the issues of pharmaceutical polymorphism. In general, the information that is useful at the early development phase includes

- Number of solid phases that exist for this drug
- Relative physical and chemical stability of these phases
- Solubility of each form in relevant media
- Resistance of metastable forms to conversion during processing
- Possible means to stabilize amorphous or metastable forms, if needed

Another major consideration at this point is to decide on the patentability of any new crystal forms discovered to have significant practical advantages over those in the original patent. Byrn and Pfeiffer (1992) have listed more than 350 patents on crystal forms in the pharmaceutical patent literature granted for showing advantages in terms of stability, formulation, solubility, bioavailability, purification, hygroscopicity, preparation/synthesis, recovery, and prevention of precipitation. More recently, patent applications regarding solid-state properties of drugs have prolifically increased. For example, patents relevant to polymorphic forms numbered over 300 from 2003 to 2006. Indeed the pharmaceutical industry has found that patents surrounding solid-state properties are advantageous for the product life-cycle management. Cabri et al. (2007) have presented cefdinir as an interesting case study and outline the strategies utilized by generic manufacturers to circumvent the innovator's solid-state patent position.

Different crystal forms can be sought by recrystallization experiments varying the solvent system, temperature, precipitation method, and level of supersaturation. Precipitation methods may include slow evaporation of the solvent, addition of antisolvents, or saturation at high temperatures followed by cooling. The solvent systems chosen for study are key aspects of these experiments. Water must be included because of its physiological significance. In addition, water tends to *contaminate* other solvents at low levels and it is often a matter of concern during product storage. In certain conditions, the usual recrystallization solvents for the drug synthesis and purification scheme and any alternate systems that may be used for scale-up of this process should also be studied. Mixtures used in the final steps of the synthetic process should be examined, including azeotropes and solvents with small amounts of miscible water. A suggested list for solvents that have been known to produce different crystalline forms is provided in Table 19.1 (Wells, 1988; Byrn and Pfeiffer, 1992; Byrn et al., 1995; Andersen, 2000; Miller et al., 2005). In general, it is prudent to include hydrogen-bond donating solvents, hydrogen-bond accepting solvents, aprotic solvents, hydrocarbon, and chlorocarbon solvents.

Solid forms isolated from these systems should be subjected to characterization techniques such as hotstage, polarized light microscopy, differential scanning calorimetry (DSC), thermogravimetric

TABLE 19.1
Partial List of Solvents Commonly Utilized for Identifying Different Crystal Forms

Water	Methanol
Ethanol	Isopropanol
Acetone	Acetonitrile
Ethyl acetate	Hexane
Dimethylformamide	Methylene chloride
Diethyl ether	Glacial acetic acid

Note: Any other solvents used in the last steps of synthesis. Aqueous mixtures with the above.