form of the drug substance administered to patients. Drug products are the subjects of companion monographs to the API in the USP. The ultimate safety and efficacy of the finally administered drug product are dependent on the assurance of the consistency of the physical and chemical properties of the API. This chapter will focus on the plethora of issues involved with the API, which must be considered when developing a generic drug product. In particular, the point of establishing specifications for critical quality attributes of the API will assure that the generic drug product, employing the API material, will have consistent in vitro/in vivo characteristics, batch after batch. As part of the routine evaluation of the compendial status of an API, in addition to the USP, the European Pharmacopeia, Japanese Pharmacopeia, British Pharmacopeia, Indian Pharmacopeia, the World Health Organization, and other "recognized" compendia should be checked to verify the presence or absence of published "official monographs" for the API.

A published overview of the regulatory oversight for both drug substances and drug products provides an excellent starting point for the particular issues that a firm faces when attempting to file an Abbreviated New Drug Application (ANDA) for an API [2]. The reference provides detailed accounting of all relevant U.S. Food and Drug Administration (FDA) documents and guidances covering the areas of concern with the focus on U.S. regulatory issues concerning APIs. Because the FDA does update "Guidances," it is important to continually scan the FDA website for guidance updates and new guidances.

SOURCES OF APIs

The three most commonly recognized categories of APIs are synthetic, semisynthetic, and natural. The latter category, natural, refers to the source of the API as being derived directly or extracted from natural sources. The category of semisynthetic indicates that a starting "intermediate" for the preparation of the API was derived from natural sources. The "isolated" intermediate is then converted synthetically to the final API. Synthetic APIs are obtained directly by chemical conversion of intermediates. It is not uncommon to see the market introduction of an API pioneer compound as a natural product, which is subsequently produced by a semisynthetic procedure. An example of the transitioning of an important API from "natural sourcing" initially to semisynthetic sourcing is paclitaxel [3,4]. In the arena of synthetic APIs, the transitioning that frequently occurs is that the initial drug product launch by the pioneer drug firm employed the API produced by a defined synthetic process. Subsequently, the pioneer product producer changes the API synthetic process. There is no requirement that the specific synthetic pathway be identified for the API as the product matures in the marketplace. It is not uncommon to see alternate "morphic" forms of the API enter the marketplace. When such changes occur for the pioneer product (originally approved NDA product), there may be labeling issues that need to be addressed for the "generic" equivalent product(s).

The USP has classified a category of drug substances as "complex active ingredients" [5]. This grouping of compounds includes biological and biotechnological drug substances and complex natural source drug substances. The traditional APIs are referred to as "noncomplex actives." This chapter will only focus on noncomplex actives.