Medicines & Healthcare products
Regulatory Agency

Consultation Response

Strategy for pharmacopoeial public quality standards for biological medicines

CPRD NIBSC MHRA

Strategy for pharmacopoeial public quality standards for biological medicines

Summary

Biological medicines are an increasingly important part of healthcare worldwide. Their quality is assured by a regulatory framework which includes compliance to public quality standards. Both documentary and physical standards work together to ensure that biological medicines are of acceptable quality for use by the patient.

In the UK, documentary standards exist as texts published in the British Pharmacopoeia. The Agency has developed a strategy for the creation of pharmacopoeial public quality standards for biological medicines.

In January 2017 a public consultation on this strategy was published, which closed 10th April 2017. This document provides the Agency's official response to the replies received.

Any questions related to this strategy can be directed to BiolStandards@mhra.gsi.gov.uk.

In this document there is:

1. Introduction

1.1 Background

In January 2017 the Agency launched a consultation on its proposed strategy for the development of pharmacopoeial standards for biological medicines. This consultation was in recognition of the increasing importance of biological medicines to global healthcare strategies and the valuable perspectives and knowledge our stakeholders hold in this area.
The Agency is committed to ensuring the quality of biological medicines through its activities in the development of pharmacopoeial quality standards. Quality helps ensure medicines work and are acceptably safe.

A key strategic aim of the Agency's corporate plan is to enable innovation and our strategy for biological pharmacopoeial standards is an important part of our portfolio of work to deliver this objective. This includes the Early Access to Medicines Scheme[1], the Innovation Office & Regulatory Advice Service for Regenerative Medicines[2] and the implementation of the Advanced

[1] https://www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams

[2] https://www.gov.uk/government/groups/mhra-innovation-office

Therapies Manufacturing Action Plan[3]. It is also aligned and complementary to UK Government proposals as outlined in the Strategy for UK Life Sciences[4] and the Life Sciences Industrial Strategy[5].

This Consultation Response document summarises the responses received, the Agency response to these and the final adopted strategy.

1.2 Responses received

A wide range of responses were received representing manufacturer trade associations, manufacturers, academia/researchers and peer organisations (Figure 1). The manufacturer-related responses spoke for national, European and international interests and encompassed all types of biological materials. These included submissions from the key trade associations: ABPI, EFPIA, IFPMA, Medicines for Europe and BGMA-BBA. Actively representing the vast majority of biopharmaceutical manufacturers. Academic and peer organisation responses were particularly focussed on Advanced Therapy Medicinal Products (ATMPs) and gave a sound basis for understanding the concerns of this emerging area of medicine.

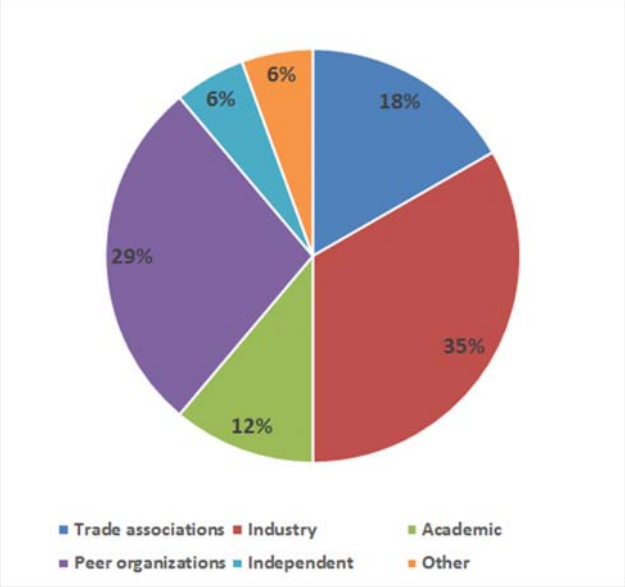

Figure 1 Percentage breakdown by responder type

1.3 Analysis methodology

The consultation response form included 6 questions designed to enable us to gain an understanding of our stakeholders' perspectives. These perspectives were related to high-level opportunities and challenges, value, innovation, unmet needs, collaboration and alternative approaches.
This has allowed us to analyse and structure the responses into key themes given below.

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[3] http://www.abpi.org.uk/our-work/mmip/Documents/Advanced-Therapies-Manufacturing-Taskforce-report.pdf

[4] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/32457/11-1429-strategy-for-uk-life-sciences.pdf

[5] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/640696/life-sciences-industrial-strategy.pdf

2. Key themes from responses

2.1 Value and innovation

Discussion in this area was wide-ranging and covered both broader strategic cases for standards as well as the value and impact of standards for specific product types. In general, responses supported the value of standardisation as an important activity in ensuring the quality of medicines.

Examples of where standards could add value included:

- providing guidance, and ensuring consistency, for product characterisation and quality control,
- ensuring analytical method performance,
- facilitating bioanalytical method development.

The draft strategy applied to all biological medicines, encompassing a wide range of products including blood products, biotechnologically produced proteins, vaccines, and ATMPs. The majority of responses focussed on biotechnologically produced proteins, such as monoclonal antibodies, or ATMPs.

Whilst acknowledging the value of standards, it was clear that many stakeholders considered both the type and function critical to ensuring that they are fit for purpose. However, this was not universal and some considered current practice acceptable.

> **Biotechnologically produced proteins** Standards should not be unnecessarily restrictive and allow for the development of new products and technologies over time. They should recognise the process-specific character of these products and focus on broader and flexible concepts of standardisation, that would enable innovation by manufacturers.
>
> **ATMPs** Due to the emerging nature and complexity of this class of products it would be important that any standards developed were not unnecessarily restrictive and did not act to inhibit innovation. Key areas where standards could add value would be in the development of shared understanding and consistency of testing methodologies.

2.2 Agency role

The Agency, through its unique incorporation of the regulatory and standard setting functions (BP and NIBSC), is well placed to make an important contribution to the development of biological standards. This includes ensuring regulatory alignment of new standards and our role in cross-Government initiatives such as the Accelerated Access Review and the Advanced Therapies Manufacturing Taskforce Action Plan.

2.3 Alternative approaches and unmet needs

Alternative approaches and unmet needs identified by stakeholders were focussed on standards for biotechnologically produced proteins, raw materials and ATMPs. Whilst the need for alternative approaches was not universal, it was a reoccurring message in numerous responses.
There was limited comment on other classes of biological medicines, e.g. vaccines, blood products, other than to confirm that current standards are fit for purpose.

2.3.1 Performance and class based monographs – A number of stakeholders proposed the exploration of two novel concepts for complex biological medicines, such as monoclonal antibody products. Both concepts have been previously advocated, publicly, in a joint International Federation of Pharmaceutical Manufacturer Associations (IFPMA) and European Generics Association (EGA) reflection paper[6].

> **Performance-based standards**, that would define the criteria for analytical method performance rather than a specific mandated analytical method, potentially enabling greater flexibility for the adoption of newer analytical technologies throughout the product lifecycle and the use of alternate methods. Physical standards would play an important role in any analytical control strategy to give assurance of method performance.
>
> **Product class based standards**, that would define Critical Quality Attributes (CQAs) and associated control strategies, including analytical techniques and methods, for specific classes of biological medicines.

2.3.2 Raw materials – Establishment of standards for raw materials were widely recommended. Control of raw materials were considered important as their properties could influence the critical quality attributes of biological bulk substances.

2.3.3 ATMPs – The exploration and development of standards for advanced therapies was seen as a useful tool in knowledge building and ensuring product quality. However, it would be critical to ensure that standards acted to support development and manufacture, and not act to restrict progress in this rapidly developing area of medicine. In light of this, there was a strong preference for non-mandatory guidance including standards for specific analytical technologies and techniques supported, where appropriate, by physical standards.

2.4 Collaboration

The opportunity to engage with the Agency on the draft strategy was commended and there was a clear desire for the Agency to continue to do this going forward. This included offers of collaboration that would enable greater understanding and added-value to standards. In the area of biotechnologically produced protein products this was particularly focussed on understanding and exploring alternative approaches and unmet needs in partnership with the Agency. For ATMPs, continued engagement would allow the identification of knowledge gaps and information sharing in newly-emerging areas.

2.5 International engagement

A range of views on the degree and type of international collaboration and activity were expressed. Consistent throughout the responses was the need for MHRA to engage with, and influence, the international regulatory and standard setting environment. This was the case for both established and emerging areas of biological medicines.

3. Our response and next steps

The draft strategy presented in the consultation document included objectives to enable the Agency to realise the key themes of vision, scope and partnerships; enabling innovation; secure

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[6] https://www.ifpma.org/wp-content/uploads/2014/10/IFPMA___EGA_-_Future_Role_of_Product_Specific_Monographs_vFinal_01.pdf

global supply chains and operational excellence from its corporate plan[7]. These objectives included a focus on engaging with others, collaboration and knowledge building and recognised that alternative approaches may also be beneficial.

This would be achieved by building on the excellence of the Agency's capability in the regulatory and standard setting fields.

The Agency has reviewed the draft strategy based on the themes identified above and our conclusions are summarised below.

3.1 Value and innovation

In general stakeholders viewed standardisation as having an important place in the assurance of quality and the enabling of innovation. Whilst standardisation was broadly supported the Agency recognises stakeholder positions that, in terms of the types and functions of standards, careful consideration is needed owing to the complexity of the materials and their developing nature.

Overall the strategy's aims and objectives were endorsed and the views of stakeholders that standards should evolve to reflect scientific and technical considerations were within the scope of the strategy.

3.2 Agency role

The Agency recognises the importance of collective working across its various centres of expertise to ensure the alignment of its activities in achieving its mission to protect public health and support wider Government activities. This was reinforced by the responses received and clearly defined within the proposed strategy.
A cross-Agency group with responsibility for the implementation of the strategy was established in 2017, and includes MHRA regulatory, Innovation Office, British Pharmacopoeia and NIBSC representatives. The Innovation Office, established 2012, acts as a point of access to regulatory information, advice and guidance that helps organisations to develop innovative medicines and devices.

3.3 Alternative approaches and unmet needs

There was a call from many stakeholders that the Agency should consider alternative types and functions of standards for biological medicines. In particular, this call focussed on the best form for standards to aid the assurance of the quality of biotechnologically produced proteins and ATMP products. It is important to note that this was not universal and varied in strength and perspective. Similar requests were not made for other areas such as blood products and vaccines.

Whilst recognising the potential value of new and alternative types of standardisation, the Agency must ensure that any move from established approaches is comprehensively assessed to understand their impact on all stakeholders and their suitability within the framework for medicines quality. The proposed strategy retains objectives to review current and alternative approaches and to establish pilot projects to explore the value of standards for biological medicines.

[7] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/350879/con261796__1_.pdf

3.4 Collaboration

Whilst the original strategy recognised the importance of collaboration it was apparent that there should be a greater emphasis on mutual knowledge building and education with stakeholders in the role and value of standards across the field.

The overarching vision statement has also been amended to reflect the importance of engaged, collaborative approaches. The strategic work programme (section 5) includes details of how we will build on the success of the consultation exercise to further engage and collaborate with our stakeholders.

3.5 International engagement

The Agency recognises the value of engagement with international peers in both the regulatory and standards setting fields and this remains a key objective within the strategy.

4. Agency pharmacopoeial biological standards strategy

Vision statement

Our vision is to work collaboratively to explore new and innovative approaches in standard setting for biological medicines to ensure the protection of public health. Ensuring we meet the needs of our stakeholders in the era of biotechnology products and advanced therapies.

Strategy statement

Biological medicines are set to be of increasing importance in the healthcare landscape over the next five years with a greater number of products and Advanced Therapy Medicinal Products (ATMPs) available as well as representing an increasing proportion of healthcare expenditure. It is important that the Agency develops a strategy for pharmacopoeial standards to ensure it continues to contribute effectively to the assurance of quality.

The strategy will be reviewed annually to ensure its continued alignment with the Agency's Corporate Plan.
This strategy contributes to key themes of our Corporate Plan:

- Vision, scope and partnerships
- Enabling innovation
- Secure global supply chains
- Organisational excellence

Over the next five years, the Agency's strategy for pharmacopoeial biological standards will be to:

- Review current, new and alternative monograph development approaches for biological medicines, in order to ensure their continued and future suitability as publicly available standards and the safeguarding of public health.
- Develop close and co-operative relationships with our stakeholders, including the biopharmaceutical industry, in the establishment of pharmacopoeial biological standards
- Build knowledge for all. Engaging with those who develop these medicines to build mutual understanding of their needs and the role standards can play in supporting them.
- Review the current portfolio of biological documentary standards and explore current and future needs for new and revised documentary and physical standards.
- Support cross-government and industry initiatives, for example the Strategy for UK Life Sciences and the Advanced Therapies Manufacturing Action Plan.
- Build close relationships with our international, regulatory and pharmacopoeial peers to share knowledge and understanding with the potential to facilitate adoption of best practice and joint working

To achieve this, the Agency will:

- Use our ability to be a fast and adaptable organisation to initiate collaborative discussions on the exploration of innovative and alternative approaches to the pharmacopoeial control of biological quality

- Work with industry and other stakeholders to increase mutual understanding of challenges in the control of biological quality and the development of pilot projects to explore potential solutions

- Bring together the combined expertise of the regulatory, biological and standard setting functions of the Agency to ensure we continue to remain at the forefront of the development of biological quality standards both in the UK and Internationally

- Continue and grow the work of the BP and NIBSC for the development of physical pharmacopoeial biological standards

- Use our data and understanding of stakeholder needs to review our portfolio of biological quality standards

5. Strategic work programme

The following work programme relates to key activities that the Agency is committed to undertaking to implement our strategy for pharmacopoeial standards for biological medicines.

The activities fall into 3 broad categories: Standards development; Engaging with users and building knowledge; Our international peers.

Standards development
Strategic objectives: • Review the current approach taken for monograph development of biologicals, including new and alternative approaches, in order to ensure their future suitability as publicly available standards and the safeguarding of public health • Review the current portfolio of biological documentary standards and explore current and future needs for new and revised documentary and physical standards.
Key themes: Value and innovation, Agency role, Collaboration, Alternative approaches and unmet needs
Activities: • To map the spectrum of biological products, from established and retained approaches for vaccines and blood products, to the need to explore new approaches in areas such as biotechnologically produced proteins and ATMPs. Establish the following working parties with representatives from MHRA regulatory, British Pharmacopoeia, NIBSC and experts from industry and academia: • Alternative approaches, for the exploration and development of pilot projects related to performance-based and class-based standards and supporting physical standards. • ATMPs, to investigate and take forward documentary and physical standard setting opportunities and build engagement with the ATMP community. • Raw materials, to investigate standard setting opportunities in the area of raw materials for biological products.

Engaging with users and building knowledge

Strategic objectives:

- Develop close and co-operative relationships with our stakeholders, including the biopharmaceutical industry, in the establishment of biological pharmacopoeial standards
- Build knowledge for all. Engaging with those who develop these medicines to build mutual understanding of their needs and the role standards can play in supporting them.
- Support cross-Government and industry initiatives, for example the Strategy for UK Life Sciences and the Advanced Therapies Manufacturing Action Plan.

Key themes: Agency role, Collaboration

Activities:

Engagement

- Host a symposium in 2018 on our pharmacopoeial biological standards work including the progression of the strategy. Subject to interest, annual updates will be provided either through symposia or online events.
- We will publish clear contact points in the organisation to enable users to engage with our staff and where appropriate host face-to-face meetings or visits.
- Publish updates on our work our work via trade journals.

Knowledge building

- We will work with our users to continue to understand the broader context of their work and the challenges they face. Through this understanding we will seek to develop, where appropriate, types of training, educational or guidance materials that may support our stakeholders.
- Maximise opportunities to visit stakeholder facilities to gain insights and build knowledge.
- Continue to play an active role in supporting wider government initiatives in the area of biological medicines. This includes an active role in the Advanced Therapies Manufacturing Taskforce, Innovate UK, and the Cell and Gene Therapy Catapult.

Our international peers
Strategic objectives: • Build close relationships with our international, regulatory and pharmacopoeial peers to share knowledge and understanding with the potential to facilitate adoption of best practice and joint working
Key themes: Agency role, International engagement
Activities: • Maintain and build on our existing close relationships with pharmacopoeial and regulatory peers and explore the possibility of developing new strategic relationships where appropriate. • Continue our participation and advocacy at international forums on the value and role of biological standards, for example the International Meeting of World Pharmacopoeias. • Continue to contribute our technical support to our international pharmacopoeial and regulatory peers.