but the (R)-isomer does not share this liability. Prior to this realization, the possibility that single enantiomers might have different biological effects had not been widely considered, and racemic drugs were routinely studied. After the thalidomide tragedy, however, scientists began to focus more heavily on single enantiomers. In the modern era, racemic drug candidates are very rare.

In related findings, an understanding of chiral stability also began to take shape as a result of the tragedy that unfolded around Thalidomide. While it is true that the two enantiomers of Thalidomide have different biological properties, the (R)-isomer still represents a significant hazard for pregnant women. This is the result of the chiral instability of the (R)-isomer in an *in vivo* setting. At physiological pH, the (R)-isomer of Thalidomide undergoes racemization to a mixture of the two isomers (Figure 2.26),

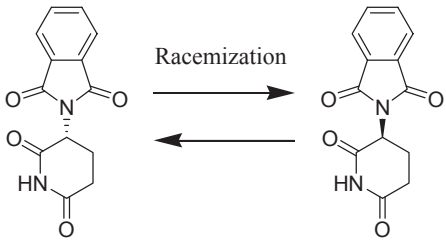

FIGURE 2.26 Thalidomide is not chirally stable *in vivo*. The (R) isomer (left) is readily converted to the (S) isomer (right). As a result, the pure (R) isomer is no safer than the originally marketed racemic material.

so even if a patient is provided only the safer (R)-isomer, the more dangerous (S)-isomer will be generated *in vivo*. In the modern drug discovery process, it is common place to check the chiral stability of possible drug candidates as a result of these findings.

REGULATORY MILESTONES

While major events such as the Thalidomide tragedy made it abundantly clear that new laws needed to be put in place to regulate the growing pharmaceutical industry, many other legislative events occurred in the absence of the substantial attention generated by a drug failure. In fact, over the course of the twentieth century, the growth of the pharmaceuticals industry has been tracked by a parallel growth in regulatory bodies responsible for oversight of the industry. The growth of the regulatory agencies was often a step behind the industry itself, as the laws granting them authority over the industry were most often reactionary in nature (i.e., developed and implemented in response to a perceived problem in the system). Over the course of the twentieth century, however, regulatory bodies such as the FDA, the European Medicines Agency (EMA), and many others across the globe have been created through legislative action with the goal of ensuring the safety of marketed drugs. Although it is well