

# VALUE & BENEFITS

The Value and Benefits of ICH to Industry

International Conference on  
Harmonisation of Technical  
Requirements for Registration of  
Pharmaceuticals for Human Use

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Japanese Pharmaceutical Manufacturers Association (JPMA)  
and PhRMA) which have been involved in ICH

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## 1.0 Executive Summary

*The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use—ICH*—is a unique project that was established in 1990. Bringing together the regulatory authorities of the European Union, Japan and the United States and experts from the pharmaceutical industry in these three regions, ICH aims to produce a single set of technical requirements for the registration of new drug products, and hence to streamline the development process.

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Since the inception of ICH 37 guidelines covering Efficacy, Quality and Safety topics in both the traditional pharmaceutical sector and the burgeoning biotechnology sector have been produced and are being implemented. The latest survey data<sup>1</sup> shows that the guidelines have reduced research duplication. Work is ongoing in the ICH organization both on the maintenance of the current guidelines and development of new guidelines, including the Common Technical Document and its electronic version. This guideline is set to revolutionize the submission procedure for regulatory staff in industry. It will afford significant time and resource savings as complex multiple submissions will be replaced by a single technical dossier to be submitted in the three regions, facilitating simultaneous submission, approval and launch of new drugs. At the same time the ICH organization is turning its sights to the dissemination of information on its guidelines to other countries, yielding additional benefits to both regulators and industry.

ICH, through its activities in the harmonization of regulatory requirements across the EU, Japan and US, is enabling industry to reduce development times by removing the duplication of studies that was previously required to gain market approval for a new drug in each of the three regions. This directly affects the bottom line through reduced development times and regulatory review times. ICH clearly enhances the competitive position of those companies that choose to operate using its standards, as well as significantly benefiting both the regulators and the patients, who, most importantly, receive crucial new treatments sooner.

Industry has three compelling reasons to support ICH and its continued efforts to further harmonize the technical requirements for the registration of innovative drugs:

- reduced development times and resources, including an end to duplicate clinical trials due to ethnicity differences
- easier simultaneous launch of a new drug in many countries (including across the three ICH regions)
- ICH guidelines—as a recognized standard— will facilitate intra-company globalization

In summary, harmonization through ICH brings important, life-saving treatments to patients faster, while releasing the pharmaceutical companies' development funds to projects that will produce the ground-breaking treatments of the future.

## 2.0 ICH—An Overview

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The establishment of ICH in 1990 was driven by a very simple principle—that the essence of rational drug development is to ask key questions and answer them with appropriate studies, and that is essential to be able to demonstrate safety, efficacy and quality to competent authorities with confidence (and is, of course, a legal requirement in all significant markets.) When the drug development activity is reduced to these fundamentals, the next logical step is to recognize that by considering the scientific principles and the technical requirements of drug development, and applying best practice and good science, scientists and regulators should be able to determine a common set of requirements that should be met to allow a new drug to be brought to the market.

ICH, then, is a unique project. It brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.<sup>2</sup> The purpose is to achieve greater harmonization in 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.

The objective of such harmonization, as stated by ICH, is a more efficient use of human, animal and material resources, and the elimination of unnecessary and unreasonable delay in the global development and availability of new medicines while maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health.

The ICH organization is administered by the ICH Steering Committee which is supported by the ICH Secretariat. Since ICH was established, each of the six co-sponsors has had two seats on the ICH Steering Committee (SC) which oversees the harmonization activities. The International Federation of Pharmaceutical Manufacturers Associations (IFPMA) provides the Secretariat and participates as a non-voting member of the Steering Committee. While the harmonization initiative relates specifically to the EU, Japan and the US (as new drug development is concentrated almost exclusively in these regions), it is recognized that other parties have a significant interest in the procedure. For this reason the World Health Organization (WHO), the Therapeutic Products Programme, Health Canada, and the European Free Trade Association (EFTA) have been invited to nominate Observers to attend the ICH Steering Committee Meetings and Expert Working Groups (EWGs). The generics industry, OTC industry and pharmacopoeial authorities have also been invited to send representatives to some of the EWGs.

The Steering Committee is advised on the technical aspects of harmonization topics by Expert Working Groups. These are joint regulatory / industry bodies, comprised of experts nominated by each of the six co-sponsors, that deal with the individual harmonization topics. Topics are grouped under the general headings of “Efficacy” (clinical testing programs and safety monitoring), “Quality” (pharmaceutical development and specifications), “Safety” (pre-clinical

toxicity and related tests) and “Multidisciplinary” (topics impacting more than one area, such as regulatory communications, including electronic communication, timing of toxicity studies in relation to clinical studies, and the Common Technical Document (CTD)).

The objective of this work is to produce harmonized tripartite guidelines that are adopted by the regulatory agencies in the three regions. Thus far 37 such guidelines have been produced,<sup>3</sup> and are currently being implemented by the regulatory agencies. The implementation and utilization of the guidelines has been monitored by periodic ICH surveys that have shown a consistent increase in utilization as penetration increases over time.<sup>1</sup> It is probably appropriate now to consider the work that has been completed and what is on-going in each technical area, and its implications for global drug development.

## 2.1 Efficacy

The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. With clinical trials being arguably the most complex, costly, time consuming and resource intensive aspect of any drug development program, it is perhaps in this area that the pharmaceutical industry is feeling the most significant impact from the outcome of ICH. To date, the ICH EWGs in the efficacy area have produced 11 finalized guidelines (see Appendix, section 6.1), which are currently being implemented by the authorities in the participating regions. Another 3 guidelines are at, or are approaching the stage of a first draft which will be issued for wider consultation. Efficacy also plays a key part in the work on the Multidisciplinary topics, and has resulted to date in one guideline which is currently in the implementation phase.

### 2.1.1 The Impact of ICH (Efficacy) on Industry

While all 11 efficacy guidelines issued thus far address significant issues in the area of clinical trials, one guideline is of particular importance to the industry. Until the introduction of the guideline “Ethnic Factors in the Acceptability of Foreign Clinical Data” (E5) in February 1998, and its subsequent implementation by the regulatory agencies of the three regions, repeat clinical trials were a fact of life in drug development if a company wished to market a drug in more than one region. This costly and time consuming activity, frequently involving the repeat of long, resource intensive Phase III clinical trials, is obviated in most cases by the introduction of this guideline. When the guidance on the influence of ethnic factors is followed, and the trials are run in accordance with the principles of GCP laid down in the ICH guideline “Good Clinical Practice: Consolidated Guideline” (E6), foreign clinical trial data may be submitted in support of a submission in any ICH region. Less than a year after the guideline was finalized Pfizer was able to apply it to great effect to gain approval of Viagra® in Japan by use of a bridging study (a key part of the E5 guideline), rather than a repeated clinical trial(s) as would have been required previously.

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“Participation in ICH has focused FDA’s attention on the organization, consistency, and scientific quality of our regulatory recommendations.”

Janet Woodcock, MD

*Director, Center for Drug Evaluation and Research, FDA*

“At Pfizer we’ve been able to use high quality data collected under GCP guidelines in one region of the world to facilitate marketing approval in another region. That gets products to patients more quickly. In the case of Viagra®, for example, we did not have to repeat Phase III trials in Japan. Every pharmaceutical company benefits from ICH—and patients benefit the most.”

Dr John Niblack

*Executive Vice-President, Pfizer*

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“The ICH harmonisation process has not only promoted a much more harmonious and productive relationship between MHW and companies of all the three ICH regions, but helped to improve access of innovative new drugs to patients, as intended, through the effective use of clinical data across the three regions. I hope ICH will continue to work to the benefit of patients worldwide by rationalising new drug review on the common scientific basis reached by ICH.”

Dr Osamu Doi  
*Councillor for Pharmaceutical and Medical Safety, Minister's Secretariat, MHW*

The importance of the two major guidelines that underpin E5 (Ethnic Factors) should not, however, be ignored. The GCP guideline finalized in May 1996 means that clinical trials are conducted according to the same rigorous standards in all three ICH regions, thus facilitating the implementation of E5 (Ethnic Factors) principles. This guideline (E6) is widely considered to be one the major achievements of the early phase of ICH, and, importantly, the consideration that was given to other major national and international GCP guidelines during the preparation of the ICH GCP guideline may also lead to its acceptance as an international standard. It is already one of the few guidelines that has led to regulatory change in the three ICH regions. Furthermore, the guideline “General Considerations for Clinical Trials” (E8), finalized in July 1997, provides a set of internationally accepted principles to be applied to trial design, further aiding the acceptance of data throughout the three regions.

Other key guidelines in the clinical area have been E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting) and E3 (Structure and Content of Clinical Study Reports). E2A led to a harmonization of expedited reporting in the three regions, defining when clinical study reports are required and the amount of detail they should contain. The guideline also ensured that reporting times are measured in calendar days rather than working days, as had been the case in some regions. These changes have resulted in a significant simplification of this type of reporting across the three regions. The guideline also led to a change in the relevant regulations. E3 (Clinical Study Reports), like E6 (GCP), was one of the major accomplishments of the early ICH process, establishing a common format for clinical study reports. This common presentation has made preparing multiple regulatory submissions a far simpler process as a single core document (with appendices) may be used in all three ICH regions. In fact, this guideline has now provided the basic framework for the CTD (Efficacy section).

If the ICH Global Cooperation Group (launched in March 1999) can achieve, by making information available and accessible, a wider international understanding and acceptance of the efficacy guidelines, access to emerging markets such as Asia and Latin America will become much easier, and new drugs should be available in this region faster than under existing conditions. Such markets are becoming increasingly important in the global economy, with the Asian market alone predicted to become 15-20% of global pharmaceutical sales.

Perhaps one of the most important outcomes of the harmonization work in the efficacy area, as well as the recognized reduction in time and resources used in a development program, is that the unified operating practices enhanced patient safety in the clinical trials process.

Already in the 1997 ICH Utilization Survey, when only seven Efficacy guidelines were available (and neither E5 or E8 had been finalized), industry was using the guidelines on an average of 74% of the time. By region, the EU had 62% utilization, Japan 77% utilization and the US had 85% utilization. Responses were extremely favorable, and indicated that the guidelines had a



positive impact on drug development programs. Some respondents noted that the availability of an international set of guidelines had facilitated the establishment of procedures across the global organization, particularly for clinical study protocols and reports. The ability of these guidelines to facilitate intra-company globalization is an important facet of ICH. The existence of a set of international harmonized guidelines is speeding intra-company globalization and easing the problems typically associated with such a process, as the content of such internal procedures is now largely defined by ICH guidelines. This will continue to be the case as ICH produces guidelines in areas such as the Common Technical Document.

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Respondents to the 1997 ICH Survey also indicated that in the Efficacy area there had been few issues with the regulatory agencies regarding the use of the guidelines, and that in following them there was general compliance with national regulations across the three regions. The survey found that research duplication was still occurring to some degree, but improvements were very evident.

## 2.2 Quality

The fourteen Quality guidelines that have been produced by ICH for implementation (see Appendix, section 6.1) in each of the ICH regions have been concerned with stability, specifications, and analytical methods validation. Five of these guidelines specifically addressed some of the issues with the quality, evaluation and specifications of biotechnological products, reflecting that biotechnology is a significant growth area for the industry.

Three guidelines are currently being revised, and a fourth is in the ICH maintenance process for minor amendments as part of a commitment by ICH to revise and improve the guidelines necessary. Furthermore, a guideline on Specifications for Chemical Products (Q6A) has recently been finalized, and a draft guideline on Good Manufacturing Practice for Active Pharmaceutical Ingredients (Q7) is soon to be released for regulatory consultation. Both of these address major areas where currently there is no industry harmonization or consensus.

### 2.2.1 The Impact of ICH (Quality) on Industry

The ICH guidelines in the Quality area have provided recommendations in two of the key areas that define bulk drug and drug product quality—stability data and impurities—and led to a significant reduction in duplicate testing. Prior to these guidelines there was no harmonized approach to the data requirements in these areas. With stability for example, it was typical to run studies at “room temperature” as defined by the company concerned, and appropriate to the locality. There was also no humidity control. This resulted in registrations in different regions requiring new stability data if the climatic zone was different to that where the original study had been conducted. ICH harmonization provided standard sets of conditions taking account of the climatic zones in each of the three regions. This means that the information

“The ICH reforms are only part of the process. It is equally important to ensure that regulatory authority staff consistently apply the ICH guidelines. Without consistent application by the regulators, the potential benefits of ICH will be greatly diminished.”

Sir Richard Sykes  
*Chairman, Glaxo Wellcome*

on stability generated in any one of the three regions is mutually acceptable in the other two areas, provided it meets the requirements of the guideline. **This removed the requirement for, and expense of, duplicate testing that had previously existed.**

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“As a result of the ICH process, it is of immense help for companies to know much more clearly, from the very beginning, what European and Japanese regulatory agencies are expecting and will accept in a new drug dossier.”

Dr Peter Corr  
*President,*

*Parke-Davis Pharmaceutical R&D*

It should also be possible for stability harmonization to positively affect the post-approval arena. Currently the majority of post-approval work in the pharmaceutical industry and by regulatory reviewers is due to variations to marketing authorizations, of which *ca* 50% is CMC (Chemistry, Manufacturing and Controls) related—ie manufacturing and packaging. This results because such changes require additional stability data. At present the requirements for stability data to support these changes are determined by differing national regulations, and typically exceed what should be required if scientific arguments are applied. Harmonization of these requirements across the three ICH regions could remove this testing burden from the pharmaceutical companies. This topic has been included in a review of the stability guidelines that commenced earlier this year, although it is not likely to be considered until the end of the review process.

The impurities guidelines (Impurities in New Drug Substances (Q3A), Impurities in New Drug Products (Q3B), and Impurities: Guideline for Residual Solvents (Q3C)) also served, as with the stability guidelines, to provide scientific agreement on the recording and reporting of impurity levels. Key areas that were addressed included the threshold limits for impurity qualification and impurity identification. Guidelines were also provided on how changes in impurity profile over the course of a development program should be managed. The result of this is that it should be possible to determine a single specification for any drug substance or product that is acceptable across the three ICH regions. This makes the supply chain far simpler, and minimizes supply error.

ICH has also produced a parallel set of guidelines covering the specific issues associated with biotechnological products. Standardization through the guidelines has been a very positive step for the biotechnology industry, and has certainly had a significant favorable impact on both development times and resource utilization. It is also anticipated that utilization of these guidelines will rise dramatically as the mainstream pharmaceutical industry works increasingly in this area.

Ten of the fourteen guidelines now being finalized were available at the time of the 1997 ICH Utilization Survey, although half of these had been implemented less than a year before the survey.<sup>4</sup> It should also be noted that there are certain time gaps between Step 4 and Step 5 in each region. Utilization across the three regions at the time was reported as 77%. The Survey aimed to assess whether the guidelines were causing regulatory issues, and for the Quality guidelines there were several reported instances (with a far higher incidence than either Efficacy or Safety). These issues are now being addressed in a revision of the relevant guidelines. In spite of these problems, companies found that duplication of research was reduced.

## 2.3 Safety

In the Safety area ICH has thus far produced twelve guidelines (of which one is multidisciplinary) (see Appendix, section 6.1) covering all the major types of pre-clinical toxicity testing required for the registration of an NCE. Prior to the ICH initiative industry and regulators agreed as to the types of study required as part of a registration package, but there was little agreement on study length, content, species requirements, dose selection and exposure levels to improve the risk/benefit assessment. These regional differences led to a considerable amount of repeat testing. Not only was this a waste of time and resources, but this was not a tenable position in an ethically and politically sensitive research area.

**Harmonization through the ICH guidelines has minimized requirements for repeat studies. The last ICH Utilization Survey in 1997 reported utilization of the Safety guidelines was the highest of the three areas. This suggests significant savings in both animal resources and time in animal testing in drug development programs. The international acceptability of studies with ICH study design was considerably increased.**

### 2.3.1 The Impact of ICH (Safety) on Industry

The guidelines in this area have very much represented industry's current best practice. By a careful examination of standard practice and the types of data that could be accessed from studies the EWGs in this area were able to determine what testing was necessary to examine any one type of toxicity, and thus to generate a standard battery of tests. This resulted in the guidelines comprehensively covering carcinogenicity testing, genotoxicity testing, reprotoxicity testing, chronic toxicity testing, and toxico-kinetics. There is also a guideline specifically concerning biotechnology derived pharmaceuticals, and a multi-disciplinary guideline for the Timing of Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (M3). The latter was particularly important as it clearly defined the safety data that must be available before human volunteers or patients may be treated with the new drug.

To summarize some of the key outcomes: there is a standard battery of tests recommended for most types of toxicity studies; timing, exact requirements (including dose) and need for toxicity studies for different indications or treatment durations have been defined; for carcinogenicity studies only one long-term study (usually carried out in a rodent species) plus one short- or mid-term study is needed (the latter are being evaluated currently, with the results available at the end of 2000); the special case of biotechnological products has also been considered. All of these should result in a reduction in duplicate testing.

As safety testing is an area of considerable research effort, both in academia and industry, an important result of, for example, the reduction in the number of long term studies that is required should be that (as well as reducing the use of animals) it will allow more resource to be diverted to other approaches to uncover potential risks like genotoxicity and carcinogenicity relevant to

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"ICH has led to streamlined regulatory requirements across geographies while preserving focus on scientific quality in submissions. These improvements have eliminated duplications of research efforts, without compromising the quality of the submission package."

August Watanabe, MD  
*President, Lilly Research Laboratories*

humans. The continual development of the models used to study toxicity is key to the industry becoming better able to evaluate the safety of new drugs, and delivering safe therapies to patients. It is on the basis of such research developments that ICH tries to keep guidelines updated and under review (eg the genotoxicity guidelines are currently being considered for review).

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“Through ICH we hope to deliver new medicines sooner to benefit patients worldwide, based on a harmonised approach to testing.

The goal of removing any duplicated or unnecessary experiments is one we strive for.”

Dr Claes Wilhelmsson,  
*Executive Director,  
Research & Development, AstraZeneca*

“The Common Technical Document will have an almost revolutionary impact on global drug development, paving the way for companies to launch their drugs more rapidly in more countries with fewer regulatory problems.”

Pedro Cuatrecasas, MD  
*Former President (R&D),  
Warner Lambert*

Utilization of these guidelines, as indicated earlier, has been high, with an average 80.5% over the three regions (seven of the thirteen now available had been implemented at the time of the 1997 survey). By region, the EU reported 77% utilization, with Japan and the US both reporting 82% utilization. Some issues had been encountered with the regulatory agencies in the regions, and likewise there was some duplicate testing required for some submissions across the three regions.

## 2.4 Common Technical Document

The Common Technical Document was adopted as an ICH topic at the Steering Committee Meeting which took place just before the ICH 4 meeting (July 1997). It is probably the most ambitious ICH project to date, and is only possible as a direct result of all the ICH guidelines produced thus far, offering potential benefits to industry far greater than any other single ICH topic.

Currently the requirements for the technical sections of a dossier differ across the three regions, and as such create a significant burden in time and resources for industry. Three separate EWGs are working on Efficacy, Quality and Safety Common Technical Documents, with a committee overseeing their activities. Already many key areas have been examined, and a general architecture for the CTD is being developed. It is hoped the finalized version of the CTD will be approved by ICH 5 (November 2000).

The value of this topic to industry must not be underestimated. Industry currently invests many thousands of man hours taking the core data required for a submission and preparing a dossier to meet the specific requirements of the regulatory agencies in the ICH regions. **The time and resource savings and resultant efficiency in dossier preparation that will be achieved by a single format for all the technical data will be extremely large.** It should also facilitate dossier review by the regulatory authorities and lead to faster review times, with the overall result of a faster time to market throughout the three ICH regions.

The work on the CTD also builds in part on the efforts of the M1 EWG which resulted in MedDRA, the Medical Dictionary for Regulatory Activities Terminology, a standardized terminology for the reporting of Adverse Drug Reactions. Furthermore, the value of the Common Technical Document activities should be considered in the context of the Electronic Standards for the Transfer of Information (ESTRI) (M2) topic, since as part of this group’s remit, they are preparing a Functional Requirements Document for an electronic Common Technical Document (e-CTD). Such a document will streamline yet further the dossier preparation and submission process, augmenting resource and time savings. On the current timeline the e-CTD will be available six months after the CTD.

## 2.5 *Electronic Standards for the Transfer of Information (ESTRI)*

The ESTRI EWG was established to harmonize electronic information transfer standards. Currently there are several other initiatives in progress on this topic that risk the creation of multiple standards. The expectation is that ICH work to harmonize these disparate initiatives will result in a single standard that promotes communication between industry and regulators as well as between regulators. Already a common standard has been selected, and work is in progress to apply this to the CTD. The time and resource savings that industry will achieve once the single standard is in place will be considerable.

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## 3.0 Implications of ICH in the Drug Development Cycle

To date there are no drug development projects that have been completely conducted following the principles of the ICH guidelines. While many drugs that have been approved have experienced the benefit of the guidelines on some or even many parts of their development activities, there has not yet been enough time for drugs to have been filed and approved having been run from Day 1—nomination of a candidate drug into a full development program—through to regulatory dossier submission using the ICH guidelines to determine the structure of the development program.

The reason for this situation is simply that many of the guidelines have only been finalized in the past two years. Implementation is also a lengthy process, and internal implementation costs risk distorting the industry's perception of the value of the ICH process. However, as new drugs pass through the full development cycle, the true benefits and value of the ICH process will be more obvious, and development activities in the future may well be redesigned as a result. The need for duplicate studies in many biological, clinical and technical areas has been minimized. For example, the ethnic factors guideline for clinical trials will facilitate a simultaneous worldwide launch (or at least in the three ICH regions), and the CTD will enable industry to prepare submissions far faster as a single technical dossier will be submitted to all competent authorities in ICH regions. The M3 guideline on the timing of safety studies with respect to clinical trials is well established, and has already had a direct impact on the drug development cycle. All of these point to a streamlined development process, bringing drugs to the global market faster using fewer resources. It is clear that ICH through its harmonization initiatives is adding significant value to drug development activities.

It is also perhaps pertinent to note that the ICH guidelines will in fact facilitate easier management of the Product Life Cycle. For example, on-going activities to harmonize stability requirements for post-approval changes will significantly reduce the workload associated with these activities today.

"I believe that the pharmaceutical industry must continue to strongly support the ICH programme. As a result of this initiative, the drug regulatory process has become smoother, quicker and less burdensome with the result that large numbers of patients all over the world are able to receive life saving and cost effective medicines sooner than was possible prior to this programme."

Prof Stuart R Walker  
*Director, CMR International*

"We know that ICH is speeding development times—and patients will receive important new drugs even more quickly when the CTD is introduced."

Dr Trevor Jones  
*Director-General, ABPI*

### **3.1 The Benefits of ICH in non-ICH Countries**

While the three ICH regions account for a large proportion of the innovative drug development and worldwide pharmaceutical sales, the importance of the other regions cannot be ignored. Already non-ICH countries are being affected by ICH guidelines as the pharmaceutical industry becomes more global. The ICH process could speed the introduction of innovative drugs into developing countries if ICH guidelines become more widespread. The faster introduction of such products will significantly benefit patients in these countries.

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In recognition of the need for information on ICH in countries outside the EU, Japan and the US, the ICH Steering Committee recently established a Global Cooperation Group. The objective of the group is to make available information on the ICH process and guidelines to non-ICH regions, and to act as a resource for the understanding, and even acceptance, of many of the guidelines. The Global Cooperation Group considers WHO involvement in this activity important to its success. It is hoped that this activity will help developing countries achieve faster access to innovative drugs.

“It is a great achievement that the basic ICH guidelines have been prepared. In the future, implementation of the ICH guidelines, identification and preparation of other necessary guidelines, including the guidelines for the clinical evaluation of drugs by therapeutic categories, revision of the existing guidelines as well as articulation of the future ICH framework will be the next challenges. Meanwhile, consistency with ICH principles should be assured in preparing new guidelines in each region. If these challenges are met, the achievements of ICH will become epoch-making.”

Mr Tohru Uwoi  
*Chairman of the Drug Evaluation  
Committee, JPMA*

### **4.0 The Future of ICH**

ICH has completed an important phase. Key guidelines are now being implemented in the areas of Efficacy, Quality and Safety in the three ICH regions. The organization has established a maintenance procedure to ensure that the guidelines continue to reflect the latest scientific developments and best practice. These maintenance activities are essential to the future of ICH, and to ensure that harmonization continues. Several more ambitious guidelines are under development, such as Good Manufacturing Practice (GMP) for Active Pharmaceutical Ingredients (APIs), Pharmacopoeial Harmonization (already achieved for some key monographs), and clinical guidelines for therapy areas (currently being run as a Pilot Project). The Common Technical Document and its electronic counterpart will be available in less than two years, both set to change procedures for regulatory dossier submission significantly.

The organization has recognized the importance of making available information on the ICH process and guidelines to non-ICH regions with the establishment of the Global Cooperation Group. As well as making information available, the group will act as a resource in the understanding, and even acceptance, of many of the guidelines.

Other topics that may now come to the fore are those such as the Harmonization of Regulatory Review Procedures. While the guidelines set a common standard for development, there is no commonality in review. By promoting greater interaction between the competent authorities, such that there is more transparency in the review process, it is a reasonable hope that a common standard of review will be achieved. Such a development is something

that the industry should actively encourage through the ICH forum, as the benefits would be significant.

To proceed with these activities the ICH organization will need to maintain a full-time Secretariat function. The Steering Committee (12 Members + Observers + Secretariat) will need to meet on at least an annual basis, if not more frequently, to oversee both the maintenance process and the new initiatives. Expert Working Groups (minimum 12 experts) will be reconvened to maintain current guidelines and to prepare new ones as required. **Investment from industry in this process will more than pay for itself as it will enable the continuation of ICH's invaluable harmonization activities which save time and resource.**

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## 5.0 Summary

Drug development is a costly, high risk activity. Drug development times have been increasing steadily over the past 30 years to an average of thirteen years today—at a cost in excess of \$500M per NCE brought to market. Every company is critically examining time / resource / quality triangles in development in an effort to improve programs and bring crucial new therapies to market faster. Hence any initiative that offers the pharmaceutical industry the opportunity to streamline development programs by setting a common quality standard in the three major market regions, reduce resource requirements by eliminating duplicate research activities, and provides the regulatory agencies with a platform from which practice and regulations can be changed to give a common standard should be actively supported. This is what ICH, through its harmonization initiatives, is providing to the industry, and will continue to do so into the 21st century.

Whilst the technical output of the ICH process is yielding many benefits to regulators and industry alike, the importance of the unique way in which ICH operates should also not be forgotten. ICH provides a forum for communication. Never before have industry and regulators sat at the same table in an international forum to discuss the science of drug development with the common goal of identifying best scientific practice and applying that uniformly across their regions. The power of this forum is such that ICH activities have led to regulatory agencies agreeing to changes in practice and regulations far faster than would have been possible otherwise, and its strength will continue to be that disharmony will be avoided across the three ICH regions. It is without doubt that in the absence of the ICH process the regulatory agencies in the three regions would have continued to diverge in their practice, and drug development within organizations would have needed to be done increasingly on a regional rather than global basis. The time and resource implications of this scenario do not need to be elaborated, nor does the increased burden on regulators that would have resulted, or perhaps most importantly, the delays it would have meant in delivering key new medicines to patients.

“Through ICH, the number of time-consuming, expensive Phase III trials required for an international launch will be reduced dramatically. This will not only save time and resources—it will save lives and improve the health of patients all over the world.”

Frank Douglas, MD, PhD  
*Executive Vice President, Hoechst  
Marion Roussel*

“JPMA can clearly see that the output of the ICH initiative is facilitating significant changes in the business environment that the Japanese pharmaceutical industry operates in.”

Mr Kazutaka Ichikawa  
*Senior Managing Director, JPMA*

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“The impact of the ICH process can now be seen by regulators when reviewing new drug applications. Consistent submissions allow an early dialogue between EMEA, the FDA and our Japanese counterparts when required. As a consequence, patients throughout the world will have a quicker access to new and better medicines.”

Dr Fernand Sauer  
*Executive Director, EMEA*

Currently the industry is in the implementation phase for the guidelines produced thus far. Implementation costs (in terms of time and resource) may well be hiding the underlying value of ICH. Once these one-time effects have passed, drugs pass through a complete development program following ICH guidelines, and are approved in the three ICH regions through the submission of a single technical dossier based on the Common Technical Document, the full value of the ICH process will be seen.

Finally, ICH looks to the future. It has established a structure to maintain the guidelines, and at the same time is looking to make available information on the ICH process and guidelines to non-ICH regions with the establishment of the Global Cooperation Group. As well as making information available, the group will act as a resource in the understanding, and even acceptance, of many of the guidelines. From an industry perspective globalization is arguably the most important issue it faces, and the ability of these guidelines to effect intra-company globalization is a facet of ICH that cannot be ignored. This is already happening within companies. Its value has not been quantified; however, the companies able to embrace these principles today will be the world leaders tomorrow. Companies who fail to see the value of harmonization—the value that is already being felt by the scientists carrying out the development, and the value that is yet to be realized in the full drug development cycle—will be left at the starting line of the industry’s globalization race.



## 6.0 Appendix

### 6.1 ICH Finalized Guidelines

#### *Efficacy*

VALUE &amp; BENEFITS

##### E1: Exposure

E1: The Extent of Population Exposure to Assess Clinical Safety

##### E2: Clinical Safety

E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting

E2B: Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports

E2C: Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs

##### E3: Study Reports

E3: Structure and Content of Clinical Study Reports

##### E4: Dose Response

E4: Dose-Response Information to Support Drug Registration

##### E5: Ethnic Factors

E5: Ethnic Factors in the Acceptability of Foreign Clinical Data

##### E6: GCP

E6: Good Clinical Practice: Consolidated Guideline

##### E7: Special Populations

E7: Studies in Support of Special Populations: Geriatrics

##### E8: Clinical Trial Design

E8: General Considerations for Clinical Trials

##### E9: Statistical Considerations

E9: Statistical Principles for Clinical Trials

#### *Quality*

##### Q1: Stability

Q1A: Stability Testing of New Drug Substances and Products

Q1B: Stability Testing: Photostability Testing of New Drug Substances and Products

Q1C: Stability Testing for New Dosage Forms

##### Q2: Analytical Validation:

Q2A: Text on Validation of Analytical Procedures

Q2B: Validation of Analytical Procedures: Methodology

**Q3: Impurities:**

**Q3A: Impurities in New Drug Substances**

**Q3B: Impurities in New Drug Products**

**Q3C: Impurities: Guideline for Residual Solvents**

**VALUE & BENEFITS**

**Q5: Biotechnological quality**

**Q5A: Viral Safety Evaluation of Biotechnology Products**

**Q5B: Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for the Production of r-DNA Derived Protein Products**

**Q5C: Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products**

**Q5D: Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products**

**Q6: Specifications**

**Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and Products: Chemical Substances**

**Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Substances**

***Safety***

**S1: Carcinogenicity**

**S1A: Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals**

**S1B: Testing for Carcinogenicity of Pharmaceuticals**

**S1C: Dose Selection for Carcinogenicity Studies of Pharmaceuticals**

**S1C(R): Addendum to the Dose Selection for Carcinogenicity Studies of Pharmaceuticals: Addition of a Dose Limit and Related Notes**

**S2: Genotoxicity**

**S2A: Genotoxicity: Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals**

**S2B: Genotoxicity: A Standard Battery of Genotoxicity Testing of Pharmaceuticals**

**S3: Kinetics**

**S3A: Note for Guidance on Toxicokinetics: the Assessment of Systemic Exposure in Toxicity Studies**

**S3B: Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies**

**S4: Toxicity**

**S4: Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing)**

S5: Reprotoxicity

S5A: Detection of Toxicity to Reproduction for Medicinal Products

S5B: An Addendum on Toxicity to Male Fertility

S6: Biotechnological Safety

S6: Preclinical Safety Evaluation of Biotechnology-Derived  
Pharmaceuticals

VALUE & BENEFITS

M3: Multidisciplinary

M3: Guideline for the Timing of Non-Clinical Safety Studies for the  
Conduct of Human Clinical Trials for Pharmaceuticals

**6.2 Sources of Further Information**

ICH guidelines . . . . . [www.ifpma.org/ich1.html](http://www.ifpma.org/ich1.html)

ICH Secretariat . . . . . [www.ifpma.org](http://www.ifpma.org)

ICH constituent parties

EU . . . . . [www.eudra.org](http://www.eudra.org)

FDA . . . . . [www.fda.gov](http://www.fda.gov)

MHW . . . . . [www.mhw.go.jp/english/](http://www.mhw.go.jp/english/)

EFPIA . . . . . [www.efpia.org](http://www.efpia.org)

JPMA . . . . . [www.jpma.or.jp/12english/index.html](http://www.jpma.or.jp/12english/index.html)

PhRMA . . . . . [www.phrma.org](http://www.phrma.org)

**6.3 Notes**

<sup>1</sup> ICH Utilization Survey, 1997. Carried out for the ICH4 International Conference.

<sup>2</sup> This group comprises the regulatory agencies for the three regions—The European Commission (EC) for the EU, the Ministry for Health and Welfare (MHW) for Japan and the Food and Drug Administration (FDA) for the USA—and the pharmaceutical industry associations —European Federation of Pharmaceutical Industries’ Associations (EFPIA) for the EU, Japanese Pharmaceutical Manufacturers Association (JPMA) for Japan and Pharmaceutical Research and Manufacturers of America (PhRMA) for the USA.

<sup>3</sup> See Appendix (section 6.1) for a full list of the current guidelines.

<sup>4</sup> The Survey generally noted that the longer a guideline had been in place, the more it was used, with utilization in some instances around 90%.

