- Safety Pharmacology: Guidance for Industry: Safety Pharmacology Studies for Human Pharmaceuticals; ICH S7A (July 2001).

Toxicology:

- Single and Repeat Dose Toxicity: Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals; ICH-M3 (Jul 1997).
- Single Dose Acute Toxicity Testing for Pharmaceuticals; PT1 (Aug 1996).

Reproductive Toxicity:

- Detection of Toxicity to Reproduction for Medicinal Products; ICH-S5A (Sep 1994).
- Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility; ICH-S5B (Apr 1996).

Pediatric Drugs:

- Draft Guidance for Industry: Nonclinical Safety Evaluation of Pediatric Drug Products (Feb 2003).

Throughout the various ICH/CDER guidances, we see the same basic points to consider when selecting an appropriate animal model. These include:

- similarity in toxicological/pharmacodynamic responsiveness;
- pharmacokinetic profiles similar to those seen in humans;
- similar metabolic profile.

3. TOXICOLOGICAL ENDPOINTS

Observations generated in a toxicity study represent discrete protocol driven points on the dose effect profile. Therefore, the outputs from these tests serve only as experiment-wise approximations of the true continuous relationship between exposure and the biological effect. Nevertheless, these points serve as valuable information upon which to base first-time-in-human dosages of new chemical entities. Pivotal terms used to describe the results of toxicological investigations include (3):

NOEL—No Effect Level: The highest exposure level at which there is no drug-related adverse or non-adverse effect observed in the target population.

NOAEL—No Adverse Effect Level: The highest exposure level at which there are no statistically or biologically significant increases in the frequency or severity of an adverse effect between the exposed population and the corresponding control group.