

Why the international harmonisation process is increasingly important

In the first of two articles, **Robin Harman** explains the increasing importance of the ICH process as the cost of bringing new medicinal products to the market continues to spiral, and greater pressures are placed on regulatory authorities to be more efficient

The registration of medicinal products has undergone many changes in scope and rationale over the past 50 years. In trying to ensure that all medicinal products conform to the three basic criteria of quality, safety and efficacy, it is not surprising that the ways in which individual countries have tried to achieve this has differed, often significantly. As a consequence, the already lengthy and expensive process for bringing a new medicinal product to the market became even more so if a manufacturer wished to market its products in as many countries as possible.

It became apparent in different countries at different times that it was important to have independent evaluation of medicinal products before they were marketed. Authorisations became a requirement in the US in the 1930s with the systems established by the Food and Drug Administration. In Japan, government regulations requiring all medicinal products to be registered started in the 1950s. In Europe, the trigger was the thalidomide tragedy of the 1960s.

In many countries globally, there was a considerable increase in the 1960s and 1970s in the laws, regulations and guidelines for reporting and evaluating the data on quality, safety and efficacy of new medicinal products. However, as the industry became more international and sought global markets, the registration of medicines remained a national responsibility. Although almost all countries based their approvals on quality, safety and efficacy, the detailed technical requirements had diverged over time. As a consequence, it became necessary for industry to duplicate many time-consuming and expensive test procedures.

The urgent need to rationalise and harmonise regulation was impelled by concerns over rising costs of health care, escalation of the cost of research and development and the need to meet the public expectation that there should be a minimum of delay in bringing new treatments to those patients that needed them.

It is now estimated to cost £350m to bring a new product to market. Equally, governments have continuously exerted



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downward pressure on the costs borne by regulatory authorities in ensuring that medicinal products are of a high standard but become available to the public at the earliest opportunity.

Initiation of ICH

The objective of creating a single market in the (then) European Community in 1981 was a major incentive towards harmonisation of regulatory requirements and the initial successes within Europe showed that harmonisation was possible. The impetus was further increased by trilateral discussions between Europe, Japan and the US. It was in Paris in 1989, at the World Health Organization Conference of Drug Regulatory Authorities (ICDRA), that specific plans for action were developed. The regulatory authorities then approached the International Federation of Pharmaceutical Manufacturers Associations, in Geneva, to

discuss a joint regulatory–industry initiative on international harmonisation.

Thus was the ICH process (the International Conference on Harmonisation of the Technical Requirements for Registration of Pharmaceuticals for Human Use) conceived.

In April 1990, the seeds of ICH were planted at a meeting hosted by the European Federation of Pharmaceutical Industries Associations in Brussels. Representatives of the regulatory agencies and industry associations of Europe, Japan and the US met initially to plan an international conference, but the meeting also discussed the wider implications and terms of reference of ICH. An ICH steering committee was established which has subsequently met at least twice a year, with the location rotating between the three regions.

At the first ICH steering committee meeting, the terms of reference were

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agreed. It was decided that the topics selected for harmonisation would be divided into quality, safety and efficacy to reflect the three basic approval criteria. It was also agreed that expert working groups (EWGs) comprising membership from each of the six main parties should be set up to discuss scientific and technical aspects of each harmonisation topic. Eleven such topics were selected for discussion at the first International Conference on Harmonisation (ICH1).

The basic principles guiding the ICH process have been summarised as:

- Development of scientific consensus through discussions between regulatory and industry experts
- Wide consultation of the draft consensus documents, through normal regulatory channels, before a harmonised text is adopted
- Commitment by regulatory parties to implement the ICH harmonised texts

The *modus operandi* for ICH work was established at this early stage: the EWGs meet in the same week as the steering committee and report on their progress to that committee.

The commitment of all parties to ICH was set out in a steering committee statement issued in Tokyo in October 1990 (Panel 1).

The process The ICH process was first drawn up at the steering committee meeting in Washington in March 1992 and amended in Tokyo in September 1992. The process incorporates “decision points” at Step 2 and Step 4, and has enabled the steering committee to monitor the progress of the topics selected for harmonisation.

The topics selected for discussion in the three EWG workshops at ICH1, particularly those for quality and safety, were broad in their scope. Although ICH1 was a successful conference, it was clear that the topics selected for harmonisation would need to be more focused, with a clearly defined and realistic objective. Thus most of the 11 ICH1 topics (which were identified as “Quality T1–T3”, “Safety T1–T4” and “Efficacy T1–T4”) were subsequently subdivided and given different codes.

At least one topic has come “full circle” since ICH1. The quality topic on “Specifications” was divided into topics on analytical validation (Q2) and impurities (Q3). These were further subdivided and developed into harmonised guidelines. Once this process had been completed, it was agreed at ICH3 that work should recommence on consolidated guidance for setting specifications for new drugs and products (Q6).

The broad safety topic from ICH1, “toxicity testing programme”, was also broken down into more manageable elements which have generated harmonised guidelines. Other topics (eg, safety testing for biotechnology products and the timing of toxicity studies in

relation to clinical trials) were put on hold, but have since been reconsidered.

Participants in the ICH process

The six founder members of ICH that are directly involved in the decision-making process represent the regulatory bodies and the research-based industry in the EU, Japan and the US. They are the European Commission of the EU, the European Federation of Pharmaceutical Industries Associations, the Ministry of Health, Labour and Welfare of Japan, the Japan Pharmaceutical Manufacturers Association, the US Food and Drug Administration and Pharmaceutical and Research Manufacturers of America (see Panel 2).

Other participants in the decision-making process include:

Observers Observers act as a link with non-ICH countries and regions. The observers to ICH are:

- The World Health Organization (WHO)
- The European Free Trade Area (EFTA), represented at ICH by Switzerland
- Canada, represented at ICH by Health Canada

International Federation of Pharmaceutical Manufacturers Associations

The IFPMA is a federation of associations representing the research-based pharmaceutical industry and other manufacturers of prescription medicines in 56 countries throughout the world. The IFPMA has been closely associated with the ICH since its in-

ception to ensure contact with the research-based industry outside the ICH regions. IFPMA runs the ICH secretariat.

ICH steering committee The ICH is administered by the ICH steering committee which is supported by the ICH secretariat. Since the ICH was established, each of the six co-sponsors has had two seats on the ICH steering committee which oversees the harmonisation activities. The IFPMA provides the secretariat and participates as a non-voting member of the steering committee.

The observers nominate non-voting participants to attend the ICH steering committee meetings.

ICH co-ordinators Fundamental to the smooth running of the ICH has been the designation, by each of the six co-sponsors, of an ICH co-ordinator to act as the main contact point with the ICH secretariat and to ensure that ICH documents are distributed to the appropriate persons within the area of their responsibility.

Each party has also established a “contact network” of experts within their own organisation or region in order to ensure that, in the discussions, they reflect the views and policies of the co-sponsor they represent. The way in which this network operates differs according to the administrative structure of the party concerned.

ICH secretariat The ICH secretariat operates from the IFPMA offices in Geneva, and is primarily concerned with preparations for, and documentation of, meetings of the steer-

Panel 1: Statement issued by the ICH Steering Committee in Tokyo, October 1990

- The parties co-sponsoring this conference, represented at the second steering committee meeting in Tokyo, 23–24 October 1990, reaffirmed their commitment to increased international harmonisation, aimed at ensuring that good quality, safe and effective medicines are developed and registered in the most efficient and cost-effective manner. These activities are pursued in the interest of the consumer and public health, to prevent unnecessary duplication of clinical trials in humans and to minimise the use of animal testing without compromising the regulatory obligations of safety and effectiveness.
- This conference will provide a unique opportunity for regulators and industry to reach consensus on the steps needed to achieve this objective through greater harmonisation of technical requirements and to set out practical and realistic targets for harmonising requirements where significant obstacles to drug development and the regulatory process have been identified.
- Recognising the substantial progress which has already been made in achieving harmonisation within Europe and through bilateral contacts between Europe, Japan, US and other regions, the conference will seek to make further progress through a trilateral approach, with clearly defined priorities, methods of work and recommendations to both industry and regulatory authorities.
- While the conference will be an important step forward, it is not seen as an end in itself, but as a stage in a developing process, at a high level, between regulators and industry.
- The conference, its preparations and follow-up activities will be conducted in an open and transparent manner and the presence of observers from other regulatory authorities and WHO is welcomed as a means of ensuring that the benefits of progress towards harmonisation can be utilised world-wide.
- The conference will not only look at existing issues but will, based on past experience, seek to minimise future divergence of new registration requirements, as a consequence of technical progress.

Panel 2: The six founder members of the ICH

The European Commission of the EU The European Medicines Evaluation Agency (EMA) was established in 1995 by the European Commission. Technical and scientific support for ICH activities is provided by the Committee for Human Medicinal Products (CHMP) (formerly the Committee for Proprietary Medicinal Products, CPMP) of the EMA.

European Federation of Pharmaceutical Industries Associations EFPIA is based in Brussels and its members are member associations in 16 countries in western Europe. A wide network of experts and country co-ordinators has been established through member associations to ensure that the federation's views within ICH are representative of the European industry.

Ministry of Health, Labour and Welfare, Japan Those affiliated to the MHLW include the National Institute of Health Sciences and academia, which carries out research and testing on drugs, vaccines and biologicals. Technical advice on ICH matters is obtained through MHLW's regulatory expert groups, with members from NIHS.

Japan Pharmaceutical Manufacturers Association The JPMA represents 90 member companies. Membership includes all the major research-based pharmaceutical manufacturers in Japan. ICH work is co-ordinated through specialised committees of industry experts who also participate in the Expert Working Groups.

Food and Drug Administration The US 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, the FDA is responsible for the approval of all drug products used in the US. The FDA consists of administrative, scientific and regulatory staff organised under the Office of the Commissioner and has several centres with responsibility for the various products which are regulated. Technical advice and experts for ICH work are drawn from the Centre for Drug Evaluation and Research and the Centre for Biologics Evaluation and Research.

Pharmaceutical Research and Manufacturers of America The PhRMA represents the research-based industry in the US. The association has 67 companies in membership which are involved in the discovery, development and manufacture of prescription medicines. There are also 24 research affiliates which conduct biological research related to the development of drugs and vaccines. PhRMA (previously known as the US Pharmaceutical Manufacturers Association, PMA) co-ordinates its technical input to ICH through its scientific and regulatory section. Special committees have been set up, of experts from PhRMA companies, to deal with ICH topics.

ing committee as well as co-ordination of preparations for expert working group meetings and six-party drafting groups. At the time of ICH conferences, the secretariat is responsible for the technical documentation and for liaison with the speakers for the conference. Organisational aspects of the conferences are handled by the industry and regulatory parties in the country where the conference takes place.

Recent changes to ICH procedures

After 10 years of ICH activities, and a reasonable degree of success in achieving the objectives of harmonisation of technical guidelines, it was decided at ICH5 in San Diego in November 2000 to revisit the aims and targets likely to be achieved over future years.

Delegates at ICH5 agreed that success had been possible because of the scientific consensus reached between the experts in both regulatory authorities and the pharmaceutical industry. Another important aspect had been the willingness of all parties to implement the harmonised guidelines and recommendations.

One further benefit that has now come to fruition has been the implementation of harmonisation of the format and content of marketing authorisation applications using the Common Technical Document format. This has now been implemented in all regions involved in the ICH process and indeed in many others outside the primary three regions.

The current large scale of successful harmonisation actions and the need for all guidelines and recommendations to keep step with an evolving scientific environment has needed greater effort on the implementation and monitoring of ICH commitments.

At ICH5, it was also agreed that one area in which increased regulatory co-operation would help enhance the protection of the health of citizens on a more international basis was that of postmarketing activities.

The important role for WHO in disseminating information and providing input beyond the ICH regions was also recognised. Moreover, the steering committee identified the need to expand its communication and dissemination of information with non-ICH parties. A more active involvement of WHO through its regional centres was suggested as one way of achieving this.

As a consequence of the discussions taking place at this time, a set of revised terms of reference of the ICH process were developed. These terms of reference were:

- 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, US and Japan in order to ensure a more timely introduction of new medicinal products, and their availability to patients

- To contribute to the protection of public health from an international perspective
- To monitor and update harmonised technical requirements leading to a greater mutual acceptance of research and development data
- To avoid divergent future requirements through harmonisation 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, where these permit a more economical use of human, animal and material resources, without compromising safety
- To facilitate the dissemination and communication of information on harmonised guidelines and their use such as to encourage the implementation and integration of common standards

Since 2000, harmonisation initiatives are now described as "major" and "minor". A major topic includes proposals for new guidelines and changes to existing guidelines which involve interpretations of statutory or regulatory requirements, changes in interpretation or policy that are more than a minor nature, usually involving complex scientific issues. Other changes are considered minor.

Major topics are handled under the full ICH process. This is based on the original "five-step" approach, which has proved extremely successful for the first phase of ICH activities. Proposals for "minor" changes to existing ICH tripartite harmonised guidelines are handled through an abbreviated maintenance process.

The full ICH process will be described in a second article.