PULSED AMPEROMETRIC DETECTION FOR LIQUID CHROMATOGRAPHY

We are seeking views from stakeholders on a proposal to include PAD (Pulsed Amperometric Detection) as a detection method for liquid chromatography (LC) procedures to determine the level of impurities and content of active pharmaceutical ingredients in medicinal substances and finished products where other detection methods may be unsuitable.

Background

LC with a UV spectrophotometric detector is the most common analytical technique used for related substances and assay tests in BP monographs. This is typically due to the nature of small chemical medicinal substances, where they are relatively polar and include strong UV chromophores. However, some medicinal substances and/or their related impurities do not absorb in the UV range, which can make it difficult to achieve the detection limits commonly required for related substances tests.

Typically such compounds, if required to be detected by UV, would be subject to a procedure to derivatise certain functional groups. The BP has received an increasing number of queries relating to the difficulty in preparation and analysis, as well as the safety and environmental impact of such procedures across the last few years and have sought alternative technologies.

PAD detectors work through the application of an electric current across electrodes. This means UV absorbance is not a pre-requisite for detection and LC-PAD may provide greater sensitivity than LC-UV for organic materials that do not contain a suitable UV chromophore.

Proposed change

The British Pharmacopoeia is proposing that PAD is used as an alternative LC detector when UV detection is not sufficiently sensitive. Where UV detection is deemed unsuitable, LC-PAD will be considered alongside existing procedures, for example: derivatisation or fluorescence detection during monograph development and revisions. LC-PAD is most likely to appear in monographs for medicinal substances and finished products containing aminoglycoside antibiotics at this time.

Reasons for change

- Introducing LC-PAD into BP monographs would offer another alternative option for improving the detection sensitivity for substances that do not contain a good UV chromophore in BP monographs. At present, the alternative options are limited, however if the situation requires, PAD can be used almost universally.
- The European Pharmacopoeia have adopted this technology in drug substance monographs for aminoglycoside antibiotics, enabling better control of impurities for these substances; it is proving difficult to match the improvement in BP monographs for aminoglycoside antibiotic products without aligning the analytical technique.
- This technology is well established, understood and accepted by industry as well as regulators.

We anticipate the following benefits to BP users through the adoption of this detector for related substances and Assay tests:

- Improved sensitivity where there is no UV chromophore, ensuring that analytical procedures are able to comply with regulatory expectations.
- Alignment with European Pharmacopoeia methodologies for drug substances, for example; aminoglycoside antibiotics.
- Alignment with industry practice, registered methods and regulatory expectations.

Planned adoption in the BP

The target adoption of PAD detection for LC methods is from the BP 2022 onwards, subject to the comments received in response to this consultation and endorsement of the recommendation by the BP Commission.

At the time of this consultation, it is anticipated that LC-PAD could be suitable for Related substances and Assay tests where LC-UV detection is not suitable. It is likely to be limited to use in monographs for aminoglycoside antibiotics at this time.

The separate principles (LC and PAD) are described in Appendix III. D and II. M of the BP respectively. Due to the maturity of this technology no additional guidance has been identified as needed to support the adoption of LC-PAD tests. An example of the draft wording to show how PAD detectors could be included within Related substances and Assay procedures in monographs can be seen in the box below.

(e) Use a post-column solution of carbonate-free sodium hydroxide solution R diluted 1 in 25 previously degassed, which is added pulse-less to the column effluent using a 375 µL polymeric mixing coil.

(f) Post-column flow rate 0.5 mL/min.

(g) Use a *pulsed amperometric detector* with a gold indicator electrode, a *silver-silver chloride* reference electrode and a stainless steel auxiliary electrode which is the cell body, held at respectively 0.00 V detection, + 0.80 V oxidation and -0.60 V reduction potentials, with pulse durations according to the instrument used.

In addition to this more general consultation, BP users will have the opportunity to comment on the specific monographs where use of a PAD detector is proposed, prior to publication of the new or revised monograph(s).

Consultation questions

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

1. What do you think about the proposal to adopt PAD as a detector to be used, where UV is not appropriate, in the determination of Related substances and content Assay in BP monographs?

2. What benefits and challenges would you experience if PAD is introduced into BP monographs?

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

How to respond

Please send your comments by email to bpcom@mhra.gov.uk with the subject 'LC -PAD for identification'.

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 as a news item on the BP website. You can subscribe to email alerts from the BP to receive updates on our activities.