British Pharmacopoeia

Public consultation response: Guidance on the application of flow cytometry for the cell and gene therapy community

Introduction

The BP wishes to thank all stakeholders for contributing views on the Guidance on the application of flow cytometry for the cell and gene therapy community. The continued cooperation and participation of our stakeholders ensures that our Advanced Therapy Medicinal Products (ATMP) work supports the needs of relevant users, and high-quality best practice guidance for ATMP analysis is produced in the interest of protecting public health.

The Agency is committed to ensuring the quality of medicines through its activities in the development of public quality standards that help to assure the safety and efficacy of medicines. The BP ATMP work is aligned to the Agency's Strategy for pharmacopoeial public quality standards for biological medicines[1] and the UK Government Life Sciences Vision[2].

This response document contains:

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

1. Report summary

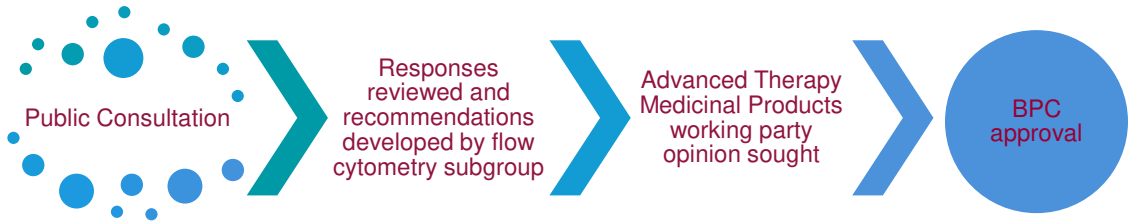
Between the 7th April to 19th May 2021, the British Pharmacopoeia (BP) sought consultation on draft guidance on the application of flow cytometry for the cell and gene therapy community. The guidance takes into account the fact that flow cytometry assays may be deployed in a range of scientific settings or environments. It recognises that the regulatory status in which the assay will be operated may influence the assay configuration and workflow. The guidance document attempts to cover assays being operated in the following environments:

- An academic research setting.
- An ATMP development programme (including GMP manufacture).
  - Within the sponsors own facilities.
  - Within outsourced contract vendors (e.g. CROs & CMOs).
- Clinical settings such as pathology laboratories for the analysis of patient samples.
- Clinical trials setting.
- Pre-clinical.

[1] https://www.gov.uk/government/consultations/strategy-for-pharmacopoeial-public-quality-standards-for-biological-medicines

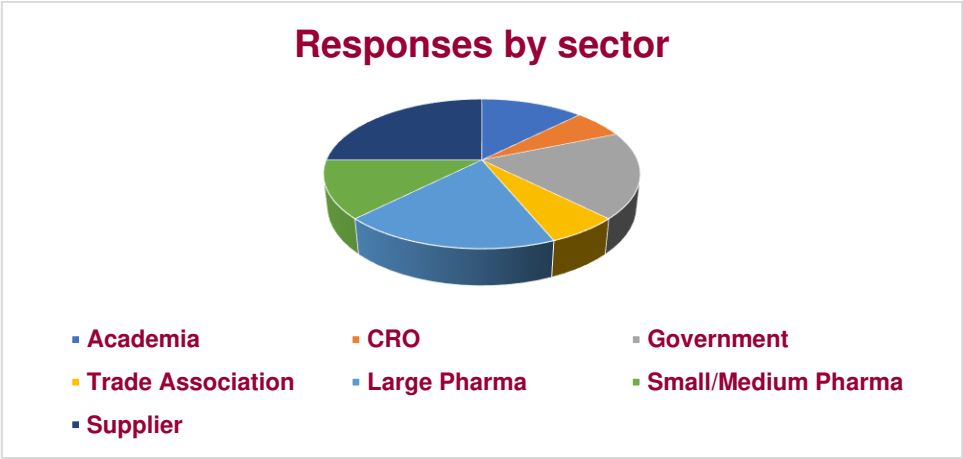
[2] https://www.gov.uk/government/publications/life-sciences-vision/life-sciences-vision-html

There were eleven responses received for the consultation, from a range of international organisations. These included trade associations, small/medium and large pharmaceutical companies, suppliers, and cell and gene therapy groups. This diverse representation, as well as the expert familiarity of many of the respondents with flow cytometry, indicates good feedback from the consultation. The extent of practical experience and wealth of knowledge from responders was evident from the detailed and balanced responses to the consultation.



2. Key themes from the responses

2.1 Response overview



The BP would like to make readers aware that although there were no responses from NHS to the public consultation, the WP ATMP and flow cytometry subgroup that drafted the guidance document includes NHS representatives.

2.2 Benefits identified by responders

Gap recognition

Guidance on how to use flow cytometry to support product development and manage patient care were stated as critically needed. Responses received were supportive of the flow cytometry guidance, they indicated a general lack of awareness of how cytometers differ in the way they acquire data, their laser/optical set-ups and the data outputs. Stakeholders considered that gaps in authoritative guidance for the application of flow cytometry in ATMP analysis exist, and that the proposed guidance would contribute to supporting users in their application of flow cytometry to ATMPs.

Key variables

The guidance recognises and addresses key variables of flow cytometry assay development, importantly including standardisation of gating and data analysis and starting material composition, and stakeholders considered the guidance to set realistic expectations of the challenges associated with using flow cytometry in the analysis of ATMPs.

Thoroughness

Responders appreciated the detail and provision of annexes for the instrument qualification, validation report, and validation protocol. The summary tables contrast similar topics such as early phase qualifications and late phase validation and were described as useful to users at all stages of development.

2.3 Potential challenges and improvements identified by responders

Cross instrument standardisation

Cross-instrument standardisation is necessary to increase confidence in the data collected and responders recommended consideration of this point.

Clarity and style

Some areas of the document required amending for clarity to ensure that the section titles accurately matched the text contained within the section. It was also suggested that some of the “background knowledge” could be removed from the document to reduce overall length. The language used was recommended to be made clearer, more concise, and be more assertive in places.

Scope

Some responders suggested additional aspects for the guidance to cover such as method lifecycle management and analysis of critical raw materials.

2.4 Usefulness

Implementation

Stakeholders indicated that that the non-mandatory nature of the guidance would allow more users greater flexibility to consider their product needs than a legally enforceable standard. It is thought that this type of document would be most useful to small start-up organisations who would need to consider the analytical process from method development and instrument qualification, through to validation.

Ease of use

The guidance is outlined in a logical order and provided a step-by-step guideline for flow cytometry assay development. It could be used as a reference for internal quality standard setting and guidance in developing flow-based analytical methods.

Alignment

Responses indicated that the cross-referencing of appropriate regulations and standards for each step was seen as beneficial.

3. Review and approval process

Guidance valued

All comments have been considered by the BP Working Party for ATMPs and changes made, as necessary the document has also been reviewed by MHRA Licensing, Clinical Trials, and Inspectorate divisions. The Working Party ATMP group is comprised of experts in flow cytometry from a range of backgrounds including industry, academia, and NHS. Final sign off will be sought from the BP Commission before the guidance is released to the ATMP community.

Technical amendments

The Working Party ATMP decided whether to make an amendment to the guidance based on experience, group knowledge, and prior agreements in relation to the scope of the document. Decisions around technical comments were made against regulatory expectations. Cross references to international regulations and guidance materials have been made intentionally due to the anticipated global usage of the guidance.

Non mandatory

The document is intended to be non-mandatory, best practice guidance and does not constitute a prerequisite for licensing approval. All products need to be considered on a case-by-case basis and this document should be combined with product knowledge to aid flow-based assay development. The document is not necessarily exhaustive of expectations, it is the user's responsibility to ensure the appropriate methods are employed for their specific product, assay, and validation plan design.

Clarity and style

Where language discrepancies, clarity and conciseness issues have been highlighted by responders, amendments have been made. The page extent of the document has been shortened by the consolidation of annexes from six down to four. The "background knowledge" remains in the document but the format may be revised in the future.

Scope

A number of new paragraphs and sections have been added to the document in response to stakeholder request, these include but are not limited to: requalification of the instrument, sample knowledge, set up, gating strategy, and data acquisition.

4. Implementation

In general, responses were supportive of the flow cytometry guidance. Changes have been made, as a result of the consultation comments to the final document, which will be published on the BP Online product during the BP 2022 edition subject to the approval of the BP Commission.

The BP will continue to listen to our stakeholders as this guidance is published to ensure that the information is relevant and that any additional support our users may need is available. Please get in touch with us by email, BiolStandards@mhra.gov.uk, if you think we can provide further advice or support.