16 March 2011
EMA/172347/2011

EMA-FDA pilot program for parallel assessment of Quality by Design applications

1. Purpose

This document explains how the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) will process the parallel review of Quality by Design (QbD) applications in a new pilot program which has been launched under the FDA-EMA Confidentiality Arrangements. It provides advice to applicants on the background and objectives of the pilot, as well on the operational steps that will be taken to coordinate the parallel review and related GMP inspections.

2. Background

The assessment of Marketing Authorisation Application (MAAs)/New Drug Applications (NDAs) including Quality by Design (QbD) or enhanced pharmaceutical development approaches, requires a good understanding of statistical, analytical and risk assessment methods that have not been systematically used by pharmaceutical industry or regulators in the past. In addition, such applications raise regulatory and scientific questions that challenge the established regulatory experience, e.g., approaches for defining a design space, adequacy of process description information in the submissions, approaches for Real Time Release Testing (RTRT), continuous process verification, continuous manufacturing, post-approval change management plans or protocols.

Several guidelines have been developed at ICH level (ICH Q8, 9, 10) in order to facilitate the implementation of Quality by Design. In addition, the Implementation Working Group (IWG) at ICH level has drafted Q&As to provide clarity and further guidance on the integrated implementation of ICH Q8, 9 and 10. However, further questions often arise on the implementation of the new approaches. In US, the now completed ONDQA CMC pilot program provided a learning experience for implementing these new concepts. In EU, the EMA PAT Team (PAT: Process Analytical Technologies) and the peer review process have served as a tool to harmonise as much as possible the assessment of applications that implement the ICH Q8-10 principles.

Taking into account the global perspective of pharmaceutical manufacturing, EMA and FDA agreed that it would be beneficial if at this early stage of implementation assessors/reviewers from US and EU exchange their views on the implementation of ICH concepts and relevant regulatory requirements using actual applications.

The pilot will operate under the U.S.-EU Confidentiality Arrangements and within the framework of the EU-US Bilateral Technical Working Group on Medicines Quality and Manufacturing.

3. Objectives

This pilot program aims at a parallel assessment by both agencies of certain Quality/CMC sections of a selected number of applications, which are relevant to QbD such as development, design space and real time release testing, in order to:

- Ensure consistent implementation between EU and US of ICH Q8, 9, 10 guidelines in the assessment process and to facilitate sharing of regulatory decisions on new regulatory concepts. Examples of such concepts include:
  - the amount and type of data to be included in the dossier/application for example:
    - Design Space development, including scale-up
    - Development, verification and lifecycle management of the different types of models used in a QbD paradigm;
  - approaches for implementing Real Time Release Testing (RTRT);
  - Design Space based on clinical relevance;
  - post-approval regulatory flexibility, including how it will be presented in the dossier/application, type and extent of data to be provided;
  - continuous processes: appropriateness of control strategy, stability requirements, and batch acceptance criteria;
  - better definition of the type of data to be assessed or inspected for QbD related aspects.
- Increase assessors/reviewers and inspectors/investigators awareness of the above regulatory concepts.
- Create a further way for EU and FDA Office of New Drug Quality Assessment (ONDQA) assessors/reviewers to share full knowledge about these applications.
- Facilitate the existing collaboration on inspections between EMA and FDA, since for most of the QbD applications that include RTRT elements a product related pre-approval inspection is envisaged.
- Better define the Assessor/Reviewer and Inspector/Investigator interaction for QbD applications.
- Develop and harmonise regulatory decisions to the greatest extent possible.

4. Scope

This voluntary pilot program will only concern New Chemical Entities/New Molecular Entities (NCE/NME) products and implementation of QbD approaches for already authorised/approved legacy products.

It will apply to new Marketing Authorisation Applications (MAAs)/New Drug Applications (NDAs), Type II Variations/Prior-approval supplements (sNDA) and Scientific Advice requests/CMC formal meeting request that include QbD/PAT elements and are submitted to:

1. Both agencies at about the same time, for MAAs/NDAs where the sponsor/applicant has agreed to a **parallel evaluation** by both agencies. Upon request from the sponsor/applicant, and where procedural timelines will allow, Type II Variations/sNDAs may also be considered on a case by case basis. Scientific Advice/CMC meeting requests submitted in parallel to both agencies, sponsors/applicants, will be handled as an 'EMA-FDA Parallel Scientific Advice'.

2. Either EMA or FDA, for MAAs/NDAs, Type II Variations/sNDAs, or Scientific Advice/CMC meetings and the agency doing the evaluation desires to obtain **consultative advice** from the other agency.

Applications for biotechnological/biological products are not included in this pilot.

Applications expected to qualify for accelerated assessment/priority review are not eligible for parallel assessment in the pilot, but could be subject to a consultative advice.

As experience is gathered, the scope could be extended in a step-wise approach to QbD/PAT applications for biological products and/or other areas of common interest, like novel dosage forms.

5. Outcomes

The expected major outcome of the pilot will be increased harmonisation of application assessment/review:

1. In the case of parallel evaluation (applications submitted to both agencies), a more harmonised response to the applicant will occur consisting of:

   - an agreed list of questions/ information requests (or responses, in the case of meetings) to the applicants for the parts of the application subject to the pilot;
   - when agreement on specific wording is not achieved, an agreed list of issues to be addressed separately with the applicant;
   - whenever feasible, joint EMA-FDA inspections will be conducted using existing programmes, to facilitate additional learning.

   Separate reports/reviews will still be issued by both agencies in accordance with regional legal requirements and organisational practices. However, the parts of the reports/reviews relevant to the pilot will be commonly addressed to the greatest extent possible taking also into account the differences in regional requirements.

2. In the case of consultative advice (applications submitted only to one Agency), a more harmonised approach for the evaluation of the QbD/PAT aspects will be attained due to the input from both parties. As above, the primary reviewer (or Rapporteur) has the option not to include the other agency's recommendations in the final assessment.

Additionally, the pilot will provide a forum for harmonizing FDA and EMA approaches, such as emerging regional practices or guidance.

EMA and FDA will evaluate the experiences gained during the pilot to help develop a common understanding on how to handle regulatory flexibility for QbD applications and translate it into common guidance:

- At the end of each parallel assessment, the differences in assessment/review approaches will be discussed within the review teams, as well as any process improvement suggestions.
- In the EU, these lessons learned will be communicated to QWP, BWP and GMP/GDP Inspectors WG.
- In the US, these lessons learned will be shared with agency personnel.
- The gaps identified in the lessons learned exercise will be proposed as new topics for discussion and guidance development by the IWG at ICH level or at regional level, as appropriate.
- A need for joint training for assessors/reviewers from the two regions will be evaluated, and plans for future trainings proposed.

- Joint presentations of key findings will be presented publically through conferences and/or publications, as appropriate.
- Provide a forum for FDA and EMA to provide comments on selected region specific guidance or internal procedures that are currently under development.

6. Duration of pilot program

The pilot will start on 1 April 2011 and will last for 3 years.

7. Outline of the procedure

7.1. Pre-submission request to EMA and FDA

Applicants willing to participate to the pilot should notify both agencies of their interest in the pilot at least 3 months prior to the anticipated submission date.

The request should include a brief description of the QbD elements in the application and the expected submission dates to both agencies. The document should be no more than 5 pages long. Reference can be made to prior communications (e.g., meeting packages, applications).

The request should be submitted to:

FDA: newdrugcmc@fda.hhs.gov

EMA: qbd-pilot@ema.europa.eu

Once requests to participate are submitted to both agencies, the project managers appointed from each Agency will discuss selection of candidate applications, using the following criteria:

- The application should include an enhanced approach to pharmaceutical development leading to the use of new approaches, e.g. design space, PAT tools, implementation of continuous process verification, reliance on models to support real time release testing, continuous manufacturing and post approval change management plans/comparability protocols).
- The approaches used in the application should provide opportunities to the assessors/reviewers to enhance their understanding of the concepts described in the overall objective.
- The application should be submitted in an appropriate timeframe to fall within the pilot period of 1 April 2011 to 31 March 2014.

The decision to accept an application into the pilot will be made within 30 days of receipt of the request for participation. Both agencies will communicate the decision to the applicant in a coordinated manner.

Where the request concerns a parallel Scientific Advice/CMC meeting requests, the principles and procedures laid out in the 'general principles' document on the handling of a 'parallel scientific advice', which is available on the FDA and EMA websites:

http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/EuropeanUnion/EuropeanUnion/EuropeanCommission/ucm114345.htm

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004147.pdf

7.2. Submission, timelines and procedural steps

The usual EMA and FDA submission requirements for NDAs/MAAs, Type II variations and sNDAs will apply. A reference to the agreed pilot participation should be included in the applicants'/sponsors' cover letter.

Participating sponsors/applicants will need to provide together with the submission, a letter allowing both FDA and EMA to share commercially confidential (including trade secret) information on the specific QbD/PAT elements that will be subject to the parallel assessment or consultative advice. Further advice will be provided to sponsors/applicants upon acceptance to the pilot program.

The exchanges between EMA and FDA on QbD aspects of the applications will occur during the normal EMA and FDA review timeframes. Review of QbD applications does not change statutory deadlines. The following steps in relation to QbD assessment will be taken:

a) Parallel evaluation

The timelines for meetings, exchange of reports, and comments between the two agencies during a parallel evaluation of QbD for MAAs/NDAs are presented in Table 1. Key steps of the process include:

- At approximately 45 days after receipt of the application ('Day 35' for EMA), a joint meeting will be held between the EMA and FDA review teams to discuss the QbD elements of the application and to agree upon the parts of the application to be subject to parallel assessment/review.
- Reports from assessors/reviewers will be sent to the other Agency 90 days after receipt of the application ('Day 80' for EMA).
- In order to ensure consistency in the evaluation of the applications, the EMA PAT Team and ONDQA - Immediate Office) will be directly involved in the process by reviewing the Assessment Reports (ARs)/Reviews and List of Questions (LoQ)/Information Requests (IRs) prior to discussing them with the other agency.
- Communications with the applicant, including the sending of the LoQ an IRs on the QbD aspects will be done independently by each agency, using existing processes (e.g for EMA, this will be included in the Day 120 LoQ).
- Co-ordination of joint meetings between the two agencies as well as communications between the sponsor/applicant and the two agencies will be facilitated by project managers from each agency.
- At the end of each parallel assessment, a Lessons Learnt exercise and identification of knowledge and process gaps will be conducted.

b) Consultative advice:

In the case that the dossier/application is submitted to only one of the agencies in addition to the above, the following steps will be taken:

- The Agency to whom the dossier/application is submitted and who is seeking consultative advice contacts the other agency to request consultative advice in accordance with the timelines presented in Table 1.
- The Agency holding the dossier/application obtains all legal clearances and agreements with the applicant/sponsor for the involvement of the other agency and provides the relevant information (relevant extracts from Modules 2 and 3).

For parallel Scientific Advice/CMC meeting requests, the principles and procedures laid out in the 'general principles' document on the handling of a 'parallel scientific advice' will apply (see also section 7.1).

In addition to the procedures outlined above for parallel assessment of QbD containing dossiers/applications, periodic meetings will be set up between the two agencies to discuss regulatory strategies for new QbD concepts, as well as discuss options for joint training.

8. End of the pilot program

At the conclusion of the pilot phase, a joint assessment on the outcomes of the pilot will be made by the EMA and FDA, and the outcome of this will be made public. The process may then be amended and the scope modified, as needed.

Table 1. Timelines and process flow for exchange of reports and comments between the two agencies during the parallel evaluation or consultative advice

Steps of the pilot parallel evaluation procedure for MAAs/NDAs	**Type of procedure**	
	EMA New MAA	**FDA New NDA**
Receipt of Dossier/Application	(Day -10)	Day 0
EMA clock start	Day 0	
FDA filing meeting		NMT Day 45
Initial meeting for high level discussion to agree upon portions of application subject to parallel assessment and the potential for a joint inspection	Day 35	Day 45
EMA-FDA Interim telecon to discuss progress	Day 60	Day 70
Exchange of completed ARs/Draft Reviews and LoQs/IRs between agencies	Day 80	Day 90
Exchange of comments on ARs and proposal for joint inspection, if applicable	Day 110	Day 120
EMA-FDA Telecon to discuss comments	Day 112	Day 122
Exchange of revised ARs/Review and agreed upon QbD issues to be sent to applicant	Day 115	Day 125
Completion of assessment/review of applicant responses and exchange of ARs/Reviews	NMT 30 days from receipt of responses	Target NMT Day 210
Exchange of comments on ARs/Reviews	NMT 50 days from receipt of responses	Target NMT Day 230
EMA-FDA Telecon to discuss comments	NMT 53 days from receipt of responses	Target NMT Day 233
Exchange of reviewed ARs/Reviews with agreed upon LoOI/deficiencies to be sent to applicant	NMT 55 days from receipt of responses	Target NMT Day 235
EMA-FDA Telecon to discuss lessons learnt upon completion of review	14 days after completion of the procedure	14 days after completion of the action
Joint report on lessons learnt	30 day after completion of the procedure	30 day after completion of the action

NOTES:

1. EMA timelines listed are after clock stop and restart upon response receipt. FDA timelines are continuous from submission date.

2. Due to the differences in timelines it would be feasible for NDAs submitted to the FDA to precede MAAs submitted to EMA by up to 30 days without adversely impacting timelines. Applications outside of the timelines can be treated as consultative advice between agencies.