

**Final Concept Paper**  
**Q8: Pharmaceutical Development**  
**dated 19 September 2003**  
*Endorsed by the ICH SC on 8 October 2003*

**Type of Harmonization Action Proposed**

It is proposed that a new tripartite guideline be developed that would describe, at a high level, the harmonised contents of Section 3.2.P.2. (Pharmaceutical Development) within the Quality Module of the Common Technical Document. It is anticipated that the guideline will be written at a level that is commensurate with the intended purpose of the Pharmaceutical Development Report, for example enabling the information contained to be used for risk assessment. Thus, the interpretation of the phrase “at a high level” should reflect this intended purpose. By this it is also meant that the guideline should be developed to describe ‘what’ is to be discussed in Section P.2 but the guideline generally would not define the ‘how’ – the details of the studies that should be carried out. This guideline will focus on principles of quality by design, and will incorporate concepts from the parallel discussions of risk management that should emerge from the proposed EWG on this topic.

**Statement of the Perceived Problem**

Currently, the EU has an implemented guideline (Note for Guidance on Development Pharmaceuticals) that describes what might be included in Section P2. More recently, the FDA has issued a draft guidance that proposes the content of P2, tailored to US regulatory expectations. However, it has been agreed within the CTD-Q IWG that a harmonised guideline would be beneficial since there is not a consistent approach for providing and evaluating this information across the three regions. Industry will benefit by being able to design scientifically based development studies to meet a single set of expectations for the ICH regions. Regulators will benefit in that they can apply their resources to the critical-to-quality elements of the product and process in a more focused and guided way.

As agreed in the discussions during the development of the CTD, CTD-Q provides a Section 3.2.P.2 where the applicant can include information on pharmaceutical development studies. The proposed guideline will elaborate the knowledge requirements that guide the technical and scientific studies that might be carried out to establish that, for example, the dosage form, formulation, manufacturing process and development, container closure system, and microbiological attributes are appropriate for the product described in the application. These are generally ‘one time’ studies that the applicant carried out in the course of the development of the drug product and are part of a background and context of scientific information that assists the Regulatory Reviewer in understanding the critical-to-quality attributes of the drug product and its manufacturing process. Potential topics to be addressed within P2 are illustrated below and could include sections on

Drug substance

- Key physicochemical characteristics and their impact on formulation and/or manufacturing process design
- Compatibility (with excipients and packaging materials)

#### Excipients

- Key physicochemical and/or biopharmaceutical characteristics

#### Drug Product

- Rationale for type of product
- Formulation development
- Overages
- Physicochemical and biological properties and their impact on product quality (risk analysis)
- Performance testing

#### Manufacturing Development

- Critical to quality manufacturing steps and process controls and their contribution to or interdependency with final product quality (risk analysis)
- Choice of sterilisation method
- Relationship of manufacturing performance and controls to end product testing (risk analysis)

Container closure system (and delivery devices)

Microbiological attributes

### **Issues to be Resolved**

Scope: what is included from e.g.,

- New chemical entities
- New biological entities
- Solid oral dosage forms
- Oral liquids
- Parenterals
- Topicals
- Inhalation
- Others?

In summary, it is proposed that the scope be the combination of the scopes described in Q6a and Q6b. In terms of the process, however, it is envisaged that the majority of the activities will use experts knowledgeable about new chemical entities: Biotech input would also be sought at the appropriate times.

Additionally, there may be merit in considering constructing the guideline to address particular unit operations in design and manufacturing processes.

The types of studies and information that should go in this section so as to be acceptable in the three regions.

Discussions are also proposed to determine the role of this section in the overall assessment process. This understanding will help frame the contents of the guideline.

The primary purpose of this section is to provide information on how development data have been transformed into knowledge of the manufacturing science and technology thus helping reviewers to gain a better understanding of product and process attributes that can influence product performance and product quality. By providing reviewers with the knowledge basis the applicant uses to judge continuous

improvement initiatives, it is hoped that the requirements for the prior approval of changes might be moderated.

A goal for the section is to help developers and manufacturers to conduct successful technology transfers and manufacturing change controls throughout the life cycle of the product. How to achieve this should be discussed.

Another key goal will be to develop a guideline that will help route field investigators through the inspection process so they can focus their inspections on the critical process steps and controls.

Initially, the Pharmaceutical Development section of CTD-Q will be used as regulatory submission document with a historical perspective. However, the knowledge and science-based discussion included within Pharmaceutical Development is intended to be applicable over the lifecycle of the product and may need to be updated as new information on the manufacturing science and technology become available. Specific topics to be addressed would be those described in the relevant sections of 3.2.P.2 of CTD-Q.

### **Background to the Proposal**

During the development of the CTD-Q format document, there was consensus among the six parties to consolidate the information described above within a single section in the registration dossier: P.2. However, the CTD-Q guideline describes the format of the section, not its content. The IWG has discussed which one of the CTD sections would most benefit from a guideline that would address content, where such a guideline does not already exist. Section P.2 was considered to be the most valuable, and this guideline will address the contents, at a high level, of this section.

It is proposed that this guideline be developed and implemented in phases. While elements of risk management and the application of this guideline during the inspection process will eventually be included, initial guideline development will focus mainly on those issues that need to be addressed for the first regulatory submission and its review process. Sections on risk management and integration of the inspection process will require close linkages with the EWG on Risk Management when that group is established.

### **Type of Expert Working Group and Resources**

A new Quality EWG should be formed that is based on the CTD-Q IWG. This is because it would be extremely beneficial if several of the EWG members were those involved in the development of CTD-Q. Additionally, as it is the intent of this guideline to reflect the needs of an integrated quality system (review and inspection), ultimately it will be necessary for the composition of the EWG to include industry and regulator members with inspection experience. To keep the size of the EWG manageable, it is suggested that the core group comprise two members from each of the ICH parties and the overall EWG be comprised of not more than three representatives from each of the ICH parties and one representative from each observer. It is recommended that the third member, that is one with manufacturing/inspection experience, be one of the members of a parallel EWG, ideally Risk Management (assuming adoption of the topic).

**Timing**

Completion of Concept Paper  
Submission to Steering Committee  
Adoption of topic by ICH Steering committee  
First EWG - Osaka  
Step 2 document  
(dependent on progress by Risk Analysis EWG)

September 15th 2003  
September 19<sup>th</sup> 2003  
October 2003  
November 2003  
end 2004