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EU LEGISLATION WITH GOOD LABORATORY PRACTICE (GLP) PROVISIONS

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1. INTRODUCTION

Good laboratory practice (GLP) is a quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported. Its purpose is to ensure the quality and integrity of the safety data submitted to regulatory authorities ('GLP receiving authorities').

The principles of GLP are applied to the non-clinical safety testing of test items contained in a range of products. The application of GLP is required by a variety of different product-specific legislation. This document lists all the EU legislation containing GLP provisions.

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2. EU LEGISLATIVE FRAMEWORK

2.1. Directive 2004/9/EC

Directive 2004/9/EC on the inspection and verification of good laboratory practice lays down the obligation for EU countries to designate the authorities responsible for GLP inspections in their territory. It also comprises reporting and internal market (mutual acceptance of data) requirements. The Directive in its Annex I contain the OECD Revised Guides for Compliance Monitoring Procedures for GLP, as well as the OECD Guidance for the Conduct of Test Facility Inspections and Study Audits, that should be followed during laboratory inspections and study audits.

2.2. Directive 2004/10/EC

Directive 2004/10/EC on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances is the second core EU GLP Directive. It contains the principles of GLP in its Annex I.

Article 1(1) of the Directive requires that "*Member States shall take all measures necessary to ensure that laboratories carrying out tests on chemical products, in accordance with Directive 67/548/EEC, comply with the principles of good laboratory practice (GLP)*". Directive 67/548/EEC is the Dangerous Substances Directive, which is repealed by the CLP Regulation (listed below) from 1 June 2015.

Article 1(2) specifies that this requirement "*shall apply also where other Community provisions provide for the application of the principles of GLP in respect of tests on chemical products to evaluate their safety for man and/or the environment.*" These other provisions are listed in this document.

3. CHEMICALS

3.1. Regulation (EC) No 1907/2006 (REACH)

REACH (Regulation (EC) No 1907/2006) is the Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals, which entered into force on 1 June 2007. It streamlines and improves the former legislative framework on chemicals of the European Union.

Article 13.4 of REACH Regulation (EC) No 1907/2006 requires that ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or the Agency.

Please note that no other international standards have been recognised to be equivalent to GLP. For further information, please refer to the relevant Q&A provided by the European Chemicals Agency (Q&A ID number 0118).

Annex XI of REACH (general rules for adaptation of the standard testing regime set out in annexes VII to X) provides for some exemptions for existing data in case that testing does not appear scientifically necessary.

For more information see also section R.4.2 (Reliability of information) in the Guidance on information requirements and chemical safety assessment.

The EU receiving authority for the REACH Regulation is the European Chemicals Agency (ECHA), which has been established to manage and in some cases to carry out the technical, scientific and administrative aspects of REACH. It receives the pre-registrations and registrations and will co-ordinate the evaluation, authorisation and restriction processes.

3.2. Regulation (EC) No 1272/2008 (CLP)

Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures aligns previous EU legislation on classification, labelling and packaging of chemicals to the GHS (Globally Harmonized System of Classification and Labelling of Chemicals).

Article 8.4 requires that where the manufacturer, importer or downstream user carries out new ecotoxicological or toxicological tests and analyses, these shall be carried out in compliance with Article 13(4) of Regulation (EC) No 1907/2006 (REACH), which establishes that ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (see above).

Article 8.5 requires that where new tests for physical hazards are carried out for the purposes of this Regulation, they shall be carried out, at the latest from 1 January 2014, in compliance with a relevant recognised quality system or by laboratories complying with a relevant recognised standard.

For these tests for physical hazards, ECHA Guidance on the Application of the CLP Criteria (July 2017) specifies that the requirement in Article 8.5 can be interpreted as follows:

(1) Compliance with the principles of good laboratory practice (GLP) (as formerly required by the DSD);

(2) Application of EN ISO/IEC 17025 General requirements for the competence of testing and calibration laboratories as amended as a relevant recognised standard;

(3) Other internationally recognised standards of comparable scope.

The EU receiving authority for Regulation (EC) No 1272/2008 is the European Chemicals Agency (ECHA).

4. BIOCIDES & PESTICIDES

4.1. Regulation (EU) No 528/2012 (biocidal products)

Regulation (EU) No 528/2012 sets the requirements for placing biocidal products on the market.

Annex II contains the information requirements for active substances:

> *"Tests performed should comply with the relevant requirements of protection of laboratory animals […] and in the case of ecotoxicological and toxicological tests, good laboratory practice, set out in Directive 2004/10/EC […] or other international standards recognised as being equivalent by the Commission or the Agency. Tests on physico-chemical properties and safety-relevant substance data should be performed at least according to international standards."*

Please note that no other international standards have been recognised to be equivalent to GLP. For further information, please refer to the relevant Q&A provided by the European Chemicals Agency (Q&A ID number 0989).

4.2. Regulation (EC) No 1107/2009 (plant protection products)

Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 is the regulation on placing plant protection products on the market. It repealed Council Directives 79/117/EEC and 91/414/EEC on 14 June 2011. Its aim is to protect human health and the environment, to harmonise the placing of plant protection products on the market, and to improve agricultural production.

Article 59(1) in chapter V of Regulation (EC) No 1107/2009 on data protection and data sharing requires that protection shall apply to test and study reports concerning the active substance, safener or synergist, adjuvants and the plant protection product, provided those tests were certified as compliant with principles of good laboratory practice (GLP).

Article 60(3) in chapter V of Regulation (EC) No 1107/2009 on the list of test and study reports requires that those lists shall include information on whether those test and study reports were certified as compliant with the principles of good laboratory practice.

Article 80(2) in chapter XI of Regulation (EC) No 1107/2009 refers to certain transitional measures.

Regulation (EU) No 283/2013 implementing Regulation (EC) No 1107/2009 as regards the data requirements for active substances and Regulation (EU) No 284/2013 implementing Regulation (EC) No 1107/2009 as regards the data requirements for plant protection products state that tests and analyses must be conducted in accordance with the principles laid down in Directive 2004/10/EC where testing is done to obtain data on the properties and/or safety with respect to human or animal health or the environment (Annex, introduction, point 3.1. for both Regulations).

The EU receiving authority for Regulation (EC) No 1107/2009 is the European Food Safety Authority (EFSA).

5. FOOD & FEEDSTUFF

5.1. Regulation (EC) No 429/2008 (feed additives)

Commission Regulation (EC) No 429/2008 of 25 April 2008 is the Regulation on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives. The objective of

this Regulation is to ensure the use of safe and good quality feeding stuff, to facilitate trade, and to protect human health, animal health, and the environment.

Annex II on general requirements to be satisfied by the dossier provided for in article 3 of the Regulation requires that studies shall be performed and documented according to appropriate quality standards (e.g. Good Laboratory Practice (GLP)). Where *in vivo* or *in vitro* studies are carried out outside the Community, the applicant shall demonstrate that the facilities concerned comply with the Organisation for Economic Cooperation and Development (OECD) principles of Good Laboratory Practice or ISO standards.

The EU receiving authority for Regulation (EC) No 429/2008 is the European Food Safety Authority (EFSA). Further information on feed additives can be found on the website of the European Commission's Directorate-General for Health and Food Safety (DG SANTE).

5.2. Regulation (EC) No 470/2009, Commission Implementing Regulation (EU) No 2017/12, and Commission Regulation (EU) 2018/782

The Commission Regulation (EC) No. 470/2009 lays down procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin. It repeals Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council; and Regulation (EC) No 726/2004 of the European Parliament and of the Council.

The Commission Implementing Regulation (EU) No. 2017/12 deals with the form and content of the applications and requests for the establishment of maximum residue limits in accordance with the above-mentioned Regulation 470/2009. The following are of relevance for GLP:

- Chapter 2 “Data for scientific risk assessment” of the Annex, under “A. Safety File” states that the dossier of safety tests shall include – among others - a discussion of the contribution that any non-GLP study can make to the overall risk assessment in cases where a study pre-dates Directive 2004/10/EC or Good Laboratory Practice status is unknown;

- Under the same sub-heading “A. Safety File”, it mentions that each study report shall include a signed statement of compliance with GLP, where applicable.

- Similarly, as mentioned in “B. Residue File”, the dossier of residue tests shall include a discussion of the contribution that any non-GLP study can make to the overall risk assessment in cases where a study pre-dates Directive 2004/10/EC or GLP status is unknown;

- Furthermore, each study report shall include a signed statement of compliance with GLP, where applicable.

Finally, Commission Regulation (EU) 2018/782 of 29 May 2018 establishes the methodological principles for the risk assessment and risk management recommendations referred to in Regulation (EC) No 470/2009.

The general principles of Annex I on methodological principles for the scientific risk assessment referred to in Article 6 of Regulation (EC) No 470/2009 mentions:

- Safety and residue tests for the establishment of maximum residue limits ('MRLs') shall be carried out in conformity with the provisions related to Good Laboratory Practice ('GLP') as laid down in Directive 2004/10/EC. If data are available that have not been generated under GLP conditions, the potential impact of this shall be addressed;

- Under "II. Safety File" it is indicated that detailed and critical summary of the safety file shall be required. Such detailed and critical summary shall discuss the GLP status of the studies submitted;

- Similarly, under "III. Residue File" it is indicated that a detailed and critical summary of the residues file shall be required for all applications. Such detailed and critical summary shall discuss the GLP status of the studies submitted.

5.3. Regulation (EU) No 234/2011 (food additives)

Commission Regulation (EU) No 234/2011 of 10 March 2011 implementing Regulation (EC) No 1331/2008 of the European Parliament and of the Council establishes a common authorisation procedure for food additives, food enzymes and food flavourings.

Article 5(7) on the general provisions on data for risk assessment requires that toxicological studies shall be conducted in facilities which comply with principles of good laboratory practice.

The EU receiving authority for Commission Regulation (EU) No 234/2011 is the European Food and Safety Authority (EFSA).

Further information on food additives can be found on the website of the European Commission's Directorate General for Health and Food Safety (DG SANTE).

5.4. Regulation (EU) No 503/2013 (GM food & feed)

Regulation (EU) No 503/2013 is an implementing regulation on applications for EU market authorisation of genetically modified food and feed.

Article 4 of this Regulation stipulates the following:

"Toxicological studies shall be conducted in facilities which comply with the:
(a) requirements of Directive 2004/10/EC; or
(b) 'OECD Principles on Good Laboratory Practice' (GLP), if carried out outside the Union.
Studies, other than toxicological studies, shall:
(a) comply with the principles of Good Laboratory Practice (GLP) laid down in Directive 2004/10/EC; or
(b) be conducted by organisations accredited under the relevant ISO standard."

5.5. Directive 2001/18/EC (GM food and feed)

Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 lays down provisions on a deliberate release into the environment of genetically modified organisms and placing on the market genetically modified organisms as or in products,

with a view to controlling risks from the release into the environment of GMOs and protecting human health and the environment.

Section 3 (Quality of data) of part C.1. of ANNEX II (Principles for the Environmental Risk Assessment) stipulates the following:

> *(a) where toxicological studies carried out to assess risk to human or animal health are provided in the e.r.a., the notifier shall provide evidence to demonstrate that they were conducted in facilities which comply with:*
>
> *(i) the requirements of Directive 2004/10/EC; or*
>
> *(ii) the 'OECD Principles on Good Laboratory Practice' (GLP), if carried out outside the Union;*
>
> *(b) where studies other than toxicological studies are provided in the e.r.a., they shall:*
>
> *(i) comply with the principles of Good Laboratory Practice (GLP) laid down in Directive 2004/10/EC, where relevant; or*
>
> *(ii) be conducted by organisations accredited under the relevant ISO standard; or*
>
> *(iii) in the absence of a relevant ISO standard, be conducted in accordance with internationally recognised standards;*

The EU receiving authority is the European Food Safety Authority (EFSA).

5.6. Implementing Regulation (EU) 2017/2469 (novel foods)

Commission Implementing Regulation (EU) 2017/2469 of 20 December 2017 lays down requirements for applications referred to in Article 10 of Regulation (EU) 2015/2283 on novel foods.

Article 5 (Scientific data requirements) requires toxicological studies to be conducted in facilities which comply with the requirements of Directive 2004/10/EC or, if they are carried out outside the territory of the Union, to follow the OECD Principles of Good Laboratory Practice.

The EU receiving authority is the European Food Safety Authority (EFSA).

5.7. Recommendation 97/618/EC (novel foods)

The Commission recommendation 97/618/EC of 29 July 1997 concerns the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients and the preparation of initial assessment reports under Regulation (EC) No 258/97.

Section 3.10 of the Commission recommendation 97/618/EC on allergenic potential specifies that studies to test the allergenic potential of novel foods should be compliant to principles of good clinical practice and good laboratory practice.

Moreover, Chapter XI of the Commission recommendation 97/618/EC on nutritional information on the novel foods requires that studies should be compliant to GLP principles, in particular regarding the numbers involved in study groups.

The EU receiving authority is the European Food Safety Authority (EFSA).

6. MEDICINAL PRODUCTS

6.1. Directive 2003/63/EC (human medicinal products)

Commission Directive 2003/63/EC of 25 June 2003 amends Directive 2001/83/EC of the European Parliament and of the Council of the 6 November 2001 on the Community code relating to medicinal products for human use.

Annex I, Introduction and general principles, Paragraph 9 requires that non-clinical (pharmaco-toxicological) studies shall be carried out in conformity with the provisions related to Good Laboratory Practice.

Section 2.2 Module 4 (Annex I, Part III of the Commission Directive) on radio-pharmaceutical precursors for radio-labelling purposes requires that for single dose and repeated dose toxicity, the results of studies carried out in conformity with the provisions related to good laboratory practice shall be provided, unless otherwise justified.

The EU receiving authority for Commission Directive 2003/63/EC is the European Medicines Agency (EMA).

6.2. Regulation (EU) No 536/2014 (clinical trials)

The Clinical Trial Regulation (Regulation No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC) entered into force on 16 June 2014 but was applied no earlier than 28 May 2016.

Article 25 of the Clinical Trial Regulation stipulates that *"non-clinical information submitted in an application dossier shall be based on data derived from studies complying with Union law on the principles of good laboratory practice, as applicable at the time of performance of those studies."*

Annex III of the Regulation requires the inclusion of *"a statement of the good laboratory practice status or equivalent standards, as referred to in Article 25(3)"* in the investigational medicinal product dossier (IMPD).

Prior to the application of the Clinical Trial Regulation, the Clinical Trial Directive (Directive 2001/20/EC) will continue to apply. This Directive does not contain any GLP requirements. However, the CT-1 guidance (Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial) requires for the IMPD that *"the protocols should meet the requirements of Good Laboratory Practice (GLP) guidelines where appropriate. The applicant should provide a statement of the GLP status of all studies."*

6.3. Regulation (EU) 2019/6 (veterinary medicinal products)

Regulation (EU) 2019/6 of 11 December 2018 repeals Directive 2001/82/EC of the European Parliament and of the Council on the Community code relating to medicinal products for veterinary use. It applies in all EU Member States as of 28 January 2022.

Paragraph 6, Introduction and general principles, Annex II of the Regulation requires that pharmacological, toxicological, residue and safety tests shall be carried out in conformity

with the provisions related to Good Laboratory Practice (GLP) laid down in Directive 2004/10/EC and Directive 2004/9/EC.

Chapter II on the presentation of particulars and documents specifies that each study report shall include a statement of compliance with good laboratory practice, if any study pre-dates studies performed in line with good laboratory principles. Each study report shall include a statement of compliance with

The EU receiving authority for Regulation (EU) 2019/6 is the European Medicines Agency (EMA).

7. COSMETICS

7.1. Regulation (EU) No 1223/2009

Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products is a recast of Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products. Most of the provisions of Regulation (EC) No 1223/2009 have become applicable from 11 July 2013.

Article 10(3) of Chapter III on safety assessment establishes the following quality requirement:

> *"Non-clinical safety studies referred to in the safety assessment according to paragraph 1 and carried out after 30 June 1988 for the purpose of assessing the safety of a cosmetic product shall comply with Community legislation on the principles of good laboratory practice, as applicable at the time of performance of the study, or with other international standards recognised as being equivalent by the Commission or the ECHA."*

To date, no other international standards have been recognised to be equivalent to GLP.

The receiving authorities for Regulation (EC) No 1223/2009 are the Member State competent authorities.

8. DETERGENTS

8.1. Regulation (EC) No 648/2004

Regulation (EC) No 648/2004 of the European Parliament and of the Council of 31 March 2004 is the Regulation on detergents. The objective of this Regulation is to harmonise the rules for the placing on the market of detergents and of surfactants for detergents.

Recital 30 of Regulation (EC) No 648/2004 states that tests specified for the biodegradability of surfactants should be carried out in laboratories meeting an internationally recognised standard, namely EN ISO/IEC17025 or the principles of good laboratory practice.

Article 5(2) on the granting of derogation states that applications for derogation shall include a technical file supplying all the information and results of tests necessary for

evaluating the safety aspects related to the specific use of surfactants in detergents failing to comply with the biodegradability limits. The tests shall be carried out on the basis of an approach defined in a technical guidance document, which will specify those tests for which the principles of good laboratory practice should be applied.

Article 7 on the testing of surfactants requires that tests on detergents shall be conducted in compliance with EN ISO/IEC standard or the principles of good laboratory practice, except for those tests for which the principles of good laboratory practice have been made mandatory.

Article 8(2) on the duties of Member States requires that each Member State shall notify to the other Member States and to the Commission the list of approved laboratories that are competent and authorised to carry out the tests required by Regulation (EC) No 648/2004. Member States have to demonstrate the competence of the above laboratories according to the standard EN ISO/IEC 17025 or verify the compliance of these laboratories with the principles of good laboratory practice.

Annex I defines standards of accreditation, good laboratory practice and animal protection concerning the laboratories that are competent and authorised to provide the necessary service for checking compliance of detergents with the requirements of this Regulation and its Annexes.

The receiving authorities for Regulation (EC) No 648/2004 are the Member State competent authorities.