Determination of equivalence – an example of comparison of impurity profiles

等效的判定 (相同产品) 一个比较杂质分布的例子

Purity/impurity profiles (manufacturing limits data)
纯度/杂质组成（生产限量资料）

- Minimum active ingredient content, TC/TK.
  有效成分最低含量，原药/母药
  - If the specification is “minimum 960g/kg”, does the “new” material comply with this?
    如果规格规定“大于960克/千克”，“新”物质符合吗？
  - Higher minimum concentrations are automatically equivalent.
    高于最低含量的产品，被自动认为是符合相同条件的
- Impurities杂质
  - Non-relevant impurities should not exceed reference profile limits by >50% or >3 g/kg, whichever is the greater.
    非相关杂质的增加不应>50％参考限量或>3克/千克
  - Lower concentrations are automatically equivalent.
    低于参考限量的产品，被自动认为相同
  - No new relevant impurities and specified relevant impurities within existing limits.
    没有新的相关杂质发生，而特定的相关杂质含量低于现有限量

Purity/impurity profiles
纯度/杂质组成

- New or higher-concentration non-relevant impurities may be accepted as equivalent in some cases.

  有时新的或高含量的非相关杂质可能会作为相同产品被接受
- Higher concentrations of relevant impurities may also be accepted as equivalent, but not if the “10% increase in hazard limit” is exceeded.

  较高含量的相关杂质可能也会作为相同产品被接受，但不得超过“10％的危险限量”
- In both cases, only if the toxicology data show no increase in hazard and no new hazards.

  以上两种情况，只有毒性资料显示危险性没有增加及没有新的危险性，才可以被接受
  - Note: the reference profiles are not changed by extending the specification to equivalent products.

    注意：参考含量不会因为相同产品规格的不同而改变

TC manufacturing specifications
原药的生产规格

	manufacturer A, g/kg 生产者 A	manufacturer B, g/kg 生产者 B
active ingredient有效成分	950	950
impurity 1 (relevant)杂质1（相关）	0.001	?
impurity 2 (relevant)杂质2（相关）	1	?
impurity 3 杂质3	31	Nd
impurity 4杂质4	10	16
impurity 5杂质5	12	24
impurity 6杂质6	9	Nd
impurity 7杂质7	11	9
impurity 8杂质8	2	Nd
impurity 9杂质9	1	Nd
impurity 10杂质10	3	nd
impurity 11杂质11	4	nd
impurity 12杂质12	?	6
acetone insolubles 丙酮不溶物	<2	<1

nd = not detected 未检出. ? = no data无数据.

Examples of additional information about TC B
原药B的其它资料

	A, g/kg	B, g/kg	Example B1 例子B1	Example B2 例子B2	Example B3 例子B3
active ingredient有效成分	950	950			
relevant impurity 1 相关杂质1	0.001	?	no data 无数据	0.001	<0.0005
relevant impurity 2 相关杂质2	1	?	cannot occur 未出现	2	<1
impurity 3 杂质3	31	nd			
impurity 4 杂质4	10	16	no hazard data 无危险性资料	no hazard data 无危险性资料	no hazard data 无危险性资料
impurity 5 杂质5	12	24	no hazard data 无危险性资料	no hazard data 无危险性资料	no hazard data 无危险性资料
impurity 6 杂质6	9	nd			
impurity 7 杂质7	11	9			
impurity 8 杂质8	2	nd			
impurity 9 杂质9	1	nd			
impurity 10 杂质10	3	nd			
impurity 11 杂质11	4	nd			
impurity 12 杂质12	?	6	no hazard data 无危险性资料	not hazardous 无危险性	relevant impurity 相关杂质
acetone insolubles 丙酮不溶物	<2	<1			

Possible conclusions可能的结论

- **Example 1例子1**
  - **if there is no evidence that impurities 4, 5 and 12 should be relevant, only requires data to show compliance with the clause for relevant impurity 1.**

    如果没有证据显示杂质4、5和12是相关杂质，只要求证明相关杂质1符合条款规定的资料

- **Example 2例子2**
  - **if there is no evidence that impurities 4 and 5 should be relevant, check to see if manufacturer B can comply with the limit of 1 g/kg for impurity 2. If not, consider raising this limit to 2 g/kg, if this is within the 10% limit for calculated increase in overall hazard.**

    如果没有证据显示杂质4和5是相关杂质，应检查制造厂商B的杂质2是否符合1克/千克的限量要求。如果不符合，如果计算的综合危险性增加不超过10%，可考虑将限量提高至2克/千克，

- **Example 3例子3**
  - **if there is no evidence that impurities 4, 5 and 9 are relevant, check the evidence for relevance of impurity 12. If it is relevant, can it occur in manufacturer A's process? If it can, the original specification of manufacturer A may have to be reviewed. If it cannot occur, a separate specification may be required for manufacturer B's TC (assuming acceptable risks).**

    如果没有证据显示杂质4、5和9是相关杂质，应检查杂质12相关性的证据。如果相关，是否也出现在A制造厂商的加工过程中？如果出现，不得不对原先的A制造厂商的技术规范进行修订。如果不出现，可对B制造厂商生产的原药制定单独的技术规范（假设风险是可接受的）