

Allowable Limits of HCP Contamination

We are not aware of limits of HCP contamination established by the FDA or any other international regulatory bodies. You should contact your regulatory body for advice and current points of view. The lack of data conclusively showing HCPs to cause safety or efficacy problems together with the fact that absolute quantitation of HCPs is rarely possible, make setting of limits a somewhat arbitrary task. We do not presume to speak for current regulatory positions on HCP detection and limits, but we can relate our considerable experience with products expressed in a variety of biological expression systems. In addition, we are pleased to offer what we feel is a rational approach to the questions of HCP contamination.

Each product submission should and will likely be considered on its own merits regarding the question of HCP contamination. Issues such as the route of administration, quantity of drug given, and frequency of dosage are all factors that could influence safety problems from HCPs. The approach should be to get HCP levels as low as reasonably possible. With advances in immunoassay approaches such as those implemented in our kits, the sensitivity and specificity of HCP analysis is significantly improved over the instances in the past where products were only analyzed using much less sensitive techniques such as Western blot and PAGE analysis. Our assays are able to detect HCP in almost all products at the final formulation stage. The concentrations of HCP in final product vary considerably from product to product. When the purification process is developed with feedback from a sensitive HCP ELISA, the levels of HCPs are typically less than 10 ppm. When a sensitive ELISA is not available during process development, it is more common to see HCP levels greater than 100 ppm and often in the ppt range. Levels of less than 100 ppm are not likely to raise much regulatory concern particularly if preclinical and Phase 1 trials have not shown safety problems. We believe the most rational and cost effective approach to achieve low levels of HCP contamination is to employ a sensitive generic ELISA methodology early in product development and not to wait until Phase 3. Such an assay will provide very valuable feedback to purification process developers to the extent that this results in very low HCP levels may help insure a more positive outcome to early clinical trials.