Response document for MHRA consultation on the application of Analytical Quality by Design concepts to pharmacopoeial standards for medicines

About You
Name: Svetlana Lyapustina

Position: IPAC-RS Secretariat

Organisation:

International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS), members listed at https://ipacrs.org/about/list-of-member-companies/

Email: svetlana.lyapustina@dbr.com

Familiarity with AQbD concepts:

None □ Awareness□ Understanding□ Knowledge□ Expertise X

Please indicate if you are responding to this consultation as an individual or on behalf of an organisation

Individual □ Organisation X

About your Organisation
Type:

□ **Generics** – *a pharmaceuticals manufacturer of any size with most of its sales from generic drug products*
□ **Large Pharma** – *a pharmaceuticals firm with annual sales of more than $2bn, and which develops and manufactures patented drug products as its primary activity*
□ **Small/ Medium Pharma** – *a pharmaceuticals firm with less than $2bn in sales, and which develops and manufactures patented drug products as its primary activity*
□ **Supplier** – *a supplier of services, materials or equipment to the pharmaceutical industry (includes testing companies, consultancies, raw materials suppliers)*
Government –
□*OMCL* □*Regulator* □*Other*
□ **Public Health** – *hospitals and medical clinics*
□ **Academia** – *universities and colleges*
X **Other (Please state)** – a not-for-profit industry association of companies that develop, manufacture or market orally inhaled and intranasal drug products.

Focus: *Please indicate your organisations focus on small and large molecules using the scale below. 3 indicates an equal focus on small and large molecules.*

Small 1□ 2X 3□ 4□ 5□ **Large**

Location (country):

Head office: USA Your site: Washington, DC

Organisation Size

Since IPAC-RS is an association of companies (each of which have different sizes), the "X" below refers to the number of member companies rather than individual persons.

1-5 □	6-50 X	51-250 □	250-1000□	1001-9999□	10,000+ □

1. What do you see as the greatest opportunities and challenges affecting the quality of medicines in the next 5 years?

The development and global implementation of analytical procedures to characterise complex drug products such as orally inhaled and nasal product.
Further globalization of supply chain.
Continued exponential growth of digitalization, automation, machine learning and AI in gathering and assessing information about quality of medicines.

2. How can AQbD concepts ensure methods are fit for purpose and how can they enable innovation? How are AQbD concepts utilised within your organisation?

AQbD, including associated concepts such as the Analytical Target Profile and risk-based scientific approaches, can help facilitate appropriate quality more effectively, by enabling operational flexibility and allowing integration of new and improved approaches for quality testing.

3. Please rank examples 1 – 5 in order of preference for presentation in the pharmacopoeia (1 is best). What advantages and disadvantages do you see in presenting AQbD information in the different examples?

Rank 1 – Example 4
Rank 2 – Example 3
Rank 3 – Example 2
Rank 4 – Example 1
Rank 5 – Example 5

Advantage of example 4 over the others is that this gives the maximum level of knowledge to the scientist conducting the method, in terms of how the method remains fit for purpose (vs the ATP requirements) and providing a range of operating parameters that the method can be modified within whilst still remaining compliant with the pharmacopoeial procedure.

Overall, the MHRA consultation paper is an interesting first step at evaluating the use of Analytical QbD concepts in the development and definition of pharmacopoeial standards. The example used is a simple one using a standard HPLC method, applied to a product manufactured using well-established tabletting procedures, with a high active substance content and a relatively non-interfering matrix. Even in such a case, the output raised many questions. This demonstrates the need for a lot more work in this area, including more complex cases such as inhalation products, before an appropriate approach can be implemented. As the paper states, further work is also required to understand how the ATP could support the evolution of pharmacopoeial procedures and lay a framework for the innovation of analytical methods in line with technological advancements.

4. What other options for the application of AQbD concepts to pharmacopoeial standards and presentation of the resulting information in the pharmacopoeia should we consider?

For aerodynamic particle size distribution of aerosolized medicines, shifts in the mass median aerodynamic diameter (MMAD) are often an informative metric. For detecting shifts in MMAD, AIM and EDA[1,2] should be considered as useful approaches during product development, and subsequently for effective and efficient quality control of commercial product.

Compared to full-resolution cascade impaction, AIM and EDA reduce the resource requirements and therefore have the potential for better characterization of the design space for Analytical Quality-by-Design purposes.

5. How can we work with you and your organisation to further develop our thinking on the application of AQbD concepts to pharmacopoeial standards?

Public consultation, direct consultation with IPAC-RS Subject Matter Experts, ad-hoc working groups with participation of regulators, industry and other stakeholders.

6. Do you have any other comments regarding the application of AQbD concepts to pharmacopoeial standards?

AQbD inclusion in Pharmacopoeia standards and the adoption of operating ranges for analytical methods should not remove the requirement to verify that a pharmacopoeial method is suitable for use. Further, when testing the quality of, for example, OINDP products, the design of the product delivery system can greatly influence the product performance. In this case, a risk assessment of the prescribed operating ranges of the analytical method should be conducted considering the likely performance characteristics of the product. Additional verification should then be conducted to demonstrate that the method remains robust within the specified operating ranges when testing the product or the operating ranges must be controlled further.

7. Would you be happy for the MHRA to contact you in order to discuss your responses in further detail?

Yes X No □

8. The MHRA may publish consultation responses. Do you want your response to remain confidential?

Yes □ Partially* □ No X

*If partially, please indicate which parts you wish to remain confidential. In line with the Freedom of Information Act 2000, if we receive a request for disclosure of the information we will take full account of your explanation, but we cannot give an assurance that confidentiality can be maintained in all circumstances. Responses to consultation will not normally be released under FOI until the regulatory process is complete.

Responses can be continued onto a separate page if required. This form should be returned by email (AQbDStds@mhra.gov.uk) to arrive by **31 August 2019.** Contributions received after that date cannot be included in the exercise.

[1] Terrence P. Tougas, Jolyon P. Mitchell, and Svetlana A. Lyapustina, (eds). Good Cascade Impactor Practices, AIM and EDA for Orally Inhaled Products. Springer, N.Y. 2013. p.225. ISBN-13: 978-1461462958. ISBN-10: 1461462959.

[2] IPAC-RS Cascade Impaction Tutorial, available at https://ipacrs.org/strategic-initiatives/cmc-product-development-test/cascade-impaction-ci/cascade-impaction-tutorial-modules Access is free. Visited August 6, 2019