Final Business Plan
Q11: Development and Manufacture Drug Substances
(chemical entities and biotechnological/biological entities)
dated 25 March 2008
Endorsed by the ICH Steering Committee on 11 April 2008

1 The Issue and Its Costs

1.1 Perceived Problems

As a consequence of different regional expectations, it is difficult for manufacturers to harmonise the technical information on drug substance (both chemical and biotechnological/biological) process development and manufacture that is included in section S2 of the Common Technical Document. Region-specific expectations regarding the level of detail that should be submitted, as well as possible differences in interpretations, can often lead to significant differences in the dossiers that are submitted in the three ICH regions.

The direct impacts of these differing expectations and interpretations are:

- industry dedicates significant resources to understand and determine how to meet regulatory expectations of individual countries and regions;
- industry dedicates significant resources to prepare region-specific data packages;
- reviewers/assessors can spend resources in the search for expected information that might not have been included because it is not expected in the submissions for other regions;
- industry often spends considerable resources to respond to queries received from the regulatory authorities, that might not be necessary if there was more uniform understanding regarding the type of data and information that is needed in submissions;
- substantial burden on industry to manage and update applications when changes are made;
- approval of dissimilar data package across different countries for the same product;
- less than timely approval of applications and, thereby, delayed availability of product to patients, as a result of data packages not meeting certain region-specific expectations;

1.2 Estimation of Costs Associated with Current Situation

1.2.1 Regulators

It is estimated that reviewers/assessors s spend considerable time searching for missing or misplaced manufacturing development information as a result of firms' misunderstanding of regional differences, to formulating questions and reviewing the answers provided by the company.

1.2.2 Industry

1.2.2.1 Understanding and meeting regulatory expectations of individual countries and regions

Considerable time and resources are spent to elaborate process development strategies due to unclear regulatory expectations. Project teams elaborate the process development plan for a given project over an extended period of time.

Additional resources are needed to generate harmonized understanding of dossier expectations between companies in order to simplify inter-company cooperation and project transfers.

1.2.2.2 Answer to queries received from the regulatory authorities

Companies need several person-days to generate, review and approve answers to each query received. A substantial percentage of the queries (about 25 % according to a survey at three companies, considering marketing authorisation applications as well as major variations and supplements) are related to the respective sections S.2.2 – S.2.6 of the documentation.

1.2.2.3 Generation of regionalised data packages and availability of the product to patients.

Resources are also spent on the generation and updating of regionalised data packages and possibly unnecessary studies performed due to unclear expectations across the three ICH regions. Costs related to delayed availability of innovative treatments to the patient should also to be considered.

2 Planning

2.1 Main Deliverables

The main deliverables are:

- Outline summarising the contents to be addressed in the future guidance;
- 4-5 working drafts;
- *Step 2* document for public comments;
- *Step 4* document addressing all public comments;
- Regular progress updates to the Steering Committee.

2.2 Resource Requirements

The working group should be a six-party expert working group (plus observers and interested parties). Due to the relative sparseness of pre-existing guidance it is anticipated that consensus building on the contents of the future guidance will require dedicated working sessions of the EWG in the form of face-to-face meetings and teleconferences.

It is anticipated that such a harmonised guideline (to *Step 2*) could be developed within an 18 month period, assuming input of 20 person-days per ICH sponsor mainly for EWG meetings over this period and additional 25 person-days of input from an appointed rapporteur (3-EWG face-to-face meetings). Additional input would be expected from observers. Progression to *Step 4* is anticipated to be less resource intensive (5 + 10 person-days, 1 face-to-face meeting).

The estimated workload is therefore 25 person-days per expert and an additional 35 person-days for the rapporteur.

2.3 Timelines and Key Milestones

The following timelines can be anticipated:

Approval of topic/Rapporteur & EWG Defined	April 2008
First EWG Meeting	June 2008
Step 2 Sign-off	4Q 2009
Step 4 Sign-off	4Q 2010

3 Impacts of the Project

3.1 Benefits

The proposed guideline fills a gap in the regulatory framework and describes the suggested contents for the 3.2.S.2.2 "Description of the manufacturing process and process controls", 3.2.S.2.3 "Control of materials", 3.2.S.2.4 "Control of critical steps and intermediates", 3.2.S.2.5 "Process validation and / or evaluation" and 3.2.S.2.6 "Manufacturing process development"-section of a regulatory submission in the ICH M4 Common Technical Document (CTD) format.

There are four major areas in which substantial cost savings are envisaged.

- the cost of assessor time wasted searching, requesting and reassessing information;
- the cost during scientific writing of the initial documentation for marketing authorisation applications;
- the cost of preparing and reviewing answers to queries and adapting documentation to regional requirements;
- the cost of keeping the various regional documentation formats up to date.

It is estimated that a reduction in queries by 30% could be achieved if the requirements for manufacturing process development were clarified. This reduction would amortise the estimated costs for generating the guideline already in the first year after implementation of the guidance.

It is re-emphasized that this estimate does not take into account

- the additional resources spent on aspects of the development programs that address region-specific issues;
- the costs related to delayed availability of innovative treatments to the patient.

The additional costs related to the above points are considered substantial as well. However, it is difficult to estimate these expenditures on an average cost basis in the context of this business plan.

3.2 Regulatory Implications

This topic being a purely technical and scientific matter, it would have no impact on the existing regional regulatory procedures and would then be eligible as an ICH topic.

4 Post hoc Evaluation

The costs of the guideline development could be evaluated after completion of *Step 4* on the basis of timesheets to be submitted by the individual experts.

The impact of the guideline on the quality of the submitted documentation could be evaluated by a survey in all agencies to evaluate the quality of the CTD sections submitted and trends in the reduction in number of questions related to sections S.2.2 to S.2.6 as a percentage of the total number of questions.

This survey could be initiated by the rapporteur 2 years after implementation of the guideline in the last participating region. The suggested survey period is two years. The rapporteur could follow-up and present the results to the Steering Committee in a timely manner after the survey has been completed, presumably 5 years after implementation of the guideline in all three regions.