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GUIDELINE ON THE EVALUATION OF CONTROL SAMPLES IN NONCLINICAL SAFETY STUDIES: CHECKING FOR CONTAMINATION WITH THE TEST SUBSTANCE

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1. INTRODUCTION

Since 1999 when the first situation was identified, several applications have revealed that samples from control animals contained levels of test substance, or antibodies against the test substance, suggesting that contamination of control animals or samples from control animals with the test substance had occurred.

The causes for contamination of controls samples may be multiple and in the majority of the situations the source of contamination has not been identified. The levels of contamination of controls samples were considered relevant/significant in some studies (e.g. carcinogenicity and reproductive toxicity) and led to their invalidation or impacted on a negative opinion for the Marketing Authorisation Application.

A survey conducted by the European Federation of Pharmaceutical Industries Association (EFPIA) shows that contamination of controls with different levels of test compound often occurs during toxicology studies, regardless of the route of administration used, the dose levels and duration of treatment.

The CPMP/ICH/384/95 Note for Guidance, Toxicokinetics: A Guidance Assessing Systemic Exposure in Toxicology Studies reads in its Note 8 that "it is often considered unnecessary to assay samples from control groups. Samples from controls may be collected and then assayed if it is deemed that this may help in the interpretation of the toxicity findings, or in the validation of the assay methods."

Significant contamination of controls may lead to the invalidation of studies due to their poor overall quality or to inappropriateness of toxicokinetic data to allow adequate interpretation of non-clinical safety studies and human risk assessment

2. SCOPE

The current guideline will give industry guidance on assaying the levels of test substance in samples from control animals in nonclinical safety studies, of reporting the findings and assessing the impact of any significant contamination in the validity of the studies.

This guideline serves the purpose of helping to verify the overall quality and validity of the nonclinical safety studies by proving that the control animals or samples were not contaminated by test article, avoiding major difficulties in evaluating the studies.

3. CONDITIONS REQUESTING CONTROLS SAMPLING AND ANALYSIS

Controls sampling and analytical procedures should be integrated in the toxicokinetic evaluation normally conducted in support of nonclinical safety studies. The analysis of samples from controls may need to be performed simultaneously with those from dosed animals.

3.1. Types of studies

For all pivotal studies that include a toxicokinetic evaluation, control samples should be collected and analysed.

In non-rodent studies, control samples should be collected and analysed in the same way as treated samples. In rodent studies, control samples should be collected and analysed in at least the general proximity of Tmax of the test substance.

3.2. Route of administration

Since contamination of control samples has been observed in studies using all routes of administration controls sampling and analyses should be performed irrespective of the route of administration.

4. CONSEQUENCES OF CONTAMINATION OF CONTROL SAMPLES AND ACTIONS TO BE TAKEN

Trace levels of contamination that are below the lower limit of quantification may in principle be considered as nonrelevant.

Contamination of control samples *in vivo* may compromise the validity and/or reliability of a study. Contamination of control samples *ex vivo* may compromise the validity and/or reliability of the corresponding toxicokinetic evaluation.

The decision on whether a study or its corresponding toxicokinetic evaluation will be invalidated depends on several aspects that need to be analysed carefully, including the extent of contamination and its impact on the validity of statistical analysis, definition of safety margins and reliability of animal exposures determined in the dosed animals

When significant contamination of control samples with the test compound at a level susceptible to impact on the validity of the study is observed, the sources of contamination should be investigated and identified. The applicant should make appropriate efforts to clarify whether contamination occurred *in vivo* or *ex-vivo*. Approaches may include, but are not exclusive to, identification of test substance in control tissues, identification of plasma metabolites in controls, or detection of antibodies against the test substance in case of a biotechnology product. Corrective measures should be taken accordingly.

When significant contamination of control samples with the test compound in nonclinical safety studies has occurred, it shall be reported appropriately. In any case the frequency, pattern and magnitude of contamination of controls should be clearly reported in the study reports and discussed with respect to its impact on the validity of the study. Irrespective of whether significant contamination of controls has been detected or not, the data from controls should be included in the toxicokinetic data in study reports. Furthermore, such findings should also be stated in the Written Summaries and highlighted in the Nonclinical Overview where discussion of their relevance and impact on the validity of the study, on the interpretation of the results and on the human risk assessment is expected.