Silver Tox Experts (TE) Call

Draft minutes, Call 10 October 2019 (10:00-11:00 CET)

1 Welcome and Introduction

1.1 Reminder on Confidentiality and Competition Law

Participants were reminded on their obligation to comply with Confidentiality and Competition Law.

1.2 Tour de table and apologies

The list of participants is available in Annex 1.

1.3 Approval of the agenda

The agenda is available on slide 3 in Annex 2. No remarks / additions; agenda approved.

1.4 Approval of the minutes of the last call (20 Sep 2019) and status of action points

Minutes of the call of 20 September were approved. A table with the status of the action points from this meeting is available on slide 4 in Annex 2. All action points have appropriately been addressed or are ongoing, or will be discussed during the call.

2 TK study test design

2.1 Selection test articles

- **AgMPs**: member companies were consulted to collect the most up-to-date information on produced micron-sized Ag forms. Based on this, the EPMF secretariat selected a possible candidate for TK testing: cf. slide 6 in Annex 2. This is a spheroidal shaped AgMP form with the lowest particle size distribution (PSD), seemingly uncontaminated by nanoforms (TBC) and which shows good uniformity. Further information on phys-chem parameters will be requested from the relevant company (e.g. coating type if present, hydrodynamic properties, …). Based on size, this is the worst case selection. However, it is a crystalline form and it is noted that amorphous forms generally have a different absorption profile so this may not be the worst case AgMP selection overall. More information on AgMP behaviour in media and dissolution may be available from US agencies / standards organisation data. **The TE agree to the collection of further information on the selected crystalline AgMP form and an amorphous AgMP form, before performing lab characterisation work to check which form is worst case.** **AP1-3**
- **AgNPs**: It has been confirmed that there are technical issues with the availability of the smallest REACH registered AgNP. During the previous TE call, it was agreed that the use of a certified reference material (CRM) used in authority programmes (e.g. OECD) would be a good alternative. Following the call, Mark Raffray circulated an overview table with possible CRM options: cf. slide 9 in Annex 2. For the NM-300K, cost is acceptable and the material is readily available. The surfactant in this material doesn't cause an issue but will influence the control to be used in the TK study.

  (Post-meeting note: Covance opinion is that surfactant levels are tolerable but will perform calculations on anticipated dosing formulations (especially for i.v. route).)

  For the nanoComposix materials, concentration may be too low to allow sufficiently high dose levels in the TK study (we might not be able to prove linearity if we don't dose high enough). For this reason,

the TE agree to select the NM-300K material for the TK study, unless the nanoComposix materials can be provided in higher concentrations. AP4

(Post-meeting note: NanoComposix stated that they are unsure about the stability of solutions higher than 3 mg/ml. They could also provide powder forms but for the amounts we would need for the TK study, pricing is not acceptable.)

2.2 Selection dose levels

Cf. slides 11-14 in Annex 2. Based on the available data from previous studies (mainly the ESTF $AgNO_3$ study and the Boudreau study with AgAc), the TE agreed on below dose levels for the **repeat dose TK segment**:

- **AgAc**: 175 – 55 – 5 mg/kg bw/d. This is in line with the DRF dose levels to support interpretation of the DRF but the low dose has been lowered to match the predicted NOEL for significant Cu/Cp oxidase effects.
- **$AgNO_3$**: 125 – 55 – 5 mg/kg bw/d. This is in line with the dose levels for AgAc but the high dose has been lowered for reasons of tolerability / to decrease the risk of losing this group because of general toxicity (absence of dose-setting information in repeat dose scenarios > 100 mg/kg bw/d; known steep dose-response for $AgNO_3$ incl. local tissue reactivity and potential for GI tract damage).
- **AgMP**: 1000 – 180 – 36 mg/kg bw/d. The high dose has been aligned to the limit dose with the expectation that this will improve our defence position as AgMP bioavailability is anticipated to be much lower. The low dose is equivalent to the mid dose for AgAc/$AgNO_3$ for reasons of comparability (= assumed reprotox benchmark dose based on Ag equivalent value).
- **AgNP**: 360 – 36 – 3.6 mg/kg bw/d. Mid dose equivalent to mid dose for AgAc/$AgNO_3$ for reasons of comparability (scaled to Ag equivalent doses). High dose expected to be above LOAEL but below MTD, with only mild toxicity anticipated based on previous studies.

Dose levels for the **single dose TK segment** (p.o. and i.v. administration) will be determined in consultation with the CRO (Covance) supported by the TK study monitor. AP5

(Post-meeting note: Covance opinion is that chosen dose levels for the repeat dose TK segment appear workable and justified. For the single dose TK segment, Covance will provide recommendations but proposed to simplify to a single i.v. route treated group per test article.)

Annexes

1. List of participants
2. Slides presented at the call

Actions

Table 1. Actions agreed at the 10 October 2019 Ag Tox Experts call

	What?	Who?	When?
Ag TK testing			
1.	Collect further information on phys-chem characterisation of one crystalline and one amorphous AgMP form from relevant companies	EPMF Sec	ASAP
2.	Check information on AgMP behaviour in media and dissolution from US agencies / standards organisations	EPMF Sec	ASAP

3.	Perform phys-chem characterisation of selected AgMP forms if not yet available	EPMF Sec	After AP1-2
4.	Order NM-300K test material for TK testing, preferably through BAM or similar organisation to get pre-characterised material	EPMF Sec	ASAP
5.	Suggest dose levels for the single dose phases of the TK study for TE agreement	M. Raffray	After discussion with Covance

Annex 1: Participants

Katrien ARIJS, consultant for EPMF (ARCHE, Belgium)

Lindsay AVEYARD, Consultant, GPC Consulting Ltd (United Kingdom) - reprotox study monitor

Arno BUTHE, Heraeus (Germany)

Eliot DEAG, Johnson Matthey (United Kingdom)

Rikki GORDON, Johnson Matthey (United Kingdom)

Olga LEMKE, BASF (Germany)

Jelle MERTENS, EPMF (Belgium)

Mark RAFFRAY, Consultant, Raffray Biosciences Ltd (United Kingdom) - TK study monitor

Nissanka RAJAPAKSE, Johnson Matthey (United Kingdom)

Steven VERBERCKMOES, Umicore (Belgium)

Sven WAECHTER, Doduco (Germany)