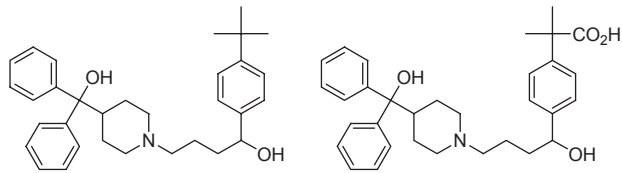
was no clear pathway forward to inhibit cholesterol synthesis. The companies that took the leap of faith that inhibition of HMG-CoA reductase would provide therapeutic relief for the prevention of cardiovascular disease received significant financial rewards in the marketplace as indicated by the success of drugs like Mevacor® (Lovastatin)[56] and Lipotor® (Atorvastatin).[57]

There are, of course, many biological targets with proven clinical utility that an organization might choose to focus on, such as phosphodiesterase-5 (PDE-5),[58] β-adrenergic receptors,[59] and 5-hydroxytryptamine (5-HT) receptors.[60] In considering whether or not to pursue known drug targets, one must keep in mind both the benefits and potential pitfalls related to previously defined targets. On the positive sides, a wealth of research and development information will be available in the literature, as companies and research institutions (universities, non-profit research institutions, etc.) patent and publish their research in order to garner support for their marketed products and research programs. The availability of research tools such as biological assays, reference compounds, and clinical trial data can provide an excellent springboard for a drug discovery program. On the other hand, the availability of this kind of information presents a significant hurdle to the development of new therapeutic agents, as any new compound or biological agent will be required to demonstrate clinical superiority to the current standard of care. Also, scientific disclosures in the literature will be available as prior art and could prevent an organization from gaining patent protection for their research (this topic will be covered in more detail in Chapter 12). If, however, one is successful in developing a new therapeutic entity based on clinically proven targets, substantial benefits can be available. Sepracor, now a division of Sunovia, for example, took the risk of developing a new antihistamine at a time when the market was dominated by Seldane® (Terfenadine).[61] They were able to demonstrate that Allegra® (Fexofenadine), a metabolite of Seldane® (Terfenadine), is significantly safer than its predecessor and quickly took over the antihistamine market (Figure 1.11).[62]



Seldane®
(Terfenadine)

Allegra®
(Fexofenadine)

FIGURE 1.11 Seldane® (Terfenadine), the first non-sedating antihistamine, dominated the market until serious safety issues were identified. It was replaced by a Allegra® (Fexofenadine), an active metabolite that is safer than the original.