

Rationalising drug development — the international harmonisation process

In the second of two articles, **Robin Harman** describes the ways in which ICH guidelines are selected and developed, and the current status of all guidelines that have been generated

In the first of these two articles (*PJ*, 14 August, p224) the reasons why the three major regions in pharmaceutical research and development (the EU, the US and Japan) decided to initiate the ICH process (the International Conference on Harmonisation of the Technical Requirements for Registration of Pharmaceuticals for Human Use) were explained. The article also described the participants in the process, the meetings that have taken place, and recent changes to the way in which guidelines are developed. This article will explain the selection and production of ICH guidelines.

Initiation of ICH harmonisation action

Proposals for harmonisation action

Suggestions for new harmonisation initiatives may arise in a number of different places, including ICH regional guideline workshops, other regional and international conferences, workshops and symposia dealing with research and development and regulatory affairs, and recognised associations, federations and societies which represent scientific and technical professionals concerned with the development, testing and registration of medicines. Formal proposals for ICH action must be channelled through one of the six parties to ICH or one of the observers on the steering committee. Proposals for action can fall into one of the following categories:

- **New types of medicinal product** Proposals for guidelines to cover new products resulting from advances in technology and techniques for producing medicines (eg, products arising from gene therapy and other developments in biotechnological and genomic research)
- **Lack of harmonisation in current technical requirements** Proposals for further harmonisation of existing requirements (eg, as a result of work on the Common Technical Document)
- **Transition to technically improved testing procedures** Proposals for action to facilitate the replacement of currently established testing procedures to more efficient and economical methods where these provide equal or better assurance of the safety and/or quality of new drug products

Robin J. Harman, PhD, MRPharmS, is a pharmaceutical and regulatory consultant based in Farnham, Surrey
(e-mail robin.harman@virgin.net)



Rex Features

- **Review of an existing ICH guideline** Proposals for significant changes to the technical aspects of an ICH guideline or proposals for a major addition to the guideline
 - **Maintenance of an existing guideline** Proposals for relatively minor modification, updating clarification or review of ICH agreements to take account of either problems with implementation, new information or new scientific knowledge.
 - **Statement of the perceived problem** Brief description with an indication of the magnitude of the problems currently caused by a lack of harmonisation or, in the case of new scientific developments, problems anticipated if harmonisation action is not taken
 - **Issues to be resolved** A summary of the main technical and scientific issues which require harmonisation
 - **Background to the proposal** Further relevant information (eg, the origin of the proposal, references to publications, discussions in other forums)
 - **Type of expert working group** Recommendation on whether the expert working group, if needed, should be a six-party group (used for topics related to the research and development of new drug substances and products) or an extended expert working group (for topics with implications beyond new drug research)
- Preparation of a concept paper** The ICH party or observer proposing a new harmonisation action must present the issue in the form of a concept paper. This provides a short summary of the proposal (maximum two pages) giving the following information:
- **Type of harmonisation action proposed** For example, a new tripartite harmonised guideline/recommendation, or an amendment/update of an existing guideline

Further documentation and reports may be annexed to the concept paper.

Selection of procedure Proposals arising for new types of medicinal product, lack of harmonisation in current requirements, improved testing procedures, and review of an existing guideline are automatically subject to the full ICH process (described below). The proposal and concept paper is sent to members of the steering committee, observers and ICH co-ordinators; the copy sent to the ICH secretariat should ask for the item to be included on the agenda for the next steering committee meeting.

Proposals for maintenance of existing guidelines, in which the sponsor believes that an abbreviated process is appropriate, should be sent to the ICH secretariat with a request that the maintenance process, rather than the full process, be initiated.

Full harmonisation process

Topic selection The steering committee agenda routinely includes an item on “pro-

posals for new topics”. The sponsoring party or observer must have circulated the concept paper to co-ordinators and the secretariat in advance, and the concept paper and any comments will be submitted to the steering committee. A preliminary determination is then made on whether the topic is of sufficient interest to all parties and can be accommodated within the ICH work programme.

The concept paper must indicate the type of EWG that is appropriate for the topic (ie, six-party membership only, or with membership extended to other interested parties). If it is considered worthwhile, and interested parties beyond the six ICH sponsors and three observers are identified as appropriate, the steering committee then invites, as appropriate, those additional parties to discussions on the topic, just before its acceptance by the steering committee as an ICH topic.

Steering committee action When a topic is adopted for harmonisation action, the steering committee:

- Confirms the objectives and expected outcome of the harmonisation action
- Confirms the composition of the EWG appointed to discuss the technical issues
- Sets a timetable and action plan for the EWG

The concept paper is then revised and updated to reflect these decisions.

Expert working groups Each of the six ICH parties (see first article, *PJ*, 13 August, p224) are asked to designate a leader for the new topic. The topic leaders participate in the EWG meetings and are the point of contact for any consultations carried out between meetings. A deputy topic leader can also be designated.

Observers to ICH are also invited to nominate an expert to the EWG. In the case of EWGs with extended membership, the secretariat invites the designated organisations to nominate an expert to participate in the EWG and act as the contact point for receipt of documents on technical issues. Other in-

Panel 1: The five-step process in developing ICH guidelines

Step 1: Consensus building

The rapporteur prepares an initial draft of a guideline or recommendation, based on the objectives set out in the concept paper, and in consultation with experts designated to the EWG. The initial draft and successive revisions are circulated for comment, giving fixed deadlines for receipt of those comments.

To the extent possible, consultation is carried out by correspondence, using fax and e-mail. Meetings of the EWG normally only take place at the time and venue of the biannual steering committee meetings. Additional formal meetings of the ICH EWG must be agreed in advance by the steering committee.

Interim reports are made to each meeting of the steering committee. If consensus is reached within the agreed timetable, the consensus text with EWG signatures (see below) is submitted to the steering committee for adoption as Step 2 of the ICH process.

Where complete consensus has not been achieved within the agreed timetable, a report will be made to the steering committee indicating the extent of agreement reached and highlighting the points on which there are differences between the parties. Experts from all parties represented on the EWG then have the opportunity to explain their position to the steering committee. The steering committee may then:

- Allow an extension of the timetable, on the basis that the EWG can give assurances that consensus could be reached within a short, specified period
- Decide to suspend or abandon the harmonisation project
- Decide to proceed to Step 2 on the basis of the current draft, notwithstanding absence of complete consensus in the EWG

Step 2, Phase 1: Sign-off by EWG members

When consensus is reached on the technical issues, all parties represented on an EWG are invited to sign the document to indicate their agreement to the consensus text which is submitted to the steering committee. Circumstances could be envisaged, however, when not all other parties are present or able to sign the consensus text. It would then be for the steering committee to decide whether to proceed to Step 2.

Step 2, Phase 2: Start of regulatory action

Step 2 is reached when the steering committee agrees, on the basis of the report from the EWG, that there is sufficient scientific consensus on the technical issues, for the draft guideline or recommendation to proceed to the next stage of regulatory consultation. This agreement is confirmed by steering committee members for each of the six ICH parties signing their assent.

Step 3: Regulatory consultation

At this stage, the guideline or recommendation embodying the scientific consensus leaves the ICH process and becomes the subject of normal wide-ranging regulatory consultation in each of the three regions. In the EU it is published as a draft Committee for Proprietary Medicinal Products guideline; in the US, it is published as a draft guidance in the Federal Register; and in Japan it is translated and issued by Ministry of Health, Labour and Welfare, for internal and external consultation.

The difference from standard national/EU procedures for consultations on guidelines is that the regulatory parties exchange information on the comments they have received in order to arrive at a single harmonised text. In addition, there is an opportunity for industry associations and regulatory authorities in non-ICH regions to comment on the draft consultation documents which are distributed using contact lists from the International Federation of Pharmaceutical Manufacturers' Associations or the World Health Organization.

A regulatory rapporteur is designated to draw up the final document and obtain agreement, in the form of a “sign-off” from the experts representing the other regulatory parties.

Step 4: Adoption of a tripartite harmonised text

At Step 4, the topic returns to the ICH forum where the steering committee receives a report from the regulatory rapporteur. If both regulatory and industry parties are satisfied that the consensus achieved at Step 2 is not substantially altered as a result of the consultation, the text is adopted by the steering committee. This adoption takes place on the signatures from the three regulatory parties to ICH, affirming that the guideline is recommended for adoption by the regulatory bodies in the three regions.

In the event that one or more parties representing industry have strong objections to the adoption of the guideline, on the grounds that the revised draft departs substantially from the original consensus or introduces new issues, the regulatory parties may agree that the revised text should be submitted to further consultation.

Step 5: Implementation

Having reached Step 4, the tripartite harmonised text moves immediately into the final step of the process: regulatory implementation. This is carried out according to the same national/regional procedures that apply to other regulatory guidelines and requirements in the EU, Japan and the US.

Information on the regulatory action taken and implementation dates are reported back to the steering committee and published by the secretariat.

interested parties and their experts may be present and can express their views to the steering committee when topics in which they have a particular interest are discussed. The agenda for the steering committee will be arranged accordingly. In order to manage the likely numbers of attendees from interested parties during the discussion of these topics, attendance is limited to one representative in addition to their expert.

Timetable and action plan The steering committee agrees a target timetable for development of scientific consensus in the EWG for each new harmonisation topic. This does not normally exceed two years.

One of the six ICH parties is designated to nominate the rapporteur and all involved parties are asked to nominate their respective experts within a fixed time limit.

Steps in the ICH process The five-step process which proved successful for the first phase of ICH activities will be maintained with appropriate modifications to accommodate the extended EWGs. The five-step process is described in Panel 1.

Abbreviated maintenance process

The maintenance process is intended to provide a rapid, flexible way of making minor changes and revisions to existing ICH guidelines. The procedure is intended to provide results quickly and efficiently using the minimum amount of resources consistent with the achievement of a scientifically valid result. As far as possible, maintenance work should be completed via a written procedure with recourse to meetings only in exceptional cases.

Contact network for maintenance of guidelines Each of the six ICH parties has established a network of experts for dealing with maintenance issues and has identified one "maintenance contact" for each Step 5 ICH guideline or implemented agreement. These maintenance contacts, in close liaison with their respective ICH co-ordinators, are empowered to deal with all maintenance issues concerning their respective guidelines.

Co-ordinators have provided the ICH secretariat with details of the maintenance contacts for each guideline. However, the first point of contact on all maintenance issues is through the ICH co-ordinators.

Procedure: maintenance network

Once a maintenance issue has been identified a concept paper is prepared (see above under full guideline process). Any issues to be resolved are stated as clearly as possible, for example, giving details of wording to be changed and the proposed new wording. The concept paper is sent to the ICH secretariat and co-ordinators. If the co-ordinators agree that the proposal constitutes a "minor" change, the maintenance process is initiated.

The review and sign-off procedure is as follows:

- The secretariat registers the maintenance proposal, designates a code number, and prepares a draft sign-off sheet identifying the proposed changes to the guideline. This is attached to the concept paper and sent to the maintenance network via the ICH co-ordinators.
- The steering committee members and observers are informed about the proposal.
- The maintenance contact from the sponsoring party (ie, the party proving the concept paper) acts as topic co-ordinator and is responsible for circulating comments and further proposals as necessary.
- After regional or internal consultation, each of the maintenance contacts indicates whether there can be agreement with the proposal made. Minor changes to the wording may be proposed.
- If agreement cannot be reached, the matter is referred to the next steering committee for a decision on establishing an expert working group and initiating the full ICH process (as described above).
- If there is agreement by all experts, the completed sign off sheet is returned to the ICH secretariat. The secretariat then circulates the signed-off proposal to the steering committee, with a request to respond within a month.

Procedure: steering committee When the steering committee receives notification that a proposal for an amendment to an ICH guideline has been agreed by the maintenance network, each party is asked to give their opinion on whether the proposal is accepted and can be implemented immediately, without further consultation. If it can, the secretariat updates and circulates the text of the ICH guideline to the steering committee and maintenance contacts. The revised text is announced and published.

Alternatively, the proposal may be accepted but with the proviso that it requires wider consultation. In such a case, it is treated as a "step 2" document (see Panel 1) for formal regulatory consultation, in accordance with the procedures set out under the full guideline process (see above). The secretariat has to obtain signatures for all six parties on the "step 2" consultation document, after which the consultation will be announced following normal procedures.

Finally, it may be decided that there are further issues to be resolved and the matter is then sent for discussion at the next steering committee. To achieve this, the secretariat informs the maintenance contacts, and the item is included on the steering committee agenda.

ICH guidelines

ICH topics are divided into four major categories (quality, safety, efficacy and multidisciplinary), and ICH topic codes are assigned according to these categories.

Quality Quality ("Q") topics are those relating to chemical and pharmaceutical quality assurance. These include Q1 — stability test-

ing, Q3 — impurity testing, Q5 — quality of biotechnological products, and Q7 — good manufacturing practices.

Safety Safety topics ("S") are those relating to *in vitro* and *in vivo* pre-clinical studies. Examples include S1 — carcinogenicity testing, S2 — genotoxicity testing, S5 — reproductive toxicology, and S7 — pharmacology studies.

Efficacy Efficacy topics ("E") are those relating to clinical studies in human subjects. Examples include E4 — dose response studies, carcinogenicity testing, E5 — ethnic factors, E6 — good clinical practices, and E7 — clinical trials.

Multidisciplinary Multidisciplinary topics ("M") are those that do not fit uniquely into one of the above categories. The multidisciplinary topics considered by ICH are M1 — medical terminology, M2 — electronic standards for transmission of regulatory information (ESTRI), M3 — timing of pre-clinical studies in relation to clinical trials, and M4 — the common technical document.

The ESTRI project includes the verification of procedures for consistent, accurate transfer of information; the evaluation of encryption technologies and key certification procedures for the transfer of regulatory information. The working group has undertaken test projects to define logical electronic communication standards to ensure the integrity of information and data exchange between pharmaceutical companies and authorities. Tests have also been conducted which involve transferring encrypted and non-encrypted files between a limited number of international centres.

Recommendations have been made on the implementation for electronic standards for the transfer of regulatory information and data (ESTRI), the core standard set, physical media (floppy disks and CD-ROM), network messaging, secure EDI transmission over the internet and electronic document and message formats.

Conclusion

The harmonisation process has been ongoing for some 15 years and has enabled companies and regulatory authorities to both produce largely one set of data for a marketing authorisation application and to give greater confidence to all regulatory authorities that the data submitted would be acceptable to all parties to the agreement. The logistical issues solved by the introduction of the common technical document have also enhanced this process.

By inference, it has also ensured that any authority outside the original tripartite agreement can have confidence in the same data that it, too, has to evaluate in order to bring novel and innovative products to its citizens. Overall the ability to bring new products to the market on a global basis has been greatly enhanced by the ICH process.