



Harmonization I

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The harmonization process of ICH Dr Yoshikazu Hayashi, Japan

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals (ICH) was established in 1990 as a joint initiative of the United States of America, the European Union and Japan, based on an idea raised at an ICDRA meeting. These three regions account for more than 90% of all new drug development in the world. The main purpose of ICH is to eliminate duplication of work and procedures caused by different regulatory requirements, to cut down on waste of resources, and to give timely access to safe, effective and good quality new drugs.

ICH is a scientific forum rather than a forum for global politics or trade negotiations. ICH is the conference on innovative drug products. ICH guidelines, which specify “how to collect data scientifically for marketing authorization”, are not mandatory, and their application thus depends on the commitment of the ICH parties.

The guidelines are produced through expert working groups (EWG) and steering committees (SC). First, experts are selected for an EWG, which prepares a rough draft guideline. The draft is considered by a steering committee before being released to the public for comments. The regulatory authorities consolidate the comments and return them to the EWG, which modifies the draft guideline accordingly. The final draft is adopted by the SC and implemented through the regulatory systems in the three regions. If a guideline is not self-explanatory, seminars or workshops may be conducted.

European contribution to a global approach to regulation

Dr Ramón Palop, Spain

The ICH requirements on registration of pharmaceutical products represent important initiatives that can lead to a reduction in costs. However, ICH has made it more difficult for countries that do not participate in the Conference to make decisions that are substantially different from those adopted by the ICH.

There are many European directives on the regulation of medicines, the most significant being Directive 93/39, which ensures mutual recognition of medication, and Regulation 2309 of the Council of Europe, which led to the establishment of the European Agency for Evaluation of Medicines.

Pharmacovigilance

There have been a number of major efforts to harmonize pharmacovigilance activities. Pharmacovigilance can be divided into risk analysis and risk management. Risk analysis includes identification of risk, quantification, and evaluation of social impact. To date, the focus of harmonization has been on the first stage of risk analysis, i.e. identification of risk. Risk identification seeks to generate a number of signals as soon as possible, by various means, e.g. through pharmaceutical laboratories, regional or national centres for monitoring of adverse drug reactions, and scientific publications. All this information is collected in national, international and regional databases, to allow generation and exchange of information among participating agencies. Once the data have been analysed, a number of actions could be taken to manage the risk, e.g. by adopting appropriate administrative measures, communicating information about the risk to health care providers and patients, and establishing specific prevention strategies.

In 1995, Europe established a system for exchange of information on suspected adverse drug reactions within 15 days. However, it was soon recognized that speedier exchange was needed; the Euroscape methodology was therefore introduced aimed at standardizing the electronic exchange of information on suspected adverse drug

reactions, regardless of origin, destination, or drug approval period. Messages can be sent from and to drug regulatory agencies, industry and WHO.

For efficient electronic transmission, data and terminology need to be standardized. This led to the development of MedDRA, a unique terminology which industry and the regulatory authorities can use for entry, retrieval and evaluation of data. A pilot project is currently under way, aiming to incorporate MedDRA into electronic submission of data, in order to decrease administration in the different agencies responsible for pharmacovigilance within the European Union.

Regulatory agencies should promote the development and maintenance of other sources of information, such as drug-related registries of disease and follow-up of specific drug-exposed populations. These should help in risk identification.

The aim of risk quantification is to confirm or refute the causal relationship. It also indicates the strength of the association between the drug and the adverse reaction, thus allowing an estimation of the public health impact. Often epidemiological studies cannot be done because of lack of time, resources or sources of information. It is therefore important to carry out monitoring in the early postmarketing phase when exposure is still low. To quantify risk, it is also necessary to keep permanent disease registries, follow up exposed populations and keep automated databases.

Much work on evaluation and risk management is still to be done. The development of measures for prevention of risk and analysis of impact of action requires greater cooperation among agencies. It is incumbent on us to implement good management practices that will allow national agencies, WHO and the pharmaceutical industry to have access to all the information necessary to protect human health with greater transparency.

The harmonization process of ICH — philosophy, process and future

Dr Yasunori Tsuruta, Japan

Much has been achieved by ICH so far, including some 40 technical guidelines on quality, safety, and efficacy, which provide the scientific basis for the testing and evaluation of new drugs. Since the fourth Conference, ICH has moved to more regulatory aspects, e.g. the Common Technical Document (CTD), MedDRA, gene technology, and establishing the Global Cooperation Group to offer direct assistance to non-ICH countries.

The ICH guidelines have contributed to the timely introduction of new products in Japan. ICH triggers changes in the regulatory environment in each region, allowing science-based discussion with industry and drug regulatory agencies. The improved quality of the data included in new drug applications after the implementation of ICH GCP and ICH E5 (concerning ethnic factors) means that the data are more widely acceptable, regardless of their origin. This facilitates acceptance of foreign clinical data.

The tighter control of clinical trials has implications for resources, including research funds, human resources, etc., and for incentives to perform such trials in Japan. ICH E5 was implemented in Japan in 1998, replacing the former guideline which required clinical trials to be performed in Japan for submissions for new drug applications.

ICH E5 will potentially allow more scope for clinical trials to be conducted in other parts of the world, by allowing a bridging study where data are available from foreign clinical trials. In Japan, the Ministry of Health and Welfare developed a system of consultation to facilitate such a study. Although still at an early stage, experience with bridging studies is gradually being accumulated.

The Common Technical Document is another notable achievement of ICH. NDA submissions should conform to CTD requirements, in order to improve communication among regulators.

With synchronized submission review, it is expected that synchronized approval of new drugs by the three regions will be achieved. Synchronized launch of new drugs may imply a wider exposure to new drugs in a short period of time. Regulators and industries should work together on mechanisms to ensure a safe roll-out of new drugs and early detection of adverse reactions.

It is of utmost importance for ICH to maintain its current momentum and to take initiatives on newly emerging issues in order to ensure timely access to new drugs for patients around the world, and to cope with the changing environment.

Impact of ICH on non-ICH countries

Dr Vesna Koblar, Slovenia

Harmonization of registration requirements leads to reduced replication of drug trials and shorter registration procedures, while maintaining the quality, safety, and efficacy of pharmaceutical products. The ICH initiative was started in 17 high-income countries, but it also has an impact on non-ICH countries, which account for 85% of the world's population. Application of measures for public health protection in these areas is related partly to their affordability.

Although ICH was not initially intended as a worldwide cooperative effort, global standardization is an inevitable consequence of ICH. For this reason, a steering committee was established by the ICH Global Cooperation Group to make information available to non-ICH countries, seek their comments on and acceptance of ICH guidelines, and thereby expand the ICH idea.

Although the common ambition of ICH and non-ICH countries is the same, there are differences between the two groups, notably in the role of essential (generic) drugs, in the concept of satisfactory levels of quality, safety, and efficacy, and in what is affordable. Public health is the first concern in non-ICH countries, where the level of technical standards has to be justified by public health needs, not by the state-of-the-art technology.

The concerns of non-ICH countries include the need for harmonized standards of quality, safety, and efficacy, and appropriate regulatory requirements, rather than global application of ICH standards, which might be too high for local industry, leading to withdrawal of products with consequent negative effects on public health. In some countries, withdrawals could have a greater public health impact than acceptance of a drug that does not meet ICH standards. On the other hand, accepting a lower standard may lead to differences in regulatory approach, double standards for quality, safety and efficacy, and double standards for public health protection.

The solution may be harmonized regulatory standards that are applicable to developed and developing countries, perhaps with WHO collaboration. The alternative is to have a double regulatory standard, one for the rich, one for the less rich.

In conclusion, if the harmonized ICH regulatory requirements are to have a positive impact on non-ICH members, they should establish the same standards of quality, safety, and efficacy, improve drug availability, avoid repetition of trials, save resources and improve public health protection. They should promote the introduction of standards of quality, safety, and efficacy based on public health need rather than state-of-the-art technology. The approach should be reviewed by a coordinator for its global applicability, with a view to protection of public health.

ICH — its value to a first-line medicines regulator

Dr Terry Slater, Australia

The Therapeutic Goods Administration (TGA) of Australia is a first-line regulator doing full evaluation of all applications for new medicines. TGA adopts the European standards unless there is a need for a unique Australian standard. Australia encourages the conduct of clinical trials, although the data required for review do not have to be drawn from Australian trials.

Australia is committed to international harmonization. The current Global Harmonization Task Force on Medical Devices is chaired by Australia, and Australia has also held the presidency of the

Pharmaceutical Inspection Cooperation Scheme (PIC/S). Australia has adopted many ICH guidelines; but some guidelines have not been adopted because they are not administratively relevant in Australia. Australia develops its own standards only when there is a specific public health need domestically, or where the EU or USA standards do not meet the public health need in that area. Australia's adoption of global ICH standards means that Australia is able to contribute to global drug development.

ICH guidelines have been used by industry and by the authorities and are of benefit to both. Benefits to industry include decreased time and cost for drug development and a better predictability of outcome. However, the guidelines do impose difficulties on small and new companies.

For the industry and the community, ICH means earlier access to safe and effective products. However, because of the limited coverage of the guidelines, many countries need to consider what factors are important locally, e.g. public health need, special climatic conditions, etc. ICH offers much and delivers much but its full value will only be realized when there is a greater focus on protecting public health.

In conclusion, ICH does not imply individual countries giving up sovereignty over decisions on which products are to be marketed. The acceptance of guidelines in principle does not mean harmonization of drug evaluation or evaluation outcome. Neither does ICH imply mutual recognition of drug evaluation. ICH is not the basis for creating a single decision-maker on whether a drug is safe and effective for the purpose and should be allowed on the entire world market.

Recommendations

1. WHO should continue involvement in the ICH Steering Committee, adopting a more proactive role by proposing topics for guideline development and expressing opinions on the potential public health implications of the guidelines proposed by ICH.

2. In the light of the wide range of regulatory environments, WHO should support non-ICH Member States and regional harmonization initiatives by evaluating the usefulness, feasibility and impact of implementing ICH guidelines.
3. WHO should continue to produce briefing notes on ICH meetings for regulatory officials of non-ICH countries and consider ways of making them widely available, including use of the Internet.
4. In order to improve access to essential drugs of good quality, especially in developing countries, WHO should assess the benefits and risks to public health of implementing selected ICH drug quality guidelines on manufacturing standards for generic products in non-ICH countries, and intensify its efforts to develop international standards and guidelines for the regulatory assessment of generic products. WHO should offer specific advice to national authorities in non-ICH countries.
5. Progress should be reported back to the ICDRA.