General Toxicity

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Abstract

Before a new small molecule candidate drug (CD) can enter human clinical trials for the first time, safety and tolerability must be assessed in preclinical rodent and nonrodent toxicology studies, both as a regulatory requirement and, more importantly, to assess, limit and manage risk to human volunteers or patients. One central premise of the testing strategy is that toxicity is exacerbated by prolonged exposure; this is clearly reflected in regulatory guidance on toxicity testing for small molecules where nonclinical toxicology studies of up to one month duration are sufficient to support dosing for up to one month in Phase I clinical trials (ICH M3(R2), 2009) whereas 6 or 9 month nonclinical studies would generally be required to support dosing for longer than 6 months and are required for registration (ICH M3(R2), 2009). Similarly, in guidelines for testing of other chemicals, longer duration toxicology studies are required to support higher volumes/longer exposure periods unless combined weight of evidence is sufficient for the purpose of classification, labelling and risk assessment. Generally, acute and chronic toxicity work begins with MTD/DRF studies that establish the maximum tolerated dose and define the dose response curve to set doses for the one-month rodent and nonrodent GLP studies. In our analysis of target organ toxicities for 77 AstraZeneca CDs in GLP toxicology testing, the most frequently affected organ in the rodent was the liver followed by adrenal glands, kidney, spleen, bone marrow and thymus. In nonrodent, liver and thymus were the most frequently affected organs, followed closely by the testis and GI tract. In chronic (3-9 months) toxicity testing, an additional 39% of TO toxicities were identified compared to observations in FTiM studies. Overall, the data from the one-month GLP studies form the basis of the risk assessment for Phase 1, are used to set starting doses and exposure limits based on the nonclinical no adverse effect level (NOAEL) and may inform any additional clinical monitoring. Data from subsequent chronic toxicology studies is used to support larger phase II and phase III clinical trials and is required for registration.