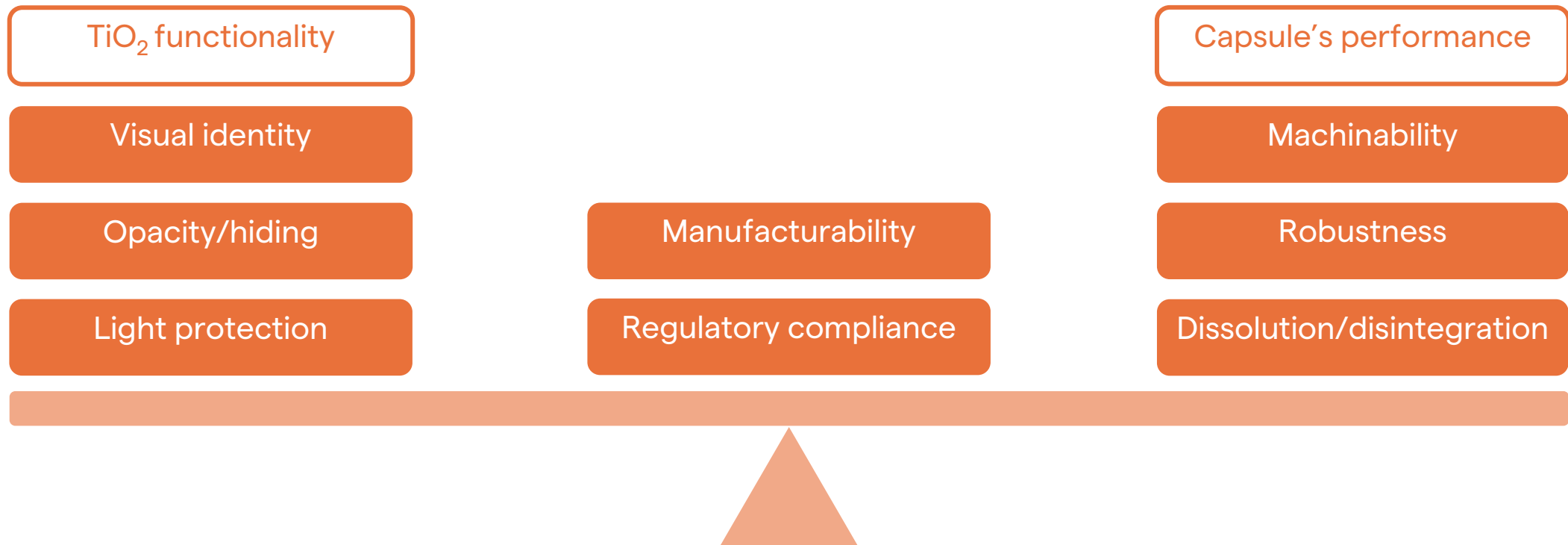
Requirements for alternative opacifiers

Combine functionality and performance

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Selected alternative(s) should match the TiO₂ functionality without impacting the key capsule's performance while complying with regulatory requirements.



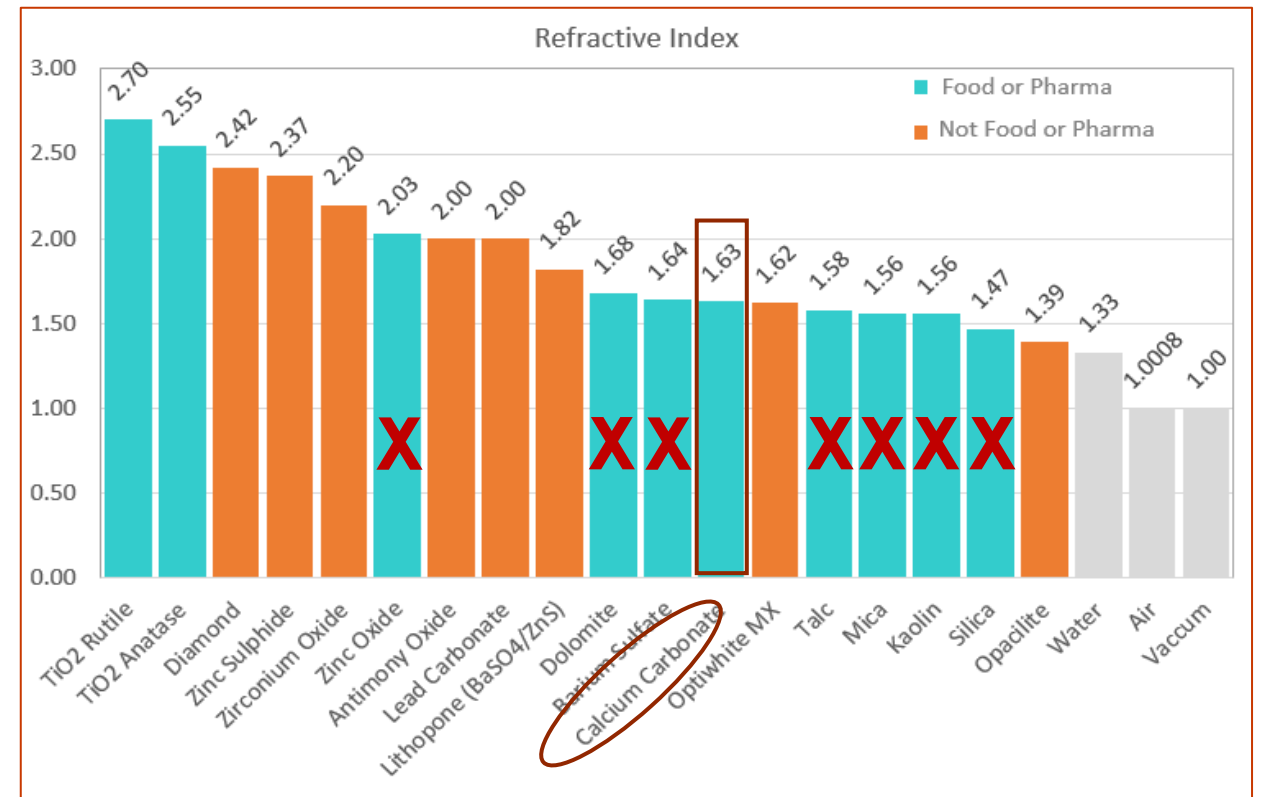
Which other substances can serve as an alternative for TiO₂ ?

Technical and regulatory challenges

Looking at combined technical and regulatory requirements for a broad set of **particulate materials** used across industries, the only viable TiO₂ alternative for oral dosage forms is **calcium carbonate** (CaCO₃).

- Authorized colorant:
 - E170 (EU)
 - 21 CFR §73.(10)70 (US)
- Limitation: refractive index much lower compared to TiO₂

Refractive indexes of different minerals/particles used in various industries with potential for use as opacifiers compared to water, air and vacuum



CaCO₃ in hard capsules

No equivalent to TiO₂

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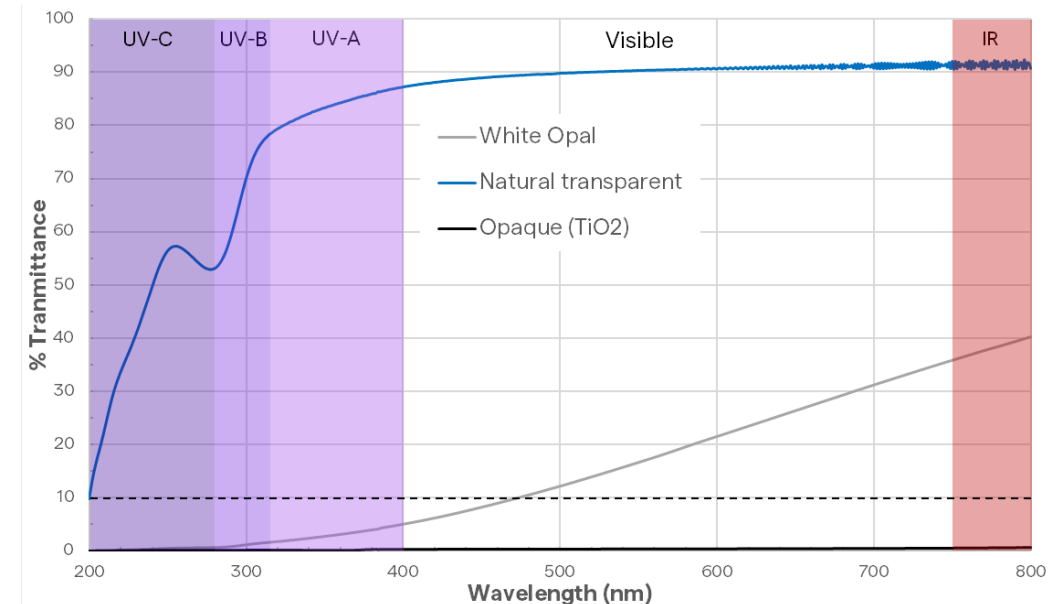
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Preserving the general capsule characteristics required compromises on the light protection and opacity

- + Robustness and machinability attained
- + Dissolution/disintegration performance preserved
- + Effective protection from the UV light
- White semi-opaque
- Only partial light protection in the visible spectra



empty capsule white powder orange pellets black pellets
(From left to right)



New opportunities can be found, when looking:

- at innovative concepts to achieve color / opacity
- beyond current EU food colorant list or US color additives listing

Reference



Lonza's solution



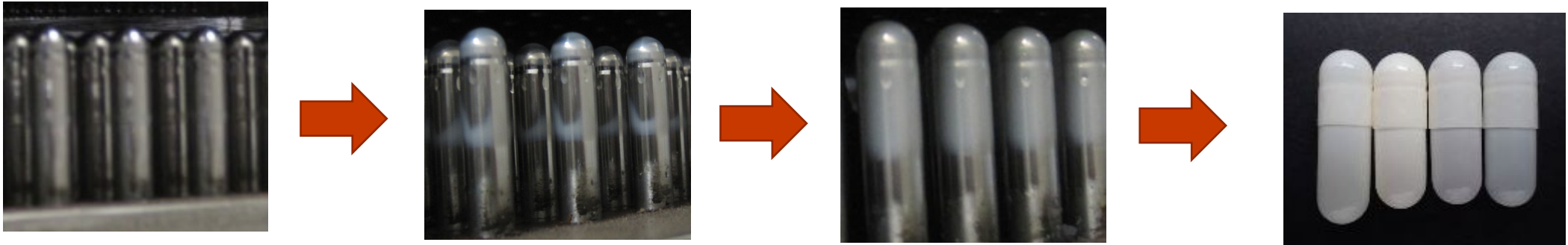
empty capsule white powder orange pellets black pellets
(From left to right in each photo)

- ⊕ Fully white, opaque
- ⊕ Complete light protection in the UV and visible spectra
- ⊕ Robustness and machinability attained
- ⊕ Dissolution/disintegration performance preserved
- ⊖ Phosphate salts NOT listed explicitly listed as food colorants (EU) or color additive (US)

Phosphate salts in hard capsules

Whiteness and opacity by crystallization

Salts are added during formulation, color is being formed in drying phase



Capsule composition and relevant regulatory references

Ingredient	Function	Regulatory References (EU, US)	
		Food	Pharma
Gelatin	Structural polymer	(EU) 853/2004, FCC	Ph. Eur, USP/NF
Tetrasodium pyrophosphate (Na ₄ P ₂ O ₇)	Colorant/Opacifier	(EU) 231/2012, FCC E 450(iii)	- (No Ph.Eur. or USP/NF monograph available)
Trisodium phosphate (Na ₃ PO ₄)	Colorant/Opacifier	(EU) 231/2012, FCC E 339(iii)	USP/NF (No Ph.Eur. monograph available)

There is no fits-it-all solution for TiO₂ replacement

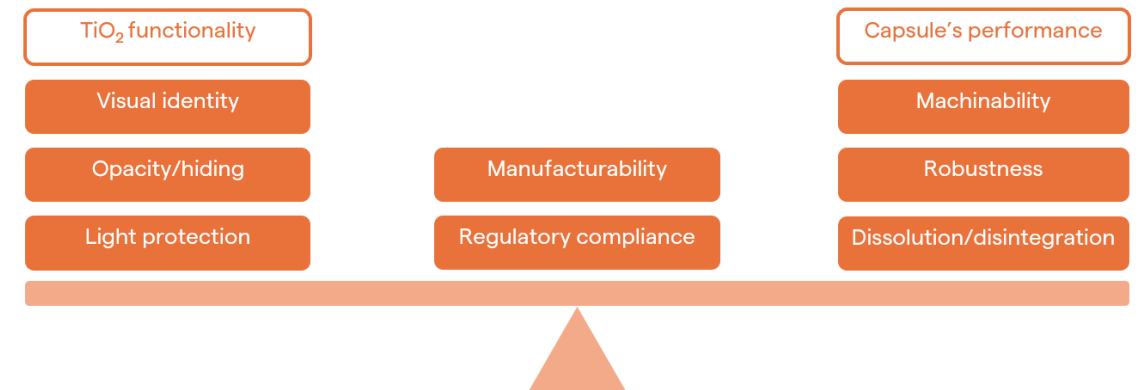
Where do we stand?

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There are strengths and opportunities in both proposed solutions, but they are not 1:1 match to TiO₂

- Different degrees of opacity and whiteness achieved
- Capsules general performance preserved
- Solutions are technical not broadly applicable
- Regulatory acceptance is not as broad as with TiO₂



- The TiO_2 ban has certainly created a void for the hard capsules industry which is difficult to fill because of technical and regulatory challenges
- Nevertheless, exploring various paths showed that there are solutions able to cover at least some of the market needs
- Having a TiO_2 alternative applicable 'across the board' will require joint efforts from different stakeholders

Thank you!

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