Regulatory Guidance – Template Numbering

Fifth and sixth level subheading numbering should be avoided within a document. Thus, the Acumen templates are built with subheadings that do not include the module number within the numbering string. For more information on eCTD numbering please see:

• M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use Guidance for Industry: https://www.fda.gov/files/drugs/published/M4-Organization-of-the-Common-Technical-Document-for-the-Registration-of-Pharmaceuticals-for-Human-Use-Guidance-for-Industry.pdf

Tips - Template Numbering

To ensure that the numbering string is not inadvertently updated to incorrect numbering, the Acumen templates arrive with the document fields locked. To unlock document fields, click on this icon in the Stylus toolbar: 

To lock fields prior to team reviews, click on the following icon in the Stylus toolbar: 

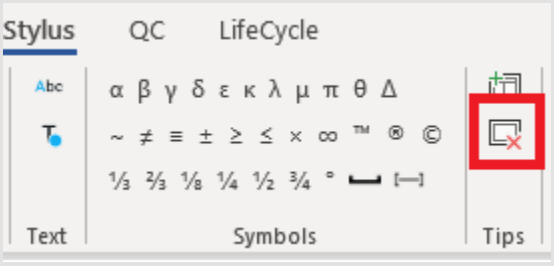
Regulatory Guidance

Regulatory Guidance informing Module 2.4:

- Guidance for Industry M4S: The CTD — Safety: https://www.fda.gov/media/71628/download

Tips - Removing Tips and/or Guidance

Once the Tips and/or Regulatory Guidance are no longer needed in the file (e.g., after the content drafting is complete or prior to publication), they can be easily removed by selecting the Stylus ribbon and clicking "Delete All Tips".



2.4 NONCLINICAL OVERVIEW

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LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Definition

Regulatory Guidance

General Aspects

The Nonclinical Overview should present an integrated and critical assessment of the pharmacologic, pharmacokinetic, and toxicologic evaluation of the pharmaceutical. Where relevant guidances on the conduct of studies exist, these should be taken into consideration, and any deviation from these guidances should be discussed and justified. The nonclinical testing strategy should be discussed and justified. There should be comment on the good laboratory practice (GLP) status of the studies submitted. Any association between nonclinical findings and the quality characteristics of the human pharmaceutical, the results of clinical trials, or effects seen with related products should be indicated, as appropriate.

Except for biotechnology-derived products, an assessment of the impurities and degradants present in the drug substance and product should be included, along with what is known of their potential pharmacologic and toxicologic effects. This assessment should form part of the justification for proposed impurity limits in the drug substance and product and be appropriately cross-referenced to the quality documentation. The implications of any differences in the chirality, chemical form, and impurity profile between the compound used in the Nonclinical studies and the product to be marketed should be discussed. For biotechnology-derived products, comparability of material used in nonclinical and clinical studies and proposed for marketing should be assessed. If a drug product includes a novel excipient, an assessment of the information regarding the excipient's safety should be provided.

Relevant, scientific literature and the properties of related products should be taken into account.

If detailed references to published, scientific literature are to be used in place of studies conducted by the applicant, this should be supported by an appropriate justification that reviews the design of the studies and any deviations from available guidances. In addition, the availability of information on the quality of batches of drug substance used in these referenced studies should be discussed.

The Nonclinical Overview should contain appropriate reference citations to the Tabulated Summaries in the following format: (Table X.X, Study/Report Number).

Content and Structural Format

The Nonclinical Overview should be presented in the following sequence:

- 2.4. NONCLINICAL OVERVIEW
- 2.4.1 Overview of the Nonclinical Testing Strategy
- 2.4.2 Pharmacology
- 2.4.3 Pharmacokinetics
- 2.4.4 Toxicology
- 2.4.5 Integrated Overview and Conclusions
- 2.4.6 List of Literature Citations

Studies conducted to establish the pharmacodynamic effects, the mode of action, and potential side effects should be evaluated, and consideration should be given to the significance of any issues that arise.

The assessment of the pharmacokinetic, toxicokinetic, and metabolism data should address the relevance of the analytical methods used, the pharmacokinetic models, and the derived parameters. It might be appropriate to cross-refer to more detailed consideration of certain issues within the pharmacology or toxicology studies (eg, impact of the disease states, changes in physiology, antiproduct antibodies, cross-species consideration of toxicokinetic data). Inconsistencies in the data should be discussed. Interspecies comparisons of metabolism and systemic exposure comparisons in animals and humans (AUC, Cmax, and other appropriate parameters) should be discussed and the limitations and utility of the nonclinical studies for prediction of potential adverse effects in humans highlighted.

The onset, severity, and duration of the toxic effects, their dose dependency and degree of reversibility (or irreversibility), and species- or gender-related differences should be evaluated and important features discussed, particularly with regard to:

Pharmacodynamics

- Toxic signs
- Causes of death
- Pathologic findings

- Genotoxic activity — the chemical structure of the compound, its mode of action, and its relationship to known genotoxic compounds
- Carcinogenic potential in the context of the chemical structure of the compound, its relationship to known carcinogens, its genotoxic potential, and the exposure data
- The carcinogenic risk to humans — if epidemiologic data are available, they should be taken into account
- Fertility, embryofetal development, pre- and postnatal toxicity
- Studies in juvenile animals
- The consequences of use before and during pregnancy, during lactation, and during pediatric development
- Local tolerance
- Other toxicity studies and/or studies to clarify special problems

The evaluation of toxicology studies should be arranged in a logical order so that all relevant data elucidating a certain effect and/or phenomenon are brought together. Extrapolation of the data from animals to humans should be considered in relation to:

- Animal species used
- Numbers of animals used
- Routes of administration employed
- Dosages used
- Duration of treatment or of the study
- Systemic exposures in the toxicology species at no observed adverse effect levels and at toxic doses, in relation to the exposures in humans at the maximum recommended human dose. Tables or figures summarizing this information are recommended.
- The effect of the drug substance observed in nonclinical studies in relation to that expected or observed in humans

If alternatives to whole animal experiments are employed, their scientific validity should be discussed.

The integrated overview and conclusions should clearly define the characteristics of the human pharmaceutical, as demonstrated by the nonclinical studies, and arrive at logical, well-argued conclusions supporting the safety of the product for the intended clinical use. Taking the pharmacology, pharmacokinetics, and toxicology results into account, the implications of the nonclinical findings for the safe human use of the pharmaceutical should be discussed (ie, as applicable to labeling).

1. OVERVIEW OF THE NONCLINICAL TESTING STRATEGY

2. PHARMACOLOGY

3. PHARMACOKINETICS

4. TOXICOLOGY

5. INTEGRATED OVERVIEW AND CONCLUSIONS

6. LIST OF LITERATURE CITATIONS