Multiple Framework Contract with Re-Opening of Competition for Scientific Services for ECHA (Reference: ECHA/2011/01)

Service Request SR 26:

Analysis of capacities and capabilities of laboratories to conduct OECD TG 443 extended one-generation reproductive toxicity study (Contract No. ECHA/2015/145)

Final Report

prepared for

ECHA

November 2015

RPA

Risk & Policy Analysts

Analysis of capacities and capabilities of laboratories to conduct OECD TG 443 extended one-generation reproductive toxicity study (OECD TG 443)

November 2015

Final Report

prepared for the European Chemicals Agency (ECHA)
by

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Quality Assurance	
Project reference / title	Analysis of capacities and capabilities of laboratories to conduct OECD TG 443 extended one-generation reproductive toxicity study
Report status	Final Report
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Approved for issue by	Peter Floyd, Director RPA
Date of issue	30 November 2015

Document Change Record			
Report	**Version**	**Date**	**Change details**
Draft Final Report	V1	15.10.15	
Final Report	V2	23.11.15	Revised in light of ECHA comments discussed (by teleconference) on 10 November 2015
Final Report	V2.1	30.11.15	Minor final edits

Contents

Glossary

AGD	Anogenital distance
CRO	Contract research organisation
DART	Developmental and reproductive toxicity
ECHA	European Chemicals Agency
EOGRTS	Extended one-generation reproductive toxicity study
EU B.*	EU standard test method as laid down in Commission Regulation (EU) No 900/2014
F1, F2	First filial generation, second filial generation
GLP	Good laboratory practice
MAD	(OECD) mutual acceptance of data
OECD TG	Organisation for Economic Co-operation and Development Test Guideline
PND	Post-natal day
REACH	Commission Regulation (EU) 2015/282 on Registration, Evaluation, Authorisation and Restriction of Chemicals
SAICM	(UN) Strategic Approach to International Chemicals Management
ToR	Terms of Reference

Executive Summary

Amendment to the information requirements of REACH Regulation (EC) No 1907/2006 Annexes saw replacement of the two-generation reproductive toxicity test guideline (OECD TG 416) with the extended one-generation reproductive toxicity study (EOGRTS; OECD TG 443).

The EOGRTS includes F1 neurotoxicity and immunotoxicity assessments, tests parental fertility and reproductive function, in addition to evaluating pre- and post-natal effects[1]. Markers of offspring (F1) development, including assessment of sexual landmarks (cohorts 1A and 1B), nervous system (cohorts 2A and 2B) and immune system (cohort 3), are monitored up to postnatal day 90 (PND 90).

Defining the global capability and capacity of CRO to conduct the EOGRTS is essential to evaluate the feasibility of chemical testing schemes. The current study is intended to establish the annual worldwide capacity of GLP-compliant EOGRTS studies via market survey and analysis of the capability, capacity and costs of relevant toxicology laboratories.

Screening of CRO directory entries (n=937) identified 122 facilities with Developmental and Reproductive Toxicity (DART) capabilities that may be able to conduct the EOGRTS. The top ten chemical companies were also identified according to their 2015 revenue, to check in-house capabilities. Contact details were extracted from company websites. Collectively 132 stakeholders were identified for participation in the study.

In close liaison with ECHA a short and simple questionnaire (in English) was created using SurveyGizmo software.

11 laboratories provided contact details and completed the survey in full and 20 facilities claimed to offer EOGRTS. Survey participants included international market leaders, in addition to a number of smaller facilities.

All the laboratories that provided contact details indicated EOGRTS capability (12/12) and 11 of those gave quantitative details regarding capacities. Other responses were qualitative - eight laboratories that participated in the survey anonymously also claimed to provide EOGRTS. Two laboratories confirmed their capability via teleconference, but did not partake in the online survey. The number of GLP-compliant contract facilities capable of conducting the EOGRTS identified in this study was 22 (20 survey responses plus two via teleconference), which corroborated the finding of a similar study performed in 2012 (n=21).

The maximum theoretical capacity of participating laboratories to conduct a basic EOGRTS was 209, 216 and 223 studies per year for 2016, 2018 and 2020, respectively. However, capacity was significantly reduced for the full EOGRTS study design to 109, 114 and 126 studies, respectively.

In consideration of parallel and competing tests, the realistic number of basic EOGRTS studies that may be conducted in 2016, 2018 and 2020 was 88, 94 and 101, respectively. In corresponding order, the realistic number for full EOGRTS for these years was 44, 49 and 61, respectively.

[1] OECD (2011): Guideline for the testing of chemicals, TG 443. Extended one-generation reproductive toxicity study. Adopted 28 July 2011. Paris. http://www.oecd-ilibrary.org/environment/test-no-443-extended-one-generation-reproductive-toxicity-study_9789264122550-en

The annual capacity was significantly greater than that identified in 2012; 209 basic study designs or 109 full studies, versus 63 EOGRTS studies previously identified. The results may suggest that market demand and availability have increased since 2012.

In order to provide estimates of 'realistic' global capacity, the figures presented above were taken as lower estimates and were then uplifted by 30% to provide upper estimates for the global capacity of laboratories offering EOGRTS.

The resulting estimated ranges for 'realistic' global capacity of EOGRTS (basic study design), considering parallel conduct of competing studies, were then 88-114, 94-122 and 101-131 for 2016, 2018 and 2020 respectively. The resulting estimated ranges for 'realistic' global capacity of EOGRTS full study design), considering parallel conduct of competing studies, were then 44-57, 49-63, 61-79 for 2016, 2018 and 2020 respectively.

Starting with the cost of the basic EOGRTS study design, extending the study to include the second generation would incur an additional 20% cost. The cost of the study with the developmental neurotoxicity and immunotoxicity cohorts (2A, 2B & 3) would be an additional 30% and 15%, respectively, and the cost of the full EOGRTS study design would be an additional 60% over the cost of the basic study design. These percentage increases for expanding and extending the basic study design are slightly higher than those identified by the 2012 study.

All participating laboratories found the ECHA guidance[2] sufficiently clear. One responder commented on situations where triggers for expansion of the study are identified during the study and on the importance of rat strain in study design.

[2] Further details of the EOGRTS required under REACH is set out in Section 7.6.4.2.3 (and associated sections and appendices) of ECHA's ***Guidance on Information Requirements and Chemical Safety Assessment - Chapter R.7a: Endpoint specific guidance***, Version 4.1, updated October 2015 and available from: http://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

1 Subject of the Service

1.1 Introduction

On the 13th March 2015, amendment to the information requirements of REACH Regulation (EC) No 1907/2006 Annexes[3] saw replacement of the two-generation reproductive toxicity study (OECD TG 416; EU B.35) with the extended one-generation reproductive toxicity study (EOGRTS; OECD TG 443; EU B.56[4]).

Adopted by the OECD Test Guidelines Programme on 28th July 2011, the EOGRTS potentially generates more toxicological information from fewer animals than the two-generation reproductive toxicity study (OECD TG 416). The increased sophistication, extent and duration of F1 offspring assessments are believed to allow adequate prediction on the reproductive toxicity without the need to assess the effects on functional fertility and reproductive performance of the F1 animals. The OECD Guidance Document 151[5] describes the conduct of the various study parts and OECD Guidance Document 117[6] describes the internal study triggers for extension of cohort 1B for those authorities which use the internal triggers.

The EOGRTS, which includes F1 neurotoxicity and immunotoxicity assessments, tests parental fertility and reproductive function, in addition to pre- and post-natal effects[7]. Markers of offspring (F1) development included assessment of sexual landmarks (cohorts 1A and 1B), nervous system (cohorts 2A and 2B) and immune system (cohort 3); these are monitored up to postnatal day 90 (PND 90). The EOGRTS assesses functional and morphological endpoints, such as epididymal sperm maturation, anogenital distance (AGD) and nipple retention, which are indicative of some endocrine modes of action (e.g. anti-androgenic).

[3] Commission Regulation (EU) 2015/282 of 20 February 2015 amending Annexes VIII, IX and X to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards the Extended One-Generation Reproductive Toxicity Study Text with EEA relevance, OJ L 50, 21.2.2015, p. 1–6, available from: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2015.050.01.0001.01.ENG

The REACH Regulation No 1907/2006 (including revisions) is available from: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02006R1907-20150601&from=EN

[4] Commission Regulation (EU) No 900/2014 of 15 July 2014 amending, for the purpose of its adaptation to technical progress, Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006, OJ L 247, 21.8.2014, p. 1–111, available from: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32014R0900

[5] OECD (2013): Guidance Document supporting OECD Test Guideline 443 on the extended one-generation reproductive toxicity test. Series on Testing and Assessment No. 151. ENV/JM/MONO(2013)10.

[6] OECD (2011): Guidance Document 117 on the current implementation of internal triggers in test guideline 443 for an extended one generation reproductive toxicity study, in the United States and Canada. Series on Testing and Assessment No. 117. ENV/JM/MONO(2011)21.

[7] OECD (2011): Guideline for the testing of chemicals, TG 443. Extended one-generation reproductive toxicity study. Adopted 28 July 2011. Paris. http://www.oecd-ilibrary.org/environment/test-no-443-extended-one-generation-reproductive-toxicity-study_9789264122550-en

A majority of EU Member States indicated their preference for the EOGRTS over the two-generation reproductive toxicity study, in order to meet the information requirement of REACH Annexes IX and X 8.7.3.

The ECHA guidance on *Information Requirements and Chemical Safety Assessment* under REACH was updated in 2015 to incorporate the detailed requirements of the EOGRTS[8].

In a statement published on the Chemical Watch Forum in 2012[9], the Head of Toxicology-Ecotoxicology at Arkema, Jean-Charles Boutonnet, suggested that the REACH Committee greatly underestimate the time scale required to complete the current workload. In light of the GLP validation requirements, demand for other regulatory *in vivo* studies (OECD TG 421, 422 and 414) and competing markets (e.g. pharma and phyto), Arkema suggest a "real" European capacity of 15 EOGRT studies per year; if true, several years will be required to complete the studies anticipated by ECHA.

Consequent to the 1981 OECD mutual acceptance of data (MAD) decision and adoption of the UN Strategic Approach to International Chemicals Management (SAICM), government incentives and investments from leading pharmaceutical companies such as Pfizer, GlaxoSmithKline and Eli Lilly, have driven the GLP-compliant CRO market in Asia, which has become an attractive location for safety assessment outsourcing[10]. Nevertheless, concern has been raised regarding the capability and capacity of CROs to meet European demands and, in 2012, a survey sponsored by ECHA (*the 2012 study*[11]) concluded that only a limited number of European CROs had the capacity to fully meet the requirements of EOGRTS (OECD TG 443).

Defining the global capability and capacity of CROs to conduct the EOGRTS is essential to evaluate the feasibility of chemical testing schemes. This is recognised in recital 13) to Regulation 2015/282 amending the REACH Annexes[12].

In order to assist ECHA with determining he market availability, the current study is intended to *establish the annual worldwide capacity of GLP-compliant EOGRTS studies* via market survey and analysis of the *capability, capacity* and *costs* of relevant toxicology laboratories.

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[8] Further details of the EOGRTS required under REACH is set out in Section 7.6.4.2.3 (and associated sections and appendices) of ECHA's ***Guidance on Information Requirements and Chemical Safety Assessment - Chapter R.7a: Endpoint specific guidance***, Version 4.1, updated October 2015 and available from: http://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

[9] Chemical Watch Forum (2014): EOGRTS capacities in Europe for REACH, Jean-Charles Boutonnet. Published October 2014. Available at: http://forum.chemicalwatch.com/discussion/143/eogrts-capacities-in-europe-for-reach [Accessed 20.05.2015].

[10] Frost & Sullivan (2010): Singapore Shifting to a Specialised CRO market: Clinical outsourcing, the new status quo. Available at: http://www.frost.com/prod/servlet/market-insight-print.pag?docid=213988299 [Accessed 20.05.2015].

[11] CEHTRA (2012): ECHA Report on Survey of Worldwide CROs: costs and practicalities of two new OECD Guidelines for testing chemical substances. CEHTRA UK Project No. ECA/RAR/110 (ECHA/2011/217) Available at: https://echa.europa.eu/documents/10162/13628/survey_report_worldwide_cros_en.pdf, hereafter referred to as the 2012 study.

[12] "*Furthermore, as stated when determining deadlines by which dossier updates providing results of EOGRTS are to be submitted, ECHA should take due account of the market availability of this testing service.*"

1.2 Results of the 2012 study

The authors of the 2012 study contacted 50 laboratories identified as potentially able to conduct the EOGRTS in 2012. 16 CROs indicated that they offered OECD TG 443 and five intended to offer the study in future. Capable laboratories that participated in the survey were predominantly based in Europe (8/16), India (2/16) and the USA (1/16). The remaining five capable CROs completed the survey anonymously. A further five CROs with Developmental and Reproductive Toxicity (DART) capabilities suggested that they did not intend to offer EOGRTS due to insufficient market demand and increased technical demands; some laboratories would need to sub-contract the immunotoxicity module (Cohort 3). The authors concluded that a minimum of 21 global CROs had the capability to conduct the EOGRTS. However, only two demonstrated experience with this test guideline (TG).

The 2012 study estimated a global capacity of 63 studies per annum, by extrapolating an average of three studies per year to the 21 capable CROs identified[13]. However, the relevance of this capacity to the chemicals industry was uncertain as "*some or more of this capacity may be utilised for pharmaceuticals and plant protection products*". The individual survey responses are summarised in Table 1-1 (based on the responses from 12 laboratories which answered in full).

Table 1-1: Annual Capacity of TG 443 EOGRTS (from the 2012 study)

Study range per year	Number of CROs	Low capacity	High capacity	Average capacity
1-5 EOGRTS studies per year	8	8	40	**24** *(8-40)*
6-10 EOGRTS studies per year	3	18	30	**24** *(18-30)*
>10 EOGRTS studies per year	1	11	11	**11** at least
Totals	**12**	**37**	**81**	**59** *(37-81)*

Source: CEHTRA (2012) ECHA Report on Survey of Worldwide CROs: Costs and Practicalities of Two New OECD Guidelines for Testing Chemical Substances (ECHA/2011/217)

Information on EOGRTS capacity was gained using study ranges. The upper and lower bounds are presented in Table 1-1. Of the 12 participating CROs, the total capacity averaged 59 studies with upper and lower bounds of 37 and 81, respectively. Whilst the authors utilised an average of three studies per year per facility for extrapolation, the raw data presented above suggests that this may have been an under-estimate.

However, in light of the amendments to REACH Annex information requirements implemented in March 2015, the findings of the 2012 study may not reflect the current EOGRTS market availability. Nevertheless, the capability and capacity identified in 2012 will be compared to the current situation.

1.3 Objectives of the study

As stated in the Specific Terms of Reference (ToR), the subject of this study is the *analysis of capacities and capabilities of laboratories to conduct the extended one-generation reproductive toxicity study (OECD TG 443) for testing chemicals substances*.

[13] 12 CROs participated in the main survey, which averaged three studies per year. Thus, the capacity was calculated by multiplying this figure by the number of capable laboratories (21).

The aim of this study is therefore to gain market intelligence on global laboratory capacities and capabilities for testing chemical substances with the extended one-generation reproductive toxicity study (OECD TG 443). In accordance with the ToR, the study considered a number of objectives. Relevant laboratories were identified and screened (GLP compliant Contract Research Organisations (GLP-CROs) and in-house laboratories) and, in close liaison with ECHA, a survey was designed and implemented to gage the global capability and capacity of EOGRTS.

The study was split into three discrete tasks: design and implementation of the survey (Task 1); analysis of survey result and follow-up clarifications (Task 2); and reporting (Task 3). This report (Task 3) has been organised as follows:

- Section 1 (this section) introduces the study and specific terms of reference;
- Section 2 summarises the methodology, detailing survey design and implementation (Task 1);
- Section 3 summarises the survey results, estimating the EOGRTS capability and capacity (Task 2); and
- Section 4 presents the conclusions.

2 Design and Implementation of Survey

2.1 Overview

Despite being identified as an *analogous* starting point, there is a lack of methodological transparency for the 2012 study, reducing the potential for replicating the study. Thus, whether the study effectively identified all relevant global GLP-compliant toxicological facilities is unclear.

This section details Task 1, the 'Design and implementation' methodology, adopted to transparently identify relevant laboratories and create an effective online survey to elucidate the global capacity of EOGRTS (OECD TG 443), as per ECHA's requirements and agreement. The extent of stakeholder engagement and survey content were governed by guidance given in teleconference with ECHA (Monday 13th July 2015) and subsequent liaison.

2.2 Method

2.2.1 Identification of relevant stakeholders

In accordance with the ToR, RPA developed a systematic method to identify and screen all relevant stakeholders. Initially, RPA screened the extensive list of global contract research organisations published by Shimek in 2011[14] for relevance to *in vivo* reproductive toxicity testing (n=770), identifying 87 GLP-compliant laboratories. Contact details of the relevant CRO were extracted from company websites.

To supplement the identified CRO 'master' list, human health toxicology laboratories listed in the Chemical Watch Global Service Providers Guide 2015[15] were screened for inclusion. Whilst overlap between methodological approaches is expected, screening of the 'ChemWatch' global guide list (n=167) identified 35 additional core providers of GLP-compliant human health toxicity testing. In total, screening (n=937) identified 122 facilities with Developmental and Reproductive Toxicity (DART) capabilities that might be able to conduct the EOGRTS. The generated list was checked against Member State lists of GLP-compliant facilities[16].

In order to account for in-house facilities of large chemical companies, the top ten global chemical companies were identified according to their 2015 revenue (in US$ billion) published by the Financial Times Global 500 List; contact details were extracted from company websites. Collectively **132 stakeholders were identified for participation in the study**, which exceeds the number of CROs identified in the 2012 study (n=50).

[14] Shimek K (2011): List of Contract Research Organizations (CROs): Version 1. Available from: https://kjshimek.wordpress.com/article/list-of-contract-research [Accessed on 18.05.2015].

[15] Chemical Watch Global Service Providers Guide 2015: A guide to global chemicals management and control services. Available from: www.chemicalwatch.com/online-guide [Accessed on 18.05.2015].

[16] http://www.oecd.org/env/ehs/testing/nationalcoordinatorsofthetestguidelinesprogramme.htm

2.2.2 Survey design

The key objective of the survey was to obtain market information on the capacity and capability of laboratories (i.e. services), rather than to extract data that may be regarded as confidential, such as cost. Thus, questions regarding the cost of study designs were presented as % increases, relative to a basic study design baseline. In close liaison with ECHA, the short and simple questionnaire (in English) was finalised on 3rd August 2015. A copy of the questionnaire (in plain format) is presented in Annex 1.

The online version incorporated additional design features and answer dependent prompts. A screen-shot of the initial questions is presented in Figure 2-1.

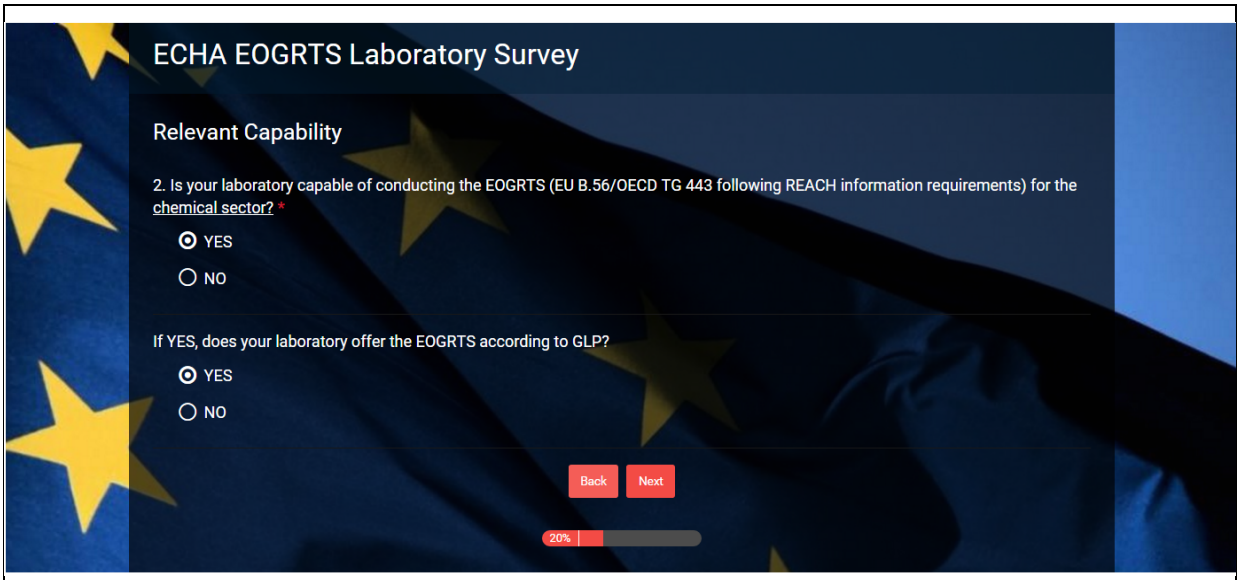

Figure 2-1: Interface of Electronic Survey to Establish Capability and Capacity of the EOGRTS (OECD TG 443)

At the end of the survey participants were given an opportunity to provide additional comment.

Invitations to participate were disseminated to a wide range of stakeholders as identified in Section 2.2.1 above. The survey was '*live*' for six weeks (4th August - 15th September 2015). Initial invites were sent on 4th August and reminder emails were sent to 62 stakeholders on 9th September 2015. Example cover emails are provided in Annex 3.

To supplement the survey results and associated research, RPA conducted a number of tele-interviews with GLP-compliant CROs, providing clarifications on the availability of facilities to conduct the EOGRTS (OECD TG 443) and aiding participation in the survey.

3 Analysis and Interpretation of Results

3.1 Overview

This section analyses and interprets the survey results, utilising RPAs collective expertise in reproductive toxicity, endocrine disruption, OECD Test Guidelines and REACH information requirements, to comment on the relevance of the survey results. The analysis provides the foundations for a view on the global 'capacity' and 'capability' to conduct EOGRTS (OECD TG 443).

Publicly available literature information on the CRO market, EOGRTS technical requirements and dossier evaluation process (i.e. REACH Annex information requirements), form the basis of supporting information. Whilst direct cost information was not collected, utilising information on the % increments for various study designs, enabled cost estimates for conducting the extended one-generation reproductive toxicity study. However, a cost range is undoubtedly more feasible, as costs may vary significantly depending on the toxicological endpoints observed in the EOGRTS cohorts.

Consideration is given to the **capacity, capability, cost** and **availability** of laboratories identified to fulfil the EOGRTS testing requirements of the REACH Annexes, forming expert conclusions on the feasibility of conducting EOGRTS given the current market conditions.

3.2 Survey response

A total of 122 GLP-compliant facilities were identified as potential EOGRTS providers and sent the link to the online survey on the 4th August 2015. Reminder emails were sent to 62 recipients (for whom there had been no initial response) on 9th September (i.e. one week before deadline) to maximise participation. As the invitation email detailed the scope of the survey, primarily only interested parties opened the link. A total of 13 laboratories emailed to confirm that they do not offer the EOGRTS (OECD TG 443) and 11 emails were undeliverable.

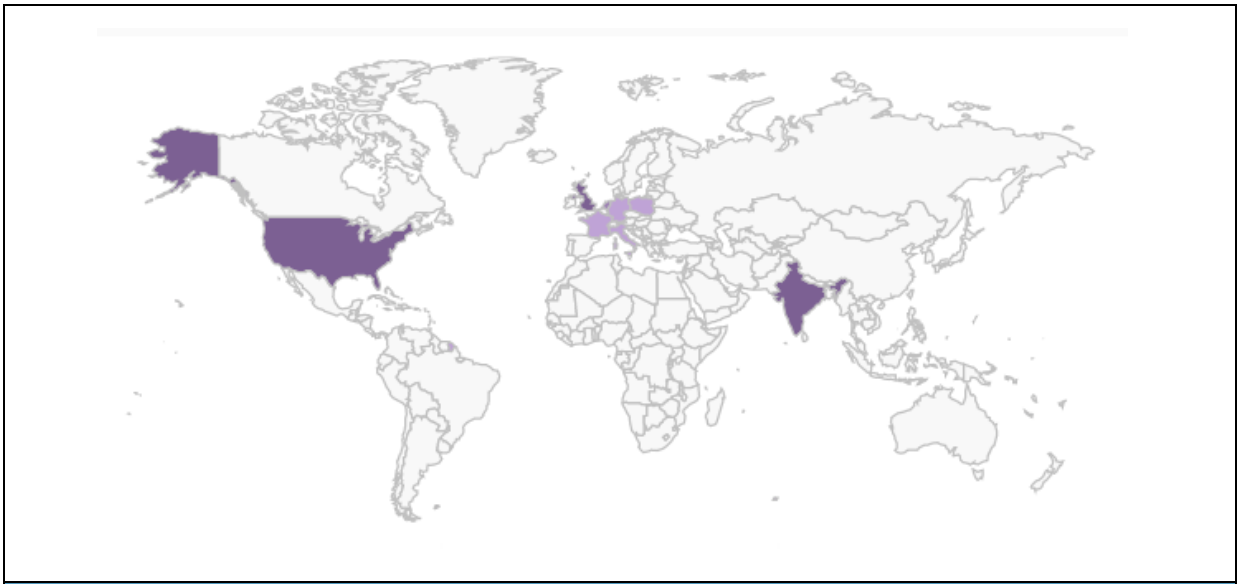

Figure 3-1: Response Location of Participating Laboratories
The survey was completed in several countries: India, United Kingdom, Netherlands, United States, Poland, Germany, Italy and France, with darker shade indicating more respondents

Inspection of the results indicated that there were numerous duplicate partial entries (indicated by the same IP address and associated responses) where participants had initiated the survey on multiple occasions. Once these were filtered out, the following observations could be made:

- 20 facilities offered EOGRTS (19 now and one planned for the future);
- 17 questionnaires were completed (but four were not offering EOGRTS);
- 12 laboratories provided contact details; and
- 11 laboratories provided contact details and completed the survey in full.

Figure 3-1 graphically presents the response location of the 17 participating laboratories that completed the survey. Survey participants included international market leaders, in addition to a number of smaller facilities.

For the purpose of analysis, in lieu of assurances regarding commercial capability, **only the complete and detailed responses provided by 11 of the participating laboratories have been formally considered in the analysis**. Thus, whilst leading CROs participated in the survey, the capability and capacity identified herein is likely to be somewhat of an underestimate.

3.3 Analysis of survey results

3.3.1 Capability

Capability is defined as "*the power or ability to do something*". All the laboratories that participated in the question regarding EOGRTS capability stated they were capable of conducting the basic study design with ten weeks pre-mating exposure of cohorts 1A and 1B, to GLP standard (11/11).

Eight anonymous laboratories that participated in the survey claimed to provide EOGRTS services, and two laboratories confirmed their capability via teleconference, but did not partake in the online survey. Unfortunately, they provided no further information as regards the numbers of tests that could be performed.

Thus, the number of GLP-compliant CROs capable of conducting the EOGRTS identified in this study was 22 (20 survey responses plus two via teleconference) which is consistent with the 2012 study (n=21). Of these, 11 CROs provided quantitative details relating to capacities, which are reflected in the total annual capacity reported in this document.

It is of note that one respondent from a leading chemical company commented that:

> *"concerning the EOGRTS, we can not explicitly name a capacity in terms of studies/year, since this depends on various parameters, such as the particular study design as well as other reproductive toxicity studies to be run in our laboratories. However, we have significant doubt that there is sufficient worldwide capacity of CROs who are actually capable and in possession of historical control data to perform the EOGRTS study in a way which we deem of sufficient quality".*

All responding facilities were also capable of extending cohort 1B to include assessment of the F2 generation (i.e. two-generation reproductive toxicity study). As presented in Table 3-1, fewer laboratories stated capability in developmental neurotoxicity (cohort 2A & 2B) and immunotoxicity (cohort 3) study designs.

Table 3-1: Capability of Laboratories to conduct TG 443 EOGRTS			
Does your laboratory have, or plan to have, capacity for EOGRTS study designs, as laid down in Annexes IX and X	**2016**	**2018**	**2020**
Basic study (ten weeks pre-mating exposure, cohorts 1A & 1B, no expansions)	100% *(11/11)*	64% *(7/11)*	64% *(7/11)*
Extension of Cohort 1B (minimum two-weeks pre-mating exposure)	100% *(11/11)*	64% *(7/11)*	64% *(7/11)*
Developmental neurotoxicity Cohorts 2A & AB	91% *(10/11)*	55% *(6/11)*	55% *(6/11)*
Developmental immunotoxicity Cohort 3	82% *(9/11)*	64% *(7/11)*	55% *(6/11)*
Full study (two weeks pre-mating exposure, cohorts 1A & 1B + expansion of cohort 1B + cohorts 2A & 2B + cohort 3	82% *(9/11)*	64% *(7/11)*	55% *(6/11)*

Participating laboratories expect the capability to decrease over subsequent years (64% (7/11) by 2018). This decreasing trend was identified in all EOGRTS study designs. These decreases may reflect the upcoming REACH registration deadline in 2018, which will necessitate the testing of studies such as OECD TGs 421, 422. With regard to planning EOGRTS study expansions, Table 3-2 summarises the possibility of *ad hoc* amendments to study design. Whilst most laboratories provided flexibility, not all facilities enabled *ad hoc* inclusion of neurotoxicity and immunotoxicity cohorts (2A, 2B & 3) based upon information collected in the early stages of an ongoing study. This cap may reflect sub-contracting requirements.

Table 3-2: Planning OECD TG 443 EOGRTS Study Expansions*		
Timing of Change	**Nature of Change**	
Is it possible to expand the EOGRTS study design…	**Prior to weaning (for inclusion of cohorts 2A & 2B and/other Cohort 3)**	**Before postnatal day 120 (for extension of cohort 1B)**
in an *ad hoc* manner before the start of the study based on newly available information	90% *(9/10)*	100% *(10/10)*
in an *ad hoc* manner during the conduct of the study based on new information	70% *(7/10)*	90% *(9/10)*
Percentage capabilities were calculated on the basis of those that participated in the question (n=10) ** Note in retrospect, this survey question could have been further refined to ensure coherence between the likely timelines of decision-making and the timelines of the study itself*		

OECD TG 443 was internationally validated with rat model species (e.g. Sprague Dawley). However, for more novel studies, laboratories also offered the EOGRTS in mice (5/10) and, in one instance, rabbits (1/10). With regards to the available routes of administration, all participating laboratories offered oral exposure pathways (Table 3-3). In addition, inhalation, intratracheal instillation, dermal, subcutaneous, intranasal and intraperitoneal routes were identified by some facilities (5/11).

Table 3-3: Routes of Administration Available for the OECD TG 443 EOGRTS	
Route of Administration	**Laboratory Capability**
Oral (dietary) Oral (drinking water) Oral (gavage)	*100% (11/11)* *91% (10/11)* *100% (11/11)*
Inhalation	*55% (6/11)*
Intratracheal instillation	*55% (6/11)*
Dermal application	*64% (7/11)*
Other	*46% (5/11)* such as: *Subcutaneous, intranasal & intraperitoneal*
Percentage capabilities were calculated on the basis of those that participated in the question (n=11)	

A number of participants provided additional comments as presented in Box 3-1.

Box 3-1: Participant Commentary on Routes of Administration
"*We have many years experience conducting OECD 416, generally by the oral route (gavage and dietary). We have also conducted OECD 416 by the inhalation route*"
"*Extensive experience with diet, drinking water, gavage and inhalation*"
"*We have been conducting reproduction studies (OECD 414, 415, 416) by oral gavage, dietary and drinking water routes for last 20 years*"
"*Intratracheal and dermal routes are possible but would be seriously challenging for the OECD 443 study*"

3.3.2 Capacity

Capacity is defined as "*the maximum amount something can contain*" or "*the amount that something can produce*". In estimates for the year 2016, the maximum theoretical tests conducted per CRO (capacity), ranged from 1 to 100 (median = 10) for basic studies and 1 to 40 (median = 7) for full studies.

Table 3-4: Annual Capacity of TG 443 EOGRTS (data for 11 laboratories which provided detailed data)				
Year of contract signature	2016	2018	2020	n =
Maximum theoretical annual capacity (under assumption that no other studies were being conducted)				
Basic study (ten weeks pre-mating exposure, cohorts 1A & 1B, no expansions)	209	216	223	*11*
Full study (two weeks pre-mating exposure, cohorts 1A & 1B + expansion of cohort 1B + cohorts 2A & 2B + cohort 3	109	114	126	*10*
'Realistic' annual capacity (given the parallel conduct of competing tests)				
Basic study (ten weeks pre-mating exposure, cohorts 1A & 1B, no expansions)	88	94	101	*11*
Full study (two weeks pre-mating exposure, cohorts 1A & 1B + expansion of cohort 1B + cohorts 2A & 2B + cohort 3	44	49	61	*10*

The maximum theoretical capacity of participating laboratories, to conduct a basic EOGRTS study design was 209, 216 and 223 studies for 2016, 2018 and 2020, respectively (Table 3-4). However, capacity was significantly reduced for the full EOGRTS study design to 109, 114 and 126 studies, respectively. These estimates are significantly higher than the capacity for 63 EOGRTS studies identified in the 2012 study.

In consideration of parallel and competing test requirements, the 'realistic' number of basic EOGRTS studies in 2016, 2018 and 2020 was estimated to be 88, 94 and 101, respectively. The realistic number of full EOGRTS for these years was 44, 49 and 61, respectively. The increasing capacity expectations conflict with the decreases in capability detailed in Section 3.3.1 - this may reflect uncertainty regarding services to be offered in future.

The total number of GLP-compliant CROs capable of conducting the EOGRTS identified in this study was 22, i.e. twice the number considered in Table 3-4 above. However, simply doubling the numbers presented would overstate the global EOGRTS capacity as the leading laboratories in this field have already been accounted for. With this in mind, the potential additional capacity will be based on an assumed 30% of the above values. The resulting 'realistic' global capacity is presented in Table 3-5.

Table 3-5: Estimated 'Realistic' Annual Capacity for TG 443 EOGRTS (for 22 laboratories)			
Year of contract signature	2016	2018	2020
Basic study (ten weeks pre-mating exposure, cohorts 1A & 1B, no expansions)	88 - 114	94 - 122	101 – 131
Full study (two weeks pre-mating exposure, cohorts 1A & 1B + expansion of cohort 1B + cohorts 2A & 2B + cohort 3	44 - 57	49 - 63	61 - 79
Note that lower estimates based on data from 11 laboratories (as presented above in Table 3-4) and upper estimates based on an assumed additional 30% capacity provided by a further 11 laboratories.			

Whilst this study has included comparable numbers of stakeholders to the 2012 study, the estimated annual capacity is significantly greater than capacity previously identified. As the methodological approaches may have varied, it is not possible to directly compare the two values for capacity. However, the results do suggest that market demand and availability has increased since 2012.

3.3.3 Cost

As detailed in Section 3.2, the survey aimed to obtain market information on the capacity and capability of laboratories, rather than extract information that may be regarded as confidential, such as cost (although, for reference, some information on costs from previous studies Is presented in Annex 3). For the purpose of this study, questions regarding cost of EOGRTS study designs were presented as % increases relative to a basic study design baseline. Table 3-6 presents the increases in cost incurred with extended EOGRTS study designs. For the full study design (i.e. two weeks pre-mating exposure, cohorts 1A & 1B, expansion of cohort 1B, cohorts 2A & 2B and cohort 3) the median additional cost was 60% (30-220% range) more than the basic study. With regard to neurotoxicity and immunotoxicity cohorts, the additional median costs were 30% (20-50%) and 15% (10-50%), respectively. The minimum cost increases were offered by Indian CROs, whilst the largest cost increases were quoted by European CROs.

Table 3-6: Cost of EOGRTS Study Design Extension				
How much additional costs do the following study elements generate	Minimum	Maximum	Median	n =
Extension of Cohort 1B (minimum two-weeks pre-mating exposure)	0%	80%	20%	9
Developmental neurotoxicity Cohorts 2A & AB	20%	50%	30%	8
Developmental immunotoxicity Cohort 3	10%	50%	15%	8
Full study (two weeks pre-mating exposure, cohorts 1A & 1B + expansion of cohort 1B + cohorts 2A & 2B + cohort 3	30%	220%	60%	8

As illustrated in Figure 3-2 (next page), the distribution of the costs for each additional element varied significantly across the respondents, with one or two indicating significantly greater costs than the majority.

With regard to the cost difference between two and ten weeks F0/P pre-mating exposure, taking the latter as the baseline, cost reductions <20% were identified by participating laboratories; four out of eleven stipulated cost reductions <6%; five suggested a cost reduction of 6-10%; and the remaining two participating laboratories stipulated a cost saving of 11-20%.

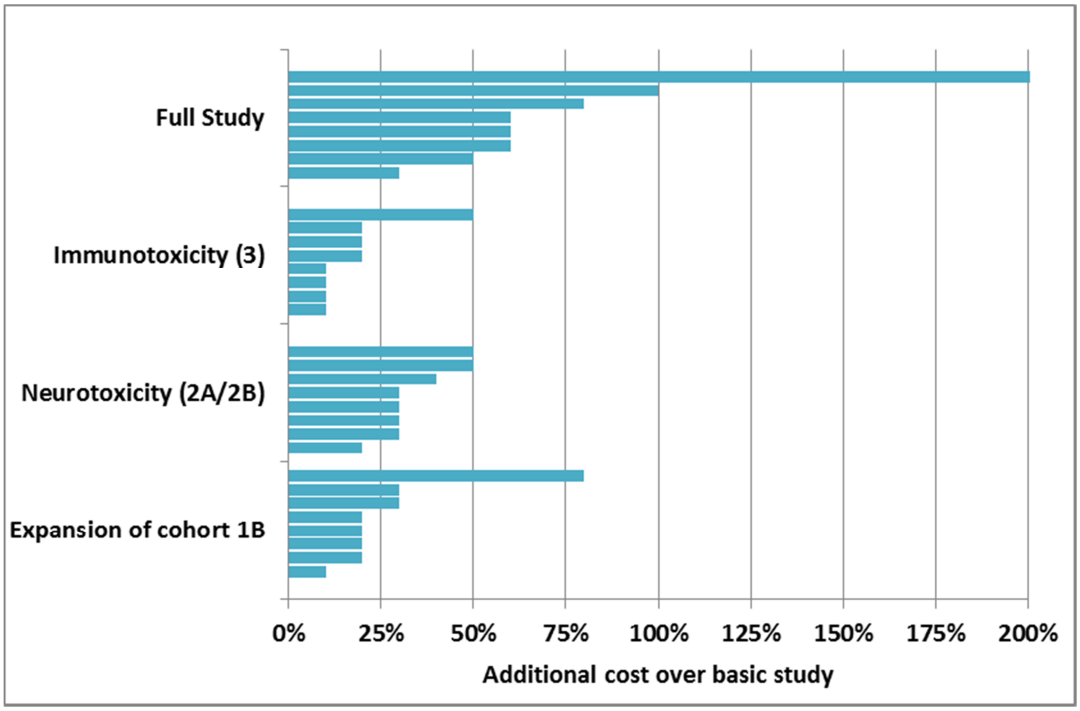

Figure 3-2: Distribution of the costs for additional elements
Note that costs have been sorted for each element, rather than by respondent

Whilst collecting cost data was deemed outside the scope of this study, the percentage figures can be compared to those previously derived in the 2012 study as shown in Table 3-7.

Table 3-7: Cost of EOGRTS Study Design Extension

How much additional costs do the following study elements generate	Median (from Table 3-5 above)	Average (from 2012 study*)
Extension of Cohort 1B (minimum two-weeks pre-mating exposure)	20%	13%
Developmental neurotoxicity Cohorts 2A & AB	30%	22%
Developmental immunotoxicity Cohort 3	15%	6%
Full study (two weeks pre-mating exposure, cohorts 1A & 1B + expansion of cohort 1B + cohorts 2A & 2B + cohort 3	60%	58%

Note: Figures derived from cost data presented in CEHTRA (2012): ECHA Report on Survey of Worldwide CROs: Costs and Practicalities of Two New OECD Guidelines for Testing Chemical Substances (ECHA/2011/217). For reference, further details on costs are presented in Annex 3.

As can be seen from Table 3-7, the figures derived for this study are generally higher but this could be due to various factors including a different sample of respondents and changing market conditions.

3.3.4 Practicalities and logistics

The EOGRTS study aims to elucidate the effects of repeated exposure to a substance during all phases of the reproductive cycle, providing information on the reproductive system, development, growth, survival and functional endpoints of offspring up to post-natal day 90 (PND 90). The study defines minimum treatment, mating, weaning and assessment periods, thus, the study itself is unlikely to fluctuate in duration[17]. However, availability of animal facilities, dose selection and breeding of animal strains may significantly impact the time to completion.

Table 3-8 summarises the median time to study completion from contract signature, for laboratories that participated in the study with the results presented graphically in Figure 3-3. The median time to complete the basic EOGRTS study design was 12 months; however, responses were widely dispersed, ranging six to 16 months. Extension of cohort 1B increased the median study duration to 16 months, whilst developmental neurotoxicity and immunotoxicity cohorts increased the median study duration to 15 and 14 months respectively. The median time for completion of the full EOGRTS study design was 16 months (range 9-24 months).

Table 3-8: Median Study Duration (months) of EOGRTS

What is the average time duration in months, from contract signature until reporting, to carry out EOGRTS?	Minimum	Maximum	Median	*n=*
Basic study (ten weeks pre-mating exposure, cohorts 1A & 1B, no expansions)	6	16	12	*10*
Extension of Cohort 1B (minimum two-weeks pre-mating exposure)	8.5	20	15.5	*10*
Developmental neurotoxicity Cohorts 2A & AB	8	18	15	*9*
Developmental immunotoxicity Cohort 3	8	18	14	*9*
Full study (two weeks pre-mating exposure, cohorts 1A & 1B + expansion of cohort 1B + cohorts 2A & 2B + cohort 3	9	24	16	*9*

[17] Further details of the EOGRTS required under REACH is set out in Section 7.6.4.2.3 (and associated sections and appendices) of ECHA's ***Guidance on Information Requirements and Chemical Safety Assessment - Chapter R.7a: Endpoint specific guidance***, Version 4.1, updated October 2015 and available from: http://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

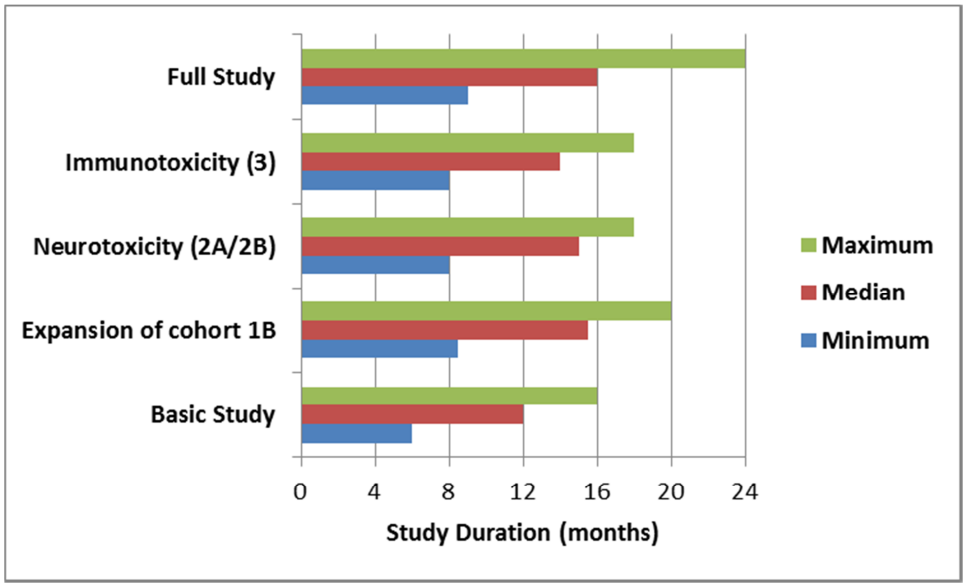

Figure 3-3: Distribution of study durations with additional elements

Collectively, the participants of this survey demonstrated experience in reproductive, developmental neurotoxicity and immunotoxicity, repeated dose and chronic toxicity/carcinogenicity studies and EOGRTS, having conducted over 1292 *in vivo* mammalian toxicology studies over the last decade for regulatory purposes in total [18] (see Table 3-9). However, and as might be expected, the table illustrates that experience is highest with established repeated dose and reproductive toxicity studies and lowest with developmental immunotoxicity studies and the EOGRTS.

Table 3-9: Participating Laboratory DART Experience

Previous experience with the following study types over the past 10 years	Number of tests undertaken					
	0	1-3	4-9	10-20	21-49	50+
Repeated dose toxicity (TG 407, 408, 417)	0%	0%	0%	0%	18%	82%
Reproductive toxicity studies (TG 414, 415, 416 etc)	0%	0%	9%	18%	9%	64%
Chronic toxicity/Carcinogenicity (TG 451, 452, 453)	0%	28%	18%	18%	18%	18%
Developmental neurotoxicity studies (TG 426)	28%	36%	18%	0%	18%	0%
Developmental immunotoxicity studies	64%	18%	9%	9%	0%	0%
EOGRTS (TG 443)	36%	46%	18%	0%	0%	0%
Percentages were calculated from the answers provided by participating laboratories (n=11).						

[18] Based upon information provided for: Reproductive toxicity studies (OECD TG 414, 415, 416, 421, 422); Developmental neurotoxicity studies (OECD TG 426); Developmental immunotoxicity studies; Repeated dose toxicity (OECD TG 407, 408, 413); Chronic toxicity/Carcinogenicity (OECD TG 451, 452, 453); and, EOGRTS (OECD TG 443). Assuming a cap of 50 studies and the median of study number ranges (upper and lower bounds), the laboratories participating in this study can be said to have conducted in excess of 1292 mammalian toxicology studies (1137-1446 range, assuming upper and lower bounds).

With regard to the EOGRTS study in particular, a total of 23 studies (minimum of 13, maximum of 33 studies) have been conducted by the laboratories participating in this study. In the 2012 study, it was reported that only two laboratories had experience in the guideline. This study has identified seven GLP-compliant laboratories with demonstrated experience in EOGRTS, potentially reflective of the amendments to the REACH information requirements subsequent to publication of the 2012 study (REACH Annexes IX and X 8.7.3).

The final section of the questionnaire focused on the clarity of the REACH requirements and ECHA guidance on reproductive toxicity (as updated July 2015[19]). Table 3-10 summarises the survey responses.

Table 3-10: Survey Participant Commentary on Available Guidance

Survey Question	Yes	No
Is the available ECHA guidance (updated July 2015) on reproductive toxicity sufficiently clear to specify and justify EOGRTS study designs, as required by REACH?	**100%**	**0%**
ECHA has provided a visualisation of the study design options – is this helpful?	**82%**	**18%**
Percentage capabilities were calculated on the basis of those that participated in the question (n=11)		

Whilst all participating laboratories found the ECHA guidance sufficiently clear (11/11), two laboratories did not find the visualisation provided for the survey particularly helpful - "*it's a little busy with symbols and footnotes*".

One respondent provided some further comments on the ECHA guidance with particular regard to a lack of clarity regarding the possible courses of action, upon identification of sufficient triggers to mate F1 animals (extend cohort 1B) and the need to stress the importance of strain selection (and likely litter size) in expansion study design.

3.3.5 EOGRTS for REACH workshop

Survey participants were asked whether they would be interested in attending a workshop on the EOGRTS under REACH. The contact details of those willing to participate in the workshop have been passed to ECHA.

[19] Since then, the guidance has been further updated with the latest version published in October 2015, as previously referenced.

4 Summary and Conclusions

4.1 Summary

Amendment to the information requirements of REACH Regulation (EC) No 1907/2006 Annexes[20] saw replacement of the two-generation reproductive toxicity test guideline (OECD TG 416) with the extended one-generation reproductive toxicity study (EOGRTS, OECD TG 443). The EOGRTS, which includes F1 neurotoxicity and immunotoxicity assessments, tests parental fertility and reproductive function, in addition to pre- and post-natal effects.

Defining the global capability and capacity of CROs to conduct the EOGRTS is essential to manage the timing of chemical testing schemes and is incorporated into recital 13) to Regulation 2015/282 amending the REACH Annexes[21].

The aim of the current study was to gain market intelligence on global laboratory capacities and capabilities for testing chemical substances with the extended one-generation reproductive toxicity study (OECD TG 443). Relevant laboratories were identified and screened (GLP compliant Contract Research Organisations (GLP-CROs) and in-house laboratories) and in close liaison with ECHA a short and simple questionnaire was created using *SurveyGizmo* software. Collectively 132 stakeholders were contacted for participation in the study.

The total number of contract research facilities that claimed to offer the EOGRTS identified in this study was 22, which corroborated the results from a similar study in 2012 (n=21). Survey responders included international market leaders, in addition to a number of smaller facilities. In addition, a leading chemical company confirmed the existence of in-house capabilities but, at the same time, questioned the global capacity to perform the EOGRTS study to a sufficient quality.

The maximum theoretical capacity of the 11 participating laboratories (which provided detailed information) to conduct a basic EOGRTS study design was 209, 216 and 223 studies per year for 2016, 2018 and 2020, respectively. Capacity was significantly reduced for performance of the full EOGRTS study design; 109, 114 and 126 studies, respectively. These estimates are significantly greater than the capacity for 63 EOGRTS studies identified in the 2012 study and suggest that market demand and availability have increased since 2012. However, in the absence of a replicable methodology, it is unclear whether the survey participants are directly comparable.

In consideration of parallel and competing tests, the realistic number of basic EOGRTS studies conducted (by the 11 participating laboratories which provided detailed information) in 2016, 2018 and 2020 was estimated to be 88, 94 and 101, respectively. With regard to the full EOGRTS study design, the capacity was estimated to be 44, 49 and 61 for 2016, 2018 and 2020, respectively. These figures could be uplifted by 30% to provide upper estimates for the global capacity of the 22 laboratories claiming to have the capability to perform an EOGRTS.

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[20] Commission Regulation (EU) 2015/282 of 20 February 2015 amending Annexes VIII, IX and X to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards the Extended One-Generation Reproductive Toxicity Study Text with EEA relevance, OJ L 50, 21.2.2015, p. 1–6, available from: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2015.050.01.0001.01.ENG

[21] *"Furthermore, as stated when determining deadlines by which dossier updates providing results of EOGRTS are to be submitted, ECHA should take due account of the market availability of this testing service."*

4.2 Conclusions

The total number of facilities that claimed to offer the EOGRTS was 22, which corroborated the 2012 study (n=21). These included the leading laboratories in this field. Nevertheless, it is possible that there are further facilities, amongst the 122 CROs identified as potential providers, which can offer the EOGRTS but did not respond to the survey.

The maximum theoretical capacity of EOGRTS (basic study design) for eleven of these laboratories (which provide detailed information) was 209, 216 and 223 studies per year for 2016, 2018 and 2020, respectively. The 'realistic' capacity of EOGRTS (basic study design), considering parallel conduct of competing studies, was 88, 94 and 101, respectively.

The maximum theoretical capacity of EOGRTS (full study design) was 109, 114 and 126 studies per year for 2016, 2018 and 2020, respectively. The 'realistic' capacity of EOGRTS (full study design), considering parallel conduct of competing studies, was 44, 49 and 61 for 2016, 2018 and 2020, respectively.

The results suggest that market demand and availability of EOGRTS has increased since 2012.

In order to provide estimates of 'realistic' global capacity, the figures presented above were taken as lower estimates and were then uplifted by 30% to provide upper estimates for the global capacity of laboratories offering EOGRTS.

The resulting estimated ranges for 'realistic' global capacity of EOGRTS (basic study design), considering parallel conduct of competing studies, were then 88-114, 94-122 and 101-131 for 2016, 2018 and 2020 respectively. The resulting estimated ranges for 'realistic' global capacity of EOGRTS full study design), considering parallel conduct of competing studies, were then 44-57, 49-63, 61-79 for 2016, 2018 and 2020 respectively.

Annex 1 ECHA EOGRTS Laboratory Survey Questionnaire

Introduction

The extended one-generation reproductive toxicity study (EOGRTS) OECD TG 443 replaced the two-generation reproductive toxicity study OECD TG 416 on 13th March 2015 as a standard information requirement in the Annexes of Regulation (EC) No 1907/2006 (REACH). The European Chemicals Agency (ECHA) is expected to process more than 300 previously suspended testing proposals and compliance check decisions, in addition to ongoing and future Evaluation processes related to this endpoint. Therefore, it is necessary to investigate the global capacities and capabilities of test animal laboratories for conducting the EOGRT study for the chemical sector. ECHA has contracted Risk & Policy Analysts (RPA) to establish which laboratories will be able to conduct this new test. A supporting letter from ECHA is here.

*Please complete your response by the **15th September 2015**.*

Please contact Dr Louise Youngs (E-mail: louise.youngs@rpaltd.co.uk, Telephone: +44 1508 528465) to ask for clarification or discuss any issues that may arise for your company in completing the questionnaire.

Please note that although your responses will not be linked to your organisation in the study report, your contact details and anonymised information concerning your responses will be passed to ECHA. If you have any particular concerns over confidentially, please indicate this in the final comment box.

1) Please provide contact details

Name:
Title:
Company Name:
Street Address:
City:
State:
Zip/Post Code:
Country:
Email Address:
Phone Number:

Relevant Capability

2) Is your laboratory capable of conducting the EOGRTS (EU B.56/OECD TG 443 following REACH information requirements) for the chemical sector?*

- YES
- NO

3) If YES, does your laboratory offer the EOGRTS according to GLP?

- YES
- NO

4) If NO, does your laboratory plan to offer the EOGRTS according to GLP to the chemical sector in future?

- YES
- NO

EOGRTS Capacity

The following questions will provide ECHA with more information on what tests are available and the associated costs.

5) Does your laboratory have, or plan to have, capacity for various study designs, as laid down in the amendments to REACH Annexes IX and X effective 13th March 2015? (please tick all that apply) ***For reference, ECHA has provided a visualisation of the study design options***

	Yes/Planned (2016)	Yes/Planned (2018)	Yes/Planned (2020)
a) Basic study (ten weeks pre-mating exposure, Cohorts 1A & 1B, no expansions)			
b) Extension of Cohort 1B (minimum two-weeks pre-mating exposure)			
c) Developmental neurotoxicity Cohorts 2A & 2B			
d) Developmental immunotoxicity Cohort 3			
e) Full study (two weeks pre-mating exposure, Cohorts 1A & 1B + Extension of Cohort 1B + Cohorts 2A & 2B + Cohort 3)			

6) Is it possible for you to expand the EOGRTS study design:
(Please tick all that apply)

	Prior to weaning (for inclusion of Cohorts 2A & 2B and/or Cohort 3)	Before postnatal day 120 (for extension of Cohort 1B)
a) In an ad hoc manner before the start of the study (for any expansion) based on newly available information?		
b) In an ad hoc manner during the conduct of the study based on new information form the study itself or from outside the study?		

7) Which routes of administration are possible at your laboratory for this study? (Please tick all that apply)

Capable of exposure via…?	
Oral (dietary)	
Oral (drinking water)	
Oral (gavage)	
Inhalation	
Intratracheal instillation	
Dermal application	
Other	

8) Please specify other possible routes of administration

9) Please provide any additional information or experience on the route of administration for OECD Test Guidelines 443 or 416

10) In addition to rats, is your facility capable of conducting the study using other species?

- YES
- NO

11) Please specify the additional species your facility is capable of conducting the EOGRTS in

EOGRTS Capacity (continued)

12) Under the assumption that no other studies were being conducted, which may compete for the facility's capacity, what is the maximum theoretical EOGRTS capacity (tests/year)?

	In 2016	In 2018	In 2020
To conduct a basic study (ten weeks pre-mating exposure, Cohorts 1A & 1B, no expansions)?			
To conduct a full study design (two weeks pre-mating exposure, Cohorts 1A & 1B + Expansion of Cohort 1B + Cohorts 2A & 2B + Cohort 3)			

13) Similar to the previous question, what is the 'realistic' annual EOGRTS capacity (tests/year), given the parallel conduct of competing tests?

	In 2016	In 2018	In 2020
To conduct a basic study (ten weeks pre-mating exposure, Cohorts 1A & 1B, no expansions)?			
To conduct a full study design (two weeks pre-mating exposure, Cohorts 1A & 1B + Expansion of Cohort 1B + Cohorts 2A & 2B + Cohort 3)			

14) What is the average time duration in months, from contract signature until reporting, to carry out EOGRTS:

- Basic study (ten weeks pre-mating exposure, Cohorts 1A & 1B, no expansion):
- Expansion of Cohort 1B (minimum two-weeks pre-mating exposure):
- Developmental neurotoxicity Cohorts 2A & 2B:
- Developmental immunotoxicity Cohort 3:
- Full study (two weeks pre-mating exposure, Cohorts 1A & 1B + Expansion of Cohort 1B + Cohorts 2A & 2B + Cohort 3):

15) How much additional cost do the following study elements generate? For the following variations, consider the EOGRTS basic study-design to equal 100% cost and attribute an additional percentage (%) cost ***i.e. additional costs equal to half of a basic study design equals 50%, while double the cost of a basic study would equal 100%***

Move the slider to the right in 10% increment values, to attribute the additional percentage cost, of the following variations

Expansion of Cohort 1B (minimum two-weeks pre-mating exposure)	0 _____[__]_____ 250
Developmental neurotoxicity Cohorts 2A & 2B	0 _____[__]_____ 250
Developmental immunotoxicity Cohort 3	0 _____[__]_____ 250
Full study (two weeks pre-mating exposure, Cohorts 1A & 1B + Expansion of Cohort 1B + Cohorts 2A & 2B + Cohort 3	0_____[__]_____250

16) Assuming that the basic EOGRTS with ten weeks F0/P pre-mating exposure equals 100%, what is the cost reduction in percent (%), of reducing pre-mating exposure to two weeks? Please select the most relevant % cost saving:

- less than 6%
- 6 - 10%
- 11 - 20%
- more than 20%

Final Comments

17) Is the available ECHA guidance, updated July 2015, on reproductive toxicity sufficiently clear to specify and justify EOGRTS study designs as required by REACH?

- YES
- NO, please explain below

Comments:

18) ECHA has provided a visualisation of the study design options - is this helpful?

- YES
- NO, please explain below

Comments:

19) Does your laboratory have previous experience with the following study types? Please indicate the number of studies conducted over the past ten years

	0	1-3	4-9	10-2	21-49	50+
Reproductive toxicity studies (OECD 414, 415, 416, 421, 422)						
Developmental neurotoxicity studies (OECD 426)						
Developmental immunotoxicity studies						
Repeated dose toxicity (OECD 407, 408, 413)						
Chronic toxicity/Carcinogenicity (OECD 451, 452, 453)						
EOGRTS (OECD TG443)						

20) Would you be interested in attending a workshop on the EOGRTS under REACH?

- YES
- NO

21) Please confirm/provide the relevant contact details to be provided to ECHA
Please note that survey responses are anonymous and will not be linked to the details provided.

First Name:
Last Name:
Company Name:
Email Address:

22) Finally, do you have any further comments or information (including concerns over confidentiality) to provide?

Thank You!

Annex 2 Invitation Emails

A2.1 Invitations to participate in survey

Dear Sir/Madam

The extended one-generation reproductive toxicity study (EOGRTS) OECD TG 443 replaced the two-generation reproductive toxicity study OECD TG 416 on 13th March 2015 as a standard information requirement in the Annexes of Regulation (EC) No 1907/2006 (REACH). The European Chemicals Agency (ECHA) is expected to process more than 300 previously suspended testing proposals and compliance check decisions, in addition to ongoing and future Evaluation processes related to this endpoint. Therefore, it is necessary to investigate the global capacities and capabilities of test animal laboratories for conducting the EOGRT study for the chemical sector.

ECHA has contracted Risk & Policy Analysts (RPA) to establish which laboratories will be able to conduct this new test. RPA has developed, in close liaison with ECHA, a questionnaire: http://www.surveygizmo.com/s3/2250390/ECHA-EOGRTS-Laboratory-Survey[22]

We would be very grateful if you could respond to the questionnaire before **15th September 2015**.

Please contact me to ask for clarification or discuss any issues that may arise for your company in completing the questionnaire.

Kind regards

Louise Youngs
4 August

Risk & Policy Analysts
1 Beccles Road, Loddon, Norfolk, NR14 6LT
Tel: +44 1508 528465
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E-mail: louise.youngs@rpaltd.co.uk

[22] Please note that this link is no longer active as the consultation has been closed.

A2.2 Follow-up reminder email

Dear Sir/Madam

We have previously attempted to contact you regarding a study for the European Chemicals Agency (ECHA), aiming to estimate the global capacity to conduct the **Extended One-Generation Reproduction Toxicity Study (EOGRTS)**. To ensure a robust estimate, it is important that we have a good response rate, particularly from leading research organisations and *in vivo* facilities.

The EOGRTS (OECD TG 443) replaced the two-generation reproductive toxicity study (OECD TG 416) on 13th March 2015 as a standard information requirement in the Annexes of Regulation (EC) No 1907/2006 (REACH). ECHA is expected to process more than 300 previously suspended testing proposals and compliance check decisions, in addition to ongoing and future Evaluation processes related to this endpoint. Therefore, it is necessary to investigate the global capacities and capabilities of test animal laboratories for conducting the EOGRT study for the chemical sector.

ECHA has contracted Risk & Policy Analysts (RPA) to establish which laboratories will be able to conduct this new test. RPA has developed, in close liaison with ECHA, a questionnaire: http://www.surveygizmo.com/s3/2250390/ECHA-EOGRTS-Laboratory-Survey.

We appreciate that some of the questions may be **commercially sensitive**, if this is the case **the questions can be left blank** and it would be extremely helpful if you could complete the other questions. To ensure that the survey is distributed to the most relevant individual(s), a PDF copy of the survey is attached to this email for your reference. We would be very grateful if you could respond to the questionnaire before **15th September 2015.**

Please contact me to ask for clarification or discuss any issues that may arise for your company in completing the questionnaire.

Kind regards

Louise Youngs
9 September

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Annex 3 Published Cost Data

Whilst collecting cost data was deemed outside the scope of this study, the table below summarises some published costs of one- and two- generation reproductive toxicity tests. All figures have been adjusted by the EU-GDP price index to €(2015).

Published Cost Data for EOGRTS and related studies (figures adjusted to €(2015))			
CEHTRA (2012)* for EOGRTS	**Minimum**	**Maximum**	**Average**
Basic Study	€ 260,000	€ 795,000	€ 431,000
Basic study with optional second generation	€ 323,000	€ 697,000	€ 489,000
Basic study with neurotox (DNT) module	€ 366,000	€ 842,000	€ 528,000
Basic study with immunotox (DIT) module	€ 280,000	€ 703,000	€ 458,000
Basic study with both modules	€ 385,000	€ 890,000	€ 591,000
Full study design	€ 447,000	€ 931,000	€ 682,000
OECD (2010) **	**Minimum**	**Maximum**	**Average**
OECD TG 416 Two-Generation Reproduction	€ 276,000	€ 287,000	€ 282,000
OECD TG 443 EOGRTS	€ 122,000	€ 796,000	€ 597,000
Fleischer (2007)***	**BauA[1]**	**Large CRO**	**Average**
OECD TG 416 Two-Generation Reproduction	€ 273,000	€ 343,000	€ 358,000

** CEHTRA (2012) ECHA Report on Survey of Worldwide CROs: Costs and Practicalities of Two New OECD Guidelines for Testing Chemical Substances (ECHA/2011/217).*

*** OECD (2010) Guidance Document on Standardised Test Guideline for Evaluating Chemicals for Endocrine Disruption. Available at: http://www.oecd.org/chemicalsafety/testing/50459967.pdf (Note that quoted US$ figures were converted to €(2010) and then adjusted to €(2015))*

**** Fleischer, M (2007): Testing Costs and Testing Capacity According to the REACH Requirements – Results of a Survey of Independent and Corporate GLP Laboratories in the EU and Switzerland. Journal of Business Chemistry 4 (3): 96-116.*

[1] *BAuA is the German Federal Institute for Occupational Safety and Health (Federal Agency)*

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