الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

General Considerations for Preclinical Studies Submissions

Version 1.0

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Saudi Food & Drug Authority

Drug Sector

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Saudi Food and Drug Authority

Vision and Mission

Vision

To be a leading international science-based regulator to protect and promote public health

Mission

Protecting the community through regulations and effective controls to ensure the safety of food, drugs, medical devices, cosmetics, pesticides and feed

Document Control

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1. Introduction

Pharmaceutical and biological products submitted for approval must satisfy quality, safety, and efficacy standards. All pharmaceutical and biological products for human use must undergo preclinical testing to establish their safety and efficacy profiles. Evaluation of preclinical components is an integral part of evaluating the benefits and risks of the pharmaceutical product before granting approval. The overall evaluation process depends on the quality of the submitted preclinical data. The types of preclinical studies required depend on the type of application. This document provides general guidance on the preclinical data requirements for drug submissions to the Saudi Food and Drug Authority (SFDA).

2. Scope

This guidance provides recommendations on the preclinical data requirements for human medicinal and biological products. It applies to data supporting clinical trials applications and marketing authorization / variation applications (including impurity qualification) of chemical and biological pharmaceutical substances and products. The information discussed in this document does not apply to veterinary and herbal product submissions. The SFDA encourages applicants to discuss the outcome of the preclinical evaluation, if needed, in the context of this guidance.

This document is composed of two parts: Part A of the document is intended as a guidance tool for applicants to ensure that the minimum required preclinical data to establish the product's safety and efficacy are included in the applicant's submission. Part B of the document is a writing guide, which provides guidance to applicants in regards to the format and content of the non-clinical data submitted to the SFDA. The SFDA reserves the right to request information or material not specifically described in this document in order to assess the safety, efficacy, or quality of a therapeutic product. Such request would be justified and well documented.

This guidance should be read in conjunction with:

RELEVANT DOCUMENTS:

- Data Requirements for Human Drugs Submission.
- Regulatory Framework for Drugs Approval.
- Guidance for Submission.
- Guideline on Strategies to Identify and Mitigate Risks for First-in-human and Early Clinical Trials with Investigational Medicinal Products.
- Guideline for Investigational New Drugs (IND) Requirements.

International Council for Harmonization (ICH) guidelines which are implemented by SFDA:

- ICH Q3A – Q3E: Impurities.
- ICH Q5A: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin.
- ICH S1A – S1C: Carcinogenicity Studies.
- ICH S2: Genotoxicity Studies.
- ICH S3A – S3B: Toxicokinetics and Pharmacokinetics.
- ICH S4: Toxicity Testing.
- ICH S5: Reproductive Toxicology.
- ICH S6: Biotechnological Products.
- ICH S7A – S7B: Pharmacology Studies.
- ICH S8: Immunotoxicology Studies.
- ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals.
- ICH S10: Photosafety Evaluation.
- ICH S11: Nonclinical Paediatric Safety.
- ICH S12: Non-clinical Biodistribution Considerations for Gene Therapy Products.
- ICH M3: Nonclinical Safety Studies.
- ICH M6: Gene Therapy.
- ICH M7: Mutagenic Impurities.

The SFDA also takes into account other guidelines established by the Stringent Regulatory Authorities (SRAs), where no corresponding ICH guidelines are present or in conjunction with ICH guidelines if they offer supporting guidance.

3. Definitions

- **Applicant:**

  Any person who submits an application to the SFDA. The terms "sponsor" and "applicant" are used interchangeably within this document.

- **Biological drug:**

  Medicinal products derived from a variety of natural sources or produced by biotechnology methods and other cutting-edge technologies. They include a wide range of products such as vaccines, blood and blood components, allergenics, advanced therapy medicinal products (ATMPs), recombinant proteins and biosimilars.

- **Biosimilar drug:**

  Therapeutic proteins are produced by recombinant deoxyribonucleic acid (DNA) technology or gene expression methods following the footsteps of one licensed reference biotechnological product. They are complex and heterogeneous in their nature; hence, they are not considered generics, but as closely similar to the innovator's drug as possible.

- **Common Technical Document (CTD):**

  An internationally harmonized format for submission for approval of pharmaceuticals. The CTD provides standardization of the presentation of the content.

- **Degradation Product:**

  An impurity resulting from a chemical change in the drug substance brought about during manufacture and/or storage of the new drug product by the effect of, for example, light, temperature, pH, water, or by reaction with an excipient and/or the immediate container closure system.

- **Generic Drug:**

  A product created to be equivalent to the innovative/brand name product in dosage form, strength, route of administration, quality, performance characteristics, and therapeutic indication(s).

  Note: A drug application will be considered as generic if the innovative product is registered in one of the SRA irrespective of whether the innovative product is registered or not at SFDA.

- **Identified Impurity:**

  An impurity for which a structural characterization has been achieved.

- **Impurity:**

  Any component of the new drug product that is not the drug substance or an excipient in the drug product.

- **Mutagenic Impurity:**

  An impurity that has demonstrated to be mutagenic in an appropriate mutagenicity test model, e.g. bacterial mutagenicity assay.

- **New Drug Applications:**

  Applications to obtain marketing authorization for new (innovator) drug products.

- **New (Innovator) Drug Product:**

  A product that includes new chemical entity, biologic, or vaccine, which is introduced by the innovator company (or the partner).

- **Non-clinical:**

- The terms non-clinical and preclinical are used interchangeably within this document. Both terms are defined as any study that is not conducted on humans, including *in-silico*, *in-vitro*, and *in-vivo* studies.

- **Permitted Daily Exposure (PDE):**

  The maximum acceptable intake per day of an impurity/residual solvent in pharmaceutical products.

- **Potential Impurity:**

  An impurity that theoretically can arise during manufacture or storage. It may or may not actually appear in the new drug substance.

- **Preclinical:**

  Refer to the definition of non-clinical.

- **Qualification:**

  The process of acquiring and evaluating data that establishes the biological safety of an individual impurity or degradation product at the level(s) specified.

- **Qualification Threshold:**

  A limit above (>) which an impurity or degradation product should be qualified.

- **Reference Drug Product:**

  Also known as the Reference Listed Drug (RLD) or Comparator Product, is an approved drug product to which new generic versions are compared to show that they are bioequivalent.

- **Specification Limit:**

  Also known as the Acceptable Limit, is the maximum acceptable concentration of an impurity in a drug substance or drug product.

- **Stringent Regulatory Authority (SRA):**

  USFDA, EMA, MHRA (UK), Swissmedic, Health Canada, TGA (Australia) and PMDA (Japan).

- **Vaccine:**

  Preparations that contain antigenic substances capable of inducing a specific and active immunity against the infecting agent or the toxin or the antigen produced by it.

- **Validation (Business & Technical):**

  The process of checking if documents satisfies a certain criterion.

4. Part A: Preclinical data requirements

Every submission to the SFDA is required to include certain preclinical data to support the safety and efficacy of the pharmaceutical product. The required preclinical data depends on the type of submission. Herein we give a guidance on the minimum preclinical data requirements per type of submission.

4.1. New drug applications

For new drug applications, a full preclinical safety and efficacy assessment is required. The preclinical assessment should aim to establish a safe starting dose and dose range for the human clinical trials (First-in-Human [FIH]), identify parameters for clinical monitoring for potential adverse effects, characterize potential toxicities with respect to target organs, dose dependence, relationship to exposure and potential reversibility, and understand the pharmacokinetic and pharmacodynamic profile of the therapeutic agent.

The preclinical data requirements will depend on the type of pharmaceutical product and type of application (i.e., marketing authorization or clinical trial application). Please refer to the relevant ICH guidelines for a more detailed description of the preclinical data requirements. Additionally, a justification based on Stringent Regulatory Authorities' (SAR) guidelines can be accepted if there are no corresponding ICH guidelines, or in conjunction with ICH guidelines if they offer supporting guidance.

The preclinical data requirements generally include safety pharmacology and pharmacodynamic studies, pharmacokinetic and toxicokinetic studies, acute toxicity studies, repeat-dose toxicity studies, local tolerance studies, developmental and reproductive studies, genotoxicity studies, and, for drugs that have special cause for concern or are intended for a long duration of use, an assessment of carcinogenic potential. Other preclinical studies that may be required on a case-by-case basis include phototoxicity studies, immunotoxicity studies, juvenile animal toxicity studies, and abuse liability studies. The relevant animal model(s) or other test systems should be carefully selected to ensure that scientifically valid information is provided. Selection factors can include the pharmacodynamic responsiveness of the model, pharmacokinetic profile, species, strain,

gender, and age of the experimental animal, relevance to humans, the sensitivity, susceptibility, and reproducibility of the test system and available background data. Justification should be provided for the selection of the particular animal model or test system. In the case of any omitted parts of the preclinical module, justifications should be explicitly discussed in the submission. For pharmaceuticals under development for indications in life-threatening or serious diseases without current effective therapy, a case-by-case approach to the preclinical evaluation can be taken, where studies can be abbreviated, omitted, deferred, or added.

For a new drug registration application or clinical trials application, the applicant must complete and provide the Preclinical Studies Submission Checklist (Appendix 1) as part of the submission. For new drug registration applications, the checklist should be added to "Section 2.4 – Non-clinical Overview". For clinical trials applications, the checklist should be submitted alongside the non-clinical studies.

Please note that the SFDA does not accept summaries of the preclinical studies alone for marketing authorization and clinical trial applications. The full study reports for all preclinical studies conducted must be provided by the applicant (see writing guide in Part 2).

4.2. New generic drug application

Generic drugs are products that are comparable to the reference product and similar in therapeutic indications, active ingredient, dosage form, strength, route of administration, and quality characteristics. In the case of using a different form of the active substance (e.g., different salt), additional information might be needed to exclude the effect of this change on the safety and efficacy of the generic product. Additionally, a summary of the impurities in the drug substance and drug product, including the specification and justification of the specification, is required.

Applications of new generic products of a non-SFDA-approved reference drug should include a comprehensive literature review of the active substance as part of module 2.4 "non-clinical overview", to support the generic product registration.

4.3. Impurities

4.3.1. Qualification of Organic Impurities

Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual organic impurity or degradation product at the proposed specification limit. The applicant is required to provide a rationale for establishing organic impurity acceptance criteria that includes safety considerations under the "justification of specification" section of the dossier.

An organic impurity/degradation product is considered qualified when it meets one or more of the following conditions:

- The proposed specification limit for the impurity or degradation product does not exceed the qualification threshold based on the maximum daily dose of the drug substance or drug product as provided in ICH Q3A and ICH Q3B guidelines.
- The proposed specification limit for the impurity is within the acceptable limit specified in the European Pharmacopeia (Ph. Eur.), British Pharmacopeia (BP), or the US Pharmacopeia (USP).
- The observed level and proposed acceptable limit for the impurity do not exceed the level that has been adequately tested in safety and toxicity studies. The study considered appropriate to qualify the degradation product will depend on a number of factors, including the patient population, daily dose, and route and duration of drug administration. The studies can be conducted on the drug product containing the impurity or degradation product or on the isolated degradation product or impurity. Information on the actual content of the impurity or degradation products in the relevant batches at the time of use in the safety and toxicity study must be included (e.g., the certificate of analysis). Additionally, the full study reports for the safety studies must be provided. All calculations to deduce the qualified impurity level, if performed, must be provided in detail.
- The observed level and proposed acceptable limit for the impurity is adequately justified by the scientific literature. The scientific literature reference must be provided and easily accessible (link or pdf document).

- The observed level and proposed acceptable limit for the impurity in the generic drug product do not exceed the level justified by the reference listed drug product when comparing the analytical profiles using the same validated analytical procedure (e.g., comparative HPLC studies). The maximum daily dose of the impurity/degradation product and the route of administration must be taken into consideration for qualification via comparative analytical studies. Analytical studies should be conducted on comparable samples (e.g., age of samples, storage conditions) to get a meaningful comparison of the impurity/degradation profiles.

4.3.1.1. Mutagenicity Assessment of Impurities

Actual impurities and degradation products that have been identified in the drug substance and drug product should be assessed for their mutagenic potential. Consider evaluating the mutagenicity of potential impurities that are likely to be present in the final drug substance. The assessment of mutagenic potential should be conducted as per ICH M7 guidelines and identified mutagenic impurities should be controlled accordingly.

4.3.2. Qualification of Residual Solvents and Elemental Impurities

Risk assessment and control strategies, if required, should be conducted for residual solvents and elemental impurities in adherence with ICH Q3C and ICH Q3D, respectively. The risk assessment should focus on assessing the levels of these substances in the drug product in relation to their permitted daily exposure (PDE) in the corresponding ICH quality guideline.

Justification should be provided in the application for any acceptance criteria that exceeds the levels the ICH Q3C or ICH Q3D recommends as safe under the "justification of specification" section of the dossier.

5. Part B: Writing Guide for Non-clinical Study Reports

5.1. Documents Format

Non-clinical overview, written and tabulated summaries, study reports, and literature references should be written in English. Documents submitted in other languages will not be taken into consideration unless they are accompanied by an official and certified translation of the original documents. SFDA retains the right to request a retranslation at any time if the accuracy of the translation appears inaccurate or incomplete. Text and tables should be prepared using margins that allow the document to be printed on both A4 paper (E.U. and Japan) and 8.5" x 11" paper (U.S.). Font sizes for text and tables should be of a style and size that are large enough to be easily legible. Times New Roman, 12-point font, is recommended. The pagination must be carefully checked for correct sequence and completeness. Positioning of page numbers is optional. Acronyms and abbreviations should be defined the first time they are used.

5.2. Non-clinical Overview

An integrated, critical assessment, and overall analysis of the pharmacological, pharmacokinetic, and toxicological evaluation of the pharmaceutical product should be provided in the nonclinical overview. ICH guidelines and other accepted guidelines related to the studies conducted should be taken into consideration. Any deviation from these guidelines should be discussed and justified. A comment related to the good laboratory practice (GLP) status of the studies submitted should be included as appropriate.

The Nonclinical Overview should be presented in the following sequence:

1. Overview of the Nonclinical Testing Strategy
2. Pharmacology
3. Pharmacokinetics
4. Toxicology
5. Integrated Overview and Conclusions
6. Literature References

5.3. Non-clinical Written and Tabulated Summaries

Nonclinical written and tabulated summaries should provide a comprehensive, factual synopsis of the nonclinical data. The study report numbers must be provided in both written and tabulated summaries. The sequence and content of the nonclinical written summary and tabulated sections should include:

- Introduction
- Written summary of pharmacology
- Tabulated summary of pharmacology
- Written summary of pharmacokinetics
- Tabulated summary of pharmacokinetics
- Written summary of toxicology
- Tabulated summary of toxicology

Details related to each section is presented below:

- **Introduction**

The purpose of this section is to familiarize the reviewer with the pharmaceutical and its proposed clinical use.

- **Written summary of Pharmacology**

In this section, the data should be presented in the following sequence:

  - Brief summary
  - Primary pharmacodynamics
  - Secondary pharmacodynamics
  - Safety pharmacology
  - Pharmacodynamics drug interactions
  - Discussion and conclusions
  - Tables and figures

- **Tabulated summary of Pharmacology**
- **Written summary of Pharmacokinetics**

In this section, the data should be presented in the following sequence:

- Brief Summary
- Method of analysis
- Absorption
- Distribution
- Metabolism (Inter-species Comparison)
- Excretion
- Pharmacokinetic drug interactions
- Other pharmacokinetic studies
- Discussion and conclusions
- Tables and figures (either here or included in text)

- **Tabulated summary of Pharmacokinetics**
- **Written summary of Toxicology**

The sequence of the Toxicology Written Summary should be as follows:

- Brief summary
- Single-dose toxicity
- Repeat-dose toxicity
- Genotoxicity
- Carcinogenicity
- Reproductive and developmental toxicity
- Studies in juvenile animals
- Local Tolerance
- Other toxicity studies
- Discussion and conclusions
- Tables and figures (either here or included in text)

- **Tabulated summary of Toxicology**

Important point to consider:

For a new drug registration application or clinical trials application, the applicant is required to complete and provide the **Preclinical Studies Submission Checklist** (Appendix 1) as part of the submission.

5.4. Non-clinical Study Reports

Study reports should be submitted in module 4 of the dossier according to the SFDA's Data Requirements for Human Drugs Submission – Content of the Dossier. Additionally, all reports should be submitted in Portable Document Format (PDF) and must fulfil the requirements of the SFDA's Guidance for Submission.

Each study should be submitted separately. If the sponsor combines multiple studies in a single file, they must include a table of contents page listing the study title, the page number, and cross-reference to each corresponding study.

Title page:

Title page should include the Study Title, Study Report number, Start and End Dates, as a minimum. Additional study identifiers (e.g., Protocol number, Testing Facility Study number, Sponsor, Quality Assurance Auditor, Study Director, Principal Investigators (PI) of the study, version/amendment number) should be included, where applicable.

Abstract:

Provide an accurate summary of research objectives, a brief overview of the experimental model and the methods used, a summary of salient findings, a brief interpretation of the data, and conclusions.

Background and Introduction:

Provide sufficient scientific background that illustrates the rationale and context for the study, as well as the experimental approach. The applicant could also describe how the experimental model used addresses the scientific objectives and how it should emulate humans' biology.

Objectives:

The purpose of the study that was conducted should be clearly stated, including the research question, research objectives, and, where appropriate, specific hypotheses being tested.

Study Design:

The study design includes brief details of the following:

- The groups being compared, including control groups. If no control group has been used, a rationale should be stated.
- The experimental unit (e.g. a single animal, litter, or cage of animals).

Materials and Methods:

Information on the test and control articles must be included in the materials section. This should include information on the article identification name/number, batch number, physical form, composition and purity (supported by Certificate of Analysis), storage conditions, and stability.

Methods should be described in enough detail. The presentation of the used methodology varies across different types of nonclinical studies. Some information could be generalized (such as providing an ethical approval statement where the applicant is required to provide information related to the authority granting ethics approval, approval number, and approval date, if applicable), whereas other details could be study-specific. For example, in the case of ***in vivo*** studies, each study report should provide details of:

1. Housing and husbandry conditions (e.g., food and water, temperature and humidity, sanitation, lighting, etc.).
2. Study design, including:
    - Details related to the groups being compared to (e.g., control groups) and the exact value of *n* in each experimental group, if applicable.
    - Details related to the experimental unit, exact number of experimental units allocated to each group, and the total number in each experiment.
    - Information related to any inclusion and exclusion criteria for animals (or experimental units) during the experiment.
    - Details related to the animals used, such as species, strain, sub-strain, sex, age or developmental stage, weight, etc.

- Information related to the provenance of animals, health/immune status, genetic modification status, genotype, if applicable.

In the case of ***in vitro*** studies, following details should be considered:

1. Information related to test compound (e.g., name, source, purity, stability, etc.) and vehicle (e.g., type, characteristics, reasons for choosing, etc.)
2. Details related to test system, including:
    - Type of system: such as cell line, primary cells, tissue, organ, embryo
    - Species and strain (as relevant) of the origin of the cells/tissue/organ source, i.e., provider of the cells/tissue/organ
    - Metabolic competence
    - The number of cell passages if cell line was used
    - Composition of the media, including use of serum, antibiotics, etc.
    - Incubation temperature, humidity, and CO2 concentration
    - Measures taken for avoiding or screening for contamination by mycoplasma, bacteria, fungi and virus
    - Administration of test compound
3. Detailed description of each protocol used in the study.
4. Details about the standards followed, if relevant (such as good cell culture practice).
5. Information related to the reliability and sensitivity of the methods.
6. Data or participation in inter-laboratory calibration/validation programs.
7. Description of parameters measured.

Statistical analysis:

Provide details of statistical methods applied, including:

1. Details of the statistical methods used for each analysis, including software used.
2. Details of any methods used to assess whether the data met the assumptions of the statistical approach.
3. Details of all quantitative and/or qualitative assessments that were performed.
4. Details related to sample size calculation, if done (i.e., explain how the sample size was decided)
5. How missing values were handled.
6. If data transformation was performed, the transformation used and a rationale for the choice of data transformation should be provided.
7. Any other information that helps the evaluators to assess the submitted studies.

Results:

Characteristics of all animals used (such as species, strain, sub-strain, sex, weight, and age) should be reported. As indicated above, the analyses could include quantitative and/or qualitative assessments. Therefore, each type of analysis could be presented differently, yet the data presented should be unambiguous, concise, and clear to the evaluators.

As an example, for quantitative analyses, for each experiment conducted, the sponsor should be providing the following (where applicable):

1. Fundamental statistical and numerical descriptions (such as significant digits, error and correlations).
2. Summary/descriptive statistics for each experimental group. For continuous data, a measure of central tendency (e.g., mean, median) and a measure of variability (e.g., quartiles, range, standard deviation) must be included. Categorical data can be expressed as counts, frequencies, or proportions.
3. Statistical significance level (i.e., p-value) should be reported, in addition to the effect size with a confidence interval (if applicable).

Data could be also presented in tables or in figures to enable information to be evaluated. The applicant should report the results of all analyses performed, even the non-statistically significant ones.

Discussions and Conclusions:

In this section, the results should be interpreted, and the significance of the findings should be discussed in light of the objective(s) of the study. The strengths and limitations of the research can also be discussed. The conclusion should clearly highlight the key findings and important outcomes of the study.

Literature References:

A list of references used should be provided in accordance with the current edition of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, International Committee of Medical Journal Editors (ICMJE). The applicant is requested to provide and attach copies of the major references cited in the Nonclinical Overview and Reports. All other references that are provided should be available upon request. Providing a list of references without in-text citations is not accepted.

Appendices:

A full list of all appendices available for the study report should be provided in this section. There is no limit on what can be placed in an appendix; yet, each appendix must be labeled with a letter (A, B, C, etc.) according to where it appears in the report and must be referred to at the appropriate point in the text (e.g., see Appendix).

6. Appendices

6.1. Appendix 1: Preclinical Studies Submission Checklist

Appendix 1: PRECLINICAL STUDIES SUBMISSION CHECKLIST

Trade name:

_____

SDR/SCTR registration number:

_____

Drug Type:

- ☐ New drug
- ☐ Generic (Multisource) drug
- ☐ Biological: Biosimilar, Blood product, Vaccine, ATMPs
- ☐ Radiopharmaceuticals
- ☐ Others: please specify ……..

Please complete and submit this checklist along with your submission package. This checklist is intended to aid both the applicant and the application reviewers in the business validation stage to ensure that the required preclinical studies have been provided.
All sections listed below have to be submitted unless for some cases where an exemption could be granted. When no information is required in a specific section or subsection, the "not applicable" option should be selected. When information is not available (i.e., no study conducted), the "not provided" option should be selected. In both cases, scientific justifications (either by providing references from the existing literature or indicating the guideline(s)) should be provided in the justification box.

	Provided	Not provided	Not applicable	Justification*
Pharmacology				
Primary pharmacodynamics Studies on the mode of action and/or effects of a substance in relation to its desired therapeutic target	☐	☐	☐	
Secondary pharmacodynamics Studies on the mode of action and/or effects of a substance not related to its desired therapeutic target	☐	☐	☐	
Safety pharmacology Studies that investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure in the therapeutic range and above	☐	☐	☐	
Pharmacodynamic drug interactions Studies that show how a drug (A) alter the effects of another drug (B) without affecting its pharmacokinetics	☐	☐	☐	
Pharmacokinetics				
Absorption Studies describe how the drug moves from the site of administration to the systemic circulation.	☐	☐	☐	
Distribution Studies describe the journey of the drug through the bloodstream to various tissues of the body	☐	☐	☐	
Metabolism Studies describe the process that breaks down the drug	☐	☐	☐	
Excretion Studies describe the removal of the drug from the body	☐	☐	☐	
Pharmacokinetic drug interactions Studies that assess if a drug alters the absorption,	☐	☐	☐	

distribution, metabolism, and/or elimination of a co-administered agent(s)				
Other pharmacokinetic studies Any other related pharmacokinetic studies that were not listed above	☐	☐	☐	
Toxicology				
Single dose toxicity Studies that elucidate the acute toxicity of a drug after administration of a single dose of a substance.	☐	☐	☐	
Repeat dose toxicity Studies that assess the general toxicological effects of a drug that occur following repeated exposure to a drug substance for a certain period of time. This includes any supportive toxicokinetic reports. The studies should be arranged by species, by route, and by duration.	☐	☐	☐	
Genotoxicity Studies that assess if a chemical compound could induce genetic damage directly or indirectly by various mechanisms. These studies include: 1. In vitro 2. In vivo	 ☐ ☐	 ☐ ☐	 ☐ ☐	
Carcinogenicity Studies that aim to identify a tumorigenic potential in animals and to assess the relevant risk in humans 1. Long-term studies 2. Short- or medium-term studies 3. Other studies	 ☐ ☐ ☐	 ☐ ☐ ☐	 ☐ ☐ ☐	
Reproductive and developmental toxicity Studies that aim to investigate the effects of a chemical substance on fertility and development 1. Fertility and early embryonic development 2. Embryo-fetal development 3. Prenatal and postnatal development, including maternal function 4. Studies in which the offspring (juvenile animals) are dosed and/or further evaluated	 ☐ ☐ ☐ ☐	 ☐ ☐ ☐ ☐	 ☐ ☐ ☐ ☐	
Local Tolerance Studies that aim to examine the potential effects of a medicinal product (active substance and excipients) at a site of application	☐	☐	☐	
Other toxicity studies, if available Any other related toxicity studies that were not listed above, including but not limited to: 1. Antigenicity 2. Immunotoxicity 3. Mechanistic studies (if not included elsewhere) 4. Dependence 5. Metabolites 6. Impurities 7. Other	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐	

* This section is mandatory if "not provided" or "not applicable" boxes were checked

SUPPLEMENTARY DETAILS (Optional)

Use this box to include additional details