5.2.4.2 Calculation of ACQ for a Level 2 Change Over

Where both therapeutic and toxicity data is available, the therapeutic data must be used. Therapeutic data could be the NED, MED or MTD, in this order of preference depending on availability of the relevant therapeutic dose information.

Based on Therapeutic Dose Information

For level 2 changeovers where therapeutic dose information is available for both APIs the ACQ must be calculated:

$$ACQ = \frac{TD_{APIa} \times MBS_{APIb}}{RAF \times MDD_{APIb}}$$

ACQ = Acceptable carryover quantity (mg) of APIa into APIb

TD_{APIa} = Therapeutic dose information on APIa (mg).

MBS = Minimum batch size of API_b (mg)

RAF = Risk Assessment Factor

MDD_{APIb} = Maximum daily dose of API_b(mg)

The risk assessment factor value is dependent on the type of therapeutic dose information used for TD_{APIa} and the mode of administration of both APIs. It is assumed that the systemic exposure of a patient to a compound is higher when administered by inhalation or parent rally than when administered topically or orally and hence a higher risk factor is used. When a product is known to be administered by more than one route the highest relevant RAF shall apply.

Risk assessment factors	Therapeutic dose information used for APIa	APIb administered topically/orally	APIb administered by inhalation/parenterally
APIa administered topically/orally	APIa nil effect dose (NED)	10	100
	APIa minimum effect dose (MED)	100	1,000
	APIa minimum therapeutic dose (MTD)	1,000	10,000
APIa administered by inhalation/ parenterally	APIa nil effect dose (NED)	10	10
	APIa minimum effect dose (MED)	10	100
	APIa minimum therapeutic dose (MTD)	100	1,000

Based on Toxicity Information

Depending on the guiding substance selected and the toxicity data available there are several options for calculating ACQ limits.

The following approach adopted from draft CPMP (Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products) Guidance must be applied for metal guiding substances. The concentration limits (ppm) for metals are calculated based on the permitted daily exposure limits and are listed in the table below.

Elements	Oral Concentration Limits (ppm)	Parenteral Concentration Limits (ppm)
Pt, Pd, Ir, Rh, Ru, Os	5	0.5
Mo, V, Ni, Cr	10	1.0
Cu, Mn	15	1.5
Zn, Fe	20	2.0

If the guiding substance is a metal the limits specified in the table above shall be used to calculate the ACQ.

$$ACQ_{metal} = \frac{CL \times MBS_{APIb}}{1{,}000{,}000}$$

MBS = Minimum batch size of APIb (mg)
ACQmetal = AcceptableCarryover Quantity (mg) into APIb
CL = Concentration Limit (ppm) from table above

With the exception of metal residues the following formula must be used to calculate the maximum allowable carry over. Where the calculated ACQ level using this methodology yields values that not practically achievable, an alternative, higher ACQ may be justified and ratified by the Drug Safety Operations Review Committee (DSORC).

$$ACQ = \frac{\text{Toxicity Value} \times MBS_{APIb}}{RAF \times MDD_{APIb}}$$

ACQ = Acceptable Carry over Quantity (mg) into APIb

Toxicity Value — Equal to NOELa, where available. If NOELa is unavailable then the Toxicity Value will be calculated.

RAF = Risk assessment factor set at 100.
Note: This RAF is based on assumption that NOEL is approximately equivalent to NED but with the additional safety factor of 10 to allow for inter-species variation.

NOELa = No observable effect level for intermediate$_a$ or APIa used in equipment for which the next use is the purification of APIb

(mg).

MBS = Minimum batch size of APIb (mg)

MDD_{APIb} = Maximum daily dose of APIb(mg)

There are a variety of types of toxicity information. If NOEL is not available then the Toxicity Value must be calculated using the following formula:

$$\text{Toxicity Value} = \frac{Tox_a \text{ (mg/kg)} \times \text{Weight (of patient in kg)}}{\text{RAFtox}}$$

Toxa = Toxicity data in mg/kg for intermediatea or APIa used in equipment for which the next use is the purification of APIb.

Weight = Weight of an average patient.
If API_b has a paediatric formulation this value is set at 15 kg
If API_b does not have a paediatric formulation this value is set at 70 kg

RAFtox = Risk assessment factor for toxicity data

The RAFtox value will be dependant on the toxicity data used:

Risk assessment factors	Toxicity data used for Toxa	APIb administered topically/orally	APIb administered by inhalation/parenterally
Topical/oral toxicity data	Oral LD_{50}	1,000	10,000
	Oral LD_{10}	100	1,000
Inhalation/ parenteral toxicity data	Parenteral LD_{50}	100	1,000
	Parenteral LD_{10}	10	100

Note: LD refers to Lethal Dose; the subscript indicates the percentage of the tested population for which the dose was lethal (i.e. 10% or 50%).

In early development the only toxicity available for the contaminant may be the result of an Ames test. This gives a positive or negative result with no indication of dose. For Ames positive material, in the absence of any other data, the ACQ must be calculated based on a maximum acceptable dose of 1.5 micrograms per day. For Ames negative material the limits in Appendix 2 shall apply.

$$ACQ = \frac{0.0015 \text{ (mg)} \times MBS_{APIb}}{MDD_{APIb}}$$

ACQ = Acceptable carryover quantity (mg) into APIb

MBS = Minimum batch size of APIb (mg)

MDD_{APIb} = Maximum daily dose of APIb(mg)

If there is other information in addition to the Ames result (i.e. the guiding substance is a known genotoxic material or subsequent testing shows that a

compound that gave an Ames positive result is/is not genotoxic) then the cleaning limit should be assessed on a case-by-case basis. DSORC should ratify the assessment in order to ensure that the approach is consistent across sites.