

Precious Metals and Rhenium Consortium Rhenium Work Group Meeting

6th December 2011, 4:30pm-7:00pm CET

1. Welcome and introduction

Angela Alderman & Caroline Braibant

Welcome and introduction

- Confidentiality and Competition Law
- Approval of the agenda
- Actions agreed at and approval of the minutes of the last meeting

Actions agreed at the 28 Jan 2011 Re WG conference call

Action	Who?	When?
Launch admin/contractual discussions with Harlan and Covance to allow early start of <i>in vitro</i> , sensitisation and mutagenicity tests	WCA and CB	Early Feb 2011
Launch APR sample request for <i>in vitro</i> , sensitisation and mutagenicity tests	CB	Early Feb 2011
Meet with Covance and Charles River to discuss dose range finding study and combined 28-day repeated dose oral toxicity and reproductive toxicity screen test in further detail	WCA, A. Alderman and M. Raffray	ASAP in Feb 2011
Formulate recommendation based on outcome of meetings with Covance and Charles River	WCA	ASAP in Feb 2011
Evaluate WCA's recommendation and decide whether to work with Charles River or Covance (in which case a possible discount should be discussed) + hold conference call if questions arise/discussion is needed	Re WG	ASAP in late Feb/early Mar 2011
Launch admin/contractual discussions with Charles River or Covance (including review of costing) to allow start of repeated dose tests in Q2	WCA and CB	ASAP in early Mar 2011
Launch APR sample request for repeated dose test	CB	Early Mar 2011
Follow-up testing programme to ensure availability of <i>in vitro</i> , sensitisation and mutagenicity test final results and repeated dose preliminary results for discussion at Dec 2011 Re WG meeting	WCA	Ongoing

Actions agreed at the 21 June 2011 Re WG conference call

Action	Who?	When?
Check whether <i>in vivo</i> mutagenicity test is subject to a testing proposal or whether it can be conducted upon unilateral decision of PMC.	WCA	In due course / if needed
Proceed with evaluation, approval and signature of contractual terms and conditions and protocol.	WCA and PMC secretariat	Jun/Jul 2011
Request Harlan to send the (~ 1 g) sample to LAB.	WCA	ASAP
Check whether CSR is required on the basis of hazard or classification.	WCA and PMC secretariat	ASAP
Prepare list of studies used to derive and support Re classifications.	WCA	15 Jul 2011
Circulate list of studies used to derive and support Re classifications to Re WG for information.	PMC secretariat	End Jul 2011
Revert to interested company with preliminary confirmation and prepare Licence to Use Agreement for discussion with/approval by Re WG.	PMC secretariat	B4 15 Sep 2011

Actions agreed at the 27 Oct 2011 Re WG conference call

What?	Who?	When?
Schematise the steps and work phases involved in the Repeat Dose/Reprotoxicity test package	WCA	ASAP
Discuss the likelihood for PEG400 to enhance the hydrophilicity, bio-availability and/or bio-accumulation of APR at an <i>ad hoc</i> conference call	WCA and PMC experts	2 Nov pm or 4 Nov am (2011)
Inform PMC on confirmed schedule	WCA	ASAP
Consider the need to perform an acute oral toxicity study	WCA	After finalisation of range-finding study and/or repeated dose study
Determine which method should be used to determine the particle size of potassium perrhenate	WCA + PMC	ASAP
Check ID Cards (especially composition) and revert with comments, corrections or comments to rondepierre@epmf.be	Re WG	End Nov 2011
Read the front page instructions and complete the questionnaire, circulate the use survey to downstream users and collect responses to it, and submit all completed questionnaires to minako.tallen@wca-environment.com	Re WG	End Nov 2011
Prepare Agenda 6 Dec 2011 Re WG meeting and include: <ul style="list-style-type: none"> - Overall progress of testing programme - Outcome of discussion on vehicle selection - Present steps and phases of Repeat Dose/Reprotox study - Confirm schedule of testing programme - Review compositions and agree on ID Cards - Review uses reported to WCA 	CB	End Nov 2011

To be discussed today/on-going

- Follow-up testing programme to ensure availability of *in vitro*, sensitisation and mutagenicity test final results and repeated dose preliminary results for discussion at Dec 2011 Re WG meeting
 - Schematise the steps and work phases involved in the Repeat Dose/Reprotoxicity test package
 - Discuss the likelihood for PEG400 to enhance the hydrophilicity, bio-availability and/or bio-accumulation of APR at an *ad hoc* conference call
 - Inform PMC on confirmed schedule
- Consider the need to perform an acute oral toxicity study
- Read the front page instructions and complete the questionnaire, circulate the use survey to downstream users and collect responses to it, and submit all completed questionnaires to minako.tallen@wca-environment.com
- Revert to interested company with preliminary confirmation and prepare Licence to Use Agreement for discussion with/approval by Re WG.
- And more...

2. Decision on vehicle selection for combined repeat dose/reprotox testing on APR

All

Choice of vehicle for OECD 422 study (1)

- definition in the TG

- Where necessary, the test substance is dissolved or suspended in a suitable vehicle. It is recommended that, wherever possible, the use of an aqueous solution/suspension be considered first, followed by consideration of a solution/emulsion in oil (e.g. corn oil) and then by possible solution in other vehicles. For non-aqueous vehicles the toxic characteristics of the vehicle must be known. The stability of the test substance in the vehicle should be determined. (OECD TG 422)
- **OBJECTIVE:**
 - Achieve significant exposure to characterise toxicity profile
 - Acceptable stability, homogeneity and ease of formulation
 - Dosability
 - No adverse effects of vehicle on test species

Choice of vehicle for OECD 422 study (2)

– Outline of history

- Choice of vehicle has been discussed with CRL (since July 2011).
- Water and corn oil were unsuccessful to formulate APR, by visual inspections.
- PEG400 was recommended by CRL as an alternative vehicle. PEG400 (40% in water) formulates a clear 'solution' of APR. Analysis in 40% PEG400/water (ICP-MS method to be most suitable method) showed that the solution to be stable for at least 10 days.
- Questions were raised by a member of the Working Group about the suitability of PEG 400 over a concern that it may potentially enhance bioavailability (27th Oct 2011). Project is currently on-hold.
- Hydroxypropyl methylcellulose (HPMC) was suggested by PMRC as a more appropriate vehicle for inorganic metal compounds (28th Nov 2011).
- Trial formulation in HPMC prepared by CRL showed that 0.5% HPMC produced an appropriate formulation (clear 'solution') of APR (visual inspection). Although the analytical development needs to be performed, this vehicle seems to be a possible alternative vehicle for APR (30th Nov 2011).
- Draft report to be issued at the end of Nov 2012, if HPMC is agreed and appears to be successful.

Choice of vehicle for OECD 422 study (3)

- discussion surrounding PEG400

PEG may over-express the potential toxicity of APR , based on the following findings for nanoparticles (Traxys, 1st Dec 2011).

- PEG is referred to pegylated surfactant polymer, and as such, as a synthetic non-ionic amphiphilic molecule (both hydrophilic and hydrophobic).
 - PEG is used to increase a molecule's *furtivité* (stealth), which allows the molecule to somewhat escape the immune system and prolong its half-life.
 - PEG is generally used because it is biocompatible, soluble in aqueous media, non-toxic, and a low immunogenicity and antigenicity.
 - PEG-coated nanoparticles or formulations of nanoparticles in PEG are used as potential drug delivery devices because of its ability to circulate for a prolonged period time and target a particular organ.
-
- Relevance of the above findings for nanoparticles to APR should be discussed.
 - PEG and CMC are considered to be suitable vehicles for organic substances. For inorganic substances, HPMC seems to be better (PMRC, 28th Nov).

Choice of vehicle for OECD 422 study (4)

- discussion surrounding PEG400

- Concerns surrounding enhanced bioavailability from use of PEG400 arise from studies using nanoparticles
- Nanoparticles are suspected of having their own unique properties with regards to bioavailability thus confounding the argument
- MMAD of APR is $\sim 138 \mu\text{m}$; therefore not comparable to a nanoparticle
- A known consequence of using PEG400 can be tissue vacuolation – this is taken into account during histopathology investigations
- The purpose of vehicles is to make test substance available therefore 'bioavailability' is a common theme to all

Choice of vehicle for OECD 422 study (5)

- Other considerations

- Bioavailability in the acute oral study – APR 'dissolved' in vegetable oil (no analysis was performed for the formulation; assumption could be made that the formulation was probably not an homogenous suspension): LD50 > 2000 mg/kg bw – no signs of toxicity from systemic absorption.
- NOAEL from 7 day drf in an agreed vehicle can be compared to the LD50 in vegetable oil to assess potential of enhanced bioavailability (JM, 18th Nov).
- *In vivo* study for toxicokinetic behaviour – expensive. Argument from animal welfare point of view.

Choice of vehicle for OECD 422 study (6)

- PEG400 and HPMC

- Both PEG400 and HPMC form clear dosing formulations, which are probably microemulsions rather than suspensions. This infers that the potential for enhancement of bioavailability could apply to both vehicles.
- CRL has experience of using both PEG400 and HPMC.
- Any known toxicity of vehicle is taken into account when study results for APR are interpreted (*e.g.* vacuolation by PEG400).

3. Status of testing programme

WCA

Study status for rhenium project

Appendix Rhenium study status & 422 for APR_2011_11_30

(APR)

- LLNA (Harlan), HLM (Covance), MLA (Covance), Isolated chicken eye (LAB), *in vivo* eye (Harlan): either finalised, draft report issued or experiment completed.
- Results of ICE and *in vivo* eye irritation (draft results) suggest that APR does not meet the criteria for classification for eye irritation.
- Ongoing study: reprotox

(Re)

- Ongoing study: bio-elution

(Potassium perrhenate)

- Ongoing study: PSD

4. Budget increase justification

All

Budget increase justification

Administrative work not sufficiently budgeted for:

- Assuming wca would not include communication with the sponsor for extended document approvals
- In terms of administrative burden the greatest time consumer has been dealing with the supply of test material. Joint effort between PMRC secretariat and wca to resolve sample supply issues

Work that was unforeseen:

- Low solubility of the test material requiring to cancel initial *in vitro* eye irritation study at Harlan and finding an alternative CRO
- Discussion on suitable test substance vehicle for the repeat-dose study at Charles River Laboratories (CRL) and suitable analytical test house
- Discussion on validity of the acute oral study based on corn oil analytics and potential need to repeat this test
- Inclusion of rhenium in the bio-elution test programme

Work still to be completed:

- Finalisation on suitable vehicle for the repeat dose/reproscreen study (with possibility of further analytical validation studies)
- Discussion and agreement on dose level selection for the definitive study
- Study monitoring to include possibly a site visit to review data and for quality assurance purposes
- Final Reports (analytical validations, dose range finding study, main study) review and any iterations required
- Bio-elution study monitoring and data assessment
- Possible acute oral toxicity study to be commissioned and monitored
- Final report review – *in vivo* eye irritation study

5. IUCLID 5 filling progress

5.1. ID cards, identification and sameness – way forward

ID Cards

- Meant as reference for identification and sameness
- Summarise REACH strategy: status, tonnage, classification, deadline, etc.
- To be used internally and externally (with SIEFs)
- Important to check relevance of content - especially composition:
 - Model coming from Ag and Refinables: are impurities listed relevant for Re materials?
 - Impurities: classification of Re material derived for high purity profiles; if impurities present which affect classification → companies to derive specific classifications and inform PMC!

Identification and sameness

- Via ID Cards
- On the basis of technical data on our materials (cf. Heraeus' proposal):

Compound	CAS	form	Parameter	Method
1) Ammonium perhenate	13598-65-7	solid	Elemental Analysis	a) ICP-OES
			identity (moleculare structure)	a) XRD
				b) IR spectroscopy/ KBr
			particle size	a) laser diffraction
			surface area	a) N-BET
2) Perrhenic acid	13768-11-1	solution	Elemental Analysis	a) ICP-OES
			identity (moleculare structure)	a) Raman spectroscopy
3) Potassium perrhenate	10466-65-6	solid (powder)	Elemental Analysis	a) ICP for Re
			identity (moleculare structure)	a) XRD
				b) IR spectroscopy/ KBr
			particle size	a) laser diffraction
			surface area	a) N-BET
4) Rhenium	7440-15-5	solid (pellets)	Elemental Analysis	a) ICP-OES
			Identity (moleculare structure)	a) XRD
			Particle size	a) Sieving
5) Rhenium	7440-15-5	solid (powder)	Elemental Analysis	a) ICP-OES
			identity (moleculare structure)	a) XRD
			particle size	a) laser diffraction
			surface area	a) N-BET

5.2. Update on use questionnaires

Data input in IUCLID

- Use information:
 - APR from 1 company (1 use);
 - Rhenium metal from 1 company (1 use);
 - Sodium rhenate from 1 company (1 use).
- RSS for APR: LLNA, ICE, MLA, HLM

6. Timeline

WCA

Overall timeline

Project Phase	Task	Current timelines	Previous timelines
III	Phy/Chem testing	31.12.11	31.12.11
	- Particle size distribution		
	Mammalian toxicity testing and report preparation		
	- Bio-elution testing, surface measurements	01.03.12 - 31.05.12	
	- <i>In vitro</i> / <i>in vivo</i> eye, skin sens, genotox	- 30.01.12	20.01.12
	- Reprotox, (acute tox)	- 15.09.12	31.05.12
IV	(Environmental modelling)		
	Composition, use pattern	01.11.11 - 28.02.12	01.11.11 - 28.02.12
V	Occupational modelling and S. 9 & 10 CSR	01.09.12 ^{*1} - 31.12.12	01.04.12 - 31.07.12
	CSA/CSR (as required)	11.12 - 02.13	07.12 - 31.10.12
	(PNECs)		
	DNELs	01.09.12 - 30.11.12	01.04.12 - 30.06.12
	Dossier available for review by the lead registrants	<u>29.02.13 (if CSR is required)^{*2};</u> <u>31.12.12 (if CSR is not required)</u>	31.10.12

*1 Based on the assumption that the draft test results are available by this date.

*2 Timeline is dependent on receiving the reprotox study results.

7. AOB, next meetings and closing remarks

Angela Alderman

- AOB?
- Next meetings and calls – Q1 2012 and Jun 2012?
- Closing remarks

THANK YOU!