Final Concept Paper
Q11: Development and Manufacture of Drug Substances
(chemical entities and biotechnological/biological entities)
dated 11 April 2008
Endorsed by the ICH Steering Committee on 11 April 2008

Type of Harmonisation Action Proposed

A new tripartite Technical Guidance is proposed for Active Pharmaceutical Ingredients (APIs harmonising the scientific and technical principles relating to the description and justification of the development and manufacturing process (CTD sections S 2.2. – S 2.6) of Drug Substances including both chemical entities and biotechnological/biological entities.

This document will take into consideration and provide examples as appropriate for describing the principles and concepts which are included in ICH guidelines on Pharmaceutical Development (Q8), Quality Risk Management (Q9) and Pharmaceutical Quality Systems (Q10). However, the approaches to, and extent of, development (e.g., traditional/empirical or systematic/enhanced) will be based on the development strategy designed by each manufacturer.

This guideline is intended to provide guidance for drug substances as defined in the scope of the ICH Guideline Q6A ("NCE") and ICH Guideline Q6B ("Biotechnological/biological").

Statement of the Perceived Problem

Background and Summary

Several aspects of technical guidance specifically related to the quality of chemical entities and biotechnological/biological drug substances have been harmonised through ICH guidelines. Although it is generally accepted that there is a strong linkage between the manufacturing process for medicinal products and their quality attributes, there is limited guidance regarding the description and justification of development and manufacturing processes for drug substances and the type and extent of information to be submitted in regulatory dossiers. During discussions at the ICH-Q Drug Substance Roundtable meeting held in Washington in September, 2007, the experts agreed that many of the principles and concepts that have been addressed in ICH guidelines Q8, Q9, and Q10 are also applicable to the development and manufacture of drug substances. The importance of an API guideline for both chemical and biotechnological/biological products was emphasised and the development of a formal concept paper and business plan was endorsed by the ICH SC in October 2007.

Therefore, it is recommended to develop a new tripartite high level Technical Guidance harmonising the scientific and technical principles relevant to the design, development and manufacture of drug substances as part of a total control strategy designed to ensure product quality and consistency. Problem Statement.

Consistent with modern global manufacturing and scientific practices (described in the ICH Quality Vision presented and endorsed in Brussels, July 2003), and economic considerations, the development and establishment of a robust manufacturing process for drug substances to deliver a product of consistent quality accounts for a significant proportion of manufacturers' resources and efforts.

While there are many similarities in the development approaches for chemical entities and biotechnological/biological drug substances, biotechnological/biological drug substances present a number of unique manufacturing and quality challenges. Therefore it will be important to identify what is common and what is different between the development and manufacturing of biotechnological/biological and chemical entities.

The guidance developed needs to take into account these similarities and differences, as appropriate. A harmonized guideline including common terminology and definitions is currently not available but would be beneficial, since it would enable a consistent approach for providing and evaluating this information across the three regions.

Additionally, there is variability in the content and level of detail requested by the various regions for evaluating the concisely described meaningful scientific knowledge gained during development. Because of a lack of guidance in the area of drug substance development and manufacturing manufacturers, no general developed harmonized approaches to demonstrating process understanding, particularly regarding sources of variability in product quality, are currently available. Additionally, region-specific requirements are conveyed to the applicants by the authorities on a case-by-case basis. In general, there is currently little consensus or agreement across the industry and the regulatory bodies with respect to manufacturing process information and justification that should be included in the dossier.

The direct impact of these currently differing approaches and uncertainties is:

- disharmony and administrative burden;
- inefficient use of industry resources to determine and comply with regulatory requirements of individual regions;
- region-specific data packages and data presentation describing manufacturing process data are submitted;
- inefficient use of reviewer/assessor and industry resources to clarify the rationale and intent of the manufacturing process data.

Issues to be Resolved

Section 3.2.S2 of the CTD is intended to provide a comprehensive understanding of the relationship of the Drug Substance quality attributes and the manufacturing process for reviewers and inspectors/facility investigators. It provides an opportunity to present the knowledge gained through the application of scientific approaches, definition of critical controls, and risk management, in the manufacture of a Drug Substance. It should define and justify the manufacturing operations and describe where the process/product robustness will permit wide operating ranges or where tighter monitoring and controls may be necessary. Enhanced understanding of manufacturing sciences and technologies can also create a basis for alternative approaches to control the quality of a product.

The content of Section S2 of the CTD will need to take into account the different technological approaches and requirements for ensuring product quality and consistency in the manufacture of chemical and biotechnological/biological drug substances.

Some examples of technical elements, which are recognised as having a strong need for harmonisation of scientific approaches, include general principles and concepts for:

- Selection of materials and components for manufacture of the Drug Substance;
- Identification and justification of key and critical manufacturing steps, process controls, process parameters, choice of analytical procedures and acceptance criteria as elements of a total control strategy designed to ensure product quality and consistency;

- The capacity of processes to reduce or remove impurities and product- related substances;
- Evaluation of process robustness;
- Suitability of scaled-down models for evaluation and validation;
- Identification and control of critical intermediates.

The goals of the proposed guideline are:

- Harmonise and encourage the submission of the relevant documents regarding the manufacturing process information and its justification;
- Outline the science-based concepts relevant to the design of a robust manufacturing process that reliably delivers a quality drug substance;
- Provide examples as appropriate of acceptable approaches for demonstrating process and product understanding;
- Facilitate the regulatory evaluation process for authorities;
- Recommend approaches for demonstrating process and product understanding;
- Address the complexity of different manufacturing processes and products;
- Accommodate variable approaches to development and corresponding information to be provided as described in Q8 and Q8R;
- Address enhanced approaches to manufacturing that can also create a basis for alternative approaches to control the quality of a product and for the application of innovative technologies for the manufacture of APIs (e.g. continuous manufacture);
- Address systematic approaches to drug substance development, application of quality risk management, and concepts such as design space, control strategies (including real-time release) over the lifecycle of the product.

Topics already covered by other ICH guidelines such as viral safety evaluation and analytical procedure validation will be cross-referenced, as appropriate.

The guideline will not address:

- Information relevant to the manufacturing process development of the Drug Product (to be covered by Q8 and Q8(R1));
- Qualification of facilities and equipment and other activities covered by GMP guidance (e.g., ICH Q7).

Type of Expert Working Group

The proposed guidance will be Technical Guidance in the Quality area for chemical and biotechnological/biological drug substances. The working group should be a six-party expert working group (plus observers Health Canada, EFTA and WHO, and interested parties WSMI, IGPA and Biotech Industry). The EWG should follow the process used by the CTD-Q EWG where biotechnological/biological and chemical experts work together and in parallel (if necessary) and will use interim teleconferences and face to face meetings as appropriate.

Proposed timing

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