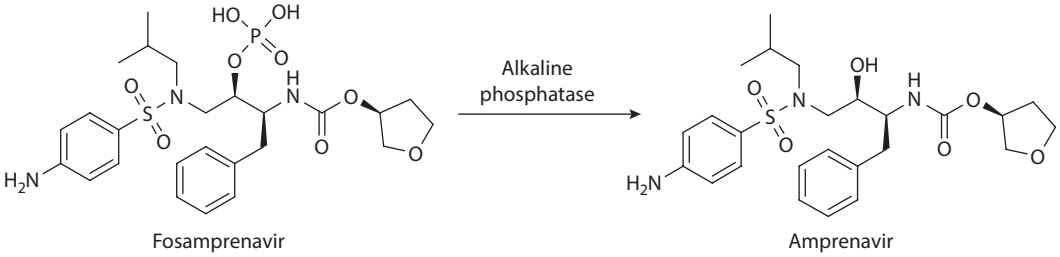

FIGURE 10.6 Structure and bioconversion of fosamprenavir to its parent drug amprenavir.

Amprenavir was marketed as 50 and 150 mg capsules and its oral formulation contained a large amount of solubilizing excipients, particularly vitamin E TPGS (d-alpha tocopherol polyethylene glycol succinate) which caused potential toxicity issues. To reduce the excipient intake and the burden of 8 capsules twice a day, approximately 10-fold more water soluble fosamprenavir which required only 2700 mg tablets twice a day, was developed (Figure 10.6). In fosamprenavir, a single phosphate group is directly attached to the free hydroxyl group of amprenavir. During its absorption, orally administered fosamprenavir is rapidly and quantitatively hydrolyzed to yield amprenavir and inorganic phosphate by gut epithelial alkaline phosphatases. Amprenavir and its phosphate prodrug fosamprenavir possess comparable therapeutical efficacy and safety profiles, but fosamprenavir provides more simplified and patient-compliant dosage regimen for HIV patients. This clinical advantage has served also as a life cycle management tool for amprenavir.

A good example of a prodrug which can overcome parenteral formulation problems of sparingly water soluble parent drug is fosphenytoin, an injectable phosphate ester of poorly water soluble anticonvulsant phenytoin, in which the phosphate group is attached to an acidic amine of the parent drug via oxymethylene spacer (Figure 10.7). Due to its limited aqueous solubility (20–30 μg/mL), the injectable formulation of phenytoin sodium salt consisted of 40% propylene glycol and 10% ethanol at a pH of 12. This formulation caused several administration problems, including severe irritation and pain at the injection site, precipitation of drug, or even death of the patient, if injected too quickly. In contrast, the significantly increased aqueous solubility of fosphenytoin (142 mg/mL) allows its formulation in purely aqueous solution with pH of about 8.5. Thus, fosphenytoin enables more safe, convenient, and rapid intravenous administration with markedly lower potential for adverse effects at the injection site. When in systemic circulation, fosphenytoin is rapidly and almost completely converted back to the phenytoin by alkaline phosphatases of blood and tissues through a chemically unstable *N*-hydroxymethyl intermediate with half-lives ranging from 7 to 15 minutes in humans. The by-products of the bioconversion of fosphenytoin include formaldehyde and inorganic phosphate.

Other examples of prodrugs with improved aqueous solubility include sulindac, miproxifene phosphate, extramustine phosphate, prednisolone phosphate, irinotecan, and fludarabine phosphate.

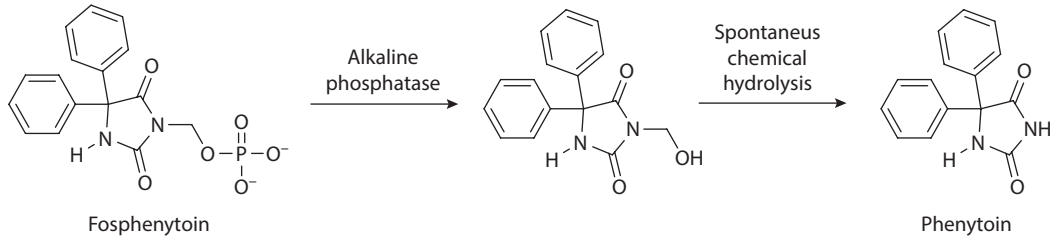

FIGURE 10.7 Bioconversion of fosphenytoin to its parent drug phenytoin.