is relatively high. In order to mitigate this risk, compounds identified as active at the 5-HT_7 receptor would likely be screened in a secondary assay to assess their capacity for modulating 5-HT_{2b} activity. Compounds that represent a risk for cardiovascular safety via 5-HT_{2b} activity can be eliminated early in the process.

Of course, the concept of screening candidate compound for activity at "nearest neighbor" targets is insufficient on its own. Screening the hypothetical 5-HT_7 modulators for 5-HT_{2b} activity will provide no insight on a candidate compound's capacity for interacting with the myriad of other potential cardiovascular targets that exist (Table 8.2). As discussed earlier,

TABLE 8.2 Exemplary Cardiovascular Drug Targets

Aldosterone receptor	Mineralocorticoid receptor
Alpha adrenergic receptor	Neutral endopeptidase
Angiotensin-converting enzyme	Nicotinic acid receptor
Beta adrenergic receptor	Prostaglandin E2 receptor
Endothelin A receptor	Vasopressin V1a receptor
L-type calcium channel	T-type calcium channel

even the largest of pharmaceutical companies do not maintain the enormous arrays of *in vitro* screens necessary to monitor for all possible untoward effects. Although the number of targets relevant to cardiovascular disease is only a subset of the total, it would still be a very large undertaking to have all of the necessary assays available in a single pharmaceutical company (The hERG assay is a notable exception. Given its importance, many companies choose to run this assay internally). Advanced candidate compounds are often screened using *in vitro* panels of cardiovascular targets at contract research organizations such as EMD Millipore,[7] Perkin Elmer,[8] and Cerep.[9] *In vitro* cardiovascular safety panels are often run on advanced candidate compounds as part of a wider *in vitro* safety assessment discussed earlier.

Failure to identify activity at in a series of *in vitro* screens designed to identify potential cardiovascular risk is good start, but it is not sufficient to fully derisk a candidate compound. *In vitro* screening, by definition, is not the same as screening a compound in an animal model. Data from *in vitro* screening assays are not a suitable substitute for testing a compound in a living system. In some organizations, the first step toward *in vivo* assessment of cardiovascular risk is the Langendorff preparation, an isolated heart perfusion model originally reported in 1898.[41] Essentially, this model consists of a heart that has been isolated from a terminally anaesthetized animal and attached to a perfusion system capable of delivering a constant