

# ICH Guidelines—Implementation of the 3Rs (Refinement, Reduction, and Replacement): Incorporating Best Scientific Practices into the Regulatory Process

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## Abstract

An overview of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is described. ICH was established through cooperation of the regulatory agencies and industrial parties of three main regions involved in pharmaceuticals: the European Union, the United States, and Japan. The purpose of the ICH is to make recommendations to achieve greater harmonization regarding interpretation and application of technical guidelines and requirements for product registration in an effort to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. The main purpose of ICH was not to foster the 3Rs per se; however, harmonization of guidelines has eliminated duplications of similar tests to satisfy the specific requirements of each region. The ICH process has contributed to mutual understanding of the regulatory requirements and has decreased the number of unnecessary animal experiments. Specific examples of the contributions of ICH harmonization to the 3Rs are described.

**Key Words:** 3Rs; drug development; International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH); ICH guidelines; pharmaceutical industry; regulatory agencies; safety and efficacy testing

## Introduction

During the 1960s and 1970s, there was a rapid increase in regulatory requirements for evaluating the safety, quality, and efficacy of new medicinal products. Even though the purposes of regulations were the same, the technical requirements varied between regulatory authorities to such an extent that industry found it necessary to duplicate many time-consuming and expensive tests to market new products internationally.

Economic risks exist in drug development. The rate of attrition for new drug development has been estimated to be as high as 1:5,000-10,000 (Lumley and Walker 1992). Both the time and costs needed for drug development increased dramatically during the 1960s and 1970s. These factors

have prompted both regulators and industry to begin to make an effort to work together for efficient drug development. Most new pharmaceuticals are developed in the European Union, the United States, and Japan. For this reason, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH<sup>1</sup>) was organized through the cooperation of regulatory and industrial parties in these regions (ICH Home Page: <<http://www.ifpma.org/ich5s.html>>).

## ICH Purpose

The purpose of the ICH is to “make recommendations on ways to achieve greater harmonization on the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines.” From the beginning, the ICH intended to prepare harmonized guidelines/guidances, or internationally accepted common texts for the development of new pharmaceuticals. Harmonization was viewed as a means of promoting efficient drug development by elimination of unnecessary duplication and by indicating rational drug developing procedures.

The ICH brought together representatives from regulatory authorities and experts from the pharmaceutical industry and academia in Europe, Japan, and the United States. They discussed scientific and technical aspects of product registration of pharmaceuticals for human use as equal partners as well as details of the testing procedures required to ensure the assessment of safety, quality, and efficacy of medicines and regulatory obligations to protect public health. Discussions on the safety and efficacy issues were based on the scientific experience of drug developments and on the current scientific knowledge.

## ICH Structure

The ICH is composed of the following components: Steering Committee, ICH Secretariat, Observers, and Expert

<sup>1</sup>Abbreviations used in this presentation: 3Rs, refinement, reduction, and replacement of animals in research and testing; EWG, expert working group; ICH, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; LD<sub>50</sub>, single lethal dose of a substance that kills half the animals in a test group value; MHLW, Japanese Ministry of Health, Labour, and Welfare.

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Working Group (EWG<sup>1</sup>). The Steering Committee oversees the harmonization activities. Each of the six cosponsors appoints an ICH Coordinator to act as the main contact point with the ICH Secretariat. They ensure that ICH documents are distributed to the appropriate contact persons within the area of their responsibility. The EWG includes subject experts who are nominated by both regulatory authorities and industry associations of the three regions.

The ICH receives support from the following organizations: In the European Union, the European Agency for the Evaluation of Medicinal Products (EMA) and the European Federation of Pharmaceutical Industries' Associations (EFPIA) represent both regulatory agencies and industry associations, respectively; in the United States, the Food and Drug Administration (FDA) and Pharmaceutical Research and Manufacturers of America (PhRMA) are included; and in Japan, the Ministry of Health, Labour, and Welfare (MHLW<sup>1</sup>) and the Japan Pharmaceutical Manufacturers Association (JPMA) are the respective organizations. In addition, the World Health Organization (WHO), the European Free Trade Area (EFTA), and Health Canada participate in the ICH as Observers on the Steering Committee. The International Federation of Pharmaceutical Manufacturers Association (IFPMA) serves as Secretariat.

## Topical Areas

ICH topics are divided into Quality, Safety (nonclinical safety studies), Clinical Efficacy, and Multidisciplinary areas. Quality includes issues relating to chemical and pharmaceutical quality assurance. Safety includes issues relating to in vitro and in vivo nonclinical safety studies. Efficacy includes matters relating to clinical studies in humans. The Multidisciplinary area addresses cross-cutting topics that do not fit uniquely into one of the above categories.

Topics in the Safety area addressed to date include carcinogenicity (S1), genotoxicity (S2), toxicokinetics and pharmacokinetics (S3), single and repeat-dose toxicity studies (S4), reproductive toxicology (S5), safety studies for biotechnological products (S6), safety pharmacology studies (S7), and timing of toxicity studies in relation to clinical studies (M3).

## Procedure for Harmonization

As a first step, representatives clarify the differences in the individual test guidelines used by the countries in each region and/or the difference in their application, the background of the difference, and the issues to be solved in the present guidelines. They then work together to distinguish the differences.

When one or several parties propose topics, the Steering Committee evaluates the need for the ICH to prepare or revise guidelines within that particular subject area. If the issues are adopted, an EWG is organized and a rapporteur is

nominated. The EWG discusses the issues and prepares the step I draft guidance. If this step is adopted by the Steering Committee, the draft will be distributed to three regions for comment as step II draft guidelines. After several months, the EWG discusses the comments and prepares step III guidelines. This document is discussed and endorsed by the Steering Committee as step IV guidelines. Each regulatory authority has an obligation to implement the guideline within each regulatory process.

## Conferences and Outputs

Since the establishment of the ICH, a total of 46 new ICH guidelines or guidances and five amendments or modifications of ICH guidelines have been made. The time needed for harmonization differs depending on the topic. If there are no large obstacles, harmonization is achieved in approximately 2 yr after establishment of an EWG.

## Contribution to Refinement, Reduction, and Replacement (3Rs<sup>1</sup>)

The main purpose of the ICH was not to foster the 3Rs per se; however, it has contributed significantly in this area. Harmonization of the guidelines eliminated duplications of similar animal tests to satisfy the specific requirement of each region. The presence of internationally accepted guidelines also supports decision making for drug development and has the tendency to decrease the conduct of unnecessary animal experiments. The ICH process has also contributed to mutual understanding for the regulatory requirements. Specific contributions of ICH harmonization to the 3Rs are described as follows:

1. There are instances, for example, in which toxicity evaluation of metabolites are needed; however, no clear understanding existed as to which metabolites should be tested. Many cases have existed in which toxicity tests have been conducted for the metabolites that essentially had already been fully evaluated by animal experiments of parent compounds. The cases in which toxicity studies of pharmaceutical metabolites are needed were defined in the first ICH congress in Brussels in 1991. The Japanese Ministry of Health and Welfare (now MHLW) defined cases in which additional toxicity studies of metabolites are required (Ohno 1992). These cases include (a) the existence of metabolites that are unique to humans; (b) instances in which much higher concentrations of specific metabolites are found in human blood than in experimental animals used in toxicity studies; and (c) where there is the formation of toxicologically or pharmacologically significant metabolites.
2. Before this ICH discussion, protocols of Japanese guidelines for single dose toxicity studies were revised to decrease the number of rodent species from two to

one and the number of animals used for the determination of lethal dose. The single dose toxicity study using a nonrodent species does not require high doses that cause severe toxic symptoms. Those changes were made clear at the ICH congress and clarified the Japanese regulations for all involved parties.

3. It is possible to replace the single lethal dose of a substance that kills half the animals in a test group value ( $LD_{50}^1$ ) in rodent or nonrodents by well-designed single dose administration, increasing dose tolerance studies involving either two rodent species or one rodent and one nonrodent species (Hayashi and Perry 1992). These authors indicated that the tests that replace the determination of the  $LD_{50}$  have a testing protocol that uses the fewest number of animals possible for the approximation of the highest nonlethal or the lowest lethal dose. In other words, preliminary dose setting studies for repeated dose toxicity studies in rodents appear to fulfill the requirement for determination of lethal dose.
4. Chronic toxicity studies (12-mo repeated dose toxicity studies) in rodents (Hayashi and Perry 1992) and in nonrodents (ICH S4 1998) have been replaced with 6- and 9-mo studies, respectively. This harmonization decreased the number of rodents by more than 80 for toxicity evaluation of pharmaceuticals with an intended therapeutic use of longer than 1 mo. In the case of the 9-mo nonrodent study, it could be started without 6-mo studies, thereby reducing the number of animals by more than 24.
5. In 1997, the ICH reduced the number of rodent species required for carcinogenicity testing from two to one, with the addition of an alternative study. Short-term alternatives, such as *in vivo* carcinogenicity studies using transgenic mice or partially hepatectomized rats, can be used instead of a second species in some testing situations. When such an alternative study is used, the number of animals needed is much less compared with the usual carcinogenicity study.
6. The guideline on "nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals" specifies the timing of each safety study in relation to the clinical trials without increasing the risk of volunteers (ICH M3 1997). Persons engaged in the decision making for clinical trials prefer to have as much toxicity data as possible. In fact, this preference may lead to toxicity testing to support each clinical trial in excess of the requirements to secure the safety of the volunteers. This guideline indicated only the standard timing of conducting nonclinical testing for ordinary drug substances. However, it would help to decide what kinds of extra toxicity tests are needed or what kinds of toxicity tests can be omitted for each candidate drug before the various steps of clinical trials. The existence of internationally accepted criteria helps to obtain consensus from institutional review boards sooner and promotes earlier decision making for further development of new drugs. Earlier decision making leads to a decrease in animal

toxicity studies conducted because many drug candidates withdraw from further development after early clinical trials.

The duration of repeated dose toxicity studies before conducting the preliminary clinical trials in Japan, and for the evaluation of effects on male reproductive organs, has been decreased from 4 to 2 wk (ICH S5B 2000; ICH M3 2000). This change also leads to earlier decision making regarding the need for animal toxicity or efficacy studies for further drug development (as described above).

## Example of the ICH Guidelines Revision

The 2-wk repeated dose toxicity study in rodents had been considered sufficient to support initial clinical trials in the European Union and the United States. However, 4-wk studies had been required in Japan before initial clinical trials of new drug candidates because 2-wk study data had been considered insufficient for detecting the toxic effects of the drug on male reproductive organs. As a result, toxicologists in MHW and JPMA conducted a validation study of a 2-wk repeated dose study for the assessment of toxicity on male reproductive organs (Sakai et al. 2000).

A total of 24 test substances covering most of the classes of testicular toxicants were used. Outcomes from 2- and 4-wk repeated dose studies were compared. The results of the validation study indicated that for most of the chemicals, toxicity on male reproductive organs could be detected by measuring organ weights and conducting traditional pathological examinations. However, if detailed sperm analysis were also included, the 2-wk study had equivalent potential to the 4-wk study for detecting the toxicity on male reproductive organs. As a result of this validation study, revisions were made to the corresponding ICH (S5B and M3) guidelines (2000).

## Conclusion

Even though many experimental animals are sometimes needed to assure the scientific validity of new ICH guidelines, the ICH has contributed much to decrease animal use through harmonization of technical requirements needed for new drug registration.

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