# Overview of Chemistry, Manufacturing, and Controls Activities

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**ADME/PK studies:**

| Non GLP | | GLP |
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| **In Vitro** | **In Vivo** | **In Vivo** |
| • Physical/chemical properties (lipophlicity (log P/log D), pKa, stability vs pH, solubility vs pH<br>• Metabolic stability<br>• Hepatic clearance<br>• Interaction with substances (CYP inhibition/ induction)<br>• Physiological characteristics (protein and tissue binding)<br>• Permeability<br>• Plasma stability, total blood/plasm partition | • Pharmacokinetic profile (concentration versus time):<br>  ○ AUC<br>  ○ Cmax<br>  ○ Tmax<br>  ○ Distribution<br>  ○ Clearance<br>  ○ Half life<br>• Bioavailability<br>• Linearity<br>• Metabolization<br>• Routes of excretion | • Toxicokinetics:<br>  ○ Pharmacokinetic profile (concentration versus time)<br>  ○ AUC<br>  ○ $C_{max}$<br>  ○ $T_{max}$<br>  ○ Distribution<br>  ○ Clearance<br>  ○ Half life<br>• Bioavailability<br>• Metabolization<br>• Routes of excretion<br>• Quantification of fluids (organs, tissues, excrement, expired air) |

**Nonclinical studies based on molecule type and application:**

| Study | Small Molecules | Large Molecules (Biologics and Recombinant Peptides) | Oncology |
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| Pharmacodynamics<br>• Primary: effect of drug on target in body<br>• Secondary: effect of drug on other aspects of body<br>• Safety (**GLP**): effect at target does and higher on key organ systems | Safety includes:<br>• In vitro (concentration-effect relationship)<br>• In vivo (dose response for respiratory, CNS, cardiovascular) | Safety includes:<br>• In vitro (concentration-effect relationship)<br>• In vivo (dose response for respiratory, CNS, cardiovascular)<br>• Choice of species to be relevant | • Proof of concept study<br>• Incorporate Safety Pharmacology into the General Toxicology study (CNS, CV, and respiratory) |

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| (respiratory, CNS, cardivascular); see ICH S7A and S7B | | | |
| Pharmacokinetics<br>• ADME: adsorption, distribution, metabolism, excretion<br>• Toxicokinetics: similar to PK, TK focuses on the adsorption and fate to the drug in the body, but specifically related to any toxic effects | Pharmacokinetics<br>• In vitro metabolism (across species microsomal metabolism)<br>• In vitro protein binding<br>• Toxicokinetics from repeat dose **GLP** toxicity study (ICH S3A) | • ADE/No M<br>• Protein binding if applicable | Pharmacokinetics<br>• In vitro metabolism (across species microsomal metabolism)<br>• In vitro protein binding<br>• Toxicokinetics from repeat dose **GLP** toxicity study (ICH S3A) |
| Toxicology:<br>• Single dose toxicity and repeated dose toxicity<br>• Initial (rat or mouse) followed by larger (dog, for example)<br>• Single dose toxicity profile:<br>o NOAEL (no observed adverse effect level<br>o Target organs of toxicity<br>o Establish doses for FIH study<br>• Repeated dose toxicity profile:<br>o Toxicity profile with repeated dosing<br>o Target organs of toxicity<br>o Reversibility of adverse effects<br>o Establish doses for FIH study<br>• Duration:<br>o Subchronic: 7, 14, 28 days and 3 months<br>o Chronic: 6, 9, and 12 months | Acute:<br>--1 rodent and 1 non-rodent<br>--Single dose or MTD<br>Chronic:<br>--1 rodent and 1 non-rodent (chosen based on similarity to human metabolism)<br>--For duration of study, see Table 1, ICH M3(R2)<br><br>• Single dose is **GLP** if it is used to determine FIH dose (more typical for biologic); else it is nonGLP.<br>• These studies could be maximum tolerated dose studies (MTD)<br>• Repeated dose study is **GLP**.<br>• Clinical MRHD is usually limited by toxicities or highest dose tested in animals.<br><br>Late Phase (3 and onward):<br>-6 month rodent and 9 month non-rodent | General Toxicology:<br>--≤ 1 mo in rodent and non-rodent<br>--2 week immunogenicity and local tolerance<br><br>• May only do single dose study and repeated dose study in non-rodent<br>• Single dose is **GLP** if it is used to determine FIH dose (more typical for biologic); else it is non GLP.<br>• These studies could be maximum tolerated dose studies (MTD)<br>• Repeated dose study is **GLP**.<br><br>Late Phase (3 and onward):<br>-6 month rodent or 6 month non-rodent | General Toxicology:<br>--3 mo in 2 species<br>--Genotoxic products: 3 mo in 1 species<br>--Similar schedule to clinical use<br><br>• Single dose is **GLP** if it is used to determine FIH dose (more typical for biologic); else it is non GLP.<br>• These studies could be maximum tolerated dose studies (MTD)<br>• Repeated dose study is **GLP**. |
| Toxicology:<br>• Genotoxicity (genetic mutations of cell); looking for damage to DNA/chromosomes<br>• ICH S2(R1)<br>• **GLP** | Genetic Toxicity:<br>--Complete prior to Phase 2<br>--In vitro Ames test<br>--In vitro and/or in vivo mammalian cell chromosomal damage evaluation | • No genotoxicity | Genetic Toxicity:<br>-- Complete prior to marketing<br>--In vitro Ames test<br>--In vitro and/or in vivo mammalian cell chromosomal damage evaluation<br>--1 species, usually rodent |
| Toxicology:<br>• Carcinogenicity (can drug cause cancer) | | | • No carcinogenicity |

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| ○ 2 year mouse or 26 week transgenetic mouse<br>○ 2 year rat | | | |
| Toxicology:<br>• Developmental and reproductive toxicity (DART)<br>○ Fertility (typically rat)<br>○ Teratology (typically rat and rabbit)<br>○ Peri- and post-natal (typically rat) | | | • Embryo-fetal development only |
| Other:<br>• Immunotoxicity (ICH S8)<br>• Photosafety (ICH S10)<br>• Abuse liability (if similar to other compounds subject to abuse or expected based on MOA) | | | |
| Dose Schedule:<br>• Determination of first human dose and dose escalation | | | |