

## Manual 038

### Appendix 2 – Risk Level Minimum Acceptance Criteria

<b>Risk Level</b>	<b>Risk Consideration</b>	<b>Minimum Acceptance Criteria for the Equipment Train</b>
0	Carry over of material within the same synthetic sequence represents the lowest risk.	The acceptance criteria must be based on technical considerations (impact on chemistry and API purity profile) and can be assessed through risk assessment. The minimum acceptance criterion (i.e. if there are no technical restrictions on the acceptable level of carry over) is that the equipment must be free from gross contamination.
1	Carry over of the intermediate/crude API into a different synthetic sequence or into final purification step of the same synthetic sequence represents a higher risk to product quality. The carryover of material into the subsequent purified API will be reduced through attrition (e.g. loss to mother liquors, screening filtrations).	Theoretically toxicological/pharmacological data could be used to calculate the ACQ, however the carry through to the following final Ape will depend on the yields of the subsequent reaction/purification steps, the relative solubility of the contaminant and the stability of the contaminant under the conditions of the succeeding steps. As all the information required to calculate an ACQ is unlikely to be available a default minimum acceptance criteria of 100 ppm w/w carry over for the guiding substance is applied (e.g. 100 mg of carry over per kg of the next product).
2	Carry over of an intermediate or an API into the purification step of an API (or post final purification step such as milling and blending) from a different synthesis represents the highest risk because of the potential for unrelated toxicity/activity effects. The likelihood of attrition is reduced as there is only one processing step (there will be some reduction in equipment in contact with solvent such as dissolution vessels and crystallisers, however there will be none in dryers and mills).	The acceptance criterion is calculated from toxicity/activity data. If there is no data available, then a default acceptance criterion of 10 ppm w/w carry over of the guiding substance is applied (e.g. 10 mg of carry over per kg of next product). If the calculated acceptance criterion is greater than 100ppm w/w, then a default limit of 100ppm w/w must be applied. If the calculated acceptable carry over limit is between 10ppm and 100ppm then the calculated limit must be applied.