British Pharmacopoeia

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TO WHOM IT MAY CONCERN

FENTANYL INJECTION BP 2020

RELATED SUBSTANCES

The use of Fentanyl Impurity A BPCRS has been revised out of the Related substances test for Fentanyl Injection in the BP 2021. The BPCRS has been replaced with peak area comparison against solution (2) to determine compliance with the limit and in-situ generation of impurity A to aid peak identification.

The Related substances test will be amended as follows, the changed text has been highlighted:

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) The injection being examined, diluted with the mobile phase if necessary, to contain the equivalent of 0.005% w/v of fentanyl.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and dilute 5 volumes of the resulting solution to 20 volumes with the mobile phase.
(3) Dissolve 5 mg of *fentanyl citrate BPCRS* in 9 mL of *water*, add 1 mL of *hydrogen peroxide solution (30 per cent)* and heat at 95° for 1 to 2 hours. Allow to cool and dilute to 25 mL with the mobile phase (generation of impurity A).
(4) Dissolve 5 mg of *fentanyl citrate BPCRS* in 10 mL of 2M *hydrochloric acid*, heat on a waterbath under a reflux condenser for 4 hours and neutralise with 10 mL of 2M *sodium hydroxide*. Evaporate to dryness on a waterbath, cool, dissolve the residue in 10 mL of *methanol* and filter. Dilute 1 volume of the filtrate to 5 volumes with the mobile phase (generation of impurity D).

Chromatographic conditions
(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Bondclone C18 10µ is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.25 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 215 nm.
(f) Inject 100 µL of each solution. Inject *methanol* as a blank prior to the solutions.
(g) For solutions (1) and (2) allow the chromatography to proceed for twice the retention time of the principal peak.

Mobile phase
0.3% w/v of *potassium dihydrogen orthophosphate* in a mixture of 4 volumes of *acetonitrile*, 40 volumes of *methanol* and 56 volumes of *water*, the solution adjusted to pH 3.2 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the retention time of fentanyl is about 9 minutes and the relative retention of fentanyl impurity A is about 1.9.

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System suitability
The test is not valid unless, in the chromatogram obtained with solution (4), the retention time of fentanyl impurity D is about 0.8 relative to fentanyl.

Limits
Identify any peaks corresponding to impurities A and D in the chromatogram obtained with solution (1), using the chromatograms obtained with solutions (3) and (4) respectively.

In the chromatogram obtained with solution (1):
the area of any peak corresponding to fentanyl impurity A is not greater than twice the area of the peak in the chromatogram obtained with solution (2) (0.5%);
the area of any peak corresponding to fentanyl impurity D is not greater than twice the area of the peak in the chromatogram obtained with solution (2) (0.5%);
the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.25%);
the sum of the areas of any *secondary peaks* apart from any peaks corresponding to fentanyl impurity A and fentanyl impurity D is not greater than three times the area of the principal peak in the chromatogram obtained with solution (2) (0.75%).
Disregard any peak obtained with the blank solution and any peak with an area less than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

Please accept this as a notice of intent to amend the monograph on behalf of the British Pharmacopoeia Commission. This letter is for information only and does not represent a legally-enforceable standard. The revised monograph will be published in a future edition of the British Pharmacopoeia - the current target publication is the BP 2021, which will come into force on 1 January 2021.

If you have any questions concerning this letter, please do not hesitate to contact the British Pharmacopoeia Secretariat (bpcom@mhra.gov.uk)
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Yours faithfully,

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Secretary & Scientific Director

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