EXPRESSION OF RELATED SUBSTANCES LIMITS: A PROPOSAL TO BEGIN MOVING TO FULLY NUMERICAL LIMITS IN BP MONOGRAPHS

We are considering a policy change and wish to seek the views of our stakeholders.

Background

Related substances tests in BP monographs for medicinal substances and products are used to control degradation products and by-products of the synthetic route used for manufacture of the drug substance.

In most liquid chromatography (LC) and gas chromatography (GC) related substances tests developed by the BP, compliance with the related substances limits is determined by comparing peak responses from the material being tested to peak responses in the other solutions listed in the test. An example of such a limit is 'the area of any peak corresponding to impurity A is not greater than the area of the peak due to API in the chromatogram obtained with solution (2) (0.5%)'. The approximate percentage of the limit is given in parentheses, in this example (0.5%), at the end of the limit statement.

Proposed change

We are proposing to begin a process of moving to fully numerical limits in related substances tests, where determined using LC and GC, in monographs developed by the BP for medicinal substances and products. This proposal will align how impurity limits are calculated in BP LC and GC related substances tests with ICH Q3B (R2) and the European Pharmacopoeia.

Reasons for change

- Guidance in ICH Q3B (R2) encourages marketing authorisation applicants to present related substances results numerically, and not in general terms such as "complies" or "meets limit";
- Through the widespread adoption of ICH principles, the majority of registered methods and finished product specifications include numerical limits;
- Queries from BP users indicate that the related substances limits given in parentheses in monographs are often treated as numerical limits;
- The European Pharmacopoeia has adopted this approach in new monographs, and revised monographs where possible.

We anticipate the following benefits to BP users:

- Closer alignment to industry practice and registered methods;
- Alignment with the European Pharmacopoeia;
- Easier determination of compliance with the related substances limits in monographs;
- Easier to use alternative procedures or external reference standards;
- A simplified expression of limits within monographs.

Planned implementation in the BP

The views expressed by stakeholders will be collated and presented to BP Commission. If this proposal is endorsed by stakeholders and BP Commission, we anticipate that the change would be applied in new monographs and on a rolling basis for monographs undergoing revision.

This would mean a longer implementation period for already published monographs but would reduce the potential impact on BP users of a global technical change in a single edition of the BP. There would be the opportunity to comment on individual monographs where fully numerical limits were applied through the usual public review windows on the BP website.

Draft wording to show how numerical limits could be included in monographs can be found in Annex 1, at the end of this document.

Consultation questions for stakeholders

Your comments are welcomed on the following questions, along with any other comments that you feel are relevant to this consultation:

1. Do you support the proposal to implement fully numerical related substances limits in BP monographs?

2. What benefits and challenges would you experience if numerical limits are introduced into the related substances tests in BP monographs?

3. What could the BP do to mitigate any challenges? For example, by providing additional guidance or adjusting implementation timings.

How to respond

Please send your comments by email to bpcom@mhra.gov.uk with the subject 'Numerical limits'.

Please tell us a little about who you are, so that we can put your comments in to context:

Job title:
Company / Organisation:
Sector: Industry / Regulator / Academia
Industry sub-sectors: Innovator / Generics / Contract Organisation / Trade Association
QC / QA / Compendial Affairs/ Regulatory Affairs / R&D

The deadline for comments is 30 September 2020.

Outcomes and feedback

Following a review of the stakeholder comments we receive and discussion by the BP Commission, the outcome of the consultation will be published on the BP website. You can subscribe to email alerts from the BP to receive updates on our activities.

Annex 1 – Draft wording to show how numerical limits could be included in BP monographs

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

(1) Shake a quantity of powdered tablets containing 0.1 g of API with 100 mL of the mobile phase. Mix, centrifuge and filter.
(2) Dilute 1 volume of solution (1) to 200 volumes with the mobile phase.
(3) 0.1% w/v of *API impurity standard BPCRS* in the mobile phase.
(4) Dilute 1 volume of solution (2) to 5 volumes with the mobile phase.

CALCULATION OF IMPURITIES
For each impurity, use the concentration of API in solution (2).
For the reporting threshold, use the concentration of API in solution (4).
For peak identification, use solution (3).
API retention time: about 10 minutes.
Relative retention: impurity A, about 0.4 and impurity B, about 0.9.
Correction factors: impurity B, multiply by 0.6.

LIMITS
Specified impurities:
impurity A, 0.5%;
impurity B, 0.3%.
Unspecified impurities: 0.2%.
Total impurities: 1.0%.
Reporting threshold: 0.1%.