Determination of equivalence

Learning objectives

After completing this *Learning unit*, you should understand:

the principles and practice of equivalence determination.

Determination of equivalence

The objective is to determine

whether or not the product of another manufacturer

(identified in this Learning Unit and the exercises as “M2”)

is **not worse** than the product (produced by the manufacturer identified as “M1”) on which the “reference” specification is based. Note that the M2 product could be better than the M1 product but this is difficult to prove, so it is only practicable to show that it is not worse.

Equivalence is a simple concept but determination is complex and requires a team of experts in various scientific disciplines.

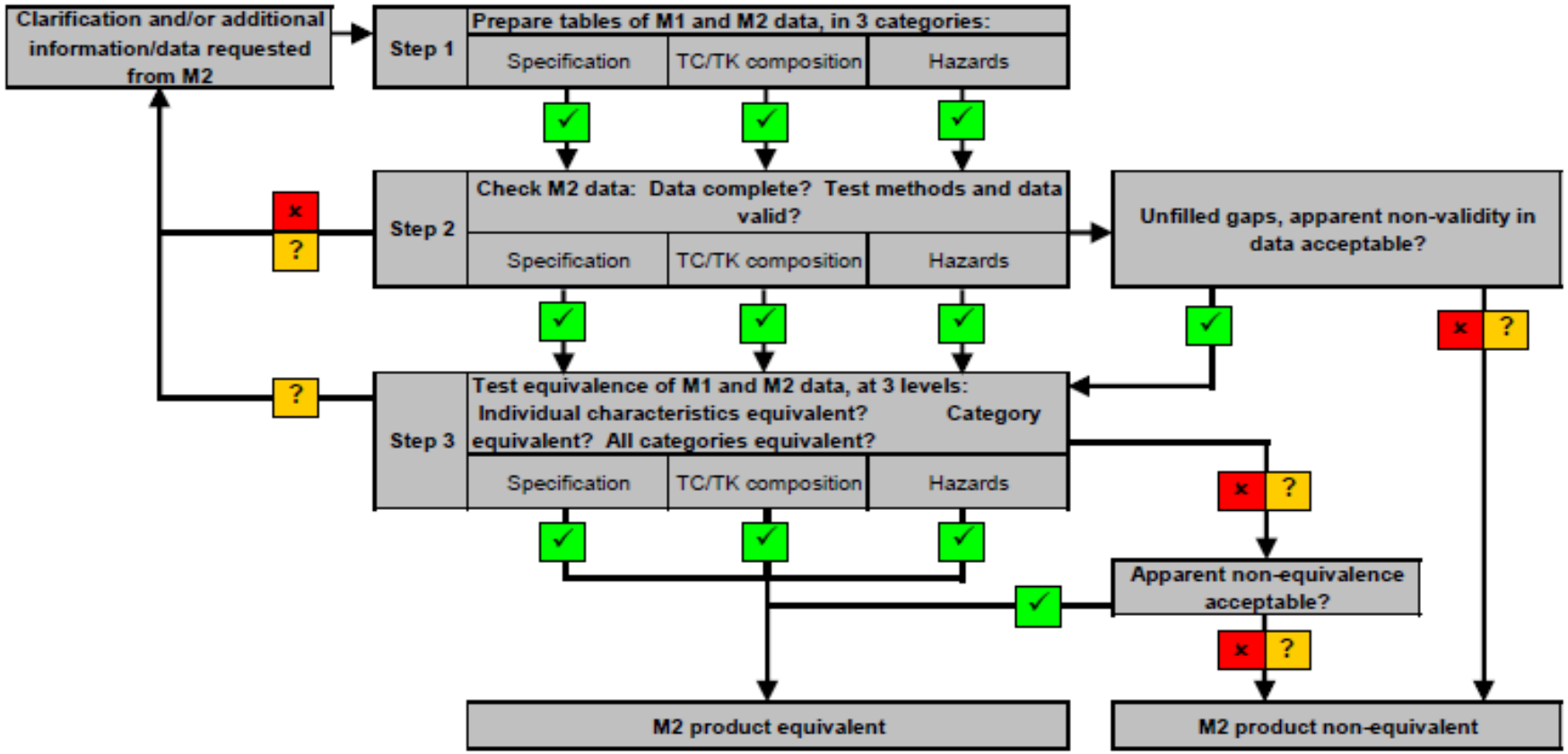
Data requirements for equivalence determination

Access to manufacturing process information and purity/impurity and hazard data from M1 and M2.

The more data available for comparison, the greater confidence in equivalence decisions.

Data are compared in a simple 3-step procedure – the complexity arises from gaps and inconsistencies which inevitably occur in the two sets of data.

Equivalence determination, overview of the 3-step procedure



Step 1, tabulate data

Characteristic of the TC or TK	Manufacturer 1 (reference)	Manufacturer 2
Active ingredient content		
active ingredient, min. g/kg	930	950
Impurity content		
impurity 1, max. g/kg (relevant)	1	2
impurity 2	10	5
impurity 3	1	5
etc...	...	...
Other specified characteristics		
pH range	4–7	5-6
etc...	...	...
Hazard data		
acute oral LD_{50}, mg/kg bw	500	650
acute dermal LD_{50}, mg/kg bw	>2000	>3000
etc...	...	...

Step 2, data checks

Are any data missing from each category?

For each component of the TC or TK, had the analytical method been acceptably validated?

For each hazard characteristic, were the tests conducted to a widely accepted guideline?

For any characteristic (composition, hazard, physical property), is there any other reason to question the validity of the reported result?

Step 3, equival. tests of each characteristic

Specification: does M2 product comply with clauses and limits of the existing specification (based on M1)?

TC or TK composition: is the manufacturing limit for any nonrelevant impurity in M2 >3 g/kg or >50% higher (whichever is the greater) than the corresponding M1 limit?

Toxicity: is M2 apparently >2x (or the factor from dosage intervals if >2) as hazardous as M1? Or, in the case of qualitative assessments, is M2 “worse” than M1?

Ecotoxicity: is M2 apparently >5x (or the factor from dosage intervals if >2) as hazardous as M1? Or, in the case of qualitative assessments, is M2 “worse” than M1?

Step 1, tabulate data

TC composition	M1 (reference)	M2	M2 data valid?	M2 equivalent?
	max./min. g/kg			
active ingredient	950	950		
impurity 1 (relevant)	0.001	–		
impurity 2 (relevant)	1	–		
impurity 3	32	ND		
impurity 4	10	16		
impurity 5	12	24		
impurity 6	9	ND		
impurity 7	11	9		
impurity 8	2	ND		
impurity 9	1	ND		
impurity 10	3	ND		
impurity 11	4	ND		
impurity 12	2	1		
impurity 13	–	6		

M1 = manufacturer 1
M2 = manufacturer 2
ND = not detected
– = no data

Step 2, check data

TC composition	M1 (reference)	M2	M2 data valid?	M2 equivalent?
	max./min. g/kg			
active ingredient	950	950	✓	
impurity 1 (relevant)	0.001	–	?	
impurity 2 (relevant)	1	–	?	
impurity 3	32	ND	?	
impurity 4	10	15	✓	
impurity 5	12	24	✓	
impurity 6	9	ND	?	
impurity 7	11	9	✓	
impurity 8	2	ND	?	
impurity 9	1	ND	?	
impurity 10	3	ND	?	
impurity 11	4	ND	?	
impurity 12	2	3	✓	
impurity 13	–	6	✓	

✓ = checked validated method, data OK, impurity 13 consistent with process used
? = unsure how to interpret the data

Step 2, check data - with additional information from M2

TC composition	M1 (reference)	M2	M2 data valid?	M2 equivalent?
	max./min. g/kg			
active ingredient	950	950	✓	
impurity 1 (relevant)	0.001	0.002	✓	
impurity 2 (relevant)	1	<1	✓	
impurity 3	32	<1	✓	
impurity 4	10	15	✓	
impurity 5	12	24	✓	
impurity 6	9	<1	✓	
impurity 7	11	9	✓	
impurity 8	2	<1	✓	
impurity 9	1	<1	✓	
impurity 10	3	<1	✓	
impurity 11	4	<1	✓	
impurity 12	2	3	✓	
impurity 13	–	6	✓	

data in red = new data from M2
✓ = yes (i.e. checked validated method, data OK)

Step 3, equivalence tests

TC composition	M1 (reference)	M2	M2 data valid?	M2 equivalent?
	max./min. g/kg			
active ingredient	950	950	✓	✓
impurity 1 (relevant)	0.001	0.002	✓	✗
impurity 2 (relevant)	1	<1	✓	✓
impurity 3	32	<1	✓	✓
impurity 4	10	15	✓	✓
impurity 5	12	24	✓	✗
impurity 6	9	<1	✓	✓
impurity 7	11	9	✓	✓
impurity 8	2	<1	✓	✓
impurity 9	1	<0.1	✓	✓
impurity 10	3	<1	✓	✓
impurity 11	4	<1	✓	✓
impurity 12	2	3	✓	✓
impurity 13	–	6	✓	✗

data in red = new data from M2

✓ = yes (i.e. checked validated method, data OK, or equivalent by this criterion)

✗ = no (i.e. non-equivalent by this criterion)

Step 3, equivalence tests

TC composition	M1 (reference)	M2	M2 data valid?	M2 equivalent?
	max./min. g/kg			
active ingredient	950	950	✓	✓
impurity 1 (relevant)	0.001	0.002	✓	✗
impurity 2 (relevant)	1	<1	✓	✓
impurity 3	32	<1	✓	✓
impurity 4	10	15	✓	✓
impurity 5	12	24	✓	✗ . → . ✓
impurity 6	9	<1	✓	✓
impurity 7	11	9	✓	✓
impurity 8	2	<1	✓	✓
impurity 9	1	<0.1	✓	✓
impurity 10	3	<1	✓	✓
impurity 11	4	<1	✓	✓
impurity 12	2	3	✓	✓
impurity 13	–	6	✓	✗ . → . ✓

✓ = yes (i.e. checked validated method, data OK, or equivalent by this criterion)

✗ . → . ✓ = not strictly equivalent but considered acceptable because no tangible change in hazards is implied

Equivalence of formulations

If the source of TC or TK incorporated into the formulation has been assessed as equivalent, and ...

If the formulated product complies with the existing specification for that formulation ...

The formulation is considered to be equivalent.

But, this test of equivalence may not be sufficient for certain products, e.g. certain slow-release LN and CS, in which the release profile is critical for efficacy.

In all cases, “equivalent” means only that basic quality characteristics are shared. It does not mean that products are equally suitable for an application or provide equal efficacy.

Incomplete or questionable data?

Gaps and limitations can occur, even in the best reference profiles.

For the particular case under review, ask the question: do the gaps and limitations prevent determination of equivalence?

Remember that new data may be costly in terms of money, time and/or animal welfare, so requests for new data must be justifiable.

“Missing” data sometimes already exist, so ask the manufacturer.

Check the study reports if data are questionable.

Validity of test methods

Specification should already be supported by suitably validated analytical and physical test methods but are the methods suitable for use with M2 products?

Were they used to generate the M2 data?

Have the analytical methods for non-relevant impurities been appropriately validated by M2? Are they considered appropriate by analysts in the evaluation team?

Hazard tests should be conducted according to widely accepted and published protocols. If not, are the tests considered appropriate by toxicologists and/or ecotoxicologists in the evaluation team?

Validity of analytical data

How were “unknowns” quantified in batch analyses?

“Unknowns” data from GC-FID or TIC from GC-EIMS are fairly reliable.

“Unknowns” data from HPLC-UV, LC-MS and LC-MS/MS tend to be unreliable.

Distinguish between “unknowns” and the unaccountable fraction.

Validity of analytical data

Are mass balance data acceptable?

A few sums slightly >1000 g/kg can arise from analytical uncertainty but, if all values exceed 1000 g/kg, or any values greatly exceed it, the analytical method(s) may provide poor accuracy.

Mass balances <980 g/kg generally should be investigated, to ensure that significant components were not undetected.

A sum of the manufacturing limits is meaningless and should not be calculated.

Validity of analytical data

What do reports of “not detected” or “not measurable” mean?

These should be expressed as “<x g/kg”.

Data on “ash”, “particulates”, inorganics, volatiles, etc., may be included in mass balance.

But it is important to avoid double-counting, so particular care is required with data for acidity/alkalinity, for example.

Validity of hazard data

Qualitative assessments can vary according to the protocol used.

In all cases where the data or assessments appear questionable, they should be checked in the study reports.

Data reported as identical to those in published literature should be checked in study reports, especially if the study details and/or several hazard characteristics appear to be identical to published data.