

References

Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food, US FDA, Center for Food Safety and Applied Nutrition, 1982 and as updated in 1993 and 2000, see also:

<http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/Redbook/ucm078044.htm>

TASK AREA 1 – GENOTOXICITY TESTING

Applicable guidelines include the ICH (International Conference on Harmonisation) S2A Guideline on Specific Aspects of Regulatory Genotoxicity Tests [Fed. Reg. 59(183): 48734, Sept. 22, 1994 and 61: 18199, April 24, 1996; see

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074925.pdf>, and S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals, July, 1997; see

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074929.pdf>. In addition, 2008 Draft Guideline S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use; see

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074931.pdf>

TASK AREA 2 – GENERAL TOXICOLOGY IN EXPERIMENTAL ANIMALS

v. CARCINOGENICITY STUDIES IN RODENTS

Applicable guidelines include S1A *The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals*

<http://docs.google.com/viewer?url=http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074911.pdf&pli=1>), S1B *Testing for Carcinogenicity of Pharmaceuticals*

<http://docs.google.com/viewer?url=http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074916.pdf>), and S1C(R2) *Dose Selection for Carcinogenicity Studies*

<http://docs.google.com/viewer?url=http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074919.pdf>

TASK AREA 3 – REPRODUCTIVE TOXICITY STUDIES IN RODENTS AND RABBITS

Applicable guidelines include, for example, USFDA Guidelines for Reproduction Studies for Safety Evaluation of Drugs for Human Use (1966); USFDA-International Committee on Harmonization (ICH) Draft Guidelines on Detection of Toxicity to Reproduction for Medicinal Products [Fed. Reg. 58(72):21074, April 13, 1993, SEE also ICH S5A

<http://docs.google.com/viewer?url=http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074950.pdf&pli=1> and ICH S5B

<http://docs.google.com/viewer?url=http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074954.pdf>]; and USEPA Guidelines for Health Assessment of Suspect Developmental Toxicants [Fed. Reg. 51(185): 34028, Sept. 24, 1986], see also:

<http://www.fda.gov/cder/guidance>.

TASK AREA 4 – SPECIALIZED STUDIES

Applicable guidelines include *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073246.pdf>

i. BIOANALYTICAL METHODOLOGY STUDIES

Applicable guidelines include: Bioanalytical Method Validation

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf>

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073381.pdf>

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073384.pdf>

ii. PHARMACOKINETIC AND PHARMACOKINETIC-PHARMACODYNAMIC STUDIES

Applicable guidances include S3A, *Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074937.pdf>), S3B *Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074938.pdf>), and *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf>

iii. BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES

Applicable guidelines include *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations*.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf>

iv. DRUG METABOLISM/DRUG INTERACTION STUDIES

Applicable guidelines include *Drug Metabolism/Drug Interaction Studies in the Drug Development. Studies In Vitro*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072104.pdf>) and *Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling*.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072101.pdf>).

v. SPECIFIC SAFETY STUDIES

Applicable guidelines include *S7A Safety Pharmacology Studies for Human Pharmaceuticals*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074959.pdf>), *S8 Immunotoxicity Studies for Human Pharmaceuticals*

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074965.pdf>

B. GENERAL PROCEDURES

i. ANIMAL FACILITY

The studies shall be conducted under the Food and Drug Administration Good Laboratory Practice Regulations as published in the Federal Register CFR Title 21, Part 58

<http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=bdba69dcdf5c19dcc5c8ed3e3a88f553&rgn=div5&view=text&node=21:1.0.1.1.22&idno=21>