Medicines & Healthcare products
Regulatory Agency

Consultation Response

MHRA response and Strategy for the Application of Analytical Quality by Design concepts to pharmacopoeial standards for medicines

August 2020

CPRD NIBSC MHRA

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Executive Summary

In June 2019 the Medicines and Healthcare products Regulatory Agency (MHRA) published a consultation on the application of Analytical Quality by Design (AQbD) principles to pharmacopoeial standards for medicines. This was accompanied by the publication of a technical review of an MHRA project to explore the application of AQbD to a pharmacopoeial Assay procedure.

The Agency has considered the responses received from stakeholders; in general, responses were supportive of the application of AQbD, with an emphasis on how public quality standards could benefit from the use of AQbD principles. The consultation outcome was further reviewed and analysed in a series of workshops within the British Pharmacopoeia's Working Party for AQbD; recurrent key themes have emerged, related to innovation, development of public quality standards, collaboration, engagement, global alignment and knowledge transfer.

As a result of the project and subsequent consultation process, the Agency has developed a clear position on the value of the application of AQbD. A strategy has been developed to implement the outcomes of the consultation which will both support and complement the evolution of developing regulatory science in this field and ensure global regulatory alignment and consistency. The following 4 strategic objectives have been identified:

- Develop and publish **new standards and guidance**.
- Further **explore the application of AQbD** concepts.
- **Build capability** across the Agency.
- **Engage and collaborate** with stakeholders.

The associated work programme aims to realise these strategic objectives through action points under the key themes: supporting and enabling innovation; laying out a process for robust inclusion of AQbD in public quality standards for the UK and encouraging collaboration, engagement and knowledge transfer.

1. Introduction

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 Analytical Quality by Design project is aligned to two of the key priorities in the Agency corporate plan[1]. To *ensure the safe production of medicines through enhanced systems* and to *support and enhance innovation*. These priorities are within the context of broader UK Government initiatives designed to support growth and enable innovation in the healthcare sector. This includes the Accelerated Access Collaborative[2] and more recently the life sciences industrial strategy[3] and associated sector deals.

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

[2] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/664685/AAR_Response.pdf

[3] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/857348/Life_sciences_industrial_strategy_update.pdf

1.1 Background

Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives and emphasises product and process understanding and process control, based on science and quality risk management. The application of Quality by Design principles to analytical methods has been explored by industry, academia, pharmacopoeias and regulators[4] for a number of years. Risk-based strategies, statistical evaluation and modelling have been widely implemented for method development. Concepts such as the Analytical target profile (ATP) have also been introduced to qualify the expected method performance.

The Agency has undertaken a collaborative project involving representatives of the British Pharmacopoeia (BP), Licensing Division, GMDP Inspectorate, Industry and Therapeutic Goods Administration (TGA) of Australia to investigate the application of AQbD principles to compendial procedures. In order to fully explore the benefits and potential challenges of implementing AQbD, the development of a pharmacopoeial assay procedure for Atorvastatin tablets was selected as a case study.

The project investigated:

- The application of risk-based approaches and Design of Experiments (DoEs) to method development and verification, to achieve an enhanced understanding of compendial procedure performance and robustness.
- Different approaches to define method performance requirements using the concept of an Analytical Target Profile (ATP), to better understand the use and value of this tool as well as to explore its relevance and applicability to compendial procedures.

A detailed technical review of the project was presented in the report "Technical Review of MHRA Analytical Quality by Design Project[5]" alongside a public consultation[6]. The consultation sought stakeholders' views on:

- The role of AQbD in the development of robust analytical methods and as a potential enabler of innovation.
- Potential application and inclusion of AQbD in published standards in the British Pharmacopoeia.

In order to gauge stakeholders' opinion and stimulate a constructive debate, the consultation proposed 5 practical examples of enhanced compendial analytical method descriptions (summarised in section 2.2.1), building on the outcome of the case study, which would include method performance requirements and /or additional knowledge gained through AQbD development.

The consultation concluded on the 31st August 2019, the outcome of the consultation is summarised and discussed in this report.

[4] https://database.ich.org/sites/default/files/Q2R2-Q14_EWG_Concept_Paper.pdf

[5] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/807416/AQbD_Technical_Document_-_Final_04_June_2019.pdf

[6] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/806198/AQbD_Consultation_document.pdf

1.2 Responses Received

Responses to the consultation were received from a range of stakeholder groups (Figure 1). There were a number of international respondents from a range of countries across three separate continents. Over 60% of responses were from the pharmaceutical manufacturing industry as well as a large number of such companies represented through key trade associations: ABPI, EFPIA and PDA and International consortiums: IPAC-RS and IQ-Consortium.

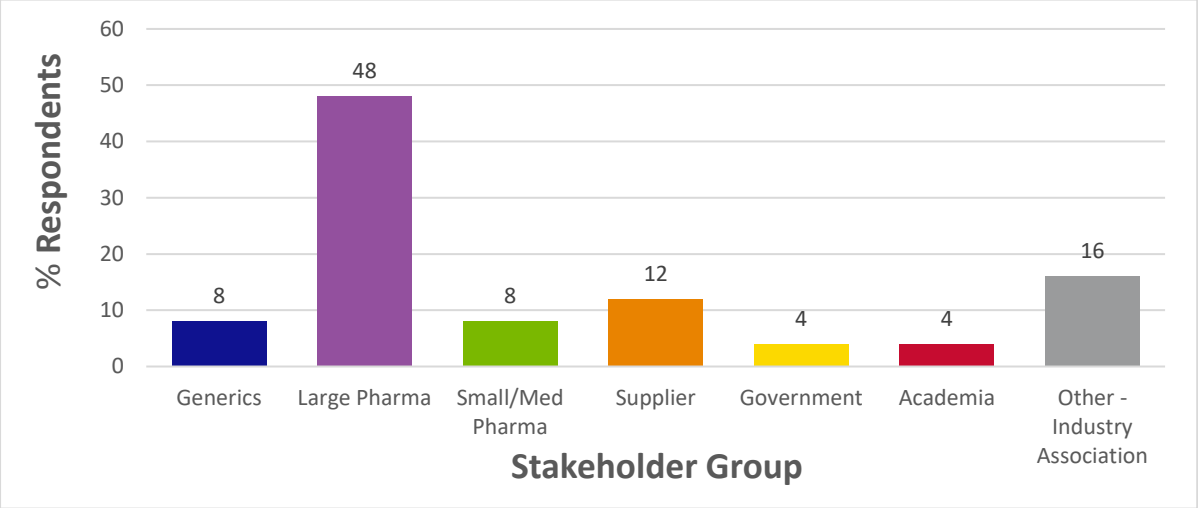

Figure 1 – Chart showing the % split of respondents by stakeholder groups. Options included: Generics Manufacturer, Large Pharma, Small/Medium Pharma, Supplier, Government, Academia, Other (Industry Association).

This representation combined with the information displayed in figure 2, which highlights the relative familiarity of the respondents with AQbD concepts, indicates the extent of implementation of AQbD across the pharmaceutical industry. The extent of practical experience and wealth of knowledge throughout our stakeholders was observed through the detailed and balanced responses to the consultation.

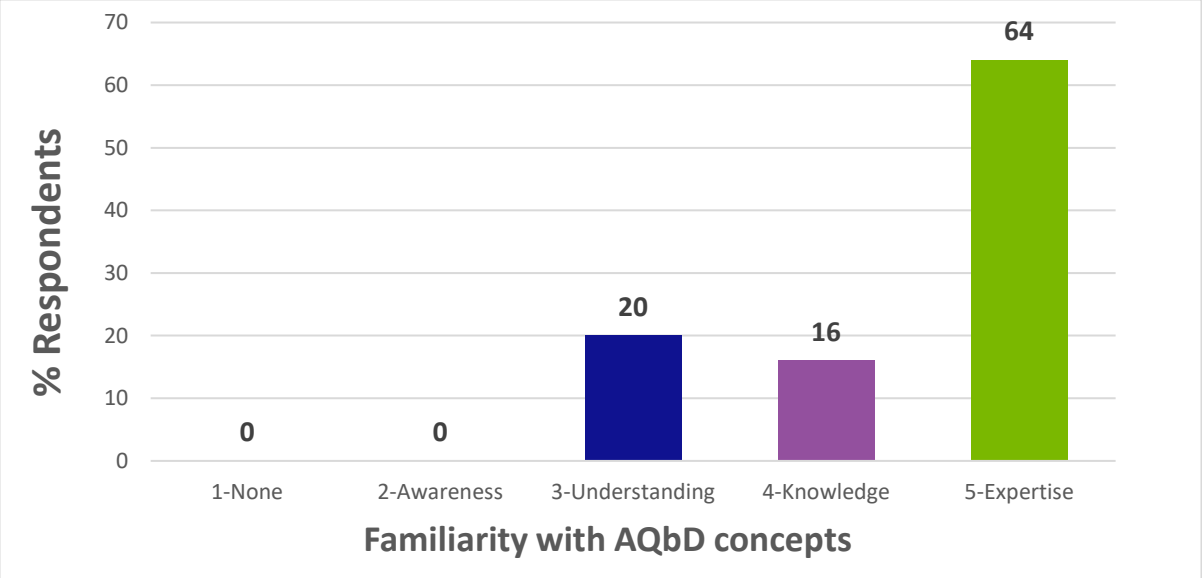

Figure 2 - Chart showing respondents indication of their Familiarity with AQbD concepts in consultation responses. Options Included: 1. None; 2. Awareness; 3. Some understanding; 4. Good knowledge; 5. Expertise

2. Key Themes from responses

Responses received were supportive of the value of AQbD concepts in pharmaceutical development & manufacturing, as well as potential application to the pharmacopoeia. In many cases the responses originated from companies and organisations with practical experience of applying AQbD in a development or manufacturing environment, as displayed in section 1.2. Key themes from these responses have been identified and are discussed in the following section.

2.1 Supporting and enabling innovation

The role of AQbD in supporting and enabling innovation for both small molecule and biological medicines was universally endorsed by stakeholders. Examples from the responses to the consultation included:

- Facilitating the development and implementation of enhanced control strategies using on line Process Analytical Technologies (PAT), to replace existing off line procedures.
- Enabling the implementation of new, improved or alternate analytical methods which had been demonstrated to comply with an Analytical Target Profile. For example, improved versions of an existing analytical method as it evolved throughout the product lifecycle, or the use of an alternative method to that published in compendia.
- Laying the foundation for enabling future analytical innovation through the knowledge and understanding of an analytical method developed using of AQbD concepts.

These aspects would ultimately be of benefit to all stakeholders through the assurance of medicines quality.

2.2 Application to public quality standards

The consultation presented 4 different options of how AQbD concepts, such as the ATP and/or operable ranges for certain parameters could be incorporated in an analytical method in a pharmacopoeial monograph, as well as an option that was akin to the current format for a pharmacopoeial monograph Assay procedure. Table 1 details the options that were available.

Option #	Description
1	Procedure only (status quo)
2	Procedure with Operable Ranges
3	Procedure with ATP
4	Procedure with ATP and Operable Ranges
5	ATP only.

Table 1 - Table representing the 5 options for the information provided in a pharmacopoeial monograph that were given in Question 3 of the Consultation,

Stakeholders were invited to rank the 5 options based on preference and provide a rationale. The respondents indicated that the inclusion of extra information pertaining to these AQbD concepts in a pharmacopoeial monograph would be fully supported based on the substantial benefits to users. The further development of the provided options in the context of broader analytical method lifecycle management concepts was a consistent feature in feedback from stakeholders.

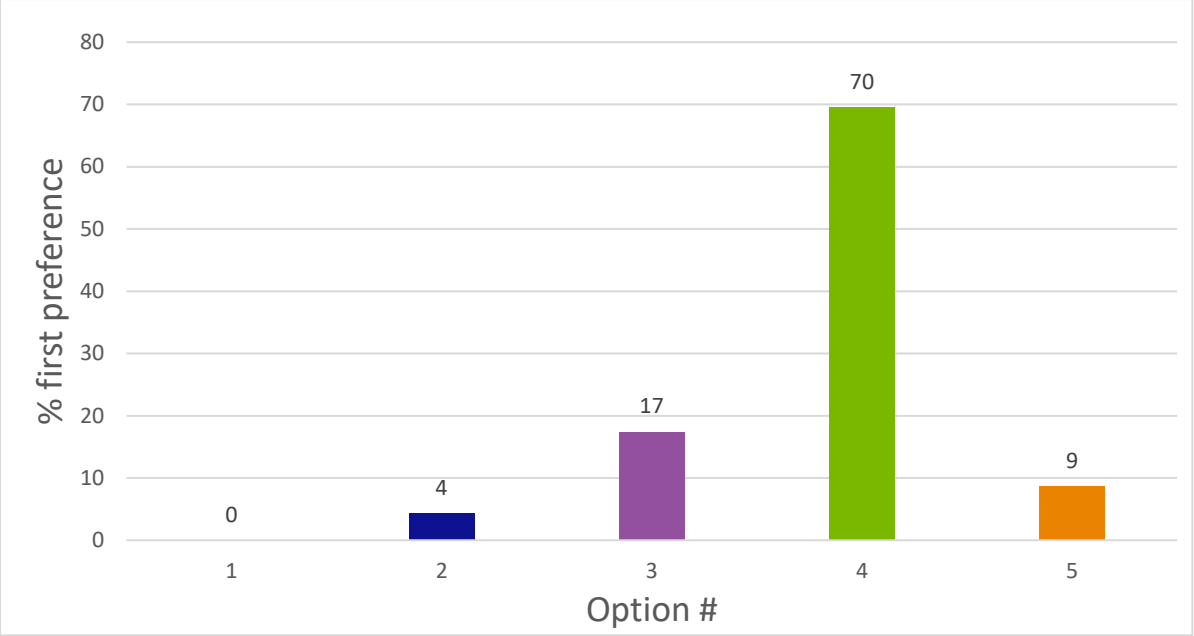

Figure 3 - Graph detailing the % of respondents that chose each option as their first preference. Option 4 (procedure with ATP and operable ranges) gaining 70% preference and no respondents choosing Option 1 (procedure only).

Figure 3 illustrates that the fourth option was significantly more popular than any of the other options presented, reflecting the preference for the inclusion of operable ranges for the analytical method parameters as well as the procedures' associated ATP. A short summary of the respondent's comments for each option is presented below.

2.2.1 Options summary

Option 1 – Description of procedure (status quo)

As the baseline option there were no perceived additional advantages in comparison to options 2-5 which enabled greater assurance that an analytical method was fit for purpose, shared maximum knowledge of the method and potentially allowed for greater flexibility.

Option 2 – Description of procedure with operable ranges

Whilst the inclusion of greater method knowledge through the inclusion of operable ranges was valued, the lack of an associated ATP was considered a significant disadvantage. There was less confidence in a method being fit-for-purpose and concern over the lack of a framework for demonstrating verification, or for the use of an alternate method and ultimately greater flexibility.

Option 3 – Description of procedure with ATP

The lack of operable ranges (as compared with options 2 and 4) was perceived as both an advantage or disadvantage depending on whether they were viewed as imparting greater knowledge to an end user or acting as a source of error if misapplied in the laboratory. However, option 3 was discussed as a clear second preference due of the presence of the ATP which gives assurance that an analytical method is fit for purpose.

Option 4 – Description of procedure with ATP and operable ranges

The advantages of this option included the value of the ATP giving assurance that the analytical method is fit for purpose and its use to enable both verification and as a tool to assess the suitability of an alternate analytical method. Ultimately, this would enable evolution of the analytical method throughout the lifecycle. This option also yielded

significant flexibility to users through the inclusion of operable ranges for the example procedure, with the caveat that the ranges should be considered indicative rather than binding, whilst also serving to share method knowledge and inform control strategies. The inclusion of an example procedure was considered beneficial to all users as a potential starting point for development or QC testing. The main advantages for this option were that it included the maximum knowledge for users, whilst allowing for potential flexibility.

Option 5 – An ATP only

Whilst this option would potentially allow for the greatest flexibility, it lacked sufficient information, such as an example procedure, and would be inconsistent with the QbD paradigm by failing to act to share knowledge.

2.2.2 Additional feedback

Stakeholders noted a number of key points related to the application of the ATP, operable ranges and the inclusion of a default analytical method, including:

- The allowance for both “AQbD” and “non-AQbD” procedures: some procedures may not benefit or require the full application of AQbD. This could reflect differing complexities and risk associated with some analytical methods.

- The application of AQbD concepts and use of statistics needed to be accessible and easy to understand for users.

- It would be important to consider the format of an ATP. Multiple formats were presented in the technical report and the selection of particular format should be justified.

- The future process for monograph development in an AQbD environment should be defined including the role of the pharmacopoeia laboratory and a collaborating manufacturer.

A wide range of options were available for the inclusion of additional information in a pharmacopoeial monograph that could be provided by AQbD concepts. Areas that would benefit from the development of further guidance included: further specific worked examples of the application of AQbD, guidance on the use of risk assessments, continued method performance verification and analytical method development background information.

2.3 Collaboration, engagement and knowledge transfer

The importance of collaboration between stakeholders in industry, pharmacopoeias and regulators was a common theme throughout the responses. This was evidenced by concerns that without international alignment the potential benefits of AQbD would not be realised: i.e. efficiency, application of new technologies, and enabling innovation. The vital role of emerging globally harmonised guidance in ICH Q2(R2), Q12 and Q14 was highlighted, as well as the role of global pharmacopoeias in their opportunities to provide additional guidance. The USP’s initiative on analytical procedure lifecycle management (including their plan to finalise USP <1220>) was considered highly relevant and a potential opportunity for collaboration.

Collaboration and engagement underpin successful knowledge management and transfer and are a key feature in the broader Quality by Design paradigm. Many organisations that develop and manufacture medicines had already embedded AQbD concepts in their own

work processes and were eager to work collaboratively with the Agency to share learnings and knowledge.

Stakeholders clearly valued the opportunity to engage with the Agency on these concepts and expressed a strong desire to maintain engagement and momentum in this area. This included offers of collaboration on the practical use of AQbD in pharmaceutical development, manufacture and quality control and the sharing of knowledge.

In addition, the development of workshops, seminars and webinars would be welcomed as a means of building on the outcomes of the consultation. It was clear that some stakeholders valued the role of the Agency and pharmacopoeia in supporting the development of capability across the sector through the creation of material to support education and learning.

3. The Agency response

The Agency AQbD project and subsequent consultation have been undertaken to develop an understanding of AQbD concepts and the views of stakeholders on their current and potential future application. This will help inform the future direction of pharmacopoeial quality standards for medicines.

The Agency has reviewed the responses received and consulted with the British Pharmacopoeia Working Party on AQbD, which is comprised of external subject matter experts from industry and other sectors. The conclusions of this review and the Agency's response to the comments summarised in section 2, are detailed in the following section.

3.1 Supporting and enabling innovation

Stakeholders view AQbD as a potentially transformative catalyst for enabling innovation for analytical methods and ultimately further supporting the assurance of medicines quality.

The Agency recognises the potential value of AQbD concepts to support and enable innovation. In line with the objective of the Agency Corporate Plan 2018-23 to support and enhance innovation, and based on the results of the consultation, further work will be undertaken to develop further knowledge and explore how these concepts can support innovation i.e.; how the application of the ATP and AQbD in public quality standards can encourage adoption of new analytical technologies and support continuous improvement throughout the product lifecycle. This will form part of the Agency's future strategy in this area and is reflected in the associated work programme.

3.2 Application to public quality standards

The positive response to the inclusion of AQbD principles in a published monograph was seen throughout the consultation responses as detailed in section 2.2. Stakeholders also indicated that specific and meaningful guidance would be required to be published alongside the implementation of these principles in the pharmacopoeia.

The Agency recognises the importance of maintaining accessibility and ease of use of the British Pharmacopoeia across the world while keeping up-to-date with advances in pharmaceutical analysis. In line with these principles, the strategy in this area will focus on how the application of AQbD in individual monographs can add value for users, and how this should be supported through the provision of supplementary information and educational materials.

The majority of consultation respondents supported future monographs comprising an example official procedure together with an ATP and operational ranges for the method (i.e. option 4), and this provides a clear direction for our future work in this area.

3.3 Collaboration, engagement and knowledge transfer

The Agency acknowledges the value of collaboration and engagement with all its stakeholders and intends to develop this network to aid knowledge transfer. To do this, the Agency will engage and collaborate with our peer organisations around the world, together with users of the pharmacopoeia, especially through national and international trade groups. Another important component will be the continued close working across the regulatory and standard setting functions of the Agency to ensure alignment between these areas of our work.

This collaborative approach was also welcomed in responses to the Agency's consultation on pharmacopoeial public quality standards for biological medicines[7]. The Agency's future strategy, including the application of AQbD to public quality standards, will be built around collaboration and engagement to ensure effective knowledge transfer between stakeholders.

The Agency will be exploring a number of opportunities to encourage engagement from all stakeholders, including; workshops, seminars and conferences to ensure alignment in the application of AQbD concepts.

4. Future strategy and work programme

An Agency strategy and associated work programme have been developed based on the outcomes of the project and consultation.

Over the next 5 years our strategic objectives for the application of AQbD concepts to the pharmacopoeia will be to:

- Develop and publish **new standards and guidance** to support the needs of users including general guidance and pharmacopoeial monographs.

- Further **explore the application of AQbD** concepts in collaboration with partners and industry. This will include further consideration of analytical procedure lifecycle management and the role of the ATP in enabling innovation.

- **Build capability** across the Agency to drive forward regulatory science in AQbD. This will include development of expertise, infrastructure and knowledge management processes to support the adoption of AQbD.

- **Engage and collaborate** with stakeholders in industry and key global partners on the development and implementation of these concepts. This will include hosting and participating in workshops and conferences and continuing to provide regular updates on progress. This will also include consideration of the role of the Agency in providing educational services in this area.

[7] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/653839/Response_to_consultation_on_strategy_for_pharmacopoeial_public_quality_standards_for_biological_medicines.pdf

To achieve this, the Agency has developed a number of action points as a work programme (section 4.1), designed using the following principles:

i. Putting patients' needs for quality medicines at the centre of our activities to develop and implement AQbD concepts in the Agency's work.

ii. Capitalising on the combined expertise of the regulatory, biological and standard setting functions of the Agency to ensure alignment between regulations and standards.

iii. Utilising international networks to ensure awareness, influence and alignment with emerging regulatory guidance on AQbD.

iv. Maximising agility and flexibility to initiate projects that support the development of emerging regulatory science.

v. Using data and understanding of stakeholders needs to inform standards development and decision making.

vi. Engaging with key partners and other stakeholders around the world to gather diverse perspectives and support global use of the BP.

4.1 Work programme

The Work programme has been developed in light of the consultation responses, supporting the strategic objectives detailed above. The work programme will be executed by the Agency with support from the British Pharmacopoeia's AQbD working party.

4.1.1 Supporting and Enabling Innovation

- Review of the membership of the British Pharmacopoeia's Working Party for Analytical Quality by Design to ensure representation across our stakeholders and a range of relevant expertise.
- Initiate further practical case studies to investigate the application of ATP models across instrumentation and emerging analytical technologies.
- Explore the opportunity of additional studies to further understand how the adoption and implementation of ICHQ12 lifecycle concepts can be utilised to realise the full benefits of AQbD.

4.1.2 Application to public quality standards

- Produce guidance and educational information in the form of Supplementary chapter/s within the British Pharmacopoeia.
- Practically investigate the application of these principles for other Critical Quality Attributes of pharmaceutical finished products and tests of the British Pharmacopoeia.
- Develop the ATP concept further with the aim of developing appropriate guidance required for implementation within the British Pharmacopoeia, while ensuring that the definition and implementation of ATP and other AQbD concepts are fully aligned with emerging international regulatory guidelines such as ICHQ14 and the revision of ICH Q2.

- Finalise the development of a monograph for atorvastatin tablets in line with ‘Option 4’ to include operable ranges for chromatographic methods alongside an example analytical target profile.

4.1.3 Collaboration, Engagement and knowledge transfer

- Collaborate with our international peers where appropriate to ensure alignment for the AQbD principles to support worldwide accessibility and understanding.
- Develop suitable workshops, seminars and forums to share knowledge across regulatory bodies, industry and academia.
- Publish updates on our work and provide clear contact points to enable stakeholders to engage directly with the Agency and where appropriate host face-to-face meetings or visits.