It is not uncommon for large companies to suddenly establish a direction through serendipitous discoveries. Alexander Fleming discovered penicillin as a result of "serendipity." Although many of the drugs that are in use today have been discovered in this way, it is a difficult route for the pharmaceutical industry to follow and breaks are few and far between. More recently, the discovery that phosphodiesterase type 5 inhibitor (originally tested as antihypertensive agents) can be a good candidate for male erectile dysfunction has changed the focus of research at Pfizer and, as a result, at several other companies.

1.3.2 Stage 2: Candidate Drug Screening (1–10 Years)

In the previous step (stage 1), a particular biological mechanism is identified or targeted; the phase that follows it involves the identification of chemicals or modalities that would interfere or interact with it and thereby identify what the industry calls "leads." This stage requires extensive screening for biological activity, a process that used to be tedious and slow; however, over the last decade, the use of techniques such as "combinatorial chemistry" and automated HTS has made it possible to identify a large number of synthetic or biosynthetic molecules.

Organizations may differ in library acquisition methods (e.g., synthesis vs. purchase), compound inclusion criteria, synthesis methodology, or how they mine their collections to uncover leads. The rationale, however, remains constant: to find new, patentable structures as efficiently as possible. Automated synthesis and HTS, pioneered during the 1990s, enabled companies to synthesize, test, and maintain compound libraries populated with hundreds of thousands—even millions—of unique compounds. Automation opened the door to new chemistry and a very large number of compounds, with a typical large pharmaceutical company possessing between 1 million and 10 million compounds in its various compound collections. The reliance on large libraries has now become an effort with diminishing returns. Now, outsourcing the lead compounds appears more plausible. This allows greater molecular diversity, expanding what may end up as a myopic view of a company. Companies such as Abbott Laboratories have done well in emphasizing chemical diversity. As combinatorial chemistry became more automated and specialized, companies created separate groups to handle synthesis, library acquisition, and compound management. Aventis, for example, maintains a 60-person combinatorial chemistry group in Tucson, Arizona, that feeds libraries of various sizes to the rest of the company. Other firms take a more traditional view, preferring not to segregate discovery-related chemical competencies. Like most large discovery organizations, Roche constructs libraries to target gene families and protein targets or to expand the chemical diversity of the company's compound collection. Roche's lead-generation strategy includes acquiring libraries from specialist compound suppliers, contracting with external partners for library synthesis, and developing libraries in-house. Roche's view on library size is in line with the current thinking, and Roche has gradually moved away from very large compound libraries. Roche uses all modern synthetic tools, including parallel synthesis, combinatorial chemistry, and solid-phase methods, principally (although not limited to) solid-phase reagents and scavengers in the latter. Resin-bound synthesis is also used but only in situations where the technique can offer an advantage such as when very large numbers of related structures are desired. In today's discovery paradigm, the prime focus is more toward activity than on numbers of compounds.