Chairperson: A. Alderman (Johnson Matthey)
Secretariat: C. Braibant (EPMF)

6December 2011, 16:30 – 19:00
MetalsConference Centre
Rue du Duc 100 – 1150 Brussels (BELGIUM)

MINUTES

AP refers to Action Points listed at the end of this document

1. **Welcome and Introduction (including progress on agreed actions at past meetings and calls).** The participants (Annex 1) were reminded on their obligation to comply with confidentiality rules and Competition Law.
   All actions agreed atthe last three conference calls (cf. slides 4-7 of Annex 2)have been completed and/or will be discussed during the meeting with the exception of the preparation of a Licence to Use for entities wishing to use data from the Registration Dossier and/or CLP notification, which should be completed in early 2012 (AP1).
   Considering the very recent circulation of the minutes of the last conference call (27 Oct 2011), thesewill be subject to approval at the next Re WG meeting or conference call (AP2). The Agenda for the meeting were approved.

2. **Decision on vehicle selection for combined repeat dose/reprotox testing on APR.** Following the impossibility to achieve the formation of a stable and homogeneous solution or suspension using water and corn oil, Charles River, WCA and the chairpersons of the Re WG and TAP agreed to use PEG400 instead.
   At the 27 Oct 2011 Re WG conference call, the possibility for PEG400 to enhance the bio-availability of APR and hence the potential for PEG400 to lead to an overexpression of APR's effects was discussed. This supposition is based on research publications having facilitated the administration of drugs by coating nanoparticles or formulations of nanoparticles containing active ingredients with PEG400. The aim of the PEG400 coating in such research programmes would be to allow the pharmaceutical molecule to escape the immune system in order to reach the target organ before it is somehow released from the virtual capsule created by the PEG400 coating and generates the desired pharmaceutical effect. It was therefore alleged that APR administered via a PEG400 solution could reach organs and have effects which would have been contained or controlled by the immune system in the event it would have been administered using another vehicle.
   Following lengthy exchanges the following was agreed:
   - As a first choice, authorities expect an aqueous solution to be used (which also enhances the absorption of APR), unless this proves to be unfeasible
   - Water and corn oil did not work: administering APR in water or corn oil could have led to underestimation of toxicity due to the fact that APR did not form a stable and homogeneous solution in either of them
   - Any other vehicle may increase the bio-availability of APR as the aim of using these vehicles is to produce a stable and homogeneous dose to be administered (even if APR would probably not form such a stable and homogeneous suspension or emulsion under normal conditions of use)
   - Carboxy methyl cellulose (CMC) and similar vehicles would tend to produce a suspension rather than a solution
   - PEG400 and Hydroxypropyl methylcellulose (HPMC) produce a fully homogeneous solution (+ micro-suspension) which is good and allows a reliable handling; for PEG400 however, ICP-MS analysis has been performed already and confirms the stability of the solution (this latter information on HPMC is not yet available and would required additional analysis and related costs)
   - A known consequence of using PEG400 can be tissue vacuolation: this will be fully taken into account during histopathology investigations
   - PEG400 and HPMC arefully guidance-compliant and have therefore higher chances of regulatory acceptance

- The results of the dose-range finding study with PEG400 will be used as a check-point to determine (in addition to the above arguments) whether or not PEG400 is the right vehicle to be used
- Any toxicity observed will be considered in relation to the doses administered to determine whether they fit an expected pattern. If unusual or exaggerated responses are observed, then further assessment of the suitability of PEG400 will be made.

3. **Status of testing programme (incl. physic-chemical, ecotox and mammtox).** Slide 3 of Annex 2 summarises the status of the testing programme of the Re project. None of the finalised tests have identified any hazard. The only on-going tests are the granulometry/dustiness and combined repeat dose/reprotox study. The bio-elution test on rhenium will most probably commence in March 2012, once the sample preparation has been agreed and a test houseresponsible for sample preparation identified. Although it is commencing later than expected, it is not affecting the overall timeline of the Re project which is led by the combined repeat dose/screening reprotox study for which results are not expected before end 2012.

4. **Budget increase justification: remaining questions from Re WG and way forward.** After the 27 Oct 2011 conference call some Re WG members expressed the need to better understand how the Re project budget for testing monitoring had increased. In follow-up of this request, WCA drafted a response which is summarised in slide 18 of Annex 2. The Re WG appreciated the level of uncertainty/learnings involved in this pioneer project and accepted the budget increase.

5. **IUCLID 5 filling progress**

   5.1. **ID Cards, identification and sameness - way forward.** One ID Card has been prepared for each in-scope Re substance and intermediate. Such ID Cards were prepared on the basis of the template used for the Ag and Refinables ID Cards and completed on the basis of information available to the PMC secretariat and the comments of the Lead Registrants. The Re WG members were requested to take a final look at the ID Cards, and at the composition tables more particularly, and to submit comments to PMC secretariat by the end of January 2012 (**AP3**).Members were reminded on the need to derive an individual classification for their materials in the event it would contain impurities other/in higher concentrations than what is typically present in the same material manufactured or imported by another potential registrant. The ID Cards will then be finalised and circulated to the Assembly for approval, before they are sent to the relevant SIEFs for information and uploaded onto the respective IUCLID 5 files for reference.
   Overall, the aim of the ID Cards is to be used as a reference in substance identification and sameness discussions. For the sameness check to take place, each potential registrant is therefore invited to generate the information listed in slide 22 of Annex 2 (**AP4-6**) and to make this information available to PMC secretariat/WCA, who will perform a screening sameness check and highlight any major issues. As regards particle size, it was made clear that some additional techniques should be recommended to the Re WG participants in the event they are require to measure the particle size and surface area of materials potentially fulfilling the definition of nanomaterial in accordance with the definition recommended by the European Commission in Oct 2011 (**AP5**).

   5.2. **Update on use questionnaires.**Due to the late sending of the questionnaire by the PMC

secretariat, only a few responses have been received by WCA so far (AP7). Meanwhile the remaining use questionnaires are sent to WCA, WCA is continuously preparing and uploading allrequired robust study summaries into the respective IUCLID 5 files.

6. **Timeline.** The overall timeline of the Re project is available in slide 26 of Annex 2. As indicated above, the timeline is led by the timing of the combined repeat dose/screening reprotox study for which results are not expected before end 2012. On the basis of the results of this study, WCA will be able to confirm whether a CSR is required (hence pushing the registration of APR to later) or not (allowing a registration submission for all Re substances and intermediates in early 2013).

7. **AOB, next meetings and closing remarks.** No other business was raised. The next conference call of the Re WG will take place on 28 Mar 2012 at 3 pm CET. The need for/date of a conference call in Jun 2012 will be discussed at the Mar 2012 conference call. The next face-to-face meeting of the Re WG will take place in Brussels on the evening of 5 Dec or on the 6 Dec 2012, back-to-back with the PMC Assembly meeting.

Annexes:

1. Agenda and list of participants
2. Slides presented at the meeting

Table 1. Actions agreed at 6 Dec 2011 Re WG meeting in Brussels

	What?	Who?	When?	Status by 26 Mar 2012
1.	Prepare LtU Agreement to share Re and Re compounds data with non-PMC Members	CB+LWG	Q1 2012	DONE
2.	Include approval of 27 Oct 2011 conference call minutes in the Agenda of the 28 Mar 2012 conference call	CB	Feb 2012	CC cancelled – action postponed
3.	Provide comments on ID Cards circulated before the meeting, and especially on proposed composition and impurities/classification to rondepierre@epmf.be	Re WG	Jan 2012	REMINDER
4.	Determine which parameters should be determined for sodium rhenate and update table in slide 22 of Annex 2	Re WG + CB	Jan 2012	DONE(*)
5.	Update table in slide 22 of Annex 2 with techniques to measure particle size and surface area of materials which may fulfil the COM Oct 2011 recommended definition of nanomaterial	CB	Mar 2012	IN PROGRESS, kick-off meeting of Nano TF held on 26 Mar 2012
6.	Send results of measurements made as per techniques listed in slide 22 of Annex 2 to braibant@epmf.be and Minako.TAllen@wca-environment.com to be used in the sameness check	Re WG	Mar 2012	REMINDER
7.	Send completed use questionnaire to rondepierre@epmf.be	Re WG	Jan 2012	REMINDER

(*) The following is proposed:

- ICP-OES for impurities

- ICP-OES for Rhenium (unless a suitable gravimetric method exists)
- Raman Spectroscopy for molecular structure or UV visible spectrometry (e.g. measurement of molar extinction coefficient at a particular concentration at a specified wavelength)