General Information

New Expression of Acceptance Criteria in the Test for Related Substances

For information of the stakeholders

In European Pharmacopoeia monographs, the acceptance criteria for related substances have so far usually been expressed in terms of comparison of peak areas ("… not more than the area of the principal peak in the chromatogram obtained with reference solution …"), which, strictly speaking, leads to a pass/fail decision but not to a true quantitative test result.

As the requirements for related substances in Ph. Eur. monographs have been adapted to the principles of ICH Guideline Q3A(R2) and VICH Guideline 10, many users have requested to apply a similar format for the expression of the acceptance criteria in Ph. Eur. monographs. An enquiry was published in Pharmeuropa 22.2.

Based on the feedback of the enquiry, it has been decided:

- *to apply the new expression of acceptance criteria by numerical values for new monographs and major revision projects, wherever possible;*
- *to maintain existing monographs in comparative style until they undergo a major revision.*

The way of expressing the criteria will not have any impact on the validity of the test as such. Respective statements to this end will be added to the General Notices and chapter 5.10. Control of impurities.

Stakeholders and groups of experts will be asked to apply the following style model when drafting or submitting text proposals.

Related substances. Liquid chromatography (*2.2.29*). *Carry out the test protected from light.*

Solvent mixture: *water R, methanol R* (10:90 *V/V*).

Test solution. Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b). Dissolve 10 mg of *modelon for peak identification CRS* (containing impurities C, D and F) in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (c). Dissolve 5.0 mg of *modelon impurity B CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 1.0 mL of the solution to 100.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 4.0 mm;

— *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: mix 10 volumes of *acetonitrile R* and 90 volumes of a 0.68 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 5.0 with *0.5 M potassium hydroxide R*;

— *mobile phase B*: mix equal volumes of *acetonitrile R* and a 0.68 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 5.0 with *0.5 M potassium hydroxide R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 – 3	60	40
3 – 16	60 → 49	40 → 51

Flow rate: 1.2 mL/min.

Detection: spectrophotometer at 238 nm.

Injection: 10 µL.

Identification of impurities: use the chromatogram supplied with *modelon for peak identification CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities C, D and F; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity B.

Relative retention with reference to modelon (retention time = about 6 min): impurity C = about 0.4; impurity G = about 0.8; impurity D = about 0.9; impurity F = about 1.2; impurity B = about 1.9.

System suitability: reference solution (b):

— *resolution*: minimum 2.5 between the peaks due to impurity D and modelon; minimum 1.5 between the peaks due to modelon and impurity F.

Calculation of percentage contents:

— for impurity B, use the concentration of impurity B in reference solution (c);

— for impurity C, multiply the peak area by the correction factor 1.5;

— for impurities other than B, use the concentration of modelon in reference solution (a).

Limits:

— *impurity B*: maximum 0.3 per cent;
— *impurity C*: maximum 0.2 per cent;
— *impurity D*: maximum 0.15 per cent;
— *unspecified impurities*: for each impurity, maximum 0.10 per cent;
— *total*: maximum 0.6 per cent;
— *reporting threshold*: 0.05 per cent.

IMPURITIES

Specified impurities: B, C, D.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical use (2034)*. It is therefore not necessary to identify these impurities for demonstration of compliance. See also *5.10. Control of impurities in substances for pharmaceutical use): E, F, G, H, I*.