CBG MEB MEDICINES EVALUATION BOARD

TiO_2: risk assessment for pharmaceuticals

I. Koval, preclinical scientific assessor

K. Notenboom, quality assessor

Dutch Medicines Evaluation Board

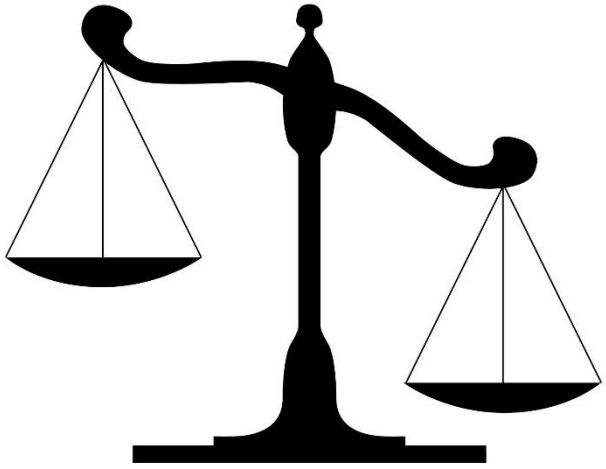
GOOD MEDICINES USED BETTER

Assessment of pharmaceuticals: benefit/risk ratio

EMA: the authorization of a medicine is recommended when the **benefits** are judged to be **greater** than its **risks**.

Benefits: favourable effects in relation to the target disease and population

Risks: undesired effects



Genotoxicity and carcinogenicity (1)

Carcinogenicity and genotoxicity: 2 endpoints relying on non-clinical data

For active pharmaceutical ingredients (API):

Genotoxicity: governed by **ICH S2**

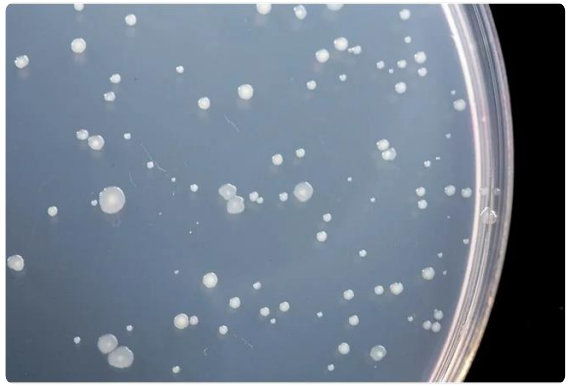
- Always required

Positive *in vivo* results would normally result in termination of development

Unless:

✓ mechanistic data demonstrate lack of clinical relevance

✓ A threshold can be identified



Exception: anticancer drugs (usually genotoxic drugs targeting rapidly dividing cells)

Genotoxicity and carcinogenicity (2)

For active pharmaceutical ingredients (API):

Carcinogenicity: governed by **ICH S1**

- Required for any pharmaceutical with expected clinical use of **at least 6 months**

Positive results would normally result in termination of development, unless clinical relevance can be ruled out or safety margins are very high

Exception: when the life-expectance in the indicated population is short (<2-3 years)

Genotoxic impurities

For impurities:

Governed by **ICH M7**

Known mutagenic carcinogens or known mutagens with unknown carcinogenic potential need to be controlled at **compound-specific limit**

or

at TTC of 1.5 µg/person/day

For a standard paracetamol tablet of 500 mg taken q.d. this would bring the maximal impurity content to 0.003% (3 ppm)

Refinement options

1) Less than lifetime exposure (LTL): table 2 from ICH M7

Table 2. Acceptable Intakes for an Individual Impurity

Duration of treatment	< 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5

This would bring the maximal content for a 500 mg tablet taken q.d. to 240 ppm

2) In anticancer pharmaceuticals (ICH S9): can be controlled at acceptable levels for non-mutagenic impurities

Conclusions

- Even in the context of risk-benefit approach, a genotoxic API without an identifiable treshold would not be approved, unless for anticancer treatment or when life expectancy is very short

- Genotoxic impurities need to be controlled at TTC level of 1.5 µg/day (3 ppm in a standard 500 mg tablet taken q.d.), unless in anticancer drugs

- In case of short use the maximal allowed content could be 240 ppm for a 500 mg tablet taken q.d.

- In practice this means that the use of TiO_2 could not be authorized, unless in anticancer drugs

Information on excipients

- Qualitative and quantitative composition of the product
- Selection of each excipient is justified with regard to **quality and safety**
  - *Dosage form*
  - *Quantities / concentration*
  - *Compatible with active substance and other excipients*

<u>Quality of excipients</u>

- Compliance with European Pharmacopoeia
- Regulations relating to **colourants** for medicinal products and foodstuffs are aligned.

Food additives and medicinal products: a legal link

- Directive 2009/35/EC: use of colours in human and veterinary medicinal products **IF** authorised in Annex II to Regulation (EC) No 1333/2008 on food additives

Consequences:

- Decision to delete TiO_2 from the list of authorised food additives is of paramount importance for its use as a colouring matter in medicinal products.

Technical uses of TiO_2

- **Colouring agent**

Enhances the white or accentuates other colours, making tablets easier to recognize by both healthcare professionals and patients.

- **Inert substance**

TiO2 is chemical inert, odourless and tasteless. It does not impact any property of the active substances of a medicine nor interacts with its excipients.

- **Typically less than 1mg per product per day**

Opacifying agent

Widely used in tablets directly as excipient or as part in special coatings, in hard/soft capsule shells.

Helps protect the active ingredients against UV/light degradation, and therefore improving the shelf life and stability of medicinal products.

Impact of change in formulation

- Composition of the product
- Coating weight or capsule shell weight
- Shape or dimensions
- Manufacturing process and process controls
- Release specification
- Analytical methods
- Packaging
- Shelf life and storage conditions

Data requirements

Data to support the change will depend on the type of product, role of the excipient in the formulation and the potential impact of the proposed change to the quality/safety/efficacy of the product, but could include:

- Usability: the change does not affect the differentiation between strengths and does not have a negative impact on taste acceptability for paediatric formulations
- Compatibility studies: new excipient should be compatible with drug substance and other excipients
- Comparative dissolution data: for solid dosage forms (tablets, capsules, etc.)
- Bioequivalence study: some excipient changes might affect bioavailability
- (Photo)Stability studies, at least three months data

Impact on medicinal products

- Reports from National Competent Authority databases and EU's Art 57 database indicate that there are **several thousand nationally authorised products per member state** containing TiO_2. There are also **hundreds of centrally authorised products** containing TiO_2
- It is **used frequently in oral solid dosage forms** (e.g., tablets, soft capsules, hard capsules, granules/powders for oral solution and oral suspensions).
- TiO2 is present in a **limited number of dosage forms administered via routes other than oral**, e.g., products for cutaneous, inhalation (capsule shells), oromucosal, sublingual, transdermal and vaginal use.
- It is present in **several essential medicines** for human including antidiabetics and antibiotics.

Conclusions

- **Widely used** as excipient in medicines (oral solid and semi-solid dosage forms)
- Mainly used as a **colour and opacifier - multiple functions**
- Each medicinal product will need **an individual review and assessment**, which will require investigation of suitable alternatives, reformulation, generation of new data related to manufacture and stability, and potentially new comparative dissolution and clinical data.
- **Global dimension** and impact on **availability**

CBG MEB

MEDICINES EVALUATION BOARD

GOOD MEDICINES USED BETTER

Main elements of Regulation

- Commission **committed to review** the necessity **to maintain titanium dioxide (E 171) or otherwise delete** it from the Union list of food additives for use as a colour in medicinal products **within three years after the date of entering into force** of this Regulation.

- **Updated EMA assessment by 1st April 2024** – Progress made to develop alternatives in new and already authorised products, impact on quality, safety, efficacy & availability

✓ **Maintain** the use of titanium dioxide in medicinal products, ***provisionally***
✓ Pressure on the pharmaceutical industry to develop alternatives