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Enzyme REACH Consortium (ERC) Data Sharing Policy

1 Introduction

The REACH Regulation no. 1907/2006 both requires and encourages multiple manufacturers and importers of the same substance to coordinate the effort to comply with their respective REACH registration obligations.

For this reason, primarily manufacturers and importers of enzymes have created an open pre-consortium which was substituted by a consortium ("ERC") with the overall purpose of facilitating a smooth REACH implementation. Reference is made to www.enzymes-reach.org.

ERC aims at producing overall policies and agreement templates to be used as appropriate in the individual enzyme SIEFs.

In order for a substance that is subject to registration obligations pursuant to REACH to be registered, a technical dossier shall be submitted, cf. article 10 of REACH. The technical dossier shall contain sufficient data on the substance characteristics and use to ensure a EU harmonized high level of human health and protection of environment. The data requirements for technical dossiers are laid down in Annex VII-X of REACH, the extent of which depend on the manufacturing or import tonnage level of the substance. Pursuant to REACH article 11 (with certain exceptions) multiple registrants of the same substance shall share certain data and submit part of the registration relating to the substance jointly.

The rules regarding data sharing among registrants of the same substance and avoidance of unnecessary testing are found in Title III of REACH. The rules set out a principle of mandatory data sharing counterbalanced by a right for the data sharing party to obtain compensation from the data recipients.

Based on and in compliance with REACH principles, ERC has developed this over all Data Sharing policy to be adopted and adapted in the individual SIEFs. The Data Sharing policy applies to data required for the mandatory joint submission, as provided for in REACH Article 11 and concerns the development of data as such, meaning gathering and selection of data, determination of data gaps and preparation of test proposals, application of data waiving arguments and read-across principles.

This policy on Data Sharing shall apply to all SIEF Members who (i) issued the adherence letter attached as Appendix 1 or (ii) are a party to the Agreement among the Members of SIEF implementing by referral the ERC policy on Data Sharing (hereinafter referred to as the "SIEF Member").

Reference is made to the ERC Cost Sharing Policy, which has been developed by the ERC to ensure a procedure of fair, transparent, equal and proportional cost mechanism for the allocation of costs and compensation for data being shared by/with SIEF members.

This document is meant as guidance only and does not substitute legal or otherwise expert advice. The ERC and its members do not accept any liability for use of this Policy or for activities contemplated and carried out under this Policy or a SIEF Agreement adhering to this policy.

2 Basic procedural principles

The task of the Lead Registrant [Where the SIEF has established a steering committee, it shall be decided within SIEF which of the tasks, obligations and part of decision authority of the Lead Registrant outlined in this policy shall be transferred to/shared with this steering committee] in cooperation with the SIEF members is to gather, develop and jointly submit the data required to register the Substance pursuant to Article 11 (1) of REACH, including determining data gaps, waivers and surrogating data.

The required data comprises:

- Classification and labelling of the Substance pursuant to section 4 of Annex VI of the REACH Regulation;
- Study summaries of the information derived from the application of Annexes VII to XI of the REACH Regulation;
- Robust study summaries of the information derived from the application of Annexes VII to XI, if required in Annex I of the REACH Regulation;
- Proposals for testing where listed in Annexes IX and X of the REACH Regulation

2.1 STEP 1 – gathering and evaluation of existing studies owned by SIEF Members

2.1.1 Study rating

Upon request from Lead Registrant and within a reasonable time frame as set by Lead Registrant, each SIEF Member shall go through own studies for evaluation of relevance for REACH purposes for this Substance.

Each study owner shall rate own relevant studies according to the Klimisch codes[1] and submit the completed checklist attached as Appendix 1 for each relevant study to the Lead Registrant (as defined in REACH article 11). Each study owner represents and warrants that it is fully aware of the applicable criteria to rate according to the Klimisch codes and that its studies were duly rated in the checklists submitted to the Lead Registrant applying the aforementioned criteria.

Upon receipt of the submitted checklists, the Lead Registrant shall consolidate all check lists submitted and distribute this consolidated check list to the Steering Committee. Lead Registrant shall be authorized to challenge, verify and validate the Klimisch rating of the candidate studies either by virtue of its function or by written request from another SIEF Member. Upon request, the study owner shall provide Lead Registrant with sufficient information/documentation[2] in order for Lead Registrant to fill this function. Lead Registrant shall be allowed to distribute such information/documentation within the SIEF, however only to SIEF Members that have undertaken confidentiality and non-use obligations either as part of the SIEF Agreement or pursuant to a separate agreement.

2.1.2 *Disagreement on Klimish rating*

In the event Lead Registrant or another SIEF Member based on the information received from the study owner disagrees with the study owner's Klimisch rating of the relevant study, it shall notify the study owner in writing of its objection and give the study owner the opportunity to verify and/or correct its rating within a period of 2 weeks from receipt of the Lead Registrant's written notification.

[1] Klimisch et al. (1997): 1= reliable without restrictions, 2= reliable with restrictions, 3= not reliable, 4= not assignable.
[2] HERA Guidance Document, February 2005, Appendix C on Data Quality, p. 73-74, as further specified in "ERC's Policy on Data Sharing" or a SIEF agreement as the case may be.

In case Lead Registrant and study owner do not find an agreement on the correct rating of the study, the Lead Registrant or another SIEF Member may impose on the study owner to submit the relevant study with all pertaining information and data to a neutral third party expert for an impartial evaluation of Klimisch rating, provided that the third party expert has committed to treat all data and information received confidential. The third party expert may be chosen by the Lead Registrant from the list of third party experts attached as Appendix 1.1 (hereinafter referred to as "Third Party Expert") and shall be asked to submit its final evaluation within a period of approximately [1] month to Lead Registrant and study owner.

The evaluation of the relevant study's Klimisch rating submitted by the Third Party Expert shall be deemed final and binding on all SIEF Members including study owner, Lead Registrant and the SIEF Member objecting to the original rating of the study owner.

Costs associated with such Third Party Expert evaluation shall be paid by the study owner in case its original rating of the study owner was corrected by the Third Party Expert.

In case the Third Party Expert confirms the original rating of the study owner and the objection was raised by the Lead Registrant alone or jointly with other SIEF Members, such costs shall be equally shared among all other SIEF Members than the study owner.

In case the Third Party Expert confirms the original rating of the study owner and the objection was raised by one or more SIEF Members without the consent of Lead Registrant, such costs shall be paid by the objecting SIEF Member(s).

2.2 STEP 2 - Selection of key studies

2.2.1 Key study and authorization

The key study is the study that has been identified from a scientific point of view as the most suitable to describe an endpoint from the perspective of quality, completeness and representativity of data.

The Lead Registrant is authorized to select in its free discretion the key study from the studies provided by the SIEF Members or available applying read-across principles pursuant to the following rules:

(i) To the extent available, the key study shall be elected from Klimisch 1 rated studies.

(ii) Only if no Klimisch 1 studies are available within SIEF, the key study may be chosen from available Klimisch 2 studies.

(iii) If the available data is not sufficient for registration purposes, Lead Registrant may decide to initiate read-across procedures.

Note: In case the cost sharing principles of the ERC Cost Sharing Policy are applicable, selection of the key study among studies of the same Klimisch rating does not imply a financial advantage to the key study owner, as owners of studies with the same Klimisch ranking as the key study will be compensated equally.

[If ECHA is entitled to request access to full study report, key study owner should be obligated to submit a copy of this to Lead Registrant upon Lead Registrant's request.]

2.2.2 Provision of Study Summaries or Robust Study Summaries

In order for Lead Registrant to be able to use the key study in the joint submission in fulfillment of the obligations in REACH article 10 (a) (iv) and (vii) relative to the endpoint treated in the said key study, a study summary respectively a robust study summary shall be drafted.

Such drafting of study summaries and robust study summaries, including any costs associated therewith, is the responsibility of the owner of the key study, and shall take place upon request by the Lead Registrant. The summary shall be submitted to Lead Registrant within a reasonable time frame as set by Lead Registrant after receipt of the Lead Registrant's request and shall be made available to SIEF Members who have signed the SIEF Agreement.

If Lead Registrant disagrees or is not satisfied with the information and data provided by the key study owner for use in the joint submission under REACH, the procedure on disagreement solution outlined in section2.1.2 shall apply.

Lead Registrant shall at any time until joint submission be entitled to reverse a decision on the use of a specific study for material and scientific reasons.

Note: Pursuant to the ERC Cost Sharing Policy only key studies actually used in the joint submission trigger the application of the agreed cost sharing mechanism for studies with the same Klimisch rating, cf. ERC Cost Sharing Policy.

2.2.3 *Letter of Access – right to refer*

Subject to the confidentiality and non-use obligations undertaken by SIEF Members pursuant to the SIEF Collaboration Agreement (if applicable) or subject to a separate confidentiality agreement if no SIEF Collaboration Agreement exists, SIEF Members shall have the right to refer to studies selected by Lead Registrant to be used in joint submission, provided that they have received a letter of access as outlined below and paid compensation according to the agreed cost sharing mechanism (which will be the ERC Cost Sharing Policy in case of a SIEF Collaboration Agreement).

Lead Registrant shall inform SIEF Members, which study (including its Klimisch rating) has been chosen as key study and for which endpoint as soon as the Lead Registrant has taken the decision. Furthermore, Lead Registrant shall inform SIEF Members without undue delay in case the Lead registrant revises the decision taken and chooses another key study.

Owners of key studies shall issue a letter of access to Lead Registrant[3] within a period of [insert time] upon written request of Lead Registrant, authorizing Lead Registrant to use the study in the joint submission and to grant to other SIEF Members or members of other SIEFs the rights to refer to the study submitted to ECHA. Lead Registrant shall hereinafter issue letters of access to the said study to all SIEF Members[4] provided that these SIEF Members pay compensation for the access right pursuant to the agreed policy on cost sharing (the ERC Cost Sharing Policy). The same applies to members of other SIEFs requesting the said study in application of read-across principles and the members of this SIEF, who have not signed the SIEF Agreement.

The access rights granted under the SIEF Agreement and pursuant to this policy shall be <u>for the purpose of registration under REACH of this Substance only</u>, unless otherwise specifically agreed. If a study is required for REACH registration of another enzyme Substance by any other Member of another enzyme SIEF, a separate request for read-across shall be submitted to the Lead Registrant or the owner of the study. The Members shall allow access to read across for other enzyme substances pursuant to the READ Across Policy set forth hereinafter provided that the party requesting access pay compensation for the access to such study in accordance with the ERC Cost Sharing Policy.

<u>2.3 Read Across</u>

[3] Template letter of access to Lead Registrant enclosed as Appendix 2
[4] Template letter of access to SIEF Members enclosed as Appendix 3

ERC considers technical enzymes to be similar enough to justify using data relating to one technical enzyme substance for another technical enzyme substance based on a case-by-case expert evaluation of relevance and scientific justification.

In the following the recommended strategy for application of read-across principles will be outlined. A list of references is attached hereto as Appendix Z.

The strategy may be applicable, if the data available within SIEF is not sufficient for registration purposes.

2.3.1 Health hazard identification

For following end points read across can be applied subject to a case-by-case expert evaluation of the specific relevance and scientific justification:

- Skin irritation *in vivo*
- Eye irritation *in vivo*
- *In vitro* gene mutation in bacteria
- *In vitro* cytogenicity in mammalian cells (chromosome aberration)
- Acute oral toxicity
- Repeated dose oral toxicity:
    - Short term (sub acute) repeated dose toxicity study (28 days)
    - Subchronic toxicity study (90 days)

In general, enzymes exhibit the same toxicological properties and although respiratory sensitizers, are considered to be of low toxicity, which is confirmed by toxicity studies performed in the industry and published safety evaluations of a variety of enzymes (1-45).

Read across for the above mentioned end points can be applied for enzyme substances with the same IUB numbers and across IUB numbers, provided that the safety of the other constituents has been established and that the toxic effect with regard to the selected end point can be considered comparable.

However, read across between enzymes of different IUB numbers should only be considered and performed when there are no studies available for the specific enzyme. In general, read across between enzymes of different IUB numbers can be performed for the majority of enzyme substances, except for proteases due to the intrinsic properties of proteases to catalyse protein degradation.

In order to perform read across between enzymes of different IUB numbers for health hazard identifications enzyme substances can be divided into two groups, proteases and non-proteases, except for genotoxicity.

With regard to genotoxicity, all enzymes can be grouped together since the overall conclusion is that enzymes are not mutagenic or clastogenic.

For acute skin and eye irritation as well as genotoxicity qualitative read across can be applied since there is typically no dose response relationship. Qualitative and quantitative read across can be applied for acute oral and repeated dose oral toxicity.

2.3.2 Environmental hazard identification

For following end points read across can be applied subject to a case-by-case expert evaluation of the specific relevance and scientific justification:

- Aquatic toxicity:
    - Short term toxicity in Daphnia (OECD 202, semi-static)

- Growth inhibition study on algae (OECD 201, static)
- Short term toxicity testing on fish (OECD 203, semi-static)

- Ready biodegradability (OECD 301A-E)

In general, enzymes exhibit the same ecotoxicological properties as confirmed by ecotoxicity studies performed in the industry.

In general the same rules for read across can be applied as described for health hazard identification, besides the fact that in order to perform read across between enzymes of different IUB numbers for environmental hazards, enzyme substances should be divided into three groups, proteases, oxidoreductases and all other enzymes, except for biodegradability.

With regard to biodegradability all enzymes can be grouped together. Qualitative read across will be applied for both aquatic toxicity and ready biodegradability since the PNEC (predicted no effect concentration) values for the majority of enzymes except for proteases and oxidoreductases is considered the highest dose tested for a given end point. As far as biodegradability concerns all enzymes are considered ready biodegradable according to the current OECD guidelines indicating a simple yes or no answer and no quantitative relationship. Aquatic toxicity tests should be performed according to current OECD guidelines and under consideration that enzymes are readily biodegradable i.e. semi-static system when possible.

2.4 Data Waiving

The data requirements of REACH may be reduced if well-founded and meticulous scientific arguments (data waiving arguments) can be provided by the registrant in accordance with the rules of ANNEX XI of REACH.

Based on a well-qualified scientific approach, ERC has drafted a memo containing an outline of arguments for waiving of data requirements for technical enzymes from non-toxigenic, non-pathogenic organisms, with the aim of facilitating a less resource demanding fulfillment of the data requirements, cf. The ERC Policy on Safety Evaluation of technical enzyme products with regard to REACH legislation.

The Memo will be published on ERC's website enzymes-reach.org

These arguments can be applied by the Lead Registrant subject to a case-by-case expert evaluation of the specific relevance and scientific justification of the arguments in relation to the enzyme Substance in question.

Where data waiving arguments are scientifically justifiable and where their application may reduce costs for the SIEF Members, such approach should be chosen.

2.5 New Studies

2.5.1 Necessary studies not involving tests on vertebrate animals

If relevant or sufficient studies to fulfill REACH data requirements of Annex VII and VIII are not available in the SIEF, and cannot be obtained by application read across principles, cf. section 2.3, or other alternative methods (QSAR etc.), and if the data requirements cannot be waived, cf. section 2.4, only one study shall be carried out by a SIEF Member acting in agreement with the other SIEF Members requiring the said study. Lead Registrant shall determine the need for new studies.

The study shall be performed by an impartial (non-SIEF member) OECD recognized contract research organization (CRO) and on test material representative for all SIEF Members. Subject to these principles, Lead Registrant shall choose the CRO to perform the study and determine the criteria for selection of test material.

Lead Registrant shall have the first right of refusal to undertake the study sponsorship, the supply of test material and the ownership of the full study report. If Lead Registrant refuses, Lead Registrant shall have the right to appoint another SIEF Member to undertake these tasks, which SIEF Member shall have the right to refuse.

The sponsor of the study shall draft the test proposal to be submitted to ECHA.

The Lead Registrant or SIEF Member undertaking the role as sponsor and supplier of test material shall have full ownership of the study. The other SIEF Members shall have the right to receive the study summary/robust study summary (with respect of confidential business information) and the right to refer to the study. All use by SIEF Members is restricted to purposes of REACH registration of the Substance in question.

The actual and not standard study and administration costs of this new study shall be shared between the SIEF members for whom the study is relevant regardless of tonnage band, cf. the ERC Cost Sharing Policy. Notwithstanding the foregoing, only the external costs incurred to the contract research organization shall be shared. The documentation for the incurrence of such costs shall be provided to SIEF Members requiring the study.

2.5.2 Necessary studies involving tests on vertebrate animals

Lead Registrant shall draft test proposal if required. For the drafting of test proposal and for the carrying out of the study, when proposal has been accepted by ECHA, the principles outlined in section 2.5.1 of this policy shall apply.

2.6 Review by an assessor

In case the Lead Registrant finds it adequate or it is requested by (a) SIEF Member (-s) to have the joint submission or parts thereof reviewed by an assessor, cf. the reference to such voluntary option in REACH, article 10 a (VIII), the Lead Registrant shall appoint and engage an assessor to undertake such review, provided that the assessor is independent and has appropriate experience.

Costs associated with a review of the joint submission or parts thereof by an assessor shall be shared equally by the SIEF Members who are subject to information requirements specified in REACH Annex VIII – X AND for whom the data being assessed is required, if the third party assessment is determined/requested by the Lead Registrant or a majority of the SIEF Members (according to voting method), unless otherwise specifically agreed by the Steering Committee.

If the third party assessment is requested by (a) SIEF Member(s) not having a majority of votes, costs associated with the requested review shall be borne by the requesting SIEF Member (-s).

Appendix 1 – LETTER OF ADHERENCE

Addressee:

Name and Address of Lead Registrant

Re:

Adherence to ERC policy on Data Sharing, dated … (the "Data Sharing Policy")

The undersigned, authorized to act in the name and on behalf of [.. *to be added: company name, registered seat and registration number with chamber of commerce or commercial register*], pre-registrant of … [*designation of the IUBMB …, EINECS….*], hereby adhere to the abovementioned Data Sharing Policy subject to the following conditions:

1. We acknowledge to have received, read and fully understood the Data Sharing Policy
2. We agree with the Data Sharing Policy and accept to apply the Data Sharing Policy for the development of data required for the mandatory joint submission, as provided for in Art. 11 of the Regulation (EC) No.1970/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH).
3. This adherence letter will become part of the Agreement to be entered into among the SIEF Members in order to manage joint submission of Core Data according to Article 11 and Article 19 of REACH (the "SIEF Agreement"). The adherence letter is, however, legally valid even if no SIEF Agreement is or will be signed. In this case, the adherence letter shall be governed by the laws of [Belgium] excluding its choice of law rules.

Place, Date

_____

[Name of the Company]

[Name of signatory]

[Title]

APPENDIX 2

[Template letter of access to LR to be added]

APPENDIX 3

[Template letter of Access to SIEF Members to be added]