explained by premature hydrolysis in the esterase-rich enterocytes during the absorption process. This indicates that complete oral bioavailability of ester prodrugs is unlikely.

The enzymes involved in prodrug bioconversion can also be polymorphic, and therefore, subject to interindividual variability in activity. Although, in general, CESs do not appear to be subject to high genetic polymorphisms in a manner that might compromise their exploitation in prodrug design, scattered evidence observed with prodrugs such as angiotensin-converting enzyme inhibitors, capecitabine, and irinotecan has nevertheless demonstrated that polymorphisms of CES genes can have some impact on the clinical variability of CES-activated prodrugs. Genetic variation in CYPs, on the other hand, is known to contribute substantially to variability in exposure as well as clinical efficacy and safety of prodrugs activating by these enzymes. CYPs that are expressed in several tissues being prominent in the liver and to lesser extent in the intestine are capable of oxidation and reduction reactions of several various, especially bioprecursor prodrugs, into their active species. Clopidogrel, codeine, tamoxifen, tegafur, and cyclophosphamide are examples of prodrugs which have demonstrated interindividual variation in prodrug exposure because of polymorphisms of CYPs. Therefore, an appropriate selection of dose of genetically defined patient subsets should enhance the efficacy and safety of prodrugs undergoing bioconversion by CYPs.

### 10.6.2 Safety Evaluation of Prodrugs

Discovery and development of prodrugs present many challenges in the safety assessment. Potential toxicity of both prodrug and promoiety as compared to the parent drug needs to be carefully evaluated. In many cases, a comparative toxicological analysis can assist in determining which toxicity is contributed by the prodrug, its intermediates, or the active drug. Two specific sources of possible toxicity in prodrugs are promoiety itself and by-products released during the bioconversion process. For example, the toxicity concern associated with the ethylene sulfide by-product released from S-acyl-2-thioethyl (SATE) prodrugs of phosphates/phosphonates has limited the advancement of these prodrugs into development. Another and more frequently discussed by-product is formaldehyde that is released during bioconversion of various double prodrugs. However, considering the normal daily formaldehyde levels in humans, it is unlikely that formaldehyde from a prodrug could adversely affect normal physiological functions. A third example of promoieties associated with possible toxicity concern is pivalic acid used as a promoiety in prodrugs such as adefovir dipivoxil, and pivampicillin. Pivalic acid is shown to interrupt carnitine homeostasis which can lead to depletion of carnitine in humans. In many cases, exposure to the pivalic acid has no or only minor toxicological impact, and in extended treatment with high doses simultaneous carnitine supplementation can be administered to avoid its deficiency. Therefore, in cases where prodrugs raise any toxicity concern, daily dose and duration of treatment should be carefully taken into consideration in the overall risk evaluation process.

### 10.6.3 Regulatory Aspects of Prodrugs

The development of a prodrug from an existing drug may represent an opportunity for life cycle management and add several years to the life of a patent. If the prodrug structure has not been disclosed previously, it can be considered as a new chemical entity (NCE) and is likely to have the added benefit of being considered as intellectual property (IP). However, for an inventive step to be acknowledged, it has to be demonstrated that the prodrug's design was not obvious to the skilled person. Difficulties in overcoming an obviousness objection may arise if the structural difference between the prodrug and parent active drug is trivial such as forming an ester of an existing drug. As of today, other widely used prodrug strategies such as amides and phosphates have overcome obviousness criteria and respective prodrugs of existing drugs have been granted NCE status. In scenarios where both the active drug and its prodrug are discovered in the same time and included in the same patent filing ensuring adequate protection of both is more straightforward. Finally, in cases