The Value and Benefits of ICH to Drug Regulatory Authorities — Advancing Harmonization for Better Health

2010

This publication salutes two decades of the ICH's groundbreaking work in harmonizing drug regulatory requirements among many global partners.

The following articles were written by the drug regulatory authorities associated with the ICH Steering Committee, Global Cooperation Group, and Regulators Forum.

We would like to thank all the technical experts, past and current, who have contributed their invaluable expertise, insights, and dedication in making the ICH a success.

If you want to go fast go alone.
If you want to go far go together.

African Proverb

The Value and Benefits of ICH to Drug Regulatory Authorities - Advancing Harmonization for Better Public Health.

JUSTINA A. MOLZON
U.S. Food and Drug Administration

OVERVIEW

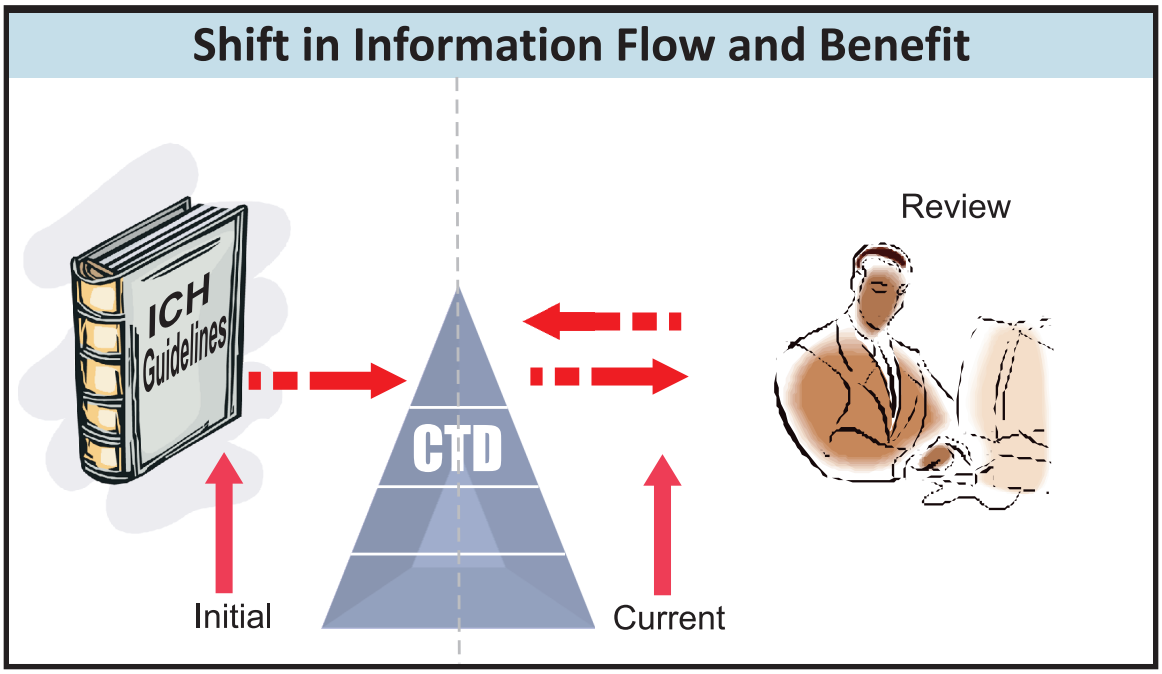
The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), launched 20 years ago, is an unparalleled undertaking. ICH brings together the drug regulatory authorities of Europe, Japan, and the United States, along with the pharmaceutical trade associations from these three regions, to discuss scientific and technical aspects of product registration. It is ICH's mission to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration, thereby reducing duplication of testing and reporting carried out during the research and development of new medicines.

In 2000, the 10th Anniversary of ICH, Dr. Caroline Nutley Loew of the Pharmaceutical Research and Manufacturers of America (PhRMA) wrote a report, *The Value and Benefits of ICH to Industry*, which detailed ICH's creation, procedures, and guideline development in the areas of safety, efficacy, and quality. Dr. Loew's report anticipated that the Common Technical Document (CTD) would revolutionize the submission procedures for industry's regulatory staff. Dr. Loew characterized the CTD as "offering potential benefits to industry far greater than any other single ICH topic," and predicted the CTD would afford significant savings in time and resources as complex multiple submissions were replaced by a single technical dossier submitted in the three ICH regions—facilitating simultaneous submission, approval, and launch of new drugs. In calling the CTD "a topic whose value to industry cannot be underestimated," Dr. Loew noted that with full incorporation of the CTD and the electronic CTD (eCTD), ICH could turn its sights to disseminating guideline information to non-ICH countries, yielding additional benefits to both regulators and industry.

Ten years later and in anticipation of ICH's 20th Anniversary, the value and benefits of ICH to regulators have been realized. Moreover, implementation of the CTD in 2003 promoted the involvement of drug regulatory authorities (DRAs) not initially part of ICH, thereby extending ICH's harmonized approach. The development of the Global Cooperation Group, which includes representatives from five regional harmonization initiatives and the newly established Regulators Forum, created to promote participation by non-ICH countries interested in implementing ICH's strategies, have also helped incorporate the CTD into regulatory processes, creating a common regulatory language that promotes faster access to life-saving treatments to patients beyond ICH regions. In recognition of the increasingly global face of drug development, ICH recently updated its logo to emphasize the benefits of harmonization for better global health.

Shift in Emphasis

Substantial benefits to DRAs resulted when ICH shifted emphasis from the input of information by industry to the output of information by regulators. This transition was made possible by the development of a common submission format—the CTD—which greatly influenced regulatory review processes, ultimately leading to a harmonized electronic submission and e-review initiatives, which, in turn, have enabled implementation of good review practices. These activities are having a global effect on information review and sharing among drug regulatory authorities.

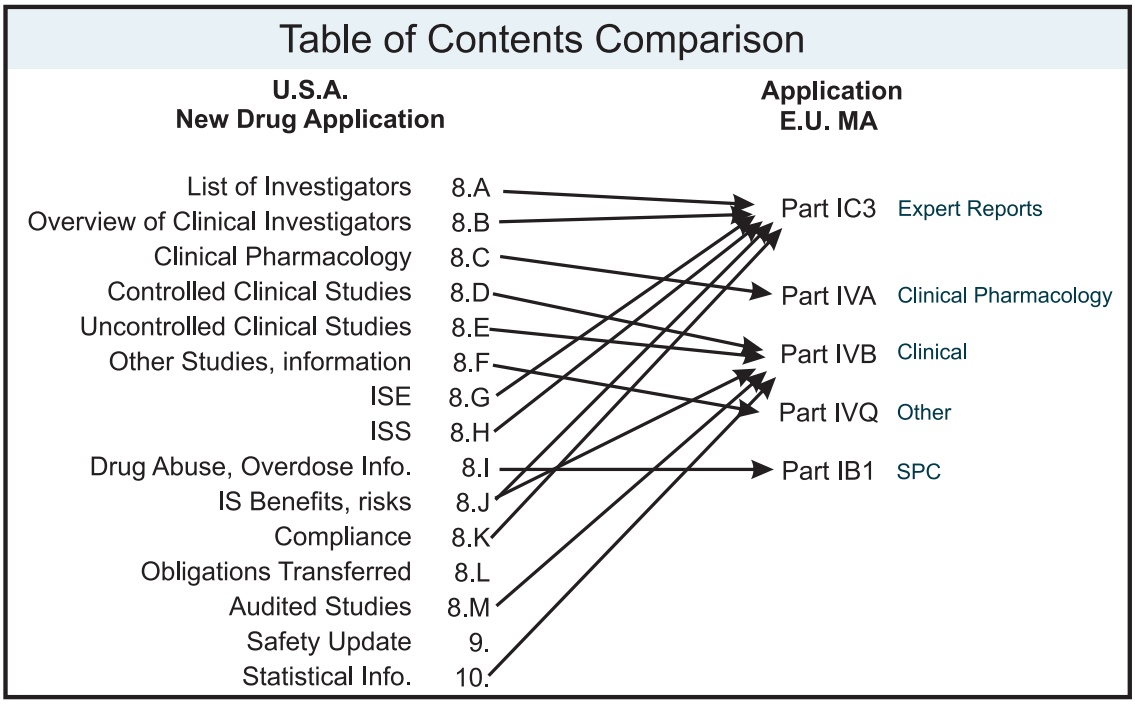


Originally, ICH focused on input by industry—the technical submission requirements for pharmaceuticals for human use. Harmonizing the differences in these requirements through ICH guidelines helped industry reduce development times and save resources. To extend the benefits of harmonization, industry proposed assembling the building blocks of information intended for inclusion in a submission into a consistent harmonized format, referred to as the CTD, which would relieve pharmaceutical companies of the time, workforce, and financial burdens of assembling a submission for one DRA and then having to reformat it for another. This new consistent format also greatly benefited the U.S. Food and Drug Administration (FDA), enabling the agency to establish templates for each of the review disciplines while promoting more consistent review practices and processes.

Prior to the advent of the CTD, regulatory reviewers received an application from one company and spent a year or more engaged in its review. When the review was completed, reviewers received the next application—most likely in a different format—and had to learn the structure of the new application. As a result, review staff were constantly on a learning curve when new assignments were received—time they could have better used reviewing the information as opposed to simply trying to find it.

When industry proposed the CTD in 1996, ICH regulators were hesitant to change their submission formats, believing it would be too disruptive to the review process. They needed convincing that harmonizing the submission format had value. Regulators asked industry to do a feasibility study. That study, conducted in May 1996, evaluated the time it took to convert an FDA new drug application into an European Medicines Agency (EMA) submission, and the reverse. It also evaluated the number and types of staff needed to carry out the conversion of the submission formats. Regulators quickly saw the potential value of harmonizing submission formats.

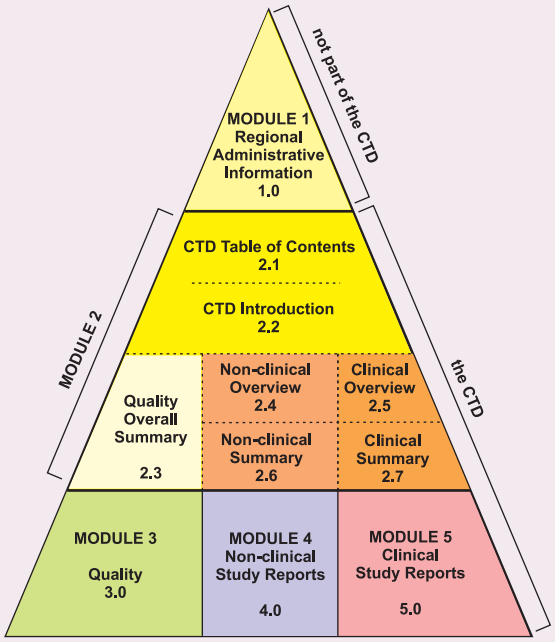
Table of Contents Comparison



Regulatory Benefits

The CTD has also made the exchange of information among drug regulatory authorities easier. For a number of years, FDA and the EMA have had a confidentiality arrangement in place allowing the sharing of confidential information, greatly increasing interactions between the two agencies. Now that submissions are received in the same format and, generally, at the same time, these interactions have become more efficient, facilitating discussions of common concerns as submissions are evaluated.

ICH regulators, impressed with the amount of time and effort involved in the conversion of one regulatory submission to another, agreed that the resources involved could be better used towards more research and development for new drug products. The regulators also realized that these conversions created a delay in submitting an application to the different ICH regions and, in turn, delayed patient access to new innovative medicine. The result of agreeing to work on a consistent format or table of contents is the ICH Common Technical Document.



Module 1 is not part of the CTD, it represents the administrative information specific to each ICH region. Module 2 is a layering of information and includes an introduction, summaries, and overviews. More complete data are contained in modules 3, 4, and 5. Countries can, in effect, focus on modules of interest. If a regulatory authority is not interested in the complete datasets in modules 3, 4, and 5, the focus can be on modules 1 and 2. This is what some less-resourced countries are now doing.

Last, and perhaps most important, the CTD has facilitated electronic submissions (the eCTD). In the past, drug applications were voluminous, delivered to FDA by the truckload due to the sheer amount of paper involved. When the agency first transitioned to electronic submissions, an application was on a compact disc or hard drive. Although this certainly helped with transportation and storage issues, it did not necessarily enhance the review process. FDA has now implemented the FDA Electronic Submission Gateway, which allows a new drug application (NDA) to be sent electronically, essentially very much like e-mail. After being assessed for completeness, a submission is immediately and fully accessible on the reviewer's desktop. This innovation has alleviated the need for industry to create and assemble the many pieces of paper that constituted a traditional paper-based product application, organize the application, box thousands of pages, load the boxes on a truck, and deliver them to FDA—all before a reviewer could even begin the assessment process.

The eCTD has proved critical to improving application submission efficiencies as well as reviewer efficiency. Besides delivering submission material to the reviewer in an expedited manner, the eCTD format has made it easier to develop standardized reviewer e-templates and review tools for each of the review disciplines.

Another benefit of a harmonized format has been the ease of developing and implementing harmonized good review practices. What is evaluated in a review is closely tied to the requested data. As a result, there is considerable similarity between ICH guidance to industry and what we consider good review practices. Because ICH regions have harmonized much of the information submitted for marketing authorization, ICH regulators could easily begin moving toward similar review practices.

In general, good review practices promote transparency and consistency, both of which are very important if industry and the public are to understand how regulatory authorities carry out their responsibilities. This is especially important because of the complexity of the disciplines and specialties involved in the review process. We needed a consistent approach to evaluating submissions and reaching conclusions, and the CTD and eCTD have helped to achieve these goals.

In summary, the CTD format influences the content of the review by imposing a consistent order of information and data. This shapes both the conduct of the review and the presentation of the results of the review and promotes good review practices and increased efficiencies. As more countries embrace ICH guidelines and the CTD format, a common regulatory language could evolve that will further promote interactions among drug regulatory authorities.

The ICH guidelines are giving medical writers improved guidance on how to interpret what FDA needs within a marketing application and provide the content to meet those needs. This in turn allows submission groups within drug development teams to focus their drug development plans and the communication around the data being generated from the execution of those plans. The end result has been faster, more concise, and higher quality submissions that ultimately not only aid regulators in their efforts to make decisions, but inevitably get health care products to patients in a more timely fashion.

DAVID CLEMOW
Scientific Communications Consultant
Medical Information Sciences, Lilly

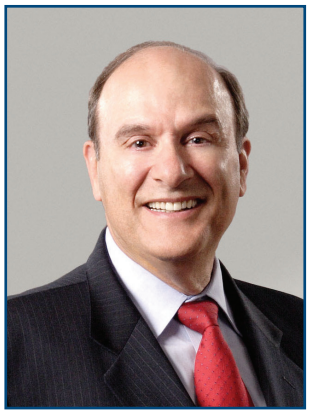
eCTD Submissions by Application Type October 2003 to October 2010

Application	No. of Sequences
IND	87,574
NDA	35,665
ANDA	23,328
BLA	11,003
MF	2,089
OTHER	951
Total	160,606

In December 2009, the U.S. Food and Drug Administration (FDA) processed its 100,000th eCTD submission. What began as a trickle in October 2003 has become a major component of FDA's regulatory processes. When coupled with the Electronic Submission Gateway we can begin to see an end-to-end, standards-based, electronic receipt, review, and dissemination environment taking shape.

ICH efforts to standardize regulatory content and processes have moved research and healthcare data standardization efforts forward in dramatic fashion, as the recent eCTD submission statistics attest.

HELLE GAWRYLEWSKI
Head Alliance Management
Johnson & Johnson



A Harmonized Marketing Application

ALEX GIAQUINTO
ICH Steering Committee
Member, PhRMA 1990 - 2003

It was nearly 20 years ago when an initial discussion of a new concept called "harmonization" took place among drug product regulators at an International Conference of Drug Regulatory Authorities. Not long afterwards, in April 1990, I attended a meeting at the European Federation of Pharmaceutical Industries and Associations (EFPIA), where the concept was explored again in greater detail—for the first time with representatives from four pharmaceutical industry associations: EFPIA, the Japan Pharmaceutical Manufacturers Association (JPMA), the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), and the Pharmaceutical Research and Manufacturers of America (PhRMA). Representatives from the regulatory agencies from Japan, the European Union, and the United States were also present. Not long after that meeting, the International Conference on Harmonisation (ICH) took its place as a pivotal organization in global pharmaceutical development and regulation. ICH's exceptional efforts in producing harmonized guidelines proved invaluable in helping both industry and regulators assess new medicines, thereby bringing those medicines to the patients who need them with new levels of efficiency and speed.

ICH's initial harmonized guideline development focused on the clinical, safety, and quality areas. It demonstrated such success that, by the mid-1990s, I was wondering how a similar strategy might benefit the application and regulatory processes. At the time, although pharmaceutical companies developed the same data in the same way for new pharmaceuticals and used the same guidelines for ICH's three regions, marketing applications in these regions varied in both how data were organized and formatted. There was also much variation in how much data were presented.

The natural question was: why couldn't we submit all this information in one uniform—or harmonized—marketing application for all three regions?

As the Third International Conference on Harmonisation (ICH 3, 1995) approached, I discussed this idea with several of my colleagues. Most of them suggested that

A Harmonized Marketing Application *(continued)*

although the current application system might be cumbersome, revamping would be even more difficult. But, schooled by remarkable ICH successes in other areas, I felt sure there was a way to accomplish the goal of a unified, or common marketing application document. I presented the idea at ICH 3, citing the number of guidelines under development or issued that, in themselves, promised to eliminate a substantial amount of experimental duplication. I identified what I believed to be a pressing need for a single approach for marketing applications.

An ICH Steering Committee meeting was held following the Conference at which I hoped to raise my concept for consideration as a guideline. But the proposal was quickly tabled until my industry colleagues and I could develop more data to support the need for such a guideline. We did so, and the ICH Steering Committee ultimately agreed to take on the topic.

While initial discussions continued to meet with objections, progress was made. Thanks to the robust and sustained efforts of numerous industry and regulatory colleagues, the innovation we had come to call the Common Technical Document (CTD) was signed off for release to the three regions by the Steering Committee at ICH 5 (2000).

A decade has since passed, and the CTD has driven fundamental changes in regulatory practice. It is the required marketing application format for many regulatory agencies, even those not initially involved in ICH. Today we have applications in a predictable format that are more accessible and readily reviewable, as they facilitate analysis and exchange of information across applications. With the change in ICH focus from input by industry to output by regulators, the CTD has been key in fostering this shift.

It is personally gratifying to see the benefits the CTD has brought with a harmonized, consensus-based approach in our global market environment. As those benefits accrue and the eCTD rapidly becomes the marketing application technique of choice, regulators are now using the principles of the CTD as a springboard to still newer and better ideas in regulatory review practices. We have certainly come a long way, and I look forward to future successes.

ICH Guideline Implementation

LENITA LINDSTROM
European Commission

Under the regulatory framework in the EU, the Committee for Medicinal Products for Human Use (CHMP), within the European Medicines Agency (EMA), is responsible for preparing scientific guidelines to help applicants prepare marketing authorization applications for medicinal products. When implementing ICH guidelines in the European Union, the CHMP adopts the harmonized text of a guideline.

The CHMP has already been involved in the ICH process at an earlier stage in that ICH topics are included in the work program of the relevant CHMP working parties or ad-hoc groups. Once adopted by the CHMP, ICH guidelines have the same status as other European scientific guidelines and replace existing guidelines on the subjects covered.

Guidelines generally take effect six months after adoption. Although applicants may, with the agreement of the competent authority concerned, choose to apply a guideline in advance of this period, competent authorities should wait until this period has expired before requiring the guideline to be taken into account.

In the EU, there are different types of pharmaceutical guidelines, which can be grouped broadly as regulatory or scientific. A regulatory guideline is a European Community document with explicit legal basis referred to in the legislative framework as intended to provide advice to applicants or marketing authorization holders, competent authorities and/or other interested parties on the best or most appropriate way to fulfill a legal obligation laid down in the pharmaceutical legislation of the EU. The basic EU legislation is thus supported by a series of guidelines published by the Commission.

Scientific guidelines are intended to provide a basis for practical

ICH Guideline Implementation (continued)

harmonization of the manner in which the EU Member States and the EMA interpret and apply the detailed requirements for the demonstration of quality, safety, and efficacy. Scientific guidelines also help facilitate the preparation of applications for marketing authorizations by the pharmaceutical industry. The scientific guidelines may relate to specific issues reflecting a harmonized EU approach, based on the most up-to-date scientific knowledge. New or updated guidelines are published by the EMA on its website. Additionally, the EMA publishes technical, procedural, and administrative guidance.

ICH guidelines are part of the scientific guidelines adopted by the CHMP. However, some ICH guidelines have been integrated into EU legislation. For example, following the adoption of the ICH Guideline Q7 *(Good Manufacturing Practice (GMP) for Active Pharmaceutical Ingredients)*, EU legislation was amended to require GMP for starting materials. Reference was made in the amended EU legislation to the fact that the principles of good manufacturing practice for active substances used as starting materials are to be adopted in the form of detailed guidelines. The European Commission subsequently modified its GMP Guideline *(Volume 4 of The rules governing medicinal products in the European Union)* on the basis of the ICH Q7 guideline.

Seasoned regulatory affairs hands recall with a mix of bemused nostalgia and frank horror the days before the electronic Common Technical Document—or, to be more exact, the days, nights, months, weekends, and holidays spent by sleep-deprived regulatory staff to build an NDA for the FDA, then deconstructing and reformatting it for EU submission. For those of us who have been around long enough to remember, there were the pre-EU days when each European country required different application formats prepared in, of course, different languages. The eCTD has changed all that, allowing both industry and regulators to focus on science and medicine, rather than on the now-unjustifiable diversity of application formats. And the world is better off.

ALBERTO GRIGNOLO
Corporate Vice President
Global Strategy and Services
PAREXEL Consulting

ICH has provided a logical framework for submission content that allows companies to use streamlined processes for developing and managing regulatory submissions globally, both within a company and between companies. The ICH initiative should continue its vital role by adding new guidelines, as well as revising existing guidelines, to meet our new electronic environment.

SUE WILSON
Senior Director, Medical Writing & Document Management
Shire Pharmaceuticals

ICH is a unique collaboration, not only among regions, but also between regulators and industry. Harmonization achievements, including pivotal milestones such as the conduct of stability studies and defining relevant thresholds for impurities testing, have been key breakthroughs. Current discussions on the new quality paradigm facilitate productive interfaces between scientific and technical innovation and regulatory constraints. Along with cooperative advances in regulatory science, ICH has brought another vital development: greater understanding of each regulatory agency's priorities and, with that, a new mutual trust that serves our larger goals of quality medicines made available to patients.

JEAN-LOUIS ROBERT
European Medicines Agency
Quality Working Party Chair

ICH guidelines have contributed to a regulatory writer's argument for using what might be called a 'hierarchy of summarization,' in which the fine details are covered at the bottom of the CTD pyramid, and information is increasingly summarized as it moves up the pyramid. Submissions built this way tend to be more consistent and easier to navigate, because the path from all the details to the summary sections is clearer. We assume this contributes to speedy and thoughtful review, and that those benefits are passed along to patients using these new therapies.

LINDA FOSSATI WOOD
MedWrite, Inc.

ICH and Domestic Regulations: Excellence Through Harmonization

TOSHIYOSHI TOMINAGA
Pharmaceuticals and Medical Devices Agency

Over the last 20 years, ICH has provided Japan's Ministry of Health, Labor, and Welfare (MHLW) with crucial momentum in bringing our national drug regulatory program to accepted international standards. Regulatory harmonization has facilitated both global acceptance of data obtained in Japan as well as MHLW's use of the world's data—realizing speedier delivery of safe and effective medicines to patients.

Among the many ICH guidelines that spurred vital change in MHLW's regulations, two in particular fueled quantum leaps for Japan's drug regulatory program: Ethnic Factors in Acceptability of Foreign Clinical Data (the fifth Efficacy Guideline, or E5), and Good Clinical Practice (E6).

Ethnic Factors in Acceptability of Foreign Clinical Data (E5)

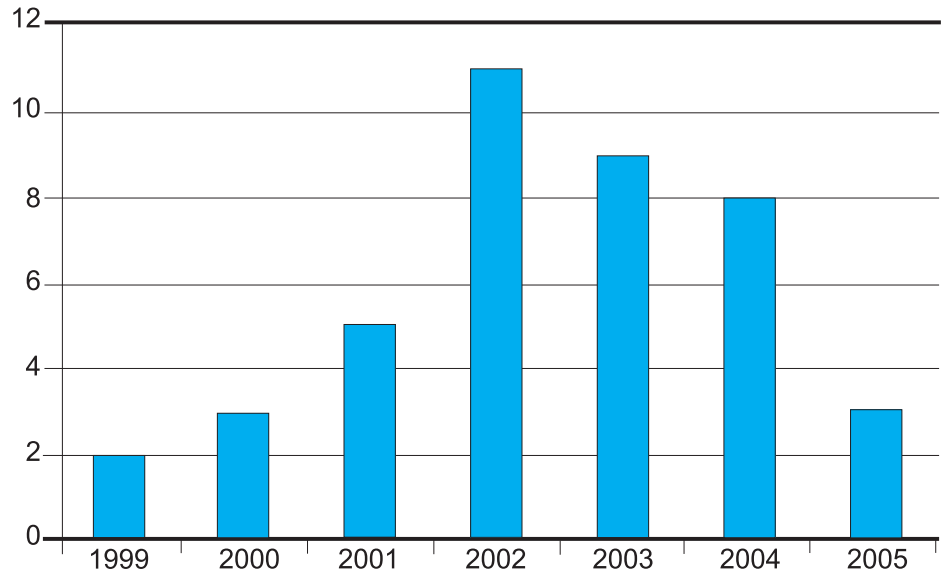
FIRST STEPS The E5 Expert Working Group (E5 EWG) began considering the effect of ethnic factors in clinical data in the early 1990s. At that time, MHLW required that applications originating outside Japan include the results of a pharmacokinetic study as well as late Phase II dose-determination and Phase III comparative studies performed on the Japanese population. This policy found its scientific basis in documented cases where race affected reactions to the same drug, but the E5 EWG offered MHLW an opportunity to further scrutinize its policies in regard to foreign clinical data. MHLW's expert, Dr. Chikayuki Naito, led the discussion as the EWG's rapporteur.

The E5 EWG wrestled with how to balance acceptable variations in drug effects among races and ethnicities while not compromising scientific rigor in an application package. Their answer—the bridging study—revolutionized Japan's drug regulatory policy.

BRIDGING STUDIES After extended discussion, the EWG reached the definition of a bridging study as "a supplemental study performed in a new region to provide pharmacodynamic or clinical data on efficacy, safety, dosage and dose regimens in the new region that will allow extrapolation of foreign clinical data to the new region." The ICH Steering Committee adopted the E5 guideline on February 5, 1998.

Six months later, MHLW replaced earlier guidelines with the E5 guideline, reducing Japan's regulatory burden and decreasing the approval time for drugs developed in foreign countries. (Fig.1 shows the number of new drug applications containing bridging data that were approved by MHLW.)

Figure 1. New Drug Applications approved by MHLW containing bridging studies



Ethnic Factors in the 21st Century

As the past decade saw pharmaceutical development trend toward multi-regional mega-trials (simultaneous subject recruitment from many populations in many parts of the world), new and complex questions emerged regarding across the board extrapolations of data. The E5 EWG was reconvened to address the issue in 2003 and in 2006 to create a series of 11 questions and answers (Q&As) that further clarified the guideline's implications in today's global clinical development landscape.

Building on the ICH E5 Guideline and subsequent Q&As, MHLW issued the guideline Basic Principles on Global Clinical Trials, which encourages inclusion of Japanese patients in global trials from an early stage and delineates key points to consider in designing such trials.

In April 2007 the health ministers of China, Korea, and Japan issued a Joint Statement and Memorandum of Cooperation, with

clinical research cited as a specific area of cooperation. MHLW, in cooperation with China's State Food and Drug Administration and Korea's Food and Drug Administration, is now exploring ethnic factors in East Asia based on ICH's E5 Guideline.

Guideline for Good Clinical Practice (E6)

When the ICH Good Clinical Practice Guideline (E6) EWG convened in the mid-1990s, Japan had only incomplete GCP guidelines—essentially a rough outline of the functions of principal investigators, study sponsors, and other key players in clinical studies, with very weak provisions for monitoring and auditing. Enrollment of study participants was allowed with oral consent.

As the EWG made progress with E6 Guideline development, vigorous debate continued in Japan. The concepts of informed consent were undeveloped at best among Japan's medical professionals, and quality assurance/quality control (QA/QC) was an overtly foreign concept. Claims were made that written informed consent defied Japanese cultural values, or that QA/QC would increase monitoring and auditing, raise administrative cost of trials—and also alienate investigators, all to the detriment of clinical development in Japan.

The ongoing debate brought fresh perspectives to the Japanese viewpoints on clinical trials, illustrating how ICH initiatives both instruct and confer benefit not only in their outcomes but also in their processes. In forging consensus the roles played by the Japanese E6 EWG experts and opinion leaders, Dr. Keiji Ueda and Mr. Osamu Ebi, cannot be overemphasized.

As the E6 Guideline reached Step 4 in 1996, MHLW embarked on a major amendment in Japan's Pharmaceutical Affairs Law (PAL), designed to implement the E6 Guideline with increased legal sanctions and enforceability. Soon after Parliament passed the amendment, MHLW issued the relevant GCP ordinances and related guidelines known collectively as Japanese GCP. On the day these rules became fully effective—April 1, 1997—Japanese clinical trials assumed globally acceptable quality, paving the way for Japan to generate globally usable clinical data. This led to GCP inspections by MHLW inspectors abroad and those by foreign inspectors in Japan and enabled exchange of inspection reports with other drug regulatory authorities. MHLW is now trying to help non-ICH countries adopt ICH GCP (E6) by sharing its expertise through GCG activities and other cooperative ventures.

For many years, Japanese investigators and institutions considered clinical trials to be a secondary task, a necessary chore of drug development, but not one they needed to pay much attention to. This attitude was primarily due to insufficient education about clinical trials in medical and graduate schools, and contributed to vigorous debate when ICH first began to consider its Good Clinical Practice Guideline (E6). But Japan has slowly come to understand the importance of E6 and of a drug research and development program that meets or exceeds global standards—in turn providing patients with the most advanced medical care available. The E6 Guideline continues to be adopted throughout Japan, and, as that process continues, E6 will be ranked as one of the most important contributions that ICH has given to Japan.

OSAMU EBI
Ex-officer,
Takeda Chemical Industries, Ltd.

ICH has provided the structural framework on which to build standardized applications to health authorities worldwide. As new information becomes available during the drug development program, it now has a place and a purpose.

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DISCUSSION

The immediate aftermath of incorporating the ICH Guideline noted above into Japan's regulations saw a significant decline in the number of clinical trials conducted in Japan (Fig. 2), a development clearly due to both the need for increased rigor in clinical trials as well as a reduced need to perform trials in Japan. Although critics objected to what they thought were drastic changes, relaxing the rules and deviating from world standards were never options for MHLW.

MHLW instead took (and continues to take) constructive measures to galvanize Japanese clinical development, such as improving the infrastructures of the trial sites and encouraging training for clinical research coordinators. As a result, the number of multi-national trials conducted in Japan has steadily increased, demonstrating the country's emergence as an international center of pharmaceutical innovation (Fig. 3).

World-class drug regulation benefits the Japanese public, and MHLW has set a clear course to pursue international regulatory harmonization. ICH is the most important mechanism Japan employs to reach that goal.

Figure 2. Clinical Trials conducted in Japan

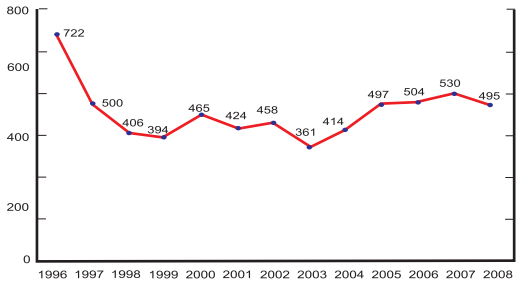
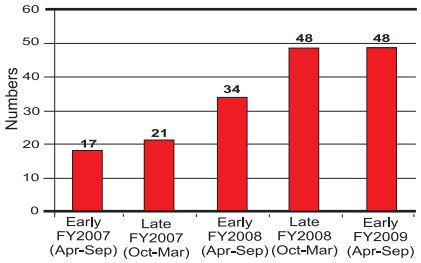


Figure 3. Multi-National Clinical Trials conducted in Japan



Revised ICH Terms of Reference

- To maintain a forum for a constructive dialogue between regulatory authorities and the pharmaceutical industry on the real and perceived differences in the technical requirements for product registration in the EU, USA and Japan in order to ensure a more timely introduction of new medicinal products, and their availability to patients;

- To contribute to the protection of public health from an international perspective;

- To monitor and update harmonised technical requirements leading to a greater mutual acceptance of research and development data;

- To avoid divergent future requirements through harmonisation of selected topics needed as a result of therapeutic advances and the development of new technologies for the production of medicinal products;

- To facilitate the adoption of new or improved technical research and development approaches which update or replace current practices, where these permit a more economical use of human, animal and material resources, without compromising safety;

- To facilitate the dissemination and communication of information on harmonised guidelines and their use such as to encourage the implementation and integration of common standards

The Global Cooperation Group – A Bridge from ICH to the World Beyond

MIKE WARD
Health Canada

For the first decade of its existence, ICH focused on the development of guidelines and standards for use in the ICH member regions (European Union, Japan, and the United States). By the late 1990s, however, ICH recognized the growing interest in ICH guidelines beyond the ICH regions. Reasons for this interest were rooted in several interrelated factors. There was a growing recognition of the utility of ICH guidelines as reference documents that define science-based principles and approaches and many of the ICH guidelines were not limited to new drugs giving them broader relevance. The globalization of industry, both innovative and generic, drove (and continues to drive) a need for common standards, and the overall trend towards global drug development strategies spurred the interest of non-ICH countries in stimulating innovation, building local capacity, and promoting earlier access to important new therapies.

In response to this growing interest, ICH created the Global Cooperation Group (GCG) in March 1999. The GCG serves to promote a better understanding of ICH guidelines and ICH itself, facilitated through open communication and fluid dissemination of information. The choice of name for the group was reflective of the desire to establish global linkages that extend beyond the three ICH regions.

From the outset, the GCG established a number of important operating principles that have guided its work to this day, notably that ICH will never impose its views on any country or region and that the GCG will work closely with WHO and other international organizations to achieve its goals.

In November 2003, a decision was made to pursue further harmonization, recognizing the need to actively engage with other harmonization initiatives showing an interest in ICH. The immediate goal was to better understand regional needs, leverage modest resources, and achieve the GCG's overall goal as captured in its mission statement: "to promote mutual understanding of regional harmonization initiatives to facilitate the harmonization process related to ICH guidelines regionally and globally and to facilitate the capacity of drug regulatory authorities and industry to utilize them." Partnerships were created with Regional Harmonization Initiatives (RHI) who were invited to attend the GCG. In June 2004, RHI representatives were invited to listen to ICH technical discussions at all levels, from Expert Working Group through Steering Committee levels.

Today, representatives from five RHIs actively participate in GCG discussions, including the Asia-Pacific Economic Cooperation (APEC),

the Association of the Southeast Asian Nations (ASEAN), the Gulf Cooperation Council (GCC), the Pan American Network for Drug Regulatory Harmonisation (PANDRH), and the Southern African Development Community (SADC).

Training is a key GCG focus, with an overall strategy for effective use of training resources, focused on developing resources and tools to maximize the effect of training efforts, including a clearing house that identifies training opportunities, public access to a growing library of training materials on the ICH website, and an evaluation template to help assess whether training objectives were achieved.

Recent workshops on clinical trial assessment and inspection have moved training beyond simply an understanding of ICH guidelines to their active application from a regulatory perspective—critical to a regulator's ability to assess studies and data developed in accordance with ICH guidelines.

Over the last decade, the GCG has established an open and productive dialogue and fostered a spirit of collaboration that has spread the message of harmonization. At the same time, ICH has gained a better understanding of the challenges faced by other regions in the use of ICH guidelines.

More recently, ICH recognized the need for further change to GCG principles and procedures to mirror the global face of drug development. This led to the November 2007 decision to create an expanded GCG with the creation of a Regulators Forum to permit the representation of individual drug regulatory authorities (DRAs) that were either a major source of active pharmaceutical ingredients (APIs), clinical trial data, or had adopted ICH guidelines. Just as the participation of DRAs is distinct and complementary to that of RHI representatives, so too are the GCG and Regulators Forum complementary.

Much progress has been made to date through the GCG in promoting a better knowledge of ICH guidelines and of the challenges faced by other regions in their use. GCG efforts have evolved from simply information sharing to active dialogue to the current results-oriented action. Important new developments will build on this progress. A pivotal factor in all of the ICH gains is exemplified by the GCG's fostering of a spirit of trust and cooperation between ICH representatives and colleagues from RHIs and DRAs—perhaps the most important key to our future success.

The strongest benefit of ICH harmonization for the Southern African Development Community (SADC) is the ease of comparability in international regulatory information. Harmonization has improved regulatory standards throughout the SADC, helped those standards be consistent with both local and national conditions and, in the process, saved time and money previously spent to consolidate divergent pharmaceutical information when more than one set of standards was required to comply with different national laws and practices. Harmonization has made a major difference in improving access to vital medicines in developing countries.

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The Regulators Forum

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The first Regulators Forum, hosted by the U.S. Food and Drug Administration, was held in Portland, Oregon, in June 2008. Regulators were invited from countries with a history of ICH guideline implementation (Australia, Chinese Taipei, Singapore, and South Korea) as were regulators from countries where major production and clinical research is done, such as Brazil, China, India, and Russia. Also in attendance were representatives from the Regional Harmonization Initiatives (RHI) also participating in the Global Cooperation Group (GCG).

The first Regulators Forum saw the formulation of a vision statement:

- To discuss and share best practices on issues related to the implementation of ICH guidelines and their impact on regulatory systems in non-ICH countries
- To assist in identifying training and capacity needs for action by the GCG. The Forum will support GCG activities and objectives and promote a more comprehensive understanding of ICH guidelines
- Create a regulator-only environment for open discussion of important issues regarding the implementation of ICH guidelines for regulators around the world
- To supplement—not replace—the GCG

A discussion also took place on the purpose, focus, and benefit of the group. There was consensus that the Forum would provide an excellent opportunity for non-ICH regulators and RHIs to learn about implementation of ICH guidelines and that participation in the ICH process would confer trust and confidence in those guidelines while developing links to other regulatory efforts and challenges.

The fourth Regulators Forum was held in St. Louis, Missouri, in October 2009. Discussions suggested that the scope of topics to be considered in the future may extend beyond the original concerns of the Forum—ICH guidelines—to include numerous other topics of common interest. But the more immediate benefits of the Forum are clear and substantive:

- Ease of communication and personal contact with increased interactivity between meetings
- Receiving updates from other regulators on current issues
- Learning from each others' experiences Analyzing differences in the interpretation of ICH guidelines

Key benefits from ICH harmonization activities and outcomes have come through the provision of common technical platforms, exemplified by the Common Technical Document (CTD) and the ICH guidelines. Although ICH requirements presented an initial challenge in adopting and adapting to guidelines, the ICH has emerged as a significant contributor to the quality, safety, and efficacy of medicinal products, bringing greater access to medicines as it delivers a beneficial impact on public health.

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Guideline Information Dissemination/Uptake in Non-ICH Countries

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As other authors have noted, it was clear from the early days of ICH that drug regulatory harmonization efforts, guidelines, and processes would affect countries and regions beyond the European Union, Japan, and the United States. At the inception of ICH, the World Health Organization (WHO), Health Canada, and European Free Trade Association (EFTA) had ICH observer status, with WHO seeking to represent the interests of non-ICH member countries.

In the early 1990s, some countries, such as Australia, sought to minimize their own unique requirements by adopting what were then seen as international best practice standards. A factor in those decisions, however, was the emerging reality: the pharmaceutical industry was increasingly globalized and the major market regulatory requirements for new and innovative medicines were best reflected in the developing ICH guidelines.

Unique regional- or country-specific standards, by placing additional and/or differing requirements on companies in respect of smaller markets, had the potential to act as barriers, delaying appropriate market access, sometimes indefinitely, for important medicines. Governments under pressure to ensure access to such medicines saw real benefit in the adoption of a generally internationally accepted standard. This was often supported by local industry as additional benefits can potentially accrue to regional pharmaceutical industry suppliers when adoption of international standards facilitates local industry entry into the global market. Effectively, the market entry standard that applies in any major market region will be applied at all stages of product delivery for products to be supplied globally.

Global production of medicines means manufacture, testing, and sale of any one product will usually encompass more than one region and, by the late 1990s, the ICH

requirements were in effect in most regions for those companies servicing the global industry.

The reality of globalization of production, in turn, obliged countries involved in medicine development at any stage, or depending on such development to meet health needs, to consider how they would ensure appropriate standards for market entry. By the end of 1999, with WHO encouragement a number of significant regional harmonization initiatives (RHI) had focused their attention on access to medicines and established groups to specifically deal with these issues. The RHI included Asia-Pacific Economic Cooperation (APEC), Association of Southeast Asian Nations (ASEAN), Gulf Cooperation Council (GCC), Pan American Network on Drug Regulatory Harmonization (PANDRH), and Southern African Development Community (SADC). The aims of the groups revolved around harmonizing technical requirements, facilitating market entry within regions, and providing appropriate skills to industry and regulators to meet regional needs.

Seven years after its implementation, the CTD has provided a great saving of resources and shortened the gap for registration in the ICH regions. The CTD is the basis for preparing a single dossier that can be submitted for registration in all ICH regions. Although this requires careful thought and planning and even more for the eCTD, as more countries decide to accept the CTD submission format, innovative medicines will be reaching many more patients all over the world with fewer hurdles and faster.

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The establishment of the Global Cooperation Group (GCG) within the ICH led to a major paradigm shift in conference principles—from regional thinking to global dimensions. The GCG helped shift the focus from information sharing to active engagement of various regions in guideline development, then expanding the international regulatory community's scope beyond guideline development to broader regulatory issues. The key lesson learned from participation in GCG is that with a little harmonization you can help regulators and industry achieve their goals with minimum cost. Harmonization is the magic word!

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Regulatory Harmonization and Public Health

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We have seen substantial improvement over the last several decades as pharmaceutical manufacturing has followed the business strategies a global marketplace demands. As globalization continues, the prevailing objective of drug regulation everywhere remains the promotion of public health. Indeed, in all cases where harmonization of registration requirements is supported by the international community, the target objective has always been, and continues to be, measurable public health gains. The main question, however, remains the same: how can regulators best contribute to the public health with the resources they have?

Value added is a relatively new phrase in science and business, and it succinctly expresses a core asset of the ICH's first two decades as public health advances have been realized through the direct benefits of harmonization: improved quality, safety, and efficacy of marketed products that mitigate the risks of harm by medicines; less time consumed and greater transparency in review and approval processes; and decreased costs for industry as a harmonized application format (CTD and eCTD) reduces the expense of preparing registration dossiers. Aside from helping drug developers and regulatory authorities, all of these value added innovations serve to increase public trust in approved medicines—a vitally important achievement in its own right.

The ICH experiment in harmonization has seen its proof borne out in practice as many approved medicines have reached and continue to reach patients in need.

As ICH launches its second 20 years, it serves to remember the lessons of the first:

- Strong commitment with allocation of necessary resources from major stakeholders involved, governments and industries alike, has contributed to the success
- Information sharing and harmonization reduces workload and improves overall regulatory performance
- Harmonization is the value added that directs expert knowledge and resources to functions that improve public and personal health and facilitates access to essential medicines
- Formation of effective networks among national regulatory authorities participating in various harmonization initiatives facilitates sharing of scarce resources; eliminates duplication of activities; saves money for all; supports cooperation, collaboration, and international understanding; facilitates in building regulatory capacity; and enhances public trust in our efforts

ICH Guidelines
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Quality Guidelines

STABILITY

Q1A(R2) 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

Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products

Q1E Evaluation for Stability Data

ANALYTICAL VALIDATION

Q2(R1) Validation of Analytical Procedures: Text and Methodology

IMPURITIES

Q3A(R2) Impurities in New Drug Substances

Q3B(R2) Impurities in New Drug Products

Q3C(R4) Impurities: Guideline for Residual Solvents

PHARMACOPOEIAS

Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions

Q4B
Annex 1 Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Residue on Ignition/Sulphated Ash General Chapter

Q4B
Annex 2 Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Test for Extractable Volume of Parenteral Preparations General Chapter

ICH Guidelines
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Q4B Annex 3	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Test for Particulate Contamination: Sub-Visible Particles General Chapter
Q4B Annex 4A	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Microbiological Examination of Non-Sterile Products: Microbial Enumeration Tests General Chapter
Q4B Annex 4B	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Microbiological Examination of Non-Sterile Products: Tests for Specified Micro-Organisms General Chapter
Q4B Annex 4C	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Microbiological Examination of Non-Sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use General Chapter
Q4B Annex 5	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Disintegration Test General Chapter
Q4B Annex 7	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Dissolution Test General Chapter
Q4B Annex 8	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Sterility Chapter General Chapter
Q4B Annex 9	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Tablet Friability General Chapter
Q4B Annex 10	Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Polyacrylamide Gel Electrophoresis General Chapter

ICH Guidelines
Finalized as of July 2010 (continued)

Q4B
Annex 11 Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Capillary Electrophoresis General Chapter

Q4B
Annex 12 Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions on Analytical Sieving General Chapter

QUALITY OF BIOTECHNOLOGICAL PRODUCTS

Q5A(R1) Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin

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

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

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

Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process

SPECIFICATIONS

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

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

GOOD MANUFACTURING PRACTICE

Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

PHARMACEUTICAL DEVELOPMENT

Q8(R2) Pharmaceutical Development

ICH Guidelines Finalized as of July 2010 (continued)

QUALITY RISK MANAGEMENT

Q9 Quality Risk Management

PHARMACEUTICAL QUALITY SYSTEM

Q10 Pharmaceutical Quality System

Safety Guidelines

CARCINOGENICITY STUDIES

S1A Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals

S1B Testing for Carcinogenicity of Pharmaceuticals

S1C(R2) Dose Selection for Carcinogenicity Studies of Pharmaceuticals

GENOTOXICITY

S2(R1) Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use (this guideline replaces and combines S2A and S2B)

TOXICOKINETICS AND PHARMACOKINETICS

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

S3B Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies

TOXICITY TESTING

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

REPRODUCTIVE TOXICITY

S5(R2) Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility

BIOTECHNOLOGICAL PRODUCTS

S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

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PHARMACOLOGY STUDIES

S7A Safety Pharmacology Studies for Human Pharmaceuticals

S7B The Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals

IMMUNOTOXICOLOGY STUDIES

S8 Immunotoxicity Studies for Human Pharmaceuticals

S9 Nonclinical Evaluation for Anticancer Pharmaceuticals

Efficacy Guidelines

CLINICAL SAFETY

E1 The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions

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

E2B(R2) Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports

E2C(R1) Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs

E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting

E2E Pharmacovigilance Planning

E2F Development Safety Update Report

CLINICAL STUDY REPORTS

E3 Structure and Content of Clinical Study Reports

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DOSE-RESPONSE STUDIES

E4 Dose-Response Information to Support Drug Registration

ETHNIC FACTORS

E5(R1) Ethnic Factors in the Acceptability of Foreign Clinical Data

GOOD CLINICAL PRACTICE

E6(R1) Good Clinical Practice: Consolidated Guideline

CLINICAL TRIALS

E7 Studies in Support of Special Populations: Geriatrics

E8 General Considerations for Clinical Trials

E9 Statistical Principles for Clinical Trials

E10 Choice of Control Group and Related Issues in Clinical Trials

E11 Clinical Investigation of Medicinal Products in the Pediatric Population

PRINCIPLES FOR CLINICAL EVALUATION BY THERAPEUTIC CATEGORY

E12 Principles for Clinical Evaluation of New Antihypertensive Drugs

CLINICAL EVALUATION

E14 The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

PHARMACOGENOMICS

E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories

E16 Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions

ICH Guidelines
Finalized as of July 2010 (continued)

Multidisciplinary Guidelines

M1 MedDRA	Medical Terminology
M2 ICSR (R2)	Electronic Transmission of Individual Case Safety Reports Message Specification
M3(R2)	Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
M4(R3)	Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use
M4Q(R1)	The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality
M4S(R2)	The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Safety
M4E(R1)	The Common Technical Document for the Registration of Pharmaceutical for Human Use: Efficacy
M5	Data Elements and Standards for Drug Dictionaries

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

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