Preclinical requirements for anticancer drugs in the EU

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Several ICH guidelines impact the preclinical requirements of anticancer drugs for the initial marketing authorisation application. For drugs for advanced cancer, the ICH S9 allows fewer preclinical studies compared to standard development. ICH S6 provides requirements for anticancer drugs which are biotechnology-derived.

Aims

To identify which preclinical studies were conducted between 2010 and 2017 for anticancer drugs and to evaluate whether the applicants followed ICH S6 and S9.

Methods

The EMA website was searched for all oncology drugs approved in 'Human medicines' that were authorised between 2010 and 2017. The EU Public Assessment Reports (EPAR) of these drugs were checked for the preclinical studies that were performed. Drugs were classified in biotechnology- (biotech) or chemical-derived (small molecule). The products were further divided into two separate groups: non-advanced and advanced cancer.

Results

For small molecules 46 drugs were approved (18 for non-advanced and 28 for advanced cancer). For biotechnology-derived 19 drugs were approved (10 products for non-advanced and 9 products for advanced cancer).

For small molecules most applicants conducted single dose and repeated dose toxicity, genotoxicity and safety pharmacology studies (for most of the studies >90%). No relevant differences were seen between the advanced and non-advanced cancer groups (Figures 1, 2, 3 & 5). Although the S9 guideline allows for some products in advanced cancer to conduct studies in only one species, most repeated dose toxicity studies were conducted in two species (>90%). S9 also allows to collect safety pharmacology data in general toxicity studies instead of performing dedicated studies. However, for more than 90% of the products dedicated studies were conducted (Figure 3). Embryofetal toxicity studies were conducted for the majority of products indicated for non-advanced cancer (Figure 4). Fertility and pre- and postnatal toxicity studies were most often not conducted (both advanced and non-advanced cancers) (Figure 4). The S9 guideline indicates that for advanced cancer these studies are not required, but does not mention that for non-advanced cancer. Full genotoxicity packages studies were conducted (Figure 5) for most of the small molecules. For biotech drugs companies seem to follow the ICH S6 guideline. Single dose toxicity studies were not always conducted (Figures 1 & 2). For safety pharmacology, applicants also made use of information from other studies or did not conduct a study (Figure 3). For biotech drugs, reproduction and genotoxicity studies were often not conducted (Figures 4 & 5).

Figure 1: repeated dose toxicity for small molecules

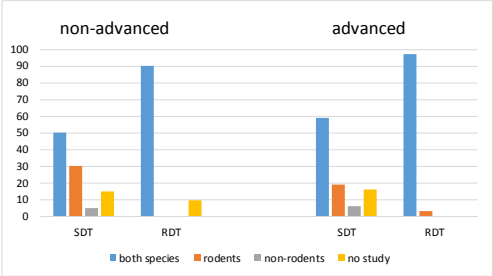


Figure 2: Repeated dose toxicity for biotech drugs

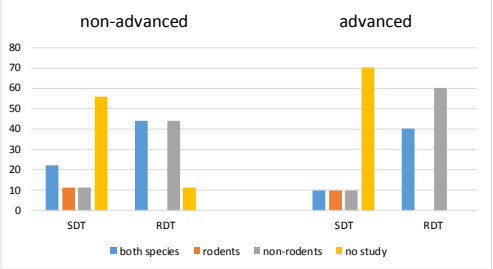


Figure 3: Safety Pharmacology

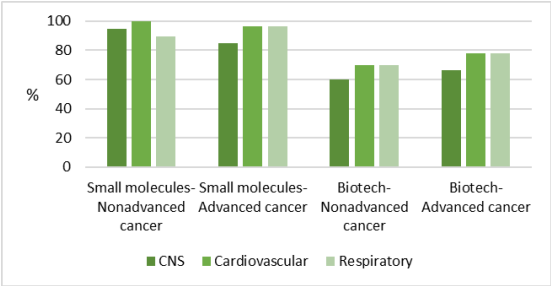


Figure 4: Reproductive Toxicity

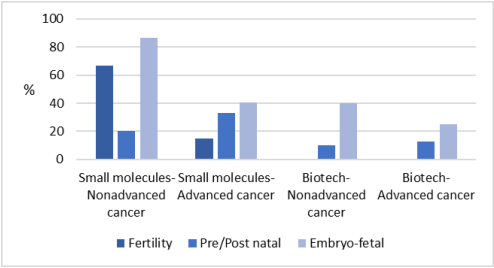
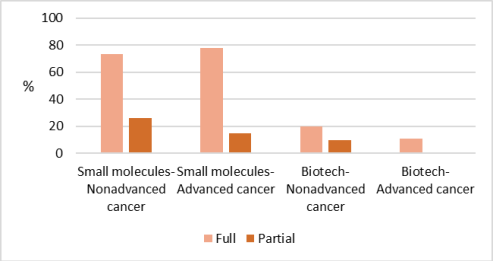


Figure 5: Genotoxicity



Conclusions

For small molecules indicated for cancer the impact of the ICH S9 guideline seems to be limited.Overall, companies seem to apply ICH S6 for the biotech drugs. In general, most of the omissions could be explained from the ICH S6 guideline and the effect of the S9 guideline seems to be limited.