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Framework for the quality assurance of 'omics technologies considering GLP requirements

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ABSTRACT

'Omics technologies are gaining importance to support regulatory toxicity studies. Prerequisites for performing 'omics studies considering GLP principles were discussed at the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) Workshop *Applying 'omics technologies in Chemical Risk Assessment*. A GLP environment comprises a standard operating procedure system, proper pre-planning and documentation, and inspections of independent quality assurance staff. To prevent uncontrolled data changes, the raw data obtained in the respective 'omics data recording systems have to be specifically defined. Further requirements include transparent and reproducible data processing steps, and safe data storage and archiving procedures. The software for data recording and processing should be validated, and data changes should be traceable or disabled. GLP-compliant quality assurance of 'omics technologies appears feasible for many GLP requirements. However, challenges include (i) defining, storing, and archiving the raw data; (ii) transparent descriptions of data processing steps; (iii) software validation; and (iv) ensuring complete reproducibility of final results with respect to raw data. Nevertheless, 'omics studies can be supported by quality measures (e.g., GLP principles) to ensure quality control, reproducibility and traceability of experiments. This enables regulators to use 'omics data in a fit-for-purpose context, which enhances their applicability for risk assessment.

1. Introduction

'Omics technologies, such as genomics, proteomics, metabolomics, and transcriptomics, are rapidly developing research technologies, and they are gaining increasing importance to support regulatory toxicity studies. The application and integration of 'omics technologies may be useful in different layers of regulatory hazard identification and assessment contributing to (i) the classification and labelling of substances, for example as part of a tiered testing strategy; (ii) weight-of-evidence approaches to elucidate

Abbreviations: ECETOC, European Centre for Ecotoxicology and Toxicology of Chemicals; GC - MS, Gas chromatography - mass spectometry; GLP, Good laboratory practice; LC - MS, Liquid chromatography - mass spectometry; NOAEL, No observed adverse effect level; OECD, Organisation for Economic Cooperation and Development; QAU, Quality Assurance Unit; qRT-PCR, quantitative real-time polymerase chain reactions; SOP, standard operating procedure.

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the modes-of-action of the substance under investigation; (iii) the substantiation of chemical similarity for read-across (ECHA, 2015; van Ravenzwaay et al., 2016); (iv) the determination of points-of-departure for hazard assessment; (v) the demonstration of species-specific effects and human health relevance (or absence thereof). Therefore, studies including 'omics technologies could make an important contribution to the risk assessment of substances (Buesen et al., 2017; Sauer et al., 2017).

Generally, regulatory toxicity studies must be performed according to principles of good laboratory practice (GLP) if they are intended to fulfil legal requirements to support the notification or regulatory approval of substances. Exceptions are, e.g., some specialized assays within the scope of immunotoxicity testing of pharmaceuticals, for which it is accepted that they might not comply fully with GLP (EMA, 2006). The Organisation for Economic Cooperation and Development (OECD) has provided a general GLP framework in its *Principles of good laboratory practice and compliance monitoring* (OECD, 1998) and a number of related OECD GLP consensus, guidance and advisory documents.

In order to use the data obtained in 'omics-based studies for regulatory purposes, it would be beneficial to also conduct these investigations according to the principles of GLP. This would serve the goals (i) to promote the consistent quality and validity of data used for determining the safety of chemical products, a primary objective of the GLP principles (OECD, 1998); (ii) to promote transparent process descriptions and thus support the traceability of study results; and (iii) to facilitate the exchange of information and enhance the regulatory impact of 'omics data, if successfully used for hazard and risk assessment purposes. All of these issues are expected to enhance the applicability of 'omics data in a regulatory context, but also in research consortia where different project partners use the same data for different purposes.

Moreover, the *OECD Council Decision on the mutual acceptance of data* (OECD, 1981) states that (eco)toxicological test data generated in any OECD member country in accordance with OECD Test Guidelines and the principles of GLP shall be accepted in other member countries. Hence, adherence to the principles of GLP also facilitates the mutual acceptance of data, and the GLP status of data avoids duplicate testing for different authorities.

'Omics technologies are part of a fast-growing scientific field that has a primary focus on the investigation of research questions. In this area, the GLP status of data is not required. However, as 'omics technologies are refined and knowledge on 'omics increases, the incentive to address questions specifically related to hazard identification and assessment using 'omics technologies is increasingly gaining importance. It is in this regulatory context that GLP conditions are relevant. However, to date, guidance is unavailable on how to conduct 'omics studies considering GLP conditions.

In addressing this deficiency, the establishment of a GLP context for collecting, storing and curating 'omics data was one of the key objectives of the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) workshop *Applying 'omics technologies in chemical risk assessment*, that took place on 10–12 October 2016 in Madrid, Spain (Fig. 1). The report of this workshop is provided in Buesen et al. (2017) in this journal Supplement.

For some aspects of 'omics studies full complicance with GLP requirements will be very difficult or virtually impossible to achieve for very special technical reasons, so that only 'GLP-like' procedures are possible meaning that procedures would be conducted as far as technically feasible in compliance with the principles of GLP, but without full GLP complicance.

Ahead of the ECETOC workshop, a first draft of a *Framework establishing a GLP(-like) context for collecting, storing and curating 'omics data* was compiled, and this draft was presented and further discussed during work stream 1 of the workshop (the term 'GLP (-like)' means in compliance with GLP or as close to GLP as technically possible). Data processing and data interpretation were not part of the GLP discussions, but were specifically addressed in work streams 2, 3, and 4 (Bridges et al., 2017; Gant et al., 2017; in this journal Supplement) (Fig. 1). The participants of the workshop, who brought in expertise with respect to transcriptomics/toxicogenomics, metabolomics and GLP, provided recommendations to advance the draft framework. These recommendations were addressed in updating the first draft, yielding the present article *Framework for the quality assurance of 'omics technologies considering GLP requirements*.

Generally, 'omics-based studies encompass three steps, i.e. (i) taking a tissue, blood, or cell sample from an *in vivo* or *in vitro* study; (ii) analysis using 'omics technologies; and (iii) scientific interpretation of the 'omics data (Fig. 2).

The concept to introduce GLP requirements for 'omics investigations raises certain challenges which are described and discussed below with respect to the different aspects that are relevant to conduct an 'omics study under GLP conditions (Section 2). Section 3 exemplarily presents the workflow of a metabolomics study to describe how GLP processes can be considered in an 'omics study. Section 4 summarizes the recommendations from the ECETOC workshop related to the quality assurance of 'omics technologies considering GLP requirements, and Section 5 provides a discussion of key issues addressed in this article and draws conclusions therefrom.

2. Application of the OECD principles of GLP to 'omics-based studies

Originally, the GLP principles were developed to promote the quality and validity of preclinical safety data. Test facilities performing GLP studies are regularly inspected for GLP compliance by national agencies based on national or agencies' GLP regulations. For some aspects (e.g. duration of archiving), these regulations can vary with agencies or nations, but the basic principles are very similar to ensure data quality and integrity. The GLP requirements established in national or agencies' regulations rely mainly on the *OECD Principles of good laboratory practice and compliance monitoring* (OECD, 1998) that serve to ensure that the evaluation of potential hazards of substances are based on safety data of sufficient quality, accuracy and reproducibility.

The OECD principles of GLP (OECD, 1998) cover specific chapters on (i) test facility organisation and personnel; (ii) quality assurance programme; (iii) facilities; (iv) apparatus, material, and reagents; (v) test systems; (vi) test and reference items; (vii) standard operating procedures (SOPs); (viii) performance of the study; (ix) reporting of study results; and (x) storage and retention of records and materials.

Of note, in 2004, the OECD published the *Advisory Document No. 14 on the application of the principles of GLP to in vitro studies* (OECD, 2004). This advisory document was developed in view of *anticipated developments in the fields of toxicogenomics, toxicoproteomics, toxicometabonomics and in various high throughput screening techniques* that were expected to enhance the importance of *in vitro* methodologies for safety testing (OECD, 2004).

As presented in further detail in the following Sub-sections, basic GLP principles that are relevant for the quality assurance of 'omics technologies considering GLP requirements, include:

- 2.1: Organisational aspects;
- 2.2: Standard Operating Procedures (SOPs);
- 2.3: Study planning;
- 2.4: Definition of raw data;
- 2.5: Data processing and storage;

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