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Mn Consortium management: How Things Get Done

Dr Derek J Knight
Director of Regulatory Affairs

**SafePharm
Laboratories**

Testing for a Safer Future

www.safepharm.co.uk

**Manganese REACH Workshop, Renaissance London Heathrow
Hotel, 10 October 2007**

SUMMARY

- Safepharma Laboratories Ltd have a Master Services Agreement to give a ‘turn-key’ registration and testing service.
- We with the Consortium Manager, the IMnI staff and consultants responsible for REACH, the REACH Technical Committee etc will provide input to the IMnI REACH Steering Committee as required.
- We provide studies under a Testing Master Services Agreement.

REACH PHASE-IN CHEMICALS OFFICE

- John Hislop BSc, Registration Supervisor (13 years experience)
- Jonathan Dale BSc MSc, Senior Registration Officer (5 years experience), on the RIP 3.3 acute toxicology WG
- Dr Ana Gomez, Registration Officer BSc PhD (with extensive registration experience)
- Christantus Tabi LLB MA, Trainee Registration Officer (with a masters degree in international law)
- 6 Trainee Registration Officers (including 1 vacancy)
- Trainee Registration Officers undertaking the Post-graduate Certificate in REACH Management at the University of Hull

SUMMARY OF REACH

- REACH: Registration, Evaluation & Authorisation (and restriction) of Chemicals
- Gradual loss of distinction between new and existing chemicals
- Review programme prioritised by tonnage & key hazardous properties
- Registration with safety data depending on tonnage
- Use existing data & surrogate data (e.g. groups and categories)
- Further higher tier testing of substances at 100 and 1000 tonnes per annum
- Data sharing, SIEFs & OSOR (one substance, one registration)
- Authorisation of uses for very high concern substances: no extra data
- Guidance: RIPs (REACH Implementation Program projects)

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ENTERING THE REVIEW PROGRAMME

- Pre-register phase-in substances June to November 2008
- ECHA data base by 1/1/09
- New manufacturers/importers can pre-register up to 12 months before the registration deadline.
- SIEF of companies supporting the substance until 1/6/18
- Mandatory sharing of old & newly-commissioned data with cost sharing
- OSOR, with opt-outs, for main registration dossier
- 12-year data protection, with cost sharing for use by new registrants

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REGISTRATION

- Register to European Chemicals Agency (ECHA)
- Phase-in for *ca* 30,000 existing substances:
(Pre-registration 1 June – 30 November 08)
 - Cat 1 and 2 CMRs at ≥ 1 tpa: 3 years, 6 months (1 December 2010)
 - R50/53 substances at ≥ 100 tpa: 3 years, 6 months (1 December 2010)
 - All substances at $\geq 1,000$ tpa: 3 years, 6 months (1 December 2010)
 - All remaining substances at ≥ 100 tpa: 6 years (1 June 2013)
 - All remaining substances at ≥ 1 tpa: 11 years (1 June 2018)
- ECHA performs completeness check (within 3 weeks for new substance or 3 months of submission deadline for phase-in substance)
- No less than 5% of dossiers to be checked for compliance

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EVALUATION OF HIGHER-TIER TESTING PROPOSALS

- Higher-tier testing programmes of Annex IX and X data to be agreed with ECHA
- *ca.* 6,000 phase-in substances draft decisions for further testing following registration:
 - Cat 1 and 2 CMRs at ≥ 1 tpa: 66 months (1 December 2012)
 - R50/53 substances at ≥ 100 tpa: 66 months (1 December 2012)
 - Remaining substances at ≥ 1000 tpa: 66 months (1 December 2012)
 - Remaining substances at ≥ 100 tpa: 9 years (1 June 2016)
 - Any other registrations: 15 years (1 June 2022)

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DOSSIER PREPARATION

- Submitted to ECHA
- Technical dossier (Annex VI data)
- Robust summaries of available safety data (Annex VII or VII + VIII)
- Proposed classification and labelling EU/GHS
- Statement whether animal testing was conducted
- Proposals for higher-tier testing (Annex IX & X)
- IUCLID electronic format (version 5.0)
- Chemical Safety Report (CSR)
- Update with significant new information

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CHEMICAL SAFETY REPORT

- For registrations at ≥ 10 t.p.a. (unless the substance is in a preparation at $< 0.1\%$ or $<$ classification trigger level)
- Risk assessment (principles of Annex I)
- Use & exposure categories with emission scenarios: Full EU life cycle
- DNELs for human exposure routes, reflecting duration & frequency
- Human health risk assessment not needed for ingredients of cosmetics & food packaging
- Environmental risk assessment for each compartment: PEC:PNEC
- Summary of CSR as an annex to SDS to inform downstream users
- PBT and vPvB assessment
- Downstream users can supplement CSR with extra uses
- RIP 3.2 & electronic tools

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ONE SUBSTANCE, ONE REGISTRATION (OSOR)

- Typically mandatory joint submission of registration (with an opt-out under specified conditions)
- Lead registrant assigned
- Certain data has to be submitted by the individual registrants (i.e. identity of the company and the substance, manufacture and use information, exposure information)

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REGISTRATION SAFETY DATA

- Annexes VII to X give standard data requirements (column 1)
- Rules for omitting tests & for additional tests to clarify hazardous properties or refine the risk assessment (column 2)
- New studies to be to standard EU/OECD methods
- New toxicological and ecotoxicological studies to GLP
- New physico-chemical studies do not have to be to GLP
- Old non-GLP data can be used if it meets quality criteria

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INTELLIGENT SAFETY EVALUATION

Annex XI of the REACH Regulation covers adapting the standard data requirements:

- existing non-standard and/or non-GLP data (evaluate ‘reliability’)
- historical human data
- weight of evidence & Expert Report
- (Q)SAR & calculation or estimation
- grouping and ‘read-across’
- data waivers, i.e. study technically impossible or scientifically impossible
- substance-tailored exposure driven testing (‘data waivers’ for low exposure)

DATA SHARING

- Substance Information Exchange Forum (SIEF) for potential registrants
- Owner of the study to provide proof of cost within one month of a request to share
- Free access to all old data (≥ 12 years)
- Data sharing and data compensation for vertebrate animal data < 12 years old is mandatory
- Costs to be shared in ‘a fair, transparent and non-discriminatory way’ (or equally, if agreement can not be reached)
- Each SIEF remains operational until 1 June 2018

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COST OF REGISTRATION TESTING

- Average for phase-in substances taking into account available studies, surrogate data & data waivers (adapted from KPMG study for the latest data requirements):
 - Annex VII: 15,000 Euro (unless exempt)
 - Annex VII & VIII: ca. 100,000 Euro
 - Annex VII to IX: 282,000 Euro
 - Annex VII to X: 323,000 Euro
- Typical very approximate costs for new substances with no surrogate data or data waivers:
 - Annex VII: ca. £30,000 to £45,000
 - Annex VII & VIII: ca. £140,000 to £185,000
 - Annex IX: Up to ca. £740,000 to £985,000 (highly variable)
 - Annex X: ca. £2,000,000 to £3,000,000 (extremely variable)
 - Also dossier preparation costs & ECA fees

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REGISTRATION SERVICE FOR IM_nI FOR REACH

- Supervision by John Hislop with oversight from Derek Knight.
- Advise on regulatory strategy.
- Help make ‘pre-registrations’ to ECHA.
- Support the Consortium in the SIEFs.
- Review existing tests, predict properties (‘surrogate data’ based ‘categories’) & ‘data waivers’ to produce a ‘data gap analysis’.

REGISTRATION SERVICE FOR IM_nI FOR REACH (continued)

- Recommend additional testing.
- Prepare the registration dossiers (in IUCLID 5 with CSRs) & assist submission to ECHA.
- Propose EU ‘dangerous’ classifications of the Mn substances & any changes under the GHS.
- Propose any additional ‘higher tier’ studies
- Update the registration dossiers as necessary & answer any questions from the ECHA.
- Scientific support.
- Copyright clearance for published studies.

TESTING MASTER SERVICE AGREEMENT FOR NEW STUDIES FOR THE IMnI

- SafePharm Laboratories can conduct the studies or place with RCC or another CRO.
- Under the Testing Master Services Agreement on the instruction of the Consortium Manager.
- Testing at SPL & RCC given priority.
- Project co-ordination & access to scientists
- GLP & standard methods.

CONCLUSIONS

- Take every opportunity to reduce cost of new studies:
 - share studies with other registrants
 - use existing & literature data
 - use non-standard data
 - make use of data waivers
 - apply intelligent testing strategy for new studies
- Extra costs may arise if further studies are triggered:
 - to investigate further from the standard studies
 - from risk assessment
 - if non-standard data are evaluated as inadequate
 - at 100 & 1,000 t.p.a. for further testing