Medicines & Healthcare products
Regulatory Agency

Public update: 2019

Strategy for pharmacopoeial public quality standards for biological medicines

CPRD NIBSC MHRA

Strategy for pharmacopoeial public quality standards for biological medicines

Summary

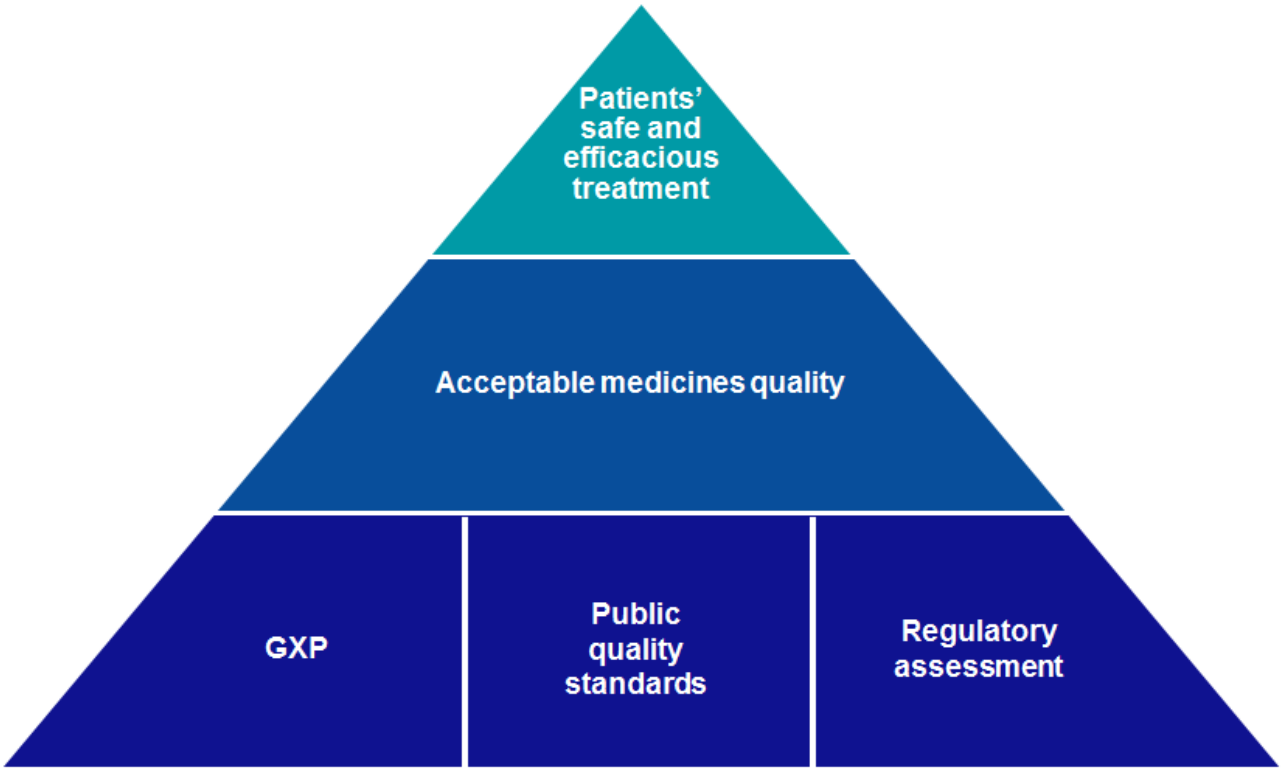
This document provides a summary of progress regarding the Medicine and Healthcare products Regulatory Agency (the Agency) Strategy for Pharmacopoeial Public Quality Standards for Biological Medicines since the publication of the Consultation Response in October 2017.

1. Introduction

In October 2017, following a public consultation, the Agency adopted its Strategy for Pharmacopoeial Public Quality Standards for Biological Medicines. The strategy and consultation had been developed as a result of the increasing importance of biological medicines to global healthcare strategies and the important role of standards in the assurance of quality and enabling of innovation.

1.1 The importance of quality

The quality of a medicine is critical to ensuring the safety and efficacy of medicines taken by patients every day. Pharmacopoeial quality standards are part of an interlinked system, together with good practice quality guidelines and regulatory assessment, that form a foundation to ensuring medicines are of an acceptable quality.



GXP – This refers to good practice quality guidelines and regulations. For medicines manufacture this refers to good manufacturing, distribution (GDP), clinical (GCP), laboratory (GLP) and pharmacovigilance (GPvP) practice.
Regulatory assessment – The independent review by a national competent authority of pharmaceutical, non-clinical and clinical data to demonstrate the quality, safety and efficacy of a medicinal product in order to evaluate its suitability for commercial supply.

1.2 The importance of innovation and life sciences

Innovation in the field of medicines and healthcare has the potential to support people throughout the world to live longer, healthier and happier lives. The importance of life sciences and innovation to public health remains recognised by the government, with commitments to supporting this included within the Life Sciences Sector Deals, Accelerated Access Collaborative and Industrial Strategy Challenge Funds.

The Agency's key strategic objectives recognise the importance of innovation as part of its public health mission within the Agency's Corporate Plan[1]. This includes work such as the Early Access to Medicines Scheme, the MHRA Innovation Office and Regulatory Advice Service for Regenerative Medicines and work with the Office for Life Sciences and Accelerated Access Collaborative.

Standards have a place in supporting and enabling innovation through the facilitation of consistent and widely applicable knowledge of quality and analytical requirements. The importance of standards and analytical technologies was recognised by stakeholders in the Agency consultation on its strategy[2] and external reports such as the Advanced Therapies Manufacturing Taskforce Action Plan[3] and the Medicines Manufacturing Industry Partnership's (MMIP) Manufacturing Vision for UK Pharma[4]. The Agency has also recently published a consultation on the application of Analytical Quality by Design to the Pharmacopoeia[5].

1.3 The Agency Strategy for Public Pharmacopoeial Standards for Biological Medicines

The strategy adopted in October 2017 set out a vision and work programme aimed at supporting the Agency's objectives and recognised and accounted for key themes from consultation responses. In addition to the value of standards, these themes included the importance of the Agency role in standardisation, consideration of how standards should address alternative and unmet needs and the desire and importance for collaborative and knowledge building approaches with all stakeholders.

The strategy and work programme have been reviewed as part of this update paper to ensure they remain aligned with government and Agency strategies and objectives. Minor editorial changes have been made to the strategy to account for changes in wording in the Agency Corporate Plan 2018 to 2023. No changes have been made to the work programme. These documents are attached as Annexes 1 and 2.

This document provides an update on the work undertaken in the implementation of the strategy and its associated work programme.

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[1] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/702075/Corporate_Plan.pdf

[2] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/653839/Response_to_consultation_on_strategy_for_pharmacopoeial_public_quality_standards_for_biological_medicines.pdf

[3] https://www.abpi.org.uk/publications/advanced-therapies-manufacturing-action-plan/

[4] https://www.abpi.org.uk/media/1344/manufacturing_vision_for_uk_pharma.pdf

[5] https://www.gov.uk/government/consultations/consultation-on-the-application-of-analytical-quality-by-design-aqbd-principles-to-pharmacopoeial-standards-for-medicines

2. Implementing the strategy

The work programme associated and published with the strategy was split into three broad categories, each aimed at realising the objectives laid out within the strategy and accounting for the themes identified within the consultation. Updates on each category are given below.

2.1 Standards development

This category relates to the technical and scientific work the Agency is exploring regarding new and alternative approaches to standards and responding to unmet needs and includes the establishment of specific working parties.

Biological medicines include a wide and diverse spectrum of products. Through cross-Agency engagement with UK and international experts, international trade associations and review of consultation feedback the priority areas to move forward initially related to advanced therapy medicinal products (ATMPs) and biotechnologically produced proteins, such as monoclonal antibodies.

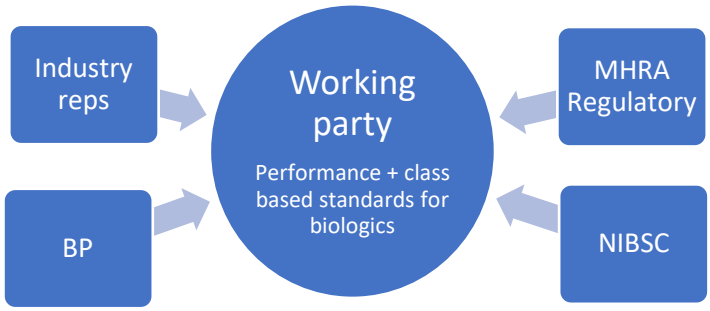
2.1.1 Biotechnologically produced proteins

These are an increasingly important part of healthcare strategies worldwide. Uses include chronic and life-threatening conditions as well as those where current treatment options are limited or unavailable. Enabling manufacturing innovation is an important component of ensuring patients receive these life changing treatments.

These complex molecules are challenging to characterise fully and are inherently variable due to the biological nature of their production processes. Their characterisation, and ultimately quality control, is supported by an ever-evolving suite of technologies and methods that allow for increased understanding over time.

Stakeholder feedback in this area focused on the potential for novel approaches to add additional value to pharmacopoeial standards by enabling the implementation of new analytical technologies and methods over time. This could help facilitate the evolution of analytics over the medicine life cycle rather than remaining fixed to a specific technology or method. In particular, performance and class-based standards were described as having the potential to unlock this additional value.

Following the publication of the strategy, a working party has been formed to explore these concepts. The working party includes international experts from innovator and biosimilar organisations supported by MHRA regulatory centre, National Institute of Biological Standards and Control (NIBSC) and British Pharmacopoeia (BP) staff to facilitate discussion around regulatory and industry expectations. The outcome of the work will be recommendations as to the value these concepts bring to the assurance of quality and support for innovation. These will be subject to review and formal endorsement by the BP Commission and the Agency Corporate Executive Team.



Through face-to-face and teleconference meetings, the working party has developed a deeper understanding of these concepts and how documentary and physical standards may need to evolve. These concepts are currently being evaluated through real-world case studies coupled with supporting laboratory assessment.

The Agency and working party recognise the importance that broader engagement will have on the understanding of performance and class-based concepts and the additional value they may support. Through the strategy the Agency has committed to maintaining collaborative and engaged approaches with stakeholders; working party discussions include input on how to achieve this.

2.1.2 Advanced Therapy Medicinal Products (ATMPs)

These medicines have the potential to be transformative to patients and healthcare globally. However, development, characterisation and production of these innovative medicines is challenging due to their high complexity and the still-emerging technologies that support them. Publications such as the Advanced Therapies Manufacturing Taskforce Action Plan[6], the MMIP's Manufacturing Vision for UK Pharma[7] and stakeholder feedback has emphasised the important role that standards can have in the development of these medicines and the technologies around them. This includes a focus on the value of widely applicable standards that could support knowledge building and facilitate analytics and characterisation.

We have focused on engaging and developing networks with stakeholders, recognising the system wide approach required for these medicines. This has included engagement across the international and national regulatory, research and manufacturing spaces including:

- The US Food and Drug Administration (FDA) Office of Tissue and Advanced Therapies
- The BioIndustry Association (BIA)
- The Cell and Gene Therapy Catapult,
- Innovate UK
- The US Standards Coordinating Body
- NHS England Specialised Commissioning
- The US National Institute for Standards and Technology (NIST)
- The US National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL)
- The US Advanced Regenerative Manufacturing Institute's BioFabUSA
- The UK's wider metrology network
- Individual manufacturing and research organisations.

Specific to understanding the potential role and options for supportive standardisation in this area we have held informal workshops and meetings with academic, research and manufacturing organisations. This has included site visits to manufacturing sites for NHS Great Ormond Street Hospital, Cancer Research UK and the Cell and Gene Therapy Catapult's Stevenage Manufacturing Centre to better understand the challenges faced in the development and production of these medicines. In July 2019, with the support of the BIA and the Cell and Gene Therapy Catapult, we

Image courtesy of the Cell and Gene Therapy Catapult

[6] http://www.abpi.org.uk/publications/advanced-therapies-manufacturing-action-plan/

[7] https://www.abpi.org.uk/publications/manufacturing-vision-for-uk-pharma-future-proofing-the-uk-through-an-aligned-technology-and-innovation-road-map/

organised an informal workshop on quality and analytics for ATMPs. This was attended by representatives from across the UK's ATMP manufacturing and analytical technology development space. A working party comprised of external and internal experts is to be established to fully consider the outputs of this workshop and the next phase of our work in this area.

Image courtesy of the Cell and Gene Therapy Catapult

2.2 Engaging with users and building knowledge

The Agency strategy recognises the importance of building close co-operative relationships and broader engagement in the area of biological medicines and the benefits this brings to all through activities such as mutual knowledge building and increased understanding. In addition to the work described above related to standards development, the Agency has also recognised and continued to support broader engagement across the biopharmaceutical and ATMP landscape.

Members of staff from the Agency have presented on the work involved in developing the strategy and how it links to the Agency's broader support for innovation at several international conferences, including the DIA's 2018 Chemistry, Manufacturing and Controls Workshop in Vienna; Bio Integrates 2019 London; and the PDA's 2019 ATMP conference in Vilnius. These events have provided important opportunities to engage with relevant stakeholders and provide visibility of the work involved in developing the strategy.

Work has also been undertaken to provide visibility to industry associations and stakeholders through smaller-scale engagement including webinars and meetings with innovator manufacturers through the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), the European Federation of Pharmaceutical Industries & Associations (EFPIA) and the Association of the British Pharmaceutical Industry (ABPI) and biosimilar associations through Medicines for Europe and the British Generic Manufacturers Association (BGMA) and the British Biosimilars Association (BBA). This has also included specialist pharmacopoeial stakeholders such as Joint Compendial Industry Meetings, a forum for updates to representatives of manufacturing companies and organisations.

To facilitate engagement with the Agency around this strategy and its associated work programme specific contact points within the Agency are included as Annex 3.

2.3 Our international peers

Building close relationships with international, regulatory and pharmacopoeial peers to share knowledge and understanding, with the potential to facilitate adoption of best practice and joint working, has been at the core of progress to date. Summarised below are bilateral meetings with peers, multilateral forums and conferences we have attended as part of this work and since the publication of the consultation response.

The UK was a founding signatory to the Convention on the Elaboration of a European Pharmacopoeia (Ph. Eur.) and provides representation and input into the relevant Ph. Eur. working parties charged with developing European standards for medicines. These standards are subsequently presented for adoption to the European Pharmacopoeia Commission (EPC), which includes the UK's delegation to the EPC. UK representation on EP groups includes staff from the MHRA regulatory centre (Licensing division), BP, NIBSC, and appointed experts. This includes the groups for monoclonal antibodies, cell and gene therapies.

In the United States the Agency has continued to meet with the Food and Drug Administration (FDA) Centre for Biological Evaluation and Research's (CBER) Office of Tissue and Advanced Therapies to develop mutual understanding of US and UK initiatives on standards to support innovation and ensure the quality of advanced therapies. This formed part of a broader set of meetings with the US medicines innovation ecosystem. In July 2019 the British Pharmacopoeia signed a memorandum of understanding with the United States Pharmacopeia (USP) which will facilitate knowledge sharing in a range of areas related to standards setting for medicines.

Image courtesy of the United States Pharmacopeia

During 2018 and 2019 the Agency had the opportunity to meet with colleagues in the Chinese National Medicinal Products Administration (NMPA) and the Chinese Pharmacopoeia Commission (ChP) to share progress on the strategic plan and maintain an ongoing dialogue on quality standards for biological medicines. This included a series of meetings and events in June 2019 in Shanghai and Xuzhou as a guest of the Chinese Pharmacopoeia Commission. These relationships with peers in China are strongly underpinned by the memorandums of understanding signed between the Agency and the NMPA, and between the ChP and the BP in 2018 and 2016 respectively.

Image courtesy of TSO

The Agency has also continued to participate in multilateral meetings and public conferences to advocate the UK position and engage with peers. The annual International Meeting of World Pharmacopoeias (IMWP) managed by the World Health Organisation (WHO) and hosted in Geneva in 2019 has provided a forum for pharmacopoeias to share knowledge and understanding on a wide array of standards setting and medicines quality challenges and opportunities. In addition, members of Agency staff have attended international conferences to build relationships across the global regulatory and pharmacopoeial system, including the PDA Pharmacopoeias Conference in 2019 and a series of other workshops, seminars and conferences across Europe.

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.

3. Forward look

Over the next 12 months the Agency will continue to progress work to support the implementation of the strategy:

Standards development	• Working party on alternative approaches for biotechnologically produced proteins – develop and carry out laboratory work to developer deeper understanding of performance and class-based concepts. • ATMPs – establish a working party to provide guidance and direction on the development of standards that support quality and innovation.
Engaging users and building knowledge	• Continue to participate in workshops and conferences to provide visibility and engagement on the progress of work.

	• Continue to engage with trade associations, manufacturers and the broader healthcare system to support mutual understanding and knowledge building. • Continue to publish public updates and consultations on the Agency's work in this area, as appropriate, to support awareness and engagement opportunities.
Our international peers	• Recognising the importance of international collaboration – we will continue to hold bilateral meetings with our peers in the pharmacopoeial and regulatory communities.

ANNEX 1 - 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 the objectives laid out in our Corporate Plan 2018 - 2023:

- We will protect public health and promote patient safety by ensuring the safety, efficacy and quality of medicines and healthcare products including through enhanced partnerships in the UK and internationally.
- We will support and enhance innovation and accelerate routes to market to benefit public health and be a magnet for life sciences.
- We will ensure the safe production and supply of medicines and healthcare products through enhanced systems and strong international partnerships.
- We will be an exemplar of organisational excellence and efficiency.

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

ANNEX 2 -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 and was published as part of the consultation response in October 2017.

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 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.

ANNEX 3 – Contact points

All enquiries related to the strategy and work being carried out can be addressed to:

BiolStandards@mhra.gov.uk