

USE OF TITANIUM DIOXIDE AS EXCIPIENT IN VETERINARY MEDICINES- INDUSTRY FEED BACK TO QWP EXPERTS/EMA QUESTIONS

QUANTITATIVE USE – DATA FROM EGGVP & ANIMALHEALTH EUROPE:

- EGGVP: 10 out of 25 MAHs are concerned
- AnimalhealthEurope: These figures are partial as not all MAHs have answered the survey. So, the figures provided below are very likely underestimated but give a first indication of the magnitude of the problem.
- EGGVP: Over 800 MAs use of TiO₂ as an excipient in the EU
- AnimalhealthEurope: About 800 MAs in the EU use TiO₂ as an excipient (for those companies who provided feedback). In that data, please note that there are a number of bee products which do contain titanium dioxide, e.g. Checkmite (7 MAs) or Polyvar (22 MAs). These products both involve a polymer matrix which contains TiO₂. Although these products were included in the count provided (no need to change the quantitative part), it is sufficiently important to specifically highlight these dosage forms as these products are critical for the health of bees and this do merit a change of the report from a qualitative perspective.
Note: It is important to mention that some MAHs are global. Therefore, based on corporate and ethical standards, those companies would act in this case worldwide, rather than EU specific only.
- EGGVP: MAs are both generic but also full dossier / WEU
- AnimalhealthEurope: Innovator products, OTC and prescription medicines.

QUALITATIVE USE:

- MAs cover the following therapeutic areas and indications
 - antiparasitic/anthelmintic
 - antibiotics
 - antidiarrheal
 - antipruritic
 - diuretic
 - peripheral vasodilator
 - antiadrenal and antithyroid.
 - Ectoparasite (neck collar)
 - Improvement of peripheral and cerebral vascular blood circulation
 - Improvement in dullness, lethargy and overall demeanour
 - Skin cancer
- Animal species:
 - Non-food producing species mainly: dogs and cats. Also horses.
 - Also minor species: pigeons, ornamental birds and zoo birds.

- Food producing species (less common): swine and poultry, cows and calves
- Purpose
 - coating agent,
 - colouring agent
 - UV blocker
- Presentations
 - Tablets
 - Capsules
 - collars
 - premixes
 - ointments
 - oral pastes

ALTERNATIVES:

Majority respondents not aware of recognized direct replacement. No feasibility assessment for alternative options is currently available as opacity, intensity of colours and protecting properties will not be comparable to TiO₂ containing formulations.

For tablets: higher coating levels (i.e. percentage of weight gain) will be required to hide API / dark substrate colour and/or to achieve comparable opacity; this may have impact on the resulting dissolution profiles of the film-coated tablets.

Photostability and palatability challenges cannot be excluded, that could lead to further product development being required. Use of less opaque coatings may impact photostability of API / tablet formulation potentially leading to less shelf life. Where TiO₂ is used as a UV-filtering or coating agent, TiO₂ is a critical excipient for the stability of the active substance in the final formulation.

TIME and COST:

Reformulation – if possible at all - would take significant time and investment to conduct the development and validation work to make the change in the formulations and receive regulatory approvals for the affected products – risk for MAs the value of investments could be disproportionate -> subsequent MAs withdrawals.

- A. if MA can justify there is no change of functional characteristics in the pharmaceutical form:
 - reformulation: 9- 12 months
 - new ingredient validation (including new supplier qualification, new analytical method qualification): 6 months
 - dissolution kinetics and stability assessment: 8 months
 - Analytical method evaluation: 6 to 9 months
 - Validation batches: 3 to 6 months stability before release Regulatory documentation preparation per formulation: 9 months

➔ Realistic case scenario: 3 to 4 years per product
- B. if MA cannot justify the absence of change of functional characteristics in the pharmaceutical form a bioequivalence study must be conducted (18 months).
- ➔ Realistic case scenario: ~5 year per product

If alternatives to TiO₂ are novel excipients, the overall timelines will increase significantly: a full pre-clinical safety package would be needed.

Finally, it should be noted that such a change will have to be done for all the countries in which the products are sold and could also involve additional country-specific requirements.

Cost: This is very hard to estimate without any idea of suitable alternatives but the cost and time associated with identifying, testing and validating an excipient could be significant and not economically viable for all impacted products.

AVAILABILITY:

TiO₂ is a critical excipient used in commercialized veterinary medicines. Potential supply disruption would be critical for majority of VMPs for which no alternative is possible / it is not known if re-formulation possible / if extended manufacturing trials are required. Supply of these product is critical and any suspension or recalls should be avoided.