level of formulation development work was prerequisite and technologies did not exist to accurately dispense a wide range of API in a capsule.

Capsule shell sizes are generally standardized with finite volumes (Rudnic and Schwartz, 2000; Capsugel, 2006) available for dispensing the API or powder blend. The capsule size selection would depend on the dose and the bulk density of the NCE. Historically, if the doses were within a reasonable range, it was feasible to dispense API directly into the capsule body utilizing manual, semiautomatic, or automatic high-speed encapsulators available for manufacturing.

Recent advances in dispensing technology for a powder into capsules have pushed the threshold, and today's technologies such as Xcelodose™ and autodose high-precision dispensing technology (Hariharan et al., 2003; Autodose and Powdernium, 2005) offer new opportunities with this dosage form. These technologies offer an opportunity to accurately dispense an NCE into a capsule shell with great flexibility in dispensing doses for Phase I trials. The stability studies and potential for interaction with formulation components are minimized using this approach. However, stability data indicating API compatibility with the capsule shell are required. Cross-linking of capsule shell and entrapment of the dispensed dose (e.g., especially low doses, 5 mg or less) are potential concerns, but advances in capsule shell material (e.g., hydroxypropyl methylcellulose [HPMC] capsule shells offered by Capsugel and Shionogi) have reduced this concern. Experience with this technology suggests that to achieve accuracy at low doses one may have to compromise on the throughput. Throughput from these machines also depends on powder flow characteristics. In cases where this technology does not accommodate dispensation owing to flow challenges, alternative approaches require some formulation efforts with one or two excipients to improve flow characteristics of the API (Mouro et al., 2006). In this case, it is necessary to show acceptable dose uniformity of capsule formulations with regular content uniformity testing. The overall distinct advantages this technology offers are reduced analytical resources, reduced formulation requirements, minimal GMP manufacturing resources, and the provision of sound documentation for each capsule produced.

PHASE II STRATEGIES FOR DRUG PRODUCT MANUFACTURING OF WATER-INSOLUBLE NEW CHEMICAL ENTITIES

The objective of Phase II clinical studies is to achieve evidence of efficacy in the target patient population and assess short-term safety. There are two types of Phase II studies: the early Phase II (or proof of concept) study that focuses on confirmation of efficacy and the late Phase II study (dose finding purpose). During the late Phase II studies, therapeutic dose ranges and dosing regimens are defined, and the minimum effective dose and maximum tolerated dose are established.

For clinical supply management, it is a challenge to recommend clinical supplies with doses that could accommodate the low and high end of the regimen. Patient compliance is a critical factor in developing the clinical dosage form. For example, if only the smallest dose is available, the number of doses would increase, and this could potentially cause patient compliance issues. Similarly, if a higher clinical dosage form is selected, this could cause limitations in the dosing regimen. The clinical study planner has to strike a balance between the lowest and highest possible doses to come up with a few doses that will allow for reasonable formulation and manufacturing of dosage form to ensure patient compliance in the clinical setting.

Typical approaches for water-insoluble compounds to make an oral dosage form are

1. to formulate with surface active agent and/or pH-modifying agent to improve aqueous solubility and wettability of the compounds,
2. to introduce micronization or nanotechnology to maximize drug dissolution from the formulation,
3. to utilize amorphous phase of the candidate compounds.

The drug product demand and forecast for conducting studies in Phase II and beyond play a key role in developing strategies for the formulation and manufacturing scale. The data for a molecule