by the FDA for the treatment of depression and marketed as Wellbutrin® in 1985. The maximum dosage approved was 600 mg three times per day, but a significant number of patients developed epileptic seizures, and the drug was withdrawn from the market in 1986. An examination of clinical data and drug pharmacokinetics demonstrated that the risk of seizure was highly dose dependent, and Wellbutrin® was relaunch in 1989 with a lower maximum dose (450 mg). While many patients were able to successfully resume drug therapy at the lower doses, patients who required higher doses for symptom relief were no longer able to use Wellbutrin®.[48]

Although it would have been possible to develop a new clinical candidate devoid of seizure risk, an alternate path forward was selected. In this case, it was hypothesized that peak plasma concentrations achieved with the highest doses were responsible for the increased risk of seizures, and that if a new dosing regimen could be designed to "smooth out" these peaks, then the risk of seizures would be eliminated. In other words, this new hypothetical formulation would allow plasma concentrations of the drug to reach therapeutically useful levels, but they would not reach concentrations required to cause seizures. This led to the development of a sustained release formulation of bupropion, Wellbutrin SR®, as a twice daily medication (FDA approved in 1996[49]), and an extended release formulation, Wellbutrin XL®, as a once daily medication (FDA approved in 2003[48]). Although modern drug discovery and development program routinely consider extended release formulations such as embedding the drug in slow dissolving polymer matrix or an osmotic pump system, this technology was a relatively new at the time. These new formulations provided greater control of plasma concentration when compared with the immediate release tablet and, as expected, lowered the peak plasma concentrations of bupropion (Figure 13.19).[50] This, in turn, allowed the drug to be used in a wider range of patients, simplified the dosing regimen, and effectively extended the patent life of the Wellbutrin® franchise for GSK. Patents covering the use of bupropion in conjunction with extended release technologies were filed well after the original bupropion patents, providing additional patent protection for both Wellbutrin SR® and Wellbutrin XL® (the patent covering Wellbutrin XL® expires in 2018).

Changes in the formulation of methylphenidate also provided improved patient outcome, while avoiding the process of developing an entirely new chemical entity. Methylphenidate was originally prepared in 1944 by Leandro Panizzon, a scientist at Ciba–Geigy Pharmaceutical Company (now Novartis). It was identified as a stimulant and was brought to market in 1954 as Ritalin® for the treatment of "chronic fatigue, lethargy, depressive states, disturbed senile behavior, psychosis associated with depression and narcolepsy." The most common use for methylphenidate, however, is the treatment of children with attention deficit disorder (ADD)