that requires intravenous injection would not go past this stage; on the other hand, for those drugs that have no alternatives, such as in cancer treatment or other diseases in which the patient is hospitalized and critically ill, any dosage form would be acceptable if the cost and reimbursement issues do not impair the commercial projections of sales. Besides delivering the drug, the dosage form must provide a stable environment through a reasonable shelf life, preferably at room temperature and sufficient bioavailability, without any food or other drug interactions. Now, it is clearly seen as to why decision-making can be very difficult at the preformulation stages of drug development.

Although most preformulation studies start during the lead optimization (LO) phase, the involvement of some studies begins much earlier, even at the lead identification stage, to rule out undesirable features, such as chirality (though at times it can be the desired target), polymorphism, hygroscopicity, and extreme stability problems. The LO takes about 2 years to complete, and this narrows the choice to no more than about 3–4 compounds, based on the fine balance of pharmacology, toxicity, and biopharmaceutic compatibility. An optimally available oral drug would be a jackpot. Given the small quantity of sample available at this stage, agreements must be reached between the preformulation and drug discovery group to obviate redundant testing. The drug discovery group may take on nuclear magnetic resonance (NMR), mass spectra, and elemental analysis, whereas the preformulation group may use almost two-thirds of the supply (generally less than 10 mg) to perform Karl Fischer, pK_a, log P/log D, initial solubility, crystal structure, hygroscopicity, stability in solution and high-performance liquid chromatography (HPLC), and other spectroscopic data. For salt forms, additional testing of dynamic vapor sorption (DVS); X-ray; differential scanning calorimetry (DSC); solubility/stability tests; polymorphism studies using DSC/differential thermal analysis (DTA)/hot-stage microscopy (HSM); crystal habit using microscopy, both light and scanning electron microscopies (SEM); and stability using temperature and humidity stress to rule out hydrate or solvate status, often using circular dichroism, require a larger sample quantity, around 100 mg.

3.3 Regulatory Requirements

3.3.1 Small Molecules/General

Regulatory agencies are continuously pushing the quality systems that appear in the early phases of drug development. The International Conference on Harmonization (ICH) offers several guidelines for the characterization of the drug substance (Table 3.1).

The physicochemical and biological properties of the drug substance, specifically designed into the drug substance (e.g., by crystal engineering), that can influence the performance of the drug product and its manufacturability should be identified and discussed. Examples of the physicochemical and biological properties that might need to be examined include solubility, water content, particle size, crystal properties, biological activity, and permeability. These properties could be interrelated and might need to be considered in combination. Some of these properties can change with time and require time studies.