Change proposal response: LC-PAD for related substances and assay testing in BP monographs

Introduction

The BP wishes to thank all stakeholders for contributing views on the change proposal. The continued cooperation and participation of our stakeholders ensures that the development and improvement of our monographs supports the needs of all users, and that we continue to maintain robust, high quality standards for pharmaceutical substances and medicinal products in the interest of protecting public health.

This response document contains:

1. Report summary
2. Key themes from the responses
3. Outcomes
4. Implementation

1. Report summary

The BP sought views from stakeholders on a proposal for use of Pulsed Amperometric Detection (PAD) as a detection method for liquid chromatography (LC) procedures, where more commonly used detectors are not suitable. The change proposal aimed to address some of the challenges faced in determining the level of impurities and assay of active pharmaceutical ingredient for organic materials that do not contain a chromophore suitable for UV detection.

The change proposal was made available on the BP website between 1 July and 30 September 2020. The purpose was to seek views from BP users, understand the benefits and challenges that users may experience if the change was adopted and how we could support users if the change proposal was adopted.

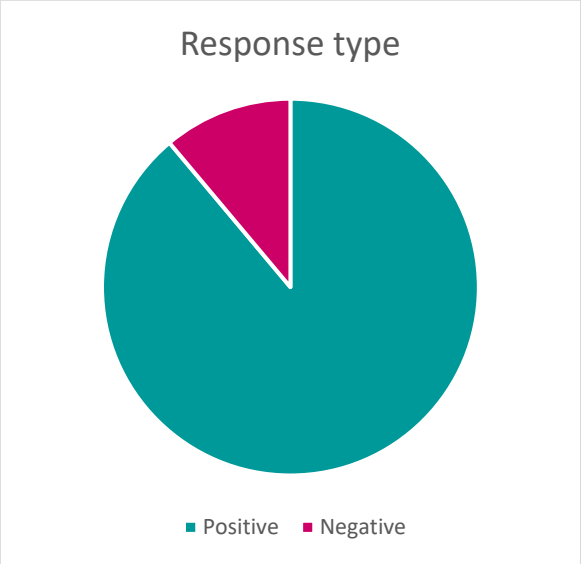
Responses were received from a range of valued stakeholders including pharmaceutical manufacturers; regulatory bodies; academia/researchers; and the healthcare sector. The responses were reviewed by the BP's New Analytical Technologies ad-hoc working group and the recommendations presented to BP Commission in November 2020, as shown below.

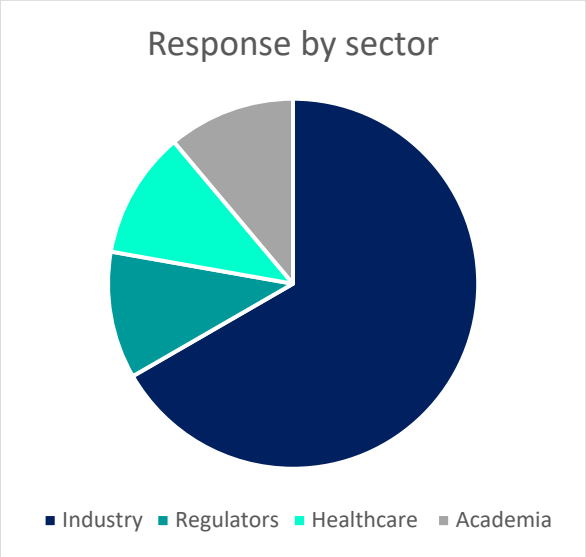
The responses we received to this change proposal were broadly in support of introducing LC-PAD as an option for related substances and assay analysis, where a UV detector is not sufficiently sensitive. As a result, BP users can expect to see LC-PAD, most likely in monographs

for medicinal substances and finished products containing aminoglycoside antibiotics, introduced from the BP 2024 onwards.

2. Key themes from the responses

2.1 Response overview





The responses demonstrated broad support for introducing this change into BP monographs.

2.2 Benefits identified by BP users

Improved methods Responses highlighted that using LC-PAD meant that complex derivatisation methods and semi-quantitative TLC methods could be avoided, improving the reliability of results.

Alignment Stakeholders informed us that alignment would be beneficial between drug product and drug substance monographs, where LC-PAD has already been adopted in European Pharmacopoeia (Ph Eur) monographs.

Mature technology Adoption of this technology was supported as it is a well-established technique for offering increased sensitivity where compounds do not have UV chromophores. It has been found to be robust and reliable in routine use.

2.3 Potential challenges faced by BP users

Equipment upgrade costs Some responses acknowledged that investment in new equipment may be a challenge for laboratories.

User experience Responders noted that although PAD is well-established, it is not widely used for pharmacopoeial applications and there may be a lack of user experience and well-defined protocols within laboratories, which would require training and resource to build-up.

2.4 Requested mitigation steps

Time An extended implementation time and advanced notification for the introduction of LC-PAD methods was seen as beneficial to BP users. This would allow sufficient time to carry out any additional activities needed to implement changes, such as acquisition of equipment, training and QMS development.

Consideration of alternatives Stakeholders requested that careful consideration was given to alternative tests before a LC-PAD method was introduced into a monograph. This would ensure that PAD would only be adopted where other methods are not suitable.

3. Outcomes

Proposal adopted Based on the predominantly positive responses to this change proposal, the BP will introduce LC-PAD related substances and assay methods in limited circumstances.

Limited adoption Where UV detection is not suitable, LC-PAD procedures may be considered alongside alternative technologies and methods during monograph development or revision. This will ensure that LC-PAD methods are introduced only where the technology offers a clear benefit to the analytical test method.

Extended implementation time Users told us that extended implementation time for LC-PAD methods would help to mitigate challenges faced by the introduction of LC-PAD methods into monographs. We have taken this on-board and will be looking to introduce this change from BP 2024 onwards.

Informed introduction Stakeholders will have the opportunity to submit comments on each monograph where a LC-PAD method is proposed. The BP intends to make draft monographs containing LC-PAD tests available before any laboratory work commences, so that stakeholders can propose alternative methods for consideration at an earlier stage in the monograph development or revision process. New and revised draft monographs are made available on the BP website for 3 month comment periods each year [1 January to 31 March; 1 April to 30 June; 1 July to 30 September and 1 October to 31 December].

Guidance The separate principles (LC and PAD) are described in BP Appendix III D and II M, respectively. Due to the maturity of this technology no additional guidance has been identified as needed to support the adoption of LC-PAD tests. The BP is committed to supporting users as this change is introduced and encourages BP users to share challenges and experiences, which may lead to future additional guidance development.

4. Implementation

BP users can expect to see LC-PAD methods in our monographs from BP 2024 onwards, in limited circumstances.

Initially, LC-PAD will be investigated where the technology is used in drug substance monographs within the European Pharmacopoeia, specifically product monographs related to the following drug substances:

- Amikacin
- Amikacin Sulfate
- Netilmicin Sulfate
- Neomycin Sulfate
- Spectinomycin Sulfate
- Spectinomycin Dihydrochloride Pentahydrate
- Tobramycin
- Framycetin Sulfate
- Gentamicin Sulfate

We encourage stakeholders with specific experience in the use of LC-PAD for these substances, to contact the BP at the email address below to support our considerations on the implementation of LC-PAD in monographs.

We will continue to listen to our stakeholders as this test is introduced to ensure that the mitigation steps we have proposed are working, and that any additional support our users may need is available. Please get in touch with us by email, bpcom@mhra.gov.uk, if you think we can provide further advice or support.