Formulation may also influence drug effects. For example, in mice, both the lethal dose (expressed as LD_{50}) and the ability to achieve some pharmacodynamic endpoint (e.g., righting reflex) for a fast acting compound (sodium pentobarbital) were significantly different when administered as an intraperitoneal injection of an aqueous solution or in a 1% carboxymethylcellulose solution. The decrease in pharmacological response with the 1% carboxymethylcellulose solution was attributed to an increase in product viscosity which, in turn, retarded drug uptake (8). This simple example underscores the influence of formulation in preclinical studies. Additional insight into potential species-specific considerations in drug formulations have been published elsewhere (9).

Excipients used in preclinical drug formulations can markedly affect the level of drug exposure. Permeability enhancers such as the bile salt sodium deoxycholate (10), fatty acids such as sodium caprate (10), and surfactants (11) such as polysorbate 80 (12), Cremophor EL (13), and vitamin E (14) can alter P-glycoprotein (P-gp) activity. P-gp is a membrane transporter protein that can affect the first-pass drug loss of many compounds. The role of P-gp in determining drug oral bioavailability is discussed later in this chapter and in Chapter 8.

Differences have been observed in the ability of the various animal species to express toxic reactions similar to that in humans (15). In a survey of the 20 chemical entities for which preclinical and clinical toxicity information was available, monkeys, rats, and mice appear to exhibit the greatest similarity to humans in adverse events. Dogs are associated with a more frequent occurrence of false-positive reactions (Table 2).

Similarly, in comparing the accuracy of the predictions of human drug toxicity generated in dogs and monkeys, Schein et al. (16) observed that monkeys and dogs tend to correctly predict bone marrow depression, gastrointestinal disturbances, and hepatotoxicity. However, these same species present with a high percentage of false positives. Of the 25 anticancer drugs investigated, dogs exhibited a particularly high rate of false positives for pathology of the stomach, small and large intestine, liver (including increases in alkaline phosphatase) and kidney (including proteinuria).

Table 2 Correlation of Toxicity to that Observed in Humans (15). Reprinted with Permission

	Rat	Mouse	Dog	Monkey
# Comparisons with humans	14	11	11	6
Similar to human (±)	71%	73%	45%	83%
False-positive	21%	—	36%	—
False-negative	7%	27%	18%	17%