Today, the pendulum has swung back toward rational design. Large libraries, despite their waning appeal, are, however, still in demand from specialty synthesis vendors. The hit rate can be improved when refined compound libraries are created from an existing hit through designing libraries for a given chemotype or pharmacophore, which amounts to the second-generation combinatorial methods coupled with computational chemistry.

Many large companies do not purify individual compounds in 100,000-entry libraries, instead preferring to bias reaction pathways toward products that are reasonably pure. Eventually, when discovery chemists settle on focused panels of between 200 and 1000 compounds, they rely on a number of tools to help them clean up these smaller libraries. One method is solid-phase scavenger reagents, which can soak up substantial amounts of impurities and side products and even drive reactions toward completion by shifting equilibrium. Simple anion- or cation-exchange resins are popular for removing anionic or cationic species, respectively. Scavengers work well to remove major impurities from individual reactions, but top-tier libraries in the 200–1000 compounds range probably require more careful cleaning up. Newer techniques such as solution-phase mixture synthesis obviate the problems associated with solid-phase synthesis, since the kinetics are easier to study in homogeneous systems.

Genomics is emerging as a useful technique in the drug selection process and has begun to play a significant role in the identification of lead compounds.

The distinct phases of stage 2 include the following:

- *Research planning*: This may involve classical structure–activity correlation studies, rational drug design modeling, HTS of libraries obtained by combinatorial chemistry, leads from natural sources, and so on.
- *Obtaining test compounds or samples*: Laboratory-scale preparation, preparation of compounds or sample libraries, determination of in vitro or animal models to test activity, and setting up of HTS.
- *Screening*: Basic pharmacological and biochemical screening. This involves the selection of "hits" and identification of active compounds. It is at this stage that the patent application for the compound will normally be filed. However, the strategies on the timing of patent filing will be discussed later.
- Preformulation studies consist of all that it takes to characterize a drug substance to enable its formulation into a practical drug delivery system. The preformulation studies begin immediately after a drug molecule (at this stage a lead) has been recognized. The process of LO integrates preformulation studies to ensure that all optimal forms of the drug (e.g., salt and crystalline forms) have been identified.

1.3.3 Stage 3: Candidate Drug Selection (1–2 Years)

With a solid chemical lead on hand, companies can create compounds with more optimal characteristics—pharmacological and formulation compatible forms that lead to nomination candidates. Ideally, the nominated candidate would have the following features:

- A simple structure
- No chiral centers