Often, the challenges experienced by an ethical pharmaceutical company in development of water-insoluble drug products revolve around the following factors:

- Active pharmaceutical ingredient (API) development and optimization of synthetic commercial route
- Therapeutic dose determination based on the therapeutic index and effective dose required to mitigate the targeted disease state
- Relatively low upfront investment in time and resources for developing a market image drug product manufacturing process

Because of the limited aqueous solubility of compounds, a small change of API particle size could make slower dissolution from dosage forms, and the increased dosing amount could cause incomplete dissolution after dosing. The altered dissolution characteristics can make systematic exposure of drug after oral administration lower than what we expect. It is important to make appropriate risk analysis when API process changes or dosing amount changes are made. The reasons why this is critical for water-insoluble drugs are that we cannot use the same strategy to bridge formulation and process changes that can be applied for Biopharmaceutics Classification System (BCS) class 1 compounds.

Table 23.2 lists the common challenges for exploratory and full development phases of drug product manufacturing. The API synthesis in early phases of development and the eventual optimization of the synthetic route for large-scale bulk API manufacturing pose numerous challenges in the development of the acceptable market image drug product. The crystalline morphology, API density, particle size, and the evolution of environmental health and safety requirements pose additional challenges to develop process understanding for drug product manufacture. The changes in morphology and particle size have a direct impact on powder flow and other key drug product attributes such as dissolution. The change in bulk density has direct impact on the scale of equipment and preference for enabling technology for successfully developing a drug product. For example, if the density of the API decreases, a large capacity blender, granulator, and so forth, may be required. Similarly, if the enabling technology is a wet granulation process involving fluid-bed technology, then for a low density API, the process may need to be modified to accommodate quick wetting of the API mass initially in the process to keep homogeneous wet granulation process in order to prevent fines during the granulation, which could cause poor powder flow and/or sticking problem. This is generally accomplished by quick wetting of the mass with low air fluidizing volume for enabling powder wetting. It is observed that if high air volumes are applied initially, the powder has a tendency to accumulate in the fluid-bed bags, thus creating undesirable fines in the granulation. However, high air volumes may be necessary if the API bulk density is high. It is necessary to adjust

TABLE 23.2
Drug Product Manufacturing Challenges

Early Development Phase (Phases I and II)	Late Development Phase (Phases III and IV)
Dose of drug molecule not known	API scale-up activities have effect on morphology
API morphology keeps changing	Optimization of drug product formulation and manufacturing processes
API synthetic route not finalized (number of synthetic steps not optimized)	Key process parameters and their effects on critical drug product attributes not well defined
Drug product manufacturing process poorly understood	Development of clinical manufacturing process and its alignment with commercial manufacturing
Drug product in-process controls not established	Commercial scale and scale-up challenges of drug products
Attrition rate is high	