so that they do not really qualify for frontloading. In case of high concern, a pilot reproduction toxicity study may be performed before start of the initial GLP regulatory studies, but in general, the standard reproduction toxicity studies including the pilot studies are performed later in the drug development parallel to clinical phase 1 or parallel to phase 2, depending on the need for inclusion of women of child-bearing potential.

11 Carcinogenicity

Carcinogenicity is a significant liability for a drug. The nonclinical assessment of the carcinogenic potential for pharmaceuticals is still based on the 2-year carcinogenicity assay in rodents. There are only few shorter-term assays in genetically modified animals (TgrasH2 and TRP53 knockout) allowing replacement of the mouse 2-year carcinogenicity assay (CHMP/SWP, 2004). The rat assay is still mandatory for drugs. The carcinogenicity assays have to be completed prior to marketing application (ICH M3 (R2) 2009).

There is a high interest to find alternative models allowing prediction of the carcinogenic risk for pharmaceuticals. However, this is difficult with no satisfying solution so far (Jacobs 2005). Hazard identification is relatively easy in case of genotoxic carcinogens (integrated in the in silico tools also used for prediction of genotoxicity; see Sect. 3). For non-genotoxic carcinogens, in silico prediction is still poor.

For chemicals, there exist some early screening strategies on how to create early signals for potential carcinogenic hazard. Ames test and structural alerts may identify DNA-reactive carcinogens and in vitro cell transformation assays (CTA) may detect non-genotoxic carcinogens. The most promising CTA is the Syrian hamster embryo cell transformation assay at pH 7 (SHE_7) (Benigni 2012). However, translation to pharmaceuticals is difficult, as a benefit-risk assessment is needed. As described in a recent review, for many marketed drugs, at least one of the carcinogenicity studies was positive and quite some of the drugs also give evidence of occurrence of human cancer (Brambilla et al. 2012). Whether in vitro screening may be helpful in early candidate selection has to be carefully decided because of the limited value for benefit-risk assessment.

12 Other Nonclinical Safety Aspects

12.1 Phototoxicity

Strategies for evaluation of phototoxic potential are well described in ICH S10 (2013). There are some prerequisites that a drug may cause phototoxicity and/or photoallergy: the compound has to absorb light within the range of natural sunlight