Validation VIEWPOINT

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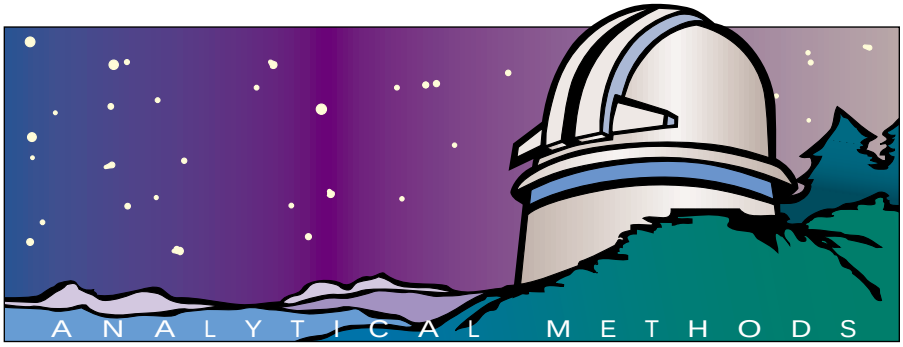

The International Conference on Harmonization

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In past "Validation Viewpoint" columns we briefly discussed the International Conference on Harmonization (ICH), but we would like to explain the organization in more detail. This month's column describes the ICH and provides an update of ICH projects and guidelines.

For years, many countries around the world had national regulatory systems to evaluate the quality, safety, and efficacy of pharmaceutical products. Although they were based on the same basic commitments, these organizations' detailed technical requirements diverged in time to an extent that the pharmaceutical industry found it necessary to duplicate many time-consuming and expensive test procedures to market new products internationally.

In response to the growing global pharmaceutical market, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals For Human Use (ICH) was conceived in 1990 at a meeting hosted by the European Federation of Pharmaceutical Industries' Associations (EFPIA) in Brussels. Since this first organizational meeting, the organization has held a biennial conference — at Brussels in 1991; Orlando, Florida, in 1993; Yokohama, Japan, in 1995; and Brussels in 1997 — as well as periodic conferences and workshops.

The founders identified a threefold initial purpose, which they called the *Terms of Reference:*

- to provide a forum for discussion between regulatory agencies and the pharmaceutical industry about the differences in the technical requirements for product registration in the three member regions;
- to identify areas in which changes in technical requirements and agreement on research and development procedures could lead to a more economical use of human, animal, and material resources without compromising safety; and
- to recommend practical ways for achieving harmonization in the interpretation and application of technical guidelines.

Although the ICH 4 meeting in Brussels brought the first phase of ICH activities to a close, the ICH steering committee entered a second phase of future harmonization activities. The term ICH, originally meant to denote an international conference on harmonization, now has become more associated with the process of harmonization than the actual conferences themselves. Indeed, many of the recommendations or guidelines developed as a result of the ICH processes have been implemented; however, more recommendations are forthcoming. We thought that this column would be an ideal opportunity to discuss the ICH in more detail, summarize its activities to date, and outline future activities as well.

THE STRUCTURE OF THE ICH

At the inaugural meeting of the ICH, representatives of the regulatory agencies and industry associations of Europe, Japan, and the United States met to establish terms of reference and create a steering committee that has met at least twice annually. The six founding parties — three regulatory and three trade associations — are the direct participants in the ICH process, along with three observer organizations.

ICH parties: *European Commission–European Union (EU):* The European Commission represents the 15 members of the European Union, and it currently is working through harmonization to achieve a single market that will allow free movement of products throughout the EU. The European Agency for the Evaluation of Medicinal Products (EMEA), based in London, was created by the European Commission to provide technical and scientific support for ICH activities.

European Federation of Pharmaceutical Industries' Associations: EFPIA is based in Brussels and has member associations in 16 countries in Western Europe. Members also include all of Europe's major research-based pharmaceutical companies. Much of the EFPIA's work concerns the activities of the European Commission and EMEA, and its work is accomplished by a network of experts and country coordinators that ensure that EFPIA's views within ICH are representative of the European pharmaceutical industry.

Ministry of Health and Welfare, Japan: In Japan, the Ministry of Health and Welfare (MHW) is responsible for the improvement and promotion of social welfare, social security, and public health. Within MHW, the Pharmaceutical Affairs Bureau is responsible for reviewing and licensing all medicinal products and acts as the focal point for ICH activities. MHW's expert groups and an affiliated organization, the National Institute of Health Sciences, distribute technical advice about ICH matters.

Japan Pharmaceutical Manufacturers Association: The membership of the Japan Pharmaceutical Manufacturers Association (JPMA) represents 90 research-based Japanese pharmaceutical manufacturers. Within JPMA, ICH activities are coordinated through specialized committees of industry experts who participate in the ICH expert working groups.

U.S. Food and Drug Administration: The U.S. Food and Drug Administration (FDA) has a wide range of responsibilities for drugs, biologicals, medical devices, cosmetics, and radiological products. The largest of the world's drug regulatory agencies, FDA is responsible for the approval of all drug products used in the United States, regardless of origin. FDA comprises administrative, scientific, and regulatory staff organized under the Office of the Commissioner, and it has several centers

with responsibility for various regulated products. The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) provide technical advice and experts for ICH activities.

Pharmaceutical Research and Manufacturers of America: Pharmaceutical Research and Manufacturers of America (PhRMA) represents the research-based pharmaceutical industry involved in the discovery, development, and manufacture of prescription medicines in the United States. The group also includes research affiliates members that conduct biological research related to the development of drugs and vaccines. PhRMA, which previously was called the U.S. Pharmaceutical Manufacturers Association, coordinates its technical input to ICH through its Scientific and Regulatory Section. Special committees of experts from PhRMA companies deal with specific ICH topics.

ICH observers: Since ICH was initiated, the organization has included official observers associated with the process to act as a link with non-ICH countries and regions. Each of the observer parties has a seat on the ICH steering committee. The ICH observers include

- the World Health Organization (WHO);
- the European Free Trade Area (EFTA), represented at ICH by Switzerland; and
- Canada, represented at ICH by the Drugs Directorate, Health Canada.

ICH administration: ICH is administered by the ICH steering committee, which is supported by the ICH Secretariat. Since ICH was established, each of the six cosponsors has filled two seats on the ICH steering committee, which oversees the harmonization activities. The International Federation of Pharmaceutical Manufacturers Association (IFPMA) is a federation of member associations representing the research-based pharmaceutical industry and other manufacturers of prescription medicines in 56 countries throughout the world. IFPMA has been closely associated with ICH since its inception to ensure contact with the research-based industry outside the ICH regions. IFPMA has two seats on the ICH steering committee and runs the ICH Secretariat.

The Secretariat also participates as a nonvoting member of the steering committee. The Secretariat operates from the IFPMA offices in Geneva, and this position's responsibilities include preparing and documenting meetings of the steering committee. The Secretariat also is responsible for coordinating expert working group meetings. WHO, the Canadian Health Protection Branch, and EFTA also nominate participants to attend the ICH steering committee meetings.

In addition, each of the six cosponsors designates an ICH Coordinator to act as the main contact point with the ICH Secretariat. The ICH Coordinator ensures that ICH documents are distributed to the appropriate persons within the areas of their responsibility.

THE ICH HARMONIZATION PROCESS

The ICH steering committee selects topics for harmonization on the basis of concept papers proposed by the ICH parties or expert working groups. A concept paper identifies the main objective of the proposed harmonization in terms of the perceived problem and the desired outcome.

Once initiated, the topic proceeds through a stepwise process, resulting in the creation of a final draft guideline that is sent to the member regulatory agencies for implementation. The stepwise process proceeds as follows:

Step 1: In the beginning, a six-party expert working group is appointed for a topic and one of them is chosen as the rapporteur. The expert working group conducts preliminary discussions about the topic, and the rapporteur prepares a first draft. This draft may be a guideline, policy statement, recommendation, or a points-to-consider document. The expert working group reviews and revises the draft until its members reach a consensus about the scientific issues. Then the expert working group forwards the draft to the steering committee for further action.

Step 2: At the next step, the six ICH parties in the steering committee approve the draft and transmit it to the three regional regulatory agencies for formal consultation. This regulatory consultation may include organizations and associations outside the ICH process, as well as IFPMA, EFPIA, JPMA, PhRMA, WHO, EFTA, and the Drugs Directorate, Health Canada. The comment period normally is six months, except when special circumstances exist.

Step 3: Next the EU, MHW, or FDA designates a regulatory rapporteur to collect comments in the three regions. The rapporteur, in consultation with the other regulatory experts, analyzes the comments and amends the Step 2 draft if necessary. If significant change results from this process and the original consensus is not maintained, one or more regulatory authorities may recirculate the amended parts of the draft for further approval. If amendment is unnecessary, the rapporteur prepares a final draft and seeks the approval of the regulatory experts from the other parties. The final draft is approved by experts designated by the regulatory parties before referral to the ICH steering committee for adoption.

Step 4: The final draft is discussed within the steering committee and approved by the three ICH regulatory parties and recommended for adoption.

Step 5: The process is complete when the full recommendations are incorporated into domestic regulations or other appropriate administrative measures, according to national–regional internal procedures.

In the United States, the full text of the guideline is published in the *Federal Register* during the comment (Step 2) and implementation (Step 5) periods. The guideline eventually will appear in the appropriate compendia, such as the *U.S. Pharmacopeia* (*USP*). Guidelines also are available via the Internet at www.fda.gov/cder/guidance/index.htm and www.fda.gov/cber/guidelines.htm. The other two regulatory parties have their own implementation process, and they make the guidelines available via the Internet as well at www.eudra.org/emea.html and www.nihs.go.jp/dig/ich/ichindex.htm.

ICH HARMONIZATION INITIATIVES

To date, ICH harmonization topics have been divided into four major categories with assigned ICH codes. The guidelines derived from each topic are commonly referred to by the ICH codes. These categories include quality topics (Q topics relating to pharmaceutical quality assurance), safety topics (S topics relating to in vitro and in vivo preclinical studies), efficacy topics (E topics relating to clinical studies in humans), and multidisciplinary topics (M topics that defy categorization).

Table I summarizes all of the quality topics initiated to date. (Readers can research S, E, and M topics at www.ich.org.) At the time this column was written, Q1, Q2, Q3, and Q5 topics had all reached Step 5 in the ICH process (considered implemented in the U.S.); Q6 guidelines are at Step 3; and Q7 is at Step 1. Topic Q4, harmonization among the major pharmacopeias, which actually started before ICH, is proceeding in parallel with the ICH.

As Table I shows, method validation guidelines fall under the quality topics in Section Q2, Validation of Analytical Procedures. The harmonized ICH text of Q2A, Definitions and Terminology, was finalized (Step 4) in October 1994. This guideline identified the validation parameters required for analytical methods. It also discussed the characteristics that must be considered during the validation of analytical procedures that are part of the registration process. Q2A, Definitions and Terminology, was published in the *Federal Register* in 1995 and is considered implemented (1). The harmonized ICH text of Q2B, Methodology, was finalized (Step 4) in November 1996. Q2B extended Q2A to include the actual experimental data required, as well as statistical interpretation for the validation of analytical procedures. Q2B also was published in the *Federal Register* in 1997 and is considered implemented (2).

Both of these guidelines significantly affect people working in the validation area, and users should consult them because these guidelines will be incorporated into the next publication of the *USP* and federal regulators have already begun to reference these documents.

Previous "Validation Viewpoint" columns have addressed these specific ICH guidelines in more detail (3–6). However, we should point out that the ICH is not a regulatory body nor is it in the business of generating duplicate guidelines. Rather, the ICH has provided clear guidance with respect to global compendia about several topics with FDA, among others, as willing participants. This participation has helped ensure that a single set of current guidelines are adopted worldwide and maintained through the normal regulatory process.

THE FUTURE OF THE ICH

At ICH 4 in Brussels, ICH released 10 guidelines for implementation and 2 for consultation (see www.ich.org), which represent significant progress. As the next logical step after agreeing on guidelines for data collection, the steering committee agreed to consider harmonizing the format and content of application documents for new product applications. At its September 1998 meeting in Tokyo, the ICH steering committee announced reports of significant progress from its expert working group on the ICH common technical document for registering new medicines.

Regulatory specialists reported that they are nearing consensus on the harmonization of the table of contents as well as the content of clinical and nonclinical summaries and tabulations (see www.ich.org). The project is well on target with a finalized document expected by the year 2000. An electronic version also is in preparation. Electronic submissions could significantly change the way in which regulatory information is provided in the future to facilitate better and more efficient management of documentation.

As mentioned previously, ICH 4 in Brussels closed the first phase of ICH activities, so ICH activities will move into a second phase with a continuing commitment to increased international harmonization. In this spirit, the ICH revised its *Terms of Reference* (see www.ich.org). The new ICH goals are

- to maintain a forum for a constructive dialogue between regulatory authorities and the pharmaceutical industry on the real and perceived differences in the technical requirements for product registration in the EU, United States, and Japan to ensure more timely introduction of new medicinal products and availability to patients;
- to monitor and update harmonized technical requirements leading to a greater mutual acceptance of research and development data;
- to avoid divergent future requirements through harmonization of selected topics needed as a result of therapeutic advances and the development of new technologies for the production of medicinal products;
- to facilitate the adoption of new or improved technical research and development approaches that update or replace current practices in situations in which these approaches permit a more economical use of human, animal, and material resources without compromising safety; and
- to facilitate the dissemination and communication of information about harmonized guidelines and their use to encourage the implementation and integration of common standards.

In addition, ICH 4 attendees decided that the six-party structure would continue as the operational basis for harmonization with the observers playing a significant role. The six founding members of ICH also agreed that the second phase of harmonization activities should continue after ICH 4 to ensure that

- a mechanism exists to harmonize new technical requirements from scientific progress and developments in innovative drug research;
- a process exists for updating and supplementing the current ICH guidelines when necessary and monitoring their use, so that the benefits of current harmonization are not lost; and
- future disharmony is prevented through early collaboration and exchange of information about newly emerging issues that originate in one of the regions.

At a recent meeting, the ICH steering committee also confirmed that a Fifth International Conference on Harmonization will be held in San Diego, California, during the week of 6 September 2000. The main focus for ICH 5 will be reporting agreements for the completion of the ICH common technical document.

TABLE I: ICH Quality Topics

Topic Name and Code	Document Name and Code
Q1: Stability	Q1A: Stability Testing of New Drugs and Products Q1B: Photostability Testing Q1C: Stability Testing: New Formulations
Q2: Analytical Method Validation	Q2A: Definitions and Terminology Q2B: Methodology
Q3: Impurities	Q3A: Impurities in New Drug Substances Q3B: Impurities in Dosage Forms Q3C: Impurities: Residual Solvents
Q4: Pharmacopeias	Q4: Pharmacopeias Harmonization
Q5: Biotechnological Quality	Q5A: Viral Safety Evaluation Q5B: Genetic Stability Q5C: Stability of Products
Q6: Specifications	Q6A: Chemical Substances Q6B: Biotechnological Substances
Q7: GMP	Q7A: GMP for Active Pharmaceutical Ingredients

FOR MORE INFORMATION

The ICH can be contacted directly at ICH Secretariat, c/o IFPMA, 30 rue de St.-Jean, P.O. Box 9, 1211 Geneva 18, Switzerland, tel. +41 (22) 340 1200, fax +41 (22) 345 8275, e-mail ich@ifpma.org, WWW www.ich.org.

Guidelines are available at the web site in PDF format, or, for a nominal fee, hard copy is available directly from the ICH. Guidelines also are available on disk in MS Word format by contacting the Secretariat.

EDITORS' NOTE

As we went to press, the 2000 *U.S. Pharmacopeia 24, National Formulary 19* was being released. All of the ICH guidelines on validation outlined in this column have been included in chapter ⟨1225⟩ on method validation. As a result, considerable more guidance is available. Because of the ICH process, the *USP* update may be the subject of a future "Validation Viewpoint" column. Until then, we urge readers to consult the new *USP* to stay current in the field.

REFERENCES

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The columnists regret that time constraints prevent them from responding to individual reader queries. However, readers are welcome to submit specific questions and problems, which the columnists may address in future columns.

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