opportunity for regulatory authorities and industry persons from non-ICH regions to comment on the draft document. The three regulatory parties review these comments with the goal of reaching a single, harmonized wording of the guideline. The final revised guideline is approved by the regulatory parties of the three regions.

Step 4: Adoption of a Tripartite Harmonized Text

Since the guideline may have been revised from that proposed by the ICH Steering Group, at Step 4 the guideline is returned to ICH and reviewed by both industry and regulatory experts to ensure that the proposals in the guideline remain acceptable subsequent to the consultation edits. If both regulatory and industry delegates are in agreement with the guideline, the text of the guideline is adopted and the guideline signed by the three regulatory parties to ICH; at this point the guideline is recommended for adoption by the regulatory bodies in the three regions.

Step 5: Implementation

The Tripartite Harmonized Guideline is implemented by the regulatory bodies. In the European Union, the Guideline is published by the European Commission in Volume III of the Rules Governing Medicinal Products in the European Union. In Japan, the Pharmaceutical and Medical Safety Bureau (PMSB) is responsible for the promulgation of the Guideline. In the United States, the Guideline is published by FDA in the Federal Register.

3. ICH NON-CLINICAL (PRECLINICAL) TOXICITY GUIDELINES

The non-clinical toxicity testing of a new drug (including biotechnological products) is a fairly well-defined process in terms of the five general areas of testing, although the actual studies and protocol elements of the studies within each of these general areas may vary depending on the class of drug and intended clinical program. In this section, ICH activity is discussed and additional comments are provided regarding study design in each of the following areas of toxicity testing:

Single-dose toxicity
Repeat-dose toxicity
Reproductive toxicity
Genetic toxicity
Carcinogenicity

A tabular listing of the ICH guidances in the "Safety" and "Multidisciplinary" categories that are specifically toxicity testing guidances is provided in Table 2. All of these guidances have reached the Step 4 adoption of the guidance text and have been implemented by the regulatory bodies from each of the three regions (Step 5).