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International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (*ICH*)

During the last 3 years, the regulatory authorities from Europe, Japan and the United States of America and experts from the pharmaceutical industry have been meeting to seek ways in which technical requirements for the regulation of new medicinal substances and products can be made uniform, to eliminate redundancies and avoid duplicate activity, with the objective of expediting the global development and availability of new medicines without loss of safeguards on quality, safety or efficacy.

This serious and comprehensive undertaking has been under the auspices of seven co-sponsors; in Europe, the Commission of the European Communities and the European Federation of Pharmaceutical Industries Association (EFPIA); in Japan, the Ministry of Health and Welfare (MHW) and the Japan Pharmaceutical Manufacturers Association (JPMA); and in the United States the Food and Drug Administration (FDA) and the Pharmaceuticals Manufacturers Association (PMA). The International Federation of Pharmaceutical Manufacturers Association (IFPMA) is the umbrella organisation for the whole of the Pharmaceutical Industry. Each of the sponsors has two seats on the ICH Steering Committee, which oversees the harmonisation process and is ultimately responsible for the international conferences. It was decided at the start of the process that the conference should be the focus for discussion of the tripartite harmonisation so that the process would be carried out in an 'open and transparent manner' and the recommendations could be presented in an open forum.

So far there have been two conferences; the first was in Brussels in November 1991 [1] and the second in Orlando in October 1993. A third is planned for Yokohama in 1995.

The Steering Committee chose three broad areas – Safety, Quality and Efficacy – over which harmonisation is being sought. To advise them the Committee established Expert Working Groups (EWG) with members drawn from the six co-sponsors, to ensure representation from industry and regulatory authorities. Each working group in turn can call on experts for comments on draft proposals.

The topics chosen for harmonisation by the ICH Steering Committee on the advice of the Expert Working Groups, are shown in Tables 1, 2 and 3. The process towards implementation of a harmonised guideline by all regulatory authorities takes place in a series of five steps, the first of which is the production of a preliminary draft by the EWG, following which comment is received from regional regulatory authorities, industry and their country's representative bodies (e.g. ABPI in UK). These comments are taken into account in the production of a Step 2 document, which when agreed by the EWG, is formally signed by the three regulatory bodies. This document is circulated for further comment during Step 3. Many drafts may be produced during this to-ing and fro-ing, leading to step 4, when the final draft is endorsed by the Steering Committee which recommends it for adoption to the three regulatory bodies. Step 5 is the incorporation of the harmonised guideline into domestic regulations and its implementation.

How is the harmonisation proceeding and what are the implications for clinical pharmacology?

Intuitively, it might be expected that harmonisation would be easier to achieve in the non-clinical areas. It might reasonably be expected that differences in culture and medical practice would be severe obstacles to agreements in the different geographical areas. However, this has not, uniformly, proved to be the case. Tables 1–3 summarise the current situation in the three areas of safety, quality and efficacy.[1]

The pre-clinical safety testing will be of considerable interest to clinical pharmacologists, particularly for innovative compounds. The LD_{50} has been discarded and replaced by rising repeat dose studies prior to starting the short and long-term toxicity. Many pharmaceutical companies have been using this approach for some time, but harmonisation will make it simpler for investigators to compare across drugs of the same class. Agreement was initially reached that both rodent and non-rodent repeat dose studies could be reduced from 12 to 6 months, which was universally welcomed as a real saving in time and test animals. Unfortunately the FDA have had second thoughts and still require 12 month non-rodent studies.

The reproductive toxicology tripartite guidelines have reached step 4, i.e. endorsed by the ICH Steering Committee, and is recommended for adoption by the three regulatory bodies.

Toxicokinetics, or the assessment of systemic exposure in toxicity studies, is of particular interest for clinical pharmacologists, and Step 2 was reached at ICH-2. There has been a definite tendency in the past to use doses administered rather than tissue exposure (area under concentration-time curve or plasma or tissue concentrations) when assessing the relationship between drug dosed and observed toxic effects. Establishing toxicokinetics as a separate topic emphasises the need to assess the relevance of pre-clinical findings to subsequent clinical safety.

Good progress has been made towards tripartite agreement in the assessment of carcinogenic potential of

[1](For a full report on the current status, readers must await the publication of proceedings of ICH-2, due out in the first quarter of 1994).

Table 1 Topics for harmonisation: safety

Topic	*Current position*
1 Toxicity testing programme for short and long term toxicity	LD_{50} abandoned. 12 month rodent studies no longer required.
2 Reproductive toxicology	Step 4 tripartite guideline – June 1993
3 Timing of toxicity studies in relation to induction of phase 1 clinical trials	Agreement not yet reached
4 Toxicokinetics: systemic exposure in toxicity studies	Step 2.
5 Safety testing for biotechnology products	Good progress, flexible approach agreed. Possible topic for ICH-3
6 Assessment of carcinogenic potential of therapeutic agents	Carcinogenicity studies not needed for compounds used only for 3 months Step 2
7 Genotoxicity testing requirements	Core test battery still under debate, but a clear progress in other areas

Table 2 Topics for harmonisation: quality

Topic	*Current position*
1 Stability testing	Step 4: Core guideline agreed by regulators: Ambiguity to be clarified. Step 2: Extension for light stability conditions under discussion. Step 1: Extension for variations being considered.
2 Analytical validation	Step 2
3 Biotechnology products	For consideration during 1994
4 Impurities in new drug substances	Step 2 – Expected March 1994 Quality – almost at consensus
5 Pharmacopoeias	Under discussion

Table 3 Topic for harmonisation: efficacy

Topic	*Current status*
1 Population exposure to assess clinical safety	Step 2 – 300–600 patients for 6 months. 100 patients for 1 year
2 Clinical Safety Data Management	Step 2 – Dealing with serious adverse events only. Must be reported within 5 working days and in writing within 15 working days.
3 Format of clinical study reports	FDA will not accept changes based on their guidelines recommended by CPMP and EPIA Further discussion in 1994
4 Good clinical practice	Step 2 – Good progress being made especially on Investigators' Brochure
5 Studies in support of Special Population: Geriatrics	Step 4 – Released for implementation
6 Ethnic factors in the acceptability of foreign data	Recognition that inter-ethnic kinetic and dynamic differences are probably less important than inter and intra subject variability. Expect to reach Step 2 in 1994
7 Dose response information to support product registration	Step 2 – Good progress. Agreement on most key areas: FDA have released guideline for comment in Federal Register.

therapeutic agents. Three topics were selected: guidelines for dose selection, defining conditions which require carcinogenicity studies and the utility of two rodent species. A step 2 guideline for dose selection was issued at ICH-2, and it is hoped that a note for guidance on defining conditions which require carcinogenicity studies will be issued by ICH-3. For genotoxicity the EWG has reached consensus on eight technical strategic issues, but has failed to define an agreed core test battery. Again it is hoped resolution will be reached before ICH-3.

The EWG on efficacy has developed a series of topics for harmonisation listed in Table 3. The section on population exposure to assess clinical safety centred around the number of patients and length of the treatment period that would achieve tripartite agreement. It was agreed that between 300–600 patients treated for 6 months would be adequate to detect most adverse events at 1% level, and 100 patients treated for 12 months was acceptable to complete the NDA safety database. US and Japan will accept filings with 6 months data with later submission of 12 month data update prior to approval. EC however, will accept filings with the 6 month data only. This would mean that the 12 month safety data and update would be filed after approval. This issue at step 2, is not finalised and further debate is required.

The clinical safety data management dealt with definitions and standards for expediting reporting. Not surprisingly, inter country differences in definition of terms proved challenging e.g. serious *vs* severe, adverse reaction *vs* adverse event and assessment of causality. Reporting time-frames were also debated; probably verbal reporting within 5 working days with written confirmation within 10 working days will be acceptable.

The document was issued at Step 2.

The format of clinical study reports was hotly debated. The FDA believes their guideline for format and content of clinical and statistical data has been 'clinically proven' for world-wide registration and were not going to be easily shifted by the European agencies. It is still anticipated that Step 2 can be finalised in March 1994.

Studies in special populations had concentrated entirely on the geriatric population. Tripartite agreement has been obtained early and the document had been released for implementation (step 4) [2].

The last two topics are of particular interest to the clinical pharmacologist. Ethnic factors in the acceptability of foreign data has proved to be less controversial than it first seemed. The Japanese have consistently maintained that they required smaller doses to produce equal efficacy to their Western counterparts in several disease areas and that the adverse event reporting patterns were different. Two studies were conducted, one on non-steroidal anti-inflammatory drugs, the other on anti-hypertensives. The results have led the Japanese investigators to conclude that differences in efficacy and safety were marginal and that differences in medical practice, methods of recording adverse events, dietary factors and so on, were probably of greater significance in explaining variability than inherent genetic factors.

This is something of a reversal from the stance adopted by the Japanese at ICH-1. Thus, step 2 was reached, at ICH-2.

The efficacy/dose-response EWG have worked steadily through a number of drafts to achieve a comprehensive document which was well received at ICH-2, at step 2. It has also been issued by the FDA as Guidelines for comment in the Federal Register [3]. These guidelines are comprehensive, practical and not prescriptive. They encourage the use of the whole data base in the clinical development programme to define a dose response, but clearly, and correctly, favour the targeted and dedicated dose-response trials. Design choices are discussed and the parallel, randomised, placebo or positive control design, given prominence. However, alternative design such as 'forced' or 'optional' titration and modelling techniques are encouraged. This is the most exciting area of the efficacy section for dynamicists and kineticists who should be encouraged to balance the traditional approach to dose-definition, with some of the newer techniques. It should also increase the dialogue between scientists in pharmaceutical companies and regulatory authorities.

Has the harmonisation process, so far, been successful? Judged in terms of progress of some of the topics to step 2, and albeit fewer to step 4, the answer is yes. That there is still the will to push on with completing the rest of the topics is also promising. But there have been disappointments, such as the reluctance to reduce the 1 year toxicity testing for non-rodent species to 6 months, as originally agreed and the inability to agree on the format of a clinical trials report format. Lack of agreement on a core genetic toxicity testing battery is perhaps more understandable in a complex technical field. There can surely be less sympathy for lack of agreement over stability testing. Whilst the three regulatory bodies have agreed a guideline, it is still not clear to industry how it will operate.

There are other measures of success. The ICH process has brought regulators and industry experts together with a common purpose. It has provided a forum for regulators of different countries to meet. However, a note of caution is necessary. None of the findings has yet been implemented and this is now the responsibility of the individual regulatory bodies. The water must be tested with a major regulatory submission that the same data will be acceptable in all countries. It is hard to believe that for example, the clinical component of a regulatory dossier would be acceptable in Japan without any data on Japanese patients, or *vice versa*.

We must wait and see.

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