(290–700 nm), it has to generate reactive species following absorption of light, and it has to distribute sufficiently to light-exposed tissues such as the skin and eye. Therefore, the initial evaluation of drug candidates with regard to phototoxicity is measuring light absorption at wavelength between 290 and 700 nm. When a compound has a molecular extinction coefficient (MEC) of greater than 1,000 L/mol/cm, it may need further evaluation (Bauer et al. 2014). An assay for detection of reactive oxygen species (ROS) may be performed, but this test is not very specific (Onoue et al. 2008). The in vitro 3T3 neutral red uptake phototoxicity test (3T3 NRU-PT) is a very well-established test with a high sensitivity, though low specificity (Lynch and Wilcox 2011; Ceridono et al. 2012, also described in OECD guideline Test No. 432 (2004)). This test can easily be used for initial evaluation of drug candidates. Depending on the outcome of the study, additional testing may be needed to check the relevance in vivo, as a positive 3T3 NRU-PT may not translate into in vivo phototoxicity (Schürmann et al. 2014). However, as such data are only needed before start of large clinical trials, such additional examinations (e.g., local lymph node assay, autoradiography study) are rarely performed during research phase.

12.2 Phospholipidosis

Drug-induced phospholipidosis is characterized by an intracellular accumulation of phospholipids and the concurrent development of concentrical lamellar bodies. It is primarily caused by an inhibition of lysosomal phospholipase activity by the drug. It has been reported not only for cationic amphiphilic (lipophilic) drugs mainly in preclinical testing but also for a few drugs in humans. The hallmark feature is the ultrastructural morphology. It can affect almost any tissue, but the lung and the liver are frequently affected in the toxicity studies. The functional human consequences are not well predictable (Reasor and Kacew 2001). Therefore, this finding may delay or even terminate the development of a drug.

As the chemical properties with a potential to cause phospholipidosis are well understood, in silico models are available to predict the potential (Orogo et al. 2012). In addition, there are in vitro models available for screening allowing moderate throughput (Kasahara et al. 2006; Morelli et al. 2006). In addition, there are biomarkers for in-life screening in animals and for testing in humans. Evaluation of peripheral blood leucocytes for morphological signs of phospholipidosis may be used as possible marker. In addition, there are some biomarkers to be tracked in blood (e.g., lysosomal phospholipids) and bronchoalveolar lavage samples (e.g., macrophage function parameters) (Monteith et al. 2006). Depending on the severity of the effect, early lesions may already be found in 2-week repeat-dose toxicity studies, but sometimes, such effects are only detected in longer-term studies.