19 April 2017
EMA/213746/2017

Report from the EMA-FDA QbD pilot program

In March 2011, the European Medicines Agency (EMA) and the United States Food and Drug Administration (US FDA) launched, under US-EU Confidentiality Arrangements, a joint pilot program for the parallel assessment of applications containing Quality by Design (QbD) elements.

The aim of this program was to facilitate the consistent implementation of QbD concepts introduced through International Council for Harmonisation (ICH) Q8, Q9 and Q10 documents and harmonize regulatory decisions to the greatest extent possible across the two regions. To facilitate this, assessors/reviewers from US and EU exchanged their views on the implementation of ICH concepts and relevant regulatory requirements using actual applications that requested participation into the program.

The program was initially launched for three years. Following its first phase, both agencies agreed to extend it for two more years to facilitate further harmonization of pertinent QbD-related topics. The program officially concluded in April 2016.

During this period, the agencies received 16 requests to participate. One submission was rejected because the approach presented was not limited to QbD applications, and another application was not reviewed because it was never filed by the applicant.

In total, two Marketing Authorisation Applications (MAA)/New Drug Applications (NDA), three variation/supplements and nine scientific advice applications were evaluated under this program. One MAA/NDA was assessed under the parallel assessment pathway, with the rest following the consultative advice route. Based on the learnings during the pilot, FDA and EMA jointly developed and published three sets of Question and Answer (Q&A) documents. These documents also addressed comments from the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), which participated as an observer, offering input to further facilitate harmonization. The objective of these Q&A documents was to generate review guides for the assessors/reviewers and to communicate pilot outcomes to academia and industry. Additionally, these documents captured any differences in regulatory expectations due to regional requirements, e.g. inclusion of process validation information in the dossier. The following topics were covered in each of the three Q&A documents:

- **Q&A (1)** published on Aug 20, 2013 included the following topics: (a) Quality target product profile (QTPP) and critical quality attributes (CQA), (b) Criticality, (c) Level of detail in manufacturing process descriptions, and (d) QbD for analytical methods[1]
- **Q&A (2)** published on Nov 1, 2013 on Design Space Verification, that included definition, presentation, justification (including potential scale-up effects) and verification of design spaces both for active substances and finished products[2]
- **Q&A (3)** published on Dec 19, 2014 included the following topics: (a) Level of detail in the dossier regarding Risk Assessment (RA), (b) Level of detail in the dossier regarding Design of Experiments (DOE) and Design Space[3]

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Additionally, the FDA-EMA pilot provided the agencies an opportunity to harmonize regulatory expectations for the following precedent-setting applications that were reviewed under the consultative advice pathway:

- The first continuous manufacturing (CM) based application submitted to both agencies. Based on the learnings from this application, the following areas related to CM were harmonized: batch definition; control of excipients; material traceability; strategy for segregation of non-conforming material; real-time release testing (RTRT) methods and prediction models; and good manufacturing practice (GMP) considerations for RTRT, validation strategy, models, and control strategy.
- A post approval supplement that included a broad based post-approval change management plan/comparability protocol. Both agencies were harmonized on the expected level of detail in the protocol and considerations for implementation of a risk based approach to evaluate the changes proposed in the protocol.

In line with the scope of the QbD pilot program, joint presentations of key findings were publically presented and discussed with stakeholders at different conferences. These included the Joint EMA-Parenteral Drug Association QbD workshop[4] organized in 2014 which also included participation from FDA and PMDA.

Overall, it is concluded that, on the basis of the applications submitted for the pilot, there is solid alignment between both Agencies regarding the implementation of multiple ICH Q8, Q9 and Q10 concepts. The FDA/EMA QbD pilot program opened up a platform for continuous dialogue which may lead to further communication on areas of mutual interest to continue the Agencies' support for innovation and global development of medicines of high quality for the benefit of patients.

Both agencies are currently exploring potential joint activities with specific focus on continuous manufacturing, additional emerging technologies, and expedited/accelerated assessments (e.g. PRIME, Breakthrough). Additionally, EMA and FDA are hosting experts from each other's organisations to facilitate dialog and explore further opportunities.

References:

1. EMA-FDA pilot program for parallel assessment of Quality-by-Design applications: lessons learnt and Q&A resulting from the first parallel assessment
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/08/WC500148215.pdf

2. FDA-EMA Questions and Answers on Design Space Verification
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/11/WC500153784.pdf

3. FDA-EMA Questions and answers on level of detail in the regulatory submissions
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/12/WC500179391.pdf

4. Joint European Medicines Agency/Parenteral Drug Association quality-by-design workshop
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2013/12/event_detail_000808.jsp&mid=WC0b01ac058004d5c3