



# ICH at 20

## AN OVERVIEW

*Betty R. Kuhnert, Section Editor*

If you've been in any area of the pharmaceutical industry for even a short period of time, you've probably heard of ICH. You may think of ICH as one or more of the specific guidelines that relate to your function in the industry (ie, in clinical E6 (GCP); in data management, M1 (MedDRA); in regulatory M4 (the CTD – Common Technical Document), etc). However, equating ICH to its guidelines is like the blind men trying to describe an elephant where one feels the trunk and says the elephant is like a snake, and the one feeling a leg says the elephant is like a tree trunk. ICH is much more than the sum of its 50 final guidelines.

ICH stands for The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Its mission is: "To achieve greater harmonization to ensure that safe, effective and high quality medicines are developed and registered in the most resource-efficient manner." The key term is "resource-efficient." Since its beginning in April 1990, ICH has worked to harmonize the criteria and documents required for approval and authorization of new medicinal products. Benefits include preventing duplication of clinical trials, minimizing the use of animal testing without compromising safety and effectiveness, and streamlining the submission preparation and regulatory assessment processes. The result is to reduce development

times and resources needed for drug development and ultimately to facilitate the access of patients to new, safe, and effective drugs.

Originally, ICH consisted of representatives of the regulatory agencies and industry associations of the three ICH regions, Japan, the US, and the European Union. In addition, representatives from other countries such as Canada, and the World Health Organization were present as observers and were quick to support the ICH initiatives. The key to success was the commitment of the ICH regulators to implement the final guidelines, and attention was directed towards facilitating the implementation of ICH Guidelines in ICH's own regions. Entering into the third decade of activity, ICH is now also focused on extending the benefits of harmonization beyond the ICH regions and involving regulators in non-ICH regions in guideline development. To further this initiative, a Global Cooperation Group was formed that has become an important subcommittee of the Steering Committee. Many other drug regulatory authorities worldwide have chosen to implement some or all of the ICH guidelines in their regulations. For example, the article in this series by Justina Molzon focuses on the relationship between the Asia-Pacific Economic Cooperation (APEC) and ICH.

The areas selected for harmonization were divided into safety, quality, and efficacy because these were the

criteria that are the basis for approval and authorization of new medicines. If a topic doesn't fit cleanly in one of the categories above, it would be put in the M or Multidisciplinary category. Accordingly, the guidelines produced by ICH, are designated by the letters E, Q, S, or M: Efficacy guidelines, such as E6 (GCP) and E3 (Clinical Study Reports), are concerned with the design, conduct, safety, and reporting of clinical trials. Quality guidelines, such as Q7 (GMP) include harmonization achievements in the areas of stability studies, defining relevant thresholds for impurities, etc. Safety guidelines, such as S1 (Need for Carcinogenicity Studies), include a comprehensive set of guidelines related to carcinogenicity, genotoxicity, and reprotoxicity. The article by Jan Willem van der Laan later in this series provides an interesting personal perspective on what it really took for harmonization related to the S1 guideline to occur. Multidisciplinary guidelines include ICH medical terminology (MedDRA, M1) and the CTD (M4). All together there are about 80 guidelines and annexes in the four categories that are either final or in various stages of development. The guidelines are guidelines and not regulations; thus, they are intended to be used in combination with regional requirements.

The ICH has also been working to facilitate international electronic communication through its Electronic Standards for the Transfer of Regulatory Information (ESTRI).



A result of this has been the Electronic Common Technical Document (eCTD), which allows for the electronic submission of the CTD from applicant to regulator. The article in this series by Nancy Katz discusses some of the competencies regulatory writers need to work effectively with the eCTD.

Early on, the benefits of ICH efforts were mostly to industry because harmonization reduced the duplication of testing and reporting necessary for submissions to multiple regulatory agencies. However, there are immense value and benefits of ICH to regulators as well. The CTD and the eCTD have revolutionized how submissions are reviewed. They have created a common regulatory language that promotes good document review practices and ultimately leads to faster access to life-saving medicines, even beyond the ICH regions. ICH has shifted its emphasis from the input of information by industry to the output of information by regulators, a transformation only made possible by the CTD. The CTD has also made the exchange of information among drug regulatory authorities easier. This is addressed in the articles in this series by Françoise de Crémiers related to E3 and how it led to the CTD, and the article by Yves Juillet on the CTD as a tool for global development and assessment.

The best place to learn more about ICH is the ICH website (<http://www.ICH.org>). There you can find information about the history and organization of ICH, how the process of harmonization actually works, and get answers to frequently asked questions such as how you can get involved in the process. I would recommend reading the

publication found there entitled, “The Value and Benefits of ICH to Drug Regulatory Authorities – Advancing Harmonization for Better Health.” This article salutes two decades of ICH’s groundbreaking work in harmonizing drug regulatory requirements among many global partners. Included are articles about how the guidelines are implemented, information about the eCTD, the impact of ICH in Japan, and more information about the ICH’s Global Cooperation Group, which is described as a “Bridge from ICH to the World Beyond.” There is also material about guideline information/ dissemination in non-ICH countries, and a list of ICH guidelines finalized as of July 2010.

Gone are the days when loading the hundreds of volumes of paper documents for a submission to a given country on a truck and watching it go down the road, was an excuse for a party before the effort began all over again for submission to the next country. Today, it doesn’t take six to nine months or longer to reformat the documents for the next submission. Also gone are most of the clinical studies done for one specific country. Instead, global clinical trials and bridging studies (E5) allow extrapolation of foreign clinical data to new regions. Thanks to ICH and improved technology, the process has gone from multiple paper submissions for various regions to a much more resource-efficient, common, standards-based, electronic submission and review process.

The articles that follow highlight some of the main contributions of ICH over the past 20 years. It should not come as a surprise that three of the five relate to the CTD, since M4 has revolutionized how submissions are prepared and reviewed. The article

by Françoise de Crémiers focuses on the birth of E3 (Clinical Study Reports) and how its development led to the CTD. The article by Yves Juillet focuses on the CTD as a tool for global development and assessment. The article by Nancy Katz focuses on competencies needed to produce an eCTD. The article by Jan-Willem van der Laan discusses the challenges and personal satisfaction of being part of the ICH safety initiatives. And finally, the article by Justina Molzon alludes to the increased globalization of pharmaceutical development and the APEC regional harmonization initiative. ■

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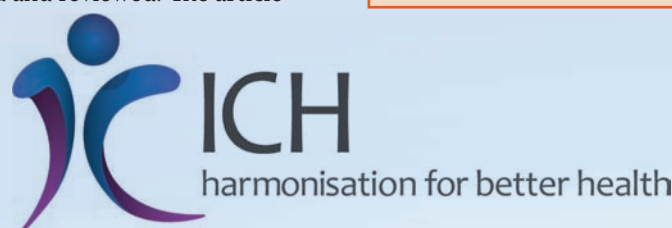
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We had planned to include an article offering the Japanese perspective on harmonization as a part of this section. However, the recent tragic events in that country prevented us from securing the article. We hope to be able to include this article in a future issue.







# THE BIRTH OF ICH E3 AND HOW IT LED TO THE CTD

*Françoise Augier de Crémiers*

**T**he concept of harmonization supported by ICH procedures and guidelines was the outcome of informal discussions that began in 1987 - 1989 between Europe, the US, and Japan. The need for harmonization was first addressed at the International Conference of Drug Regulatory Authorities (ICDRA) in Paris in 1989. An ICH preparatory meeting was held in 1990 in Brussels with Dr. F. Sauer (European Commission), Dr. Nelly Baudrihaye (EFPIA), Dr. Shirota (JPMA), Dr. Osuma Doi (MHWP), Professor J.M. Alexandre (CHMP), Dr. E. Esber (FDA), and A. Jaquinto (PhARMA), establishing the preliminary ICH framework. These architects were the builders of the ICH process, which provided for true collaborative development of international guidelines between drug development experts and regulators from the three regions.

The concept, the procedure with the different steps, and the guidelines to be selected were decided at the first ICH conference held in Brussels in November 1991. The ICH E3 guideline (The Structure and Content of the Clinical Study Report) was one of the first topics selected, along with the ICH E6 guideline (GCP). ICH E3 was the first step aimed at harmonizing the clinical documentation of drug development, and resulted in the harmonized

clinical study report. The topic was officially selected in March 1992, and the final ICH E3 guideline was implemented in the three regions in 1995/1996. The highly motivated ICH E3 expert working group was created in 1992 and was initially under European leadership until step 2 was achieved. At that time, computers and IT support were not effective enough, and the secretariat was supported by US and EU industry resources. This assistance was of the utmost importance for the review process by the three regions' experts during the ICH working meetings and intermediate consultation periods.

It should be noted that the three regional medical writers' associations also played a significant role in the development of the E3 guideline. They brought to the table practical experiences through forums such as DIA workshops that allowed exchanges of views between drug developers and regulators. These discussions brought to light potential pitfalls as well as positive items. Their participation was greatly appreciated and facilitated the ICH E3 implementation through changes to international company SOPs so that they would be applicable for a clinical study performed in any of the three regions and later Canada.

Parts of the clinical study report guideline were based on the US

Food and Drug Administration (FDA) guideline entitled Format and Content of the Clinical and Statistical Section of New Drug Applications – July 1988. The statistical part of the clinical study report closely resembles the FDA guideline, with certain modifications. However, after extensive initial comparative analyses and evaluations, the FDA guideline underwent significant changes to take into account ethical requirements and to make it compatible with EU, USA, and Japanese regulations. The ICH E3 guideline also took into consideration the different regional Health Authority approaches and philosophies regarding drug assessment.

The “modularity principle” was applied. A common core format allowed preparation of a worldwide core clinical study report that would be acceptable to all Regulatory Authorities. This core clinical study report was to be completed with appendices. Each appendix was to be considered as a separate module, meeting specific regional regulatory requirements, depending on the three regions' regulations. Taking the principle of modularity into consideration, the core report and appendices could be separated. This approach would avoid unnecessary duplication, and waste of resources and time. A common format would not only benefit the industry, but



potentially also allow patients faster access to new medicines.

Although the intended scope of the ICH E3 guideline was to cover pivotal efficacy and safety studies, the basic principles and structure described could also be applied to other areas such as pharmacokinetic/pharmacodynamic studies. The ICH E3 guideline was to be used in conjunction with other ICH guidelines dealing with efficacy and safety.

Subsequently, worldwide industry surveys were conducted by PhRMA to find out how long it took to convert a registration dossier prepared in one region for submission to another region once the drug development process was complete. The results presented to the ICH Steering Committee were based on recent experiences from eight different companies and showed that ten months were needed to convert a US/NDA into an EU/MAA! This was the starting point for the ICH Steering Committee's decision to set up the ICH CTD expert working groups. Different groups addressed the different parts of the registration dossier related to quality, safety (nonclinical), efficacy, and multidisciplinary topics.

Thus, the success of ICH E3 led to the birth of the ICH CTD efficacy expert working groups. Continuity with the previous expert working group was ensured by involving Dr. R. Temple and Dr. F. de Crémiers, who had been involved with E3. The ICH CTD-efficacy guideline was intended to harmonize the structure and format (or table of contents) of the clinical part of the "common" registration dossier in order to benefit from standardized sets of tables, tabular overviews, and tabular listings. The modularity principle was again applied to allow for regional requirements. Moreover, guidance documents regarding an overall written clinical summary, as well as an executive summary, were prepared. These allowed "unique" summaries providing identical information and formatted in the same way that as a result, could be submitted simultaneously to the three regions and Canada. Modular appendices for specific regional requirements still remained, such as the US Integrated Safety Summary. Global companies could provide this document in the EU submission as an appendix referenced in the Table of Contents.

In conclusion, the ICH E3 guideline and the ICH CTD efficacy guideline have proven to be

acceptable, standardized formats for the preparation of global clinical submissions. The modular formats have saved time and resources, and have greatly facilitated early access to new innovative medicines. In addition, the common formats have facilitated discussions and exchanges between drug developers and regulators, and have led to better dialogue in terms of public health needs for the patients. ■



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# THE CHALLENGE AND SATISFACTION OF GLOBALIZATION *A Personal Perspective*

*Jan Willem van der Laan*

**G**lobalization in the regulatory field of human medicines cannot be discussed without the important initiative of the ICH, a short abbreviation for a long name: International Conference on Harmonisation of Technical Requirements for Medicines for Human Use.

This name also defines the boundaries: only technical requirements, not the language. Whether it is “harmonization” or “harmonisation” is not important.

## **First Experience: Carcinogenicity**

In January 1992 I got the chance to participate in the ICH process by joining the Carcinogenicity Expert Working Group at their first meeting in Whitehall in London. The topic of carcinogenicity is complex, consisting of different aspects such as dose selection and a possible discussion of the relevance of the two individual rodent species.

This first process revealed differences in thinking between the various geographic areas, including the representatives who attended the meeting. The representatives from Japan (Ministry of Health, Labor and Welfare, MHLW) and the USA (FDA) consisted of a battery of experts, including at least one carcinogenicity expert. In addition, the FDA had just started the Carcinogenicity Assessment Committee to achieve consistency across divisions in their

decisions regarding carcinogenicity study protocols and interpretation of results. In Europe, however, the individual (national) nonclinical-assessment groups were (and still are) rather small. Therefore, my first task was to learn about the main issues in carcinogenicity testing. With a huge number of papers in my suitcase, I started my career with ICH.

An important factor in the ICH was the interaction between industry and regulators as equivalent partners. The input from industry prevented the regulatory parties from being too theoretical in their requirements, leading to real discussions about how to assess safety for humans. On the other hand, industry was asking for detailed guidance that might eventually be too prescriptive, preventing thinking by the industrial experts themselves.

*Globalization is multidisciplinary.* Defining the need for carcinogenicity studies required that clinical expertise be brought into the group when we discussed the duration of clinical treatment for patients. Contact with the clinical experts at ICH was easy in the so-called Caucus meetings taking place during ICH meetings.

*Globalization should be data driven.* The FDA had conducted an overview of the ratios in exposure of rats versus humans for a series of pharmaceuticals. This database clearly showed the limitations of having a general requirement of a

range of exposure of animals over humans. It showed also that the use of extremely high doses (because of low toxicity) was limited. A variety of endpoints had to be defined, such as the maximum tolerable dose, the maximum feasible dose, the exposure-based maximum dose (with the factor 25), and a few others.

The issue of species choice led us to build a database in Europe. A problem in Europe was the lack of a central administration, as the European Medicines Agency (EMA) was not yet established. Therefore, we decided as a Dutch group to cooperate with Germany.<sup>1</sup> This database taught us a lot about the value of the carcinogenicity studies in the pharmaceutical field, ie, that the contribution of mouse studies to carcinogenic evidence was low, although we had to admit that the relevance of the rat studies was also rather low. After having reached agreement in general terms under the excellent chairmanship of Lars Ekman, a Swedish representative of the pharmaceutical industry, most of the time was spent on the text of the guidance documents.

One specific moment is worth mentioning. We had just finished the document on the Need for Carcinogenicity Studies (S1A), with a short preview of the next decade announcing the use of transgenic animals. We then started with the next document, the Choice of Species (S1B), and the FDA representative



proposed including the possibility of using transgenic mice. From a European viewpoint, I would reduce the requirements to one species, the rat, being unhappy with these mice. I explicitly indicated that this position would be not acceptable for the EU. The FDA representative could also not handle this situation, and started reading a newspaper. At that time, the chairman announced a break in the meeting. During this break, emotions settled down, and the discussion on transgenics was deferred to a later stage. As a result of this meeting I was invited by the FDA representative to join the FDA for a month, and to spend a month at his home. The MEB (Medicines Evaluation Board) sponsored my flight. I became a temporary FDA employee, and this was a great experience.

*Globalization leads to friendship.* My work with my host Joe DeGeorge, led to a lasting friendship. I had also the opportunity to meet several pharm-tox colleagues from CDER and CBER, which was important for the future work in ICH.

*Globalization brings about cooperation: ICH, HESI, and DIA.*<sup>2</sup> The discussions in ICH led to a new global initiative, within ILSI (International Life Sciences Institute)-HESI (Health and Environmental Science Institute) located in Washington, DC, to evaluate transgenic and other models. This project was important and led to encounters with the challenges in the ICH process. DIA played an important role in this process, by taking the opportunity to organize a meeting discussion in Noordwijk in 1997 on "Alternative Models in Carcinogenicity Testing."

This first experience in globalization was challenging because of the different issues in the field, but very satisfying as changes in the strategy for testing drug safety could be initiated, and more importantly as friendships resulted from these intense discussions.

### Second Experience: Immunotoxicity

*Globalization should be data driven.* Another challenge was the topic of immunotoxicity. The process started in our institute in the 1980s, where strategies to detect immunotoxicity were developed for environmental chemicals such as tributyltin oxide (TBTO) under the leadership of the late Sjef Vos. The Safety Working Party (SWP) invited him in 1989 to introduce immunotoxicity in the pharmaceutical arena, but the topic required more data. In the early 1990s, the Medicines Evaluation Board supported a program to validate an approach in immunotoxicity by conducting animal testing with a range of pharmaceuticals. These studies were led by Eric de Waal and Henk van Loveren. At the same time, my own research was on opiates, because of questions about their immunosuppressive potency in drug abusers infected with HIV.

*Globalization should be led by scientific discussion.* When all these studies were finished and most of the data were published, a process was started to bring this topic into the global regulatory environment. A DIA workshop in January 1995 in Arlington, VA, was devoted to this topic. One day was spent on immunotoxicity in close cooperation with immunotoxicologists in the US and especially within FDA (Ken Hastings) and NIEHS (National Institute on Environmental Health

Sciences) (Mike Luster). An explicit driving force was Jack Dean. In Arlington, it became clear that the time was ripe to extend the topic. Therefore, another DIA workshop was held in 1996 in Montreux, resulting in recommendations. This was an important step in the globalization of this topic, as leading immunotoxicologists from the US and Japanese pharmaceutical industry participated.<sup>3</sup>

Despite these workshops, the strategies of the different regulatory parties were different. The EU incorporated a paragraph on immunotoxicity testing in their Guideline on Repeated Dose Toxicity finalized in 2000, whereas the FDA released their first draft document in April 2001, and a Japanese draft document was published in December 2001.

Soon after the publication of these guidances, the issue of immunotoxicity was brought to the table at ICH. In November 2001, a third DIA workshop was organized again in Noordwijk in the Netherlands to discuss the situation. The conclusions of this meeting were published in the *Drug Information Journal*.<sup>4</sup>

*Globalization should be data-driven.* In February 2002 the different approaches were discussed in Brussels, but it was decided just to gather data, and to continue to learn from experience in the pharmaceutical industry. We spent nearly two years on this. In July 2003, we proceeded by analyzing the database in Brussels. Despite the small amount of data, we decided to proceed and to ask the industry for more input in the meantime. Eventually the survey



contained 45 compounds. Only six were positively scored as immunotoxic in functional tests without being positive in other respects.<sup>5</sup> At that time an important realization was that the European request for routinely conducting immunotoxicity studies might be regulatory overkill. This recognition brought into play the possibility of harmonization of this topic between the various regions. (*Globalization may be painful.*)

The final point can be briefly stated: the challenge was to maintain the most important aspects of the immunotoxic risks in the documents, without overemphasizing the need for functional screening.

From this second experience we again learned that guidance documents have to be based on sound data, and harmonization can be reached only through further analysis of the way things work in industry. It is important that in the field of toxicity testing of human pharmaceuticals, companies will take some risk by conducting studies.

### Third Experience: Regulatory Language and Safety Testing of Biotechnology-derived Proteins

In 2006 the SWP was asked to evaluate the existing guidelines and to think about the possibility of adding new issues to the ICH list of topics. On behalf of the SWP, I wrote a short notice, and we made a list of topics as a proposal for a brainstorming meeting.

The brainstorming discussion took place in June 2006 in Yokohama with a rather straightforward outcome. It was chaired by Professor Tohru Inoue, representing the Japanese authorities who were hosting the meeting, and by

me, representing the initiator, the EU. The following were among the many topics that were discussed.

*Globalization is accepting differences in legislative culture.* The topic that was expected to be a quick-win, ie, a very small revision of S1C took 18 months with legalistic discussions with FDA, turned out to be a nice learning experience. There is specific regulatory language that is sometimes difficult to understand. As a non-native speaker I learned that “warranted” is not a commonly used word in the American and English language. However, it is commonly used to express that a certain test is needed or “called for.” But since the discussion on the S1C, we have a list of “unwanted” words, which apparently express a requirement or statement too strongly. For example, the word “acceptable” is not acceptable, and the word “appropriate” is more appropriate, unless we really believe that a certain approach is acceptable. It might be difficult to accept that a certain region might be so dominant in the character of the wording, but in fact that is one of the challenges in harmonization... to accept the legalistic approach of one of the parties. In the same way, the US parties have to respect the opinion of the EU that the use of animals should be reduced as much as possible.

Another outcome of the brainstorming session was the request for revision/updating of the Guideline on Preclinical Testing of Biotechnology-derived Proteins. It was, however, decided that this revision could be done only after evaluation of the experience gathered thus far. This decision was an important aspect of the process.

It was therefore important to organize regional meetings to discuss the evidence available at that time on the different topics that needed to be harmonized. In Europe, together with the EFPIA Safety Group and the Immunotoxicity Summer School, we organized a day in Lyon to discuss the “hot items,” eg, the duration of chronic toxicity studies, reproduction toxicity, immunogenicity, and carcinogenicity.

Together with a student, I took the challenge of the reproduction toxicity studies for this type of compound. This led us deep into the differences between human and animal placental physiology.<sup>6</sup>

Other datasets were gathered on the character of chronic toxicity, tissue cross-reactivity, and carcinogenicity of biotechnology-derived pharmaceuticals.

As a whole, the process was very satisfying in this respect, as all of these reviews have substantially improved the knowledge of regulatory experience in this field.

*Globalization is respecting each other's way of organization.* The process of updating/revising the S6 Guidance is close to being finalized, as we have been waiting a few months for final agreement among the pharm-tox assessors of the FDA. This might be frustrating sometimes, but that's all in the game, and therefore it is a challenge.

### Other Experience: World Health Organization

*Globalization is involvement with developing countries.* The ICH is not the only organization with a global impact. In fact the WHO has an older tradition. My involvement is in the



vaccine field, as the institute where I am working has held an important role with respect to vaccines since the first half of the 20th century, when it developed the national vaccination program for children. The character of the work for WHO is different, as the lead is more in the organization itself, in this case in the Unit for Biological Standardization. Meetings organized by WHO are bigger than the Expert Working Groups in ICH, and more multidisciplinary in design. In most cases there is explicit representation from the developing countries, which are hardly present in ICH. Also, the topics in the vaccine field are different and more applied to specific types of products, such as plant vaccines, DNA vaccines, and malaria, dengue, and yellow fever vaccines. From that point of view, the work is very satisfying since it is influential in the daily life of developing countries.

One of the challenges in the WHO vaccine field is the introduction of the ICH system of the Common Technical Dossier. The development of a vaccine requires a close interaction between the biotechnological process of the production of a vaccine, and the proof-of-concept testing or safety testing. The differentiation between master seed, working seed, and final lots is very important in the vaccine field and is not always easy to compare with the different stages of development of a common human pharmaceutical. From that point of view it is also not easy to make a strong distinction between Module 3 (Quality part) and Module 4 (Nonclinical testing part) of the CTD. Testing of neurovirulence (translated as central nervous system toxicity) belongs to the testing of the master seed or working seed, in the common human pharmaceuticals part of

early development, whereas testing the safety of local tolerance should be conducted with the final product, ie, the first final lot. It is a real challenge to harmonize these types of principles.

### Personal Globalization

*Globalization is experiencing brotherhood.* Traveling around in the world is a challenge as such, meeting people in different cultures, in different environments and with their own specialties. For me an additional value is meeting and experiencing brotherhood with people all over the world.

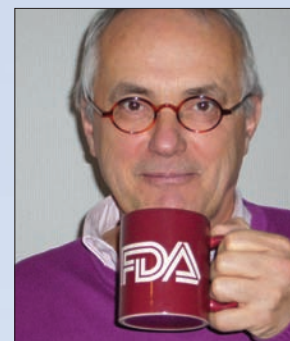
*Conclusion: Globalization is a challenge in various respects, but gives a high level of satisfaction.*

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# THE CTD

## A TOOL FOR GLOBAL DEVELOPMENT AND ASSESSMENT

*Yves Juillet*

**H**armonization is not an objective as such. The aim of this activity is to create a substantial uniformity between the requirements in different regions to facilitate the access of patients to new drugs. It should limit unnecessary delays in drug development and also avoid animal and human study duplications. In doing that, it saves regulatory authorities and industry both time and money.

When the ICH process started in the early 1990s, only harmonization of the dossier content was considered. At that time it was not even conceivable to think of harmonization of the format. The first success of the ICH guideline implementations made this project possible.

At the end of the 1990s, when the work started, the objectives of the CTD were clearly stated:

- Reduce the time and resources needed to compile the applications for different regulatory authorities
- Make preparation of the file easier
- Facilitate regulatory reviews and communication between authorities and applicants
- Facilitate the exchanges of regulatory information between authorities. (Harmonized numbering allows easy reference to the same part of the dossier.)

### CTD Definition and Reality

The CTD has been defined as an agreed-upon common format for registration applications. In theory, it was not concerned with the content. In practice, the development of the CTD project required a lot of effort to verify that the words had the same meaning in the three ICH regions (and they did not). This exercise then led to a thorough review of the content of the registration dossier. This review was needed to clearly identify each part of the CTD (granularity) to allow for harmonized numbering.

Even more difficult was the harmonization of the application summaries. The word “summary” did not have the same meaning, nor did the sections have the same length, in the different regions.

### What Has Been Achieved?

Ten years after implementation, it is possible to clearly state that the CTD has been a success. It is now totally adopted in the three ICH regions, even if there are slight differences. In practice, these differences are limited to a few paragraphs. The main differences are still the length of the summaries and the remaining requirement in the US for the ISS (Integrated Summary of Safety).

It is interesting to note that during the CTD implementation phase there were no major changes, only very minor ones, and it was adopted easily by regulatory authorities and industry.

The review process was also made easier for both regulatory authorities and the day-to-day work of assessors, showing that the logic behind the development of the CTD was correct.

Thanks to its robustness, it has been possible to develop an eCTD, whose objectives go far beyond the simple electronic submission, and include facilitating the review process itself.

It is interesting to note that one of the main aims, “To facilitate the exchange between regulatory authorities” has been a real success, as evidenced by ongoing regular contacts between regions regarding topics such as pharmacovigilance and scientific advice. This is not a surprise for Europeans, who knew that the European registration system only started to emerge when the European format and the expert reports were finalized and adopted.

The data are impressive. In December 2009, less than 10 years after the CTD launch (ICH San Diego 2000), the US FDA processed its 100,000th eCTD !

### The CTD as a Global Tool

The CTD was initially developed by ICH for the ICH countries/regions.

Some additional countries, ICH observers (Canada, Switzerland), and Australia immediately adopted the format.



A major step towards globalization was taken in 2004, when the Regional Harmonization Initiatives (ASEAN, APEC, GCC, SADC and PANDRH) led to invitations to regulatory authorities from different countries such as China or India to become members of the ICH Global Cooperation Group. This quickly led to a better understanding of the ICH process and results.

Even when not always formally implemented, the CTD is now present in most of the regions.

It is clear that the CTD, which allows for a better global understanding of regulatory requirements, has helped these countries not only to develop their own registration processes, but to participate more and more in the development of new ICH guidelines.

The CTD is also the tool that is clearly used by emerging countries to attract industry sponsors to place clinical trials in these regions. It is now impossible for these countries to play a key role without adopting the ICH guidelines, including the CTD and Good Clinical Practices.

In addition, it allows the regulatory authorities to develop contacts and cooperation among the different agencies, in particular with the most stringent authorities.

### The CTD, an Easily Adaptable Tool

Often compared to a pyramid, the CTD is composed of modules and submodules. Each part could be compared to stones or bricks.

The composition of the dossier would not be the same if a new compound or generic were considered. For generics, only some parts of the CTD are required: Module 1 (administrative information), Module 2 (Summaries), Module 3 (Quality part), Module 4 (usually not necessary), Module 5 (usually limited to bioequivalence studies).

It seems clear that regulatory authorities in different parts of the world have neither the same needs nor the same means. They often don't need all the stones, nor are they able to use them. Even in the least developed countries, the use of the CTD Module 2 (summaries) will help authorities to get needed information and will allow them to question agencies in more developed countries.

It is interesting to see that the harmonization initiative, which has just started in Africa, is clearly based on the use of the CTD. The CTD is now considered the common ground on which the different countries/regions will be able to build their own harmonization activity little by little.

When the CTD exercise started, the question was: "Will the CTD save time and money?" The answer is clearly "yes" and much more. It has allowed all stakeholders from the different countries to be and to stay on the same page. It is now the adopted and indispensable framework for all regulatory activity from development to marketing, while still allowing for regional variations in ICH and non-ICH countries.

The CTD is a success story led by a few people who were optimistic enough to make things happen despite the difficulties and conservatism present within both industry and the regulatory authorities at the time. It will be the basis for further harmonization activities. ■



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# EFFECTIVE eCTD WRITING

## FIVE ESSENTIAL COMPETENCIES<sup>1</sup>

Nancy R. Katz

**H**ow does a writer effectively create documents for a drug submission based on the Common Technical Document (CTD), and in particular, a CTD that will be submitted electronically (an “eCTD”)? This article describes five essential competencies that enable the delivery of eCTD-compliant documents.<sup>2</sup>

- An understanding of the rationale for the CTD: standardization, transparency, and effective reviews.
- An understanding of the structure (pyramid and Greek temple) and content of the CTD, as well as of the individual documents that comprise the CTD.
- The ability to create regulatory-compliant, scientifically accurate, linkable, clearly written documents, which, taken together, contain consistent messages that contribute to the case for drug approval.

- The ability to reuse content.
- Finally, and not altogether incidentally: the ability to get along with others and work as part of a team.

### An Understanding of the Rationale for the eCTD: Standardization, Transparency, and Effective Reviews

The CTD template was developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (for short, “ICH”; see [www.ich.org](http://www.ich.org)). Composed of representatives of regulatory authorities as well as experts from the pharmaceutical industries of three world regions, the European Union, Japan, and the United States, ICH members discuss and recommend processes related to the development of pharmaceutical products. ICH’s goal is harmonization, or put another way, standardization. ICH seeks agreement regarding the interpretation and application of guidelines and technical

requirements for the registration of new medicines. Three desired outcomes of harmonization are 1) reduction of duplicate testing and research; 2) intelligent and economical use of resources (human, animal, and material); and 3) elimination of “unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health” ([www.ich.org](http://www.ich.org)).

A drug application submitted in CTD format supports the goal of ICH by eliminating redundant applications: one CTD-based drug application can be submitted to and accepted for review by regulatory agencies in any country of each of the three ICH regions. An electronically based application (that is, an eCTD) further supports ICH’s goal by enabling efficient reviews, allowing reviewers almost instantaneous access to electronic documents and source data, hyperlinked to one another via an XML backbone, and ensures transparency, allowing reviewers to

1. Portions of this article were published in *Your Career as a Biopharmaceutical Regulatory Writer in Choosing the Right Regulatory Career*, edited by Peggy J. Berry, 2010; RAPS and *The eCTD and beyond: a primer for regulatory writers*. DIA Global Forum; 2010; April:16-21.  
2. For a thorough discussion of competencies for medical writers, many of whom write eCTD-compliant documents, see Woolley KL and Clemow D. Development and use of an international medical writer competency model. DIA Global Forum; 2010; June: 8-11.



trace the reasoning and data upon which the scientific conclusions of the application are based.

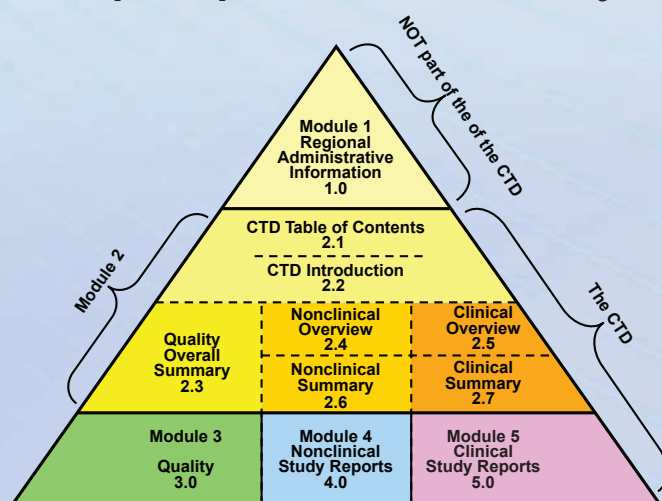
### An Understanding of CTD Structure and Content: The Pyramid and the Greek Temple

The CTD has five sections, referred to as “modules”; traditionally, the modules are depicted as part of a

mainly of reports (and associated study protocols) of in vitro and in vivo studies (pharmacokinetic, pharmacodynamic, toxicologic, and immunologic) of the drug in animals. Module 5, the “Efficacy” section, contains clinical information. It consists mainly of reports (and associated study protocols) of studies of the drug in human

2 — and postmarketing reports. Modules 3, 4, and 5 contain many subsections not depicted in the graphic; specifications for these modules are provided in the ICH’s M4 guidances, listed at the end of this article.

(Some nomenclature is useful at this point: Regulatory writers who write the documents for Module 3 and 4 are sometimes called *technical writers*. Those who write documents for Module 5 are often called *medical writers*. But this distinction is blurring fast, and is not always useful. A writer who writes documents for any of the CTD modules is properly called a *regulatory writer*.)



(This graphic was created as a slide for a DIA presentation by Christopher Preston and is reproduced with his permission.)

This is a most useful way to conceptualize the CTD; the next sections examine the pyramid from the base up.

pyramid:

**Modules 3, 4, and 5.** As the graphic shows, these modules form the base of the pyramid. Module 3, the “Quality” section, contains the chemistry, manufacturing, and controls (CMC) information. It consists mainly of reports of studies (and associated study protocols) conducted to characterize the pharmaceutical nature of the drug and ensure its purity. Module 4, the “Safety” section, contains nonclinical information. It consists

subjects. Included in this module are reports of pharmacokinetic, pharmacodynamic, toxicologic, and immunologic studies in human subjects as well as the phase 1, 2, and 3 clinical studies (including safety narratives for individual study subjects). Other Module 5 documents are the integrated summary of safety (ISS) and the integrated summary of efficacy (ISE) — these are in fact integrated analyses of safety and efficacy datasets and differ from the summaries of clinical safety and efficacy found in Module

**Module 2.** This module, with its seven subsections, summarizes the content of the three modules at the base of the pyramid and conveys the main, overarching messages of the drug application. Section 2.1 is the table of contents for Module 2 (its function is now subsumed by the XML electronic backbone), and Section 2.2 is a brief introduction to all of Module 2. Section 2.3 summarizes the content of Module 3. Sections 2.4 and 2.6 summarize the content of Module 4, and Sections 2.5 and 2.7 summarize the content of Module 5. Thus, the Module 2 subsections are to the CTD as the abstract of a journal article is to the main text of the article. Specifically, Module 3 is analogous to the body of a journal article describing the quality of the drug, and Section 2.3, the *Quality Overall Summary*, is analogous to the abstract of that article. As in the case of Module 3, Modules 4 and 5 are analogous to the body of a journal article describing



the safety (nonclinical studies) and efficacy (clinical studies) of a drug. However, unlike Section 2.3, which summarizes the content of Module 3 in one section, two Module 2 subsections are required to summarize Module 4, and two are required to summarize Module 5. The first layer of summary for Module 4 is Section 2.4, the *Nonclinical Overview*. This section is an overview, comparable to the part of a journal abstract that summarizes

5: Section 2.5 provides the overview and Section 2.7 provides the details.

The traditional pyramid of the CTD does not quite capture this concept. To understand the relationship of the Module 2 subsections to their respective modules at the base of the pyramid, it is useful to visualize the CTD as a Greek temple. (You will have to use your imagination here.)

**Module 1.** This module is not

Management plans, and 4) Clinical Investigator's Brochure (IB). The latter is a document prepared for the investigator. It summarizes current nonclinical and clinical data about the drug under investigation and provides a description of the drug's active and inactive ingredients.

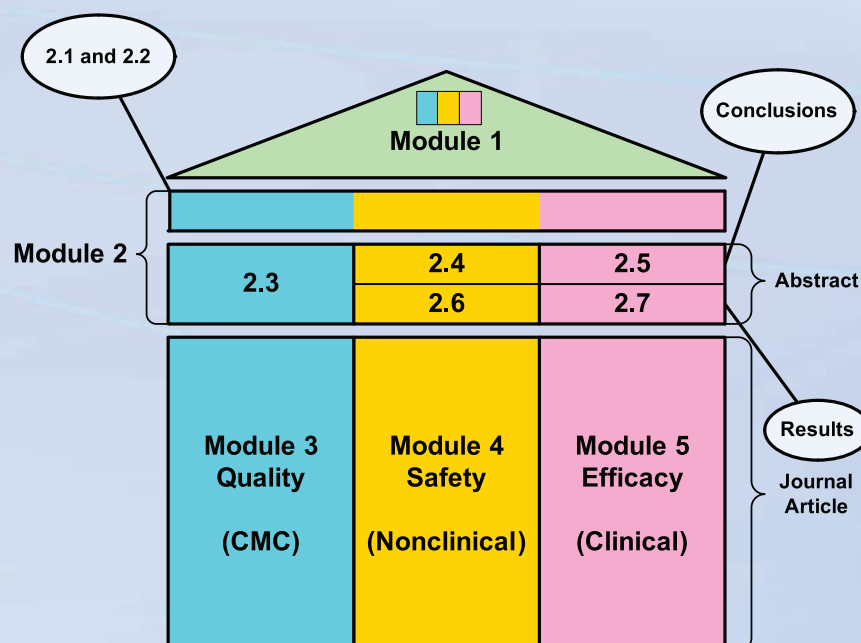
### The Ability to Create Regulatory-Compliant, Scientifically Accurate, Linkable, Clearly Written Documents, Which, Taken Together, Contribute to the Case for Drug Approval

Creating a document that meets these specifications can be daunting. Be encouraged by the fact that successful, seasoned regulatory writers are mere mortals who have learned how to do this.

a) *Regulatory-compliant, scientifically accurate documents:*

Competencies that allow achievement of this standard include knowledge of the following:

1. Regulations and guidelines governing the relevant documents in the CTD submission (Please contact the author for this information.)
2. Data and how to work with it: The regulatory writer should understand basic biostatistical principles as well as the underlying principles of programming, data entry, data interpretation, and coding of adverse events and drugs (via specialized dictionaries such as the Medical Dictionary for Regulatory Activities [MedDRA] and the World Health Organization [WHO] Drug dictionary).



(This graphic was developed by the author; she has used it in many DIA presentations.)

the *conclusions* section of an article. The second layer of summary for Module 4 is Section 2.6, the *Nonclinical Summary*. More detailed than Section 2.4, it is comparable to the portion of a journal abstract that summarizes the *methods and results* sections of an article. The same relationship applies to the subsections that summarize Module

properly part of the CTD. It is an administrative section, consisting of documents specific to the region in which the drug is being submitted (that is, the European Union, Japan, or the United States). Some documents included in Module 1 are the 1) General Investigational Plan, 2) Label (sometimes called the Package Insert [PI]), 3) Risk



3. Process of drug development, including principles and practices of clinical studies: The regulatory writer should understand protocol design, both nonclinical and clinical, including the logistics involved in running studies; principles of safety reporting, including reporting of serious adverse events (SAEs); creation of the final study report for a clinical trial; and basic clinical laboratory tests and interpretation of chest X-rays and electrocardiograms (ECGs).
4. Characterization and mechanism of action of the drug under development: The regulatory writer should understand the basics of the chemistry, manufacturing, and control of the drug, including the drug substance and the final drug product as well as the pharmacology of the drug, including its pharmacokinetics and pharmacodynamics (that is, what the body does to the drug and what the drug does to the body).
5. The indication (that is, disease or condition) under investigation: The regulatory writer should understand the etiology of the targeted condition (eg, asthma, multiple sclerosis, diabetes, obesity, infections caused by Gram-negative or Gram-positive pathogens resistant to current antibiotics), current treatments for the indication, and the immunological response of the body to the drug in healthy individuals and individuals with the proposed condition for treatment.

*b) Linkable documents:* More and more, regulatory authorities worldwide are expressing a preference for electronic submission of CTD-based drug applications. To comply, the regulatory writer must ensure that any document created as part of a submission be linkable to an XML backbone, the technological core of the eCTD. Competencies allowing realization of this standard include: 1) strong knowledge of basic software programs (eg, MS Word, especially the Styles feature, MS PowerPoint, MS Excel, and Adobe Acrobat); 2) ability to create and format tables (in MS Word), figures (in Prism or other graphing software), and study diagrams (in MS Visio or other drawing software); 3) ability to use and maintain templates; and 4) knowledge of how to archive and retrieve documents.

*c) Clearly written, well argued documents:* A regulatory writer tells the story of the drug, but more importantly, argues the case for its approval. Competencies that allow this include a thorough understanding of the efficacy and safety of the drug, a command of basic writing skills (eg, organization and logic as well as mastery of syntax, grammar, and punctuation), and knowledge of scientific style, including the in-house style of the sponsor for whom the regulatory writer works.

*d) Consistent messages:* A message, in regulatory parlance, is the translation of quantitative data

into a *valid* qualitative statement. To the best of your ability, ensure that any message in any document you create is a valid message. For example, if you write, in the discussion section of a clinical study report, that the drug “is well tolerated in the patient population tested,” ensure that the statement can be backed up by summary tables of adverse events as well as data in individual patient listings. Be sure also, that the same message (with supporting data) appears in the Clinical Overview (Section 2.5), the Summary of Clinical Safety (Section 2.7.4), and the Integrated Summary of Safety (Section 5.3.5.3). And especially make sure that the message hasn’t evolved into something inaccurate such as “this drug is safe for anyone and everybody.” (No joke, drift like this happens.)

### The Ability to Reuse Content

The CTD contains information and data that are repeated over and over in different contexts throughout the application. Access to building blocks of content, sometimes referred to as “topics,” allows re-use (often called “repurposing”) of information and rapid creation of documents that are more often than not written under tight timelines and by multiple authors. Sponsors may create topics by 1) establishing a folder on a common drive with files that contain standardized language and information, 2) approving the content of particular document (eg, the most current clinical study report) for re-use, or 3) employing sophisticated software that allows direct access of approved “topics”



into the document a writer is creating. Often, the writer is asked to work with subject matter experts (the clinician, biostatistician, toxicologist) to create the topics in the first place.

### **Finally, and Not Altogether Incidentally: The Ability to Get Along with People and Work as Part of a Team**

A regulatory writer does not work alone. Creation of regulatory-compliant, scientifically accurate, internally consistent documents results from successful teamwork and interaction with others. A writer obtains data and other information from people in all parts of an organization; works with others to craft interpretations of the data (“messages,” discussed above); circulates documents for review; adjudicates comments from colleagues; and finalizes a document for publication into an electronic format. In addition, the writer performs less glamorous tasks: ensures that abbreviations are used consistently throughout all documents; indicates, often by using blue font, which text needs to be linked to another part of the document, or another document in the submission; and ensures consistency of voice throughout the submission (eg, does your sponsor say “in the opinion of the Investigator, the drug contributed to a clinical benefit for the patient” or “The Investigator judged the drug to benefit the patient”? It is certainly true that “a foolish consistency can be the hobgoblin of little minds” (Ralph Waldo Emerson, *Self-Reliance*, 1841); however, an intelligent consistency certainly promotes ease of reading and timely reviews.

The writer also realizes that team review may result in re-conceptualization of the structure and content of a document, and that consequently, that writer may have to revise the document from the ground up. (For example, just imagine that at the last minute the sponsor changes the indication for the drug from “therapy for patients with moderate asthma” to “therapy for patients with mild-to-moderate asthma,” and envision the changes the writer must make.)

A successful document for eCTD submission depends on the writer’s willingness to get along with and learn from others and, when necessary, engage in ego subordination and/or intelligent assertiveness. For instance, a reviewer may insist that a well cadenced sentence crafted by the writer be turned into a grammatical but awkward piece of prose; in this case, the writer is silent. On the other hand, if the sponsor considers 20,000 pages of text an acceptable Summary of Clinical Safety, that writer is responsible for diplomatically and firmly pointing out that the guidance for that section specifies a much lower limit. If such behavior does not come naturally, many courses sponsored under the loose category of “leadership” and “management” exist that teach people how to work and play together on the job. Interpersonal skills are serious skills, and a lack of them will ruin the career of any writer who wants to be part of an eCTD submission team.

In addition, the writer who writes eCTD-compliant documents must keep in training. A writer should regularly perform a gap analysis, identifying areas that impede his or her ability to function (for instance, do you need to learn about Bayesian analyses or the latest FDA guidance about where to place the ISS and the ISE in the CTD?) and have a development plan that enables ways to plug those gaps. The world of drug development is never static, and in this fast-paced environment, a successful writer is one who keeps learning.

### **Summary and Conclusion**

The eCTD is here to stay. A drug application in eCTD format enables efficient reviews by regulatory agencies, which in turn allow faster delivery of new medicines to those in need. A writer participates in this effort by creating scientifically accurate, clearly written, eCTD compliant documents. Such a writer will always be a valued member of a drug development team. ■



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# APEC AND EFFORTS FOR REGULATORY HARMONIZATION

*Justina Molzon*

## Introduction

The Asia-Pacific Economic Cooperation (APEC) is a forum for Pacific Rim economies to promote economic cooperation throughout the Asia-Pacific region. It was established in 1989 in response to the growing recognition that the Asia-Pacific region had numerous comparative and complementary advantages. APEC's goal is to raise living standards and education levels via sustainable economic growth and to foster a sense of community and appreciation of shared interests among Asia-Pacific countries. It does this by promoting trade, sustainable economic growth and prosperity of member economies through policy alignment and economic and technical cooperation.

APEC currently has 21 members, including most countries with a coastline on the Pacific Ocean.

This article will describe how recent developments within the APEC Life Sciences Innovation Forum (LSIF) are important in advancing a more strategic, coordinated and sustainable approach to regulatory harmonization and cooperation among medical product regulatory authorities.

## Background

APEC is a unique forum operating on a basis of nonbinding commitments, open dialogue, and equal respect for views of all participants. Decisions are by consensus, and commitments are on a voluntary basis.

At APEC meetings held at Los Cabos, Mexico in October 2002, APEC

Leaders endorsed a proposal to establish the Life Science Innovation Forum (LSIF). This reflected the belief that life sciences innovation was important in promoting the improvement of both public health and economic development in the APEC economies. Perceived as an annual forum, LSIF would serve to promote policy discussion and projects aimed at advancing life sciences innovation. From the outset, harmonization was seen as a prerequisite to promoting innovation and a key element of robust health systems.

LSIF was well positioned to serve as an enabler of harmonization as its role was not to produce harmonized documents, such as ICH, but to promote the use of existing international guidelines. Participation in LSIF was voluntary, and this ensured participation of those economies interested and committed to cooperation and harmonization. Further, APEC funding was available to advance proposed projects focused on harmonization and a series of workshops on anti-counterfeiting, clinical trial evaluation, and Good Clinical Practices (GCP) inspection and ICH Quality guidances were offered throughout the APEC region.

APEC leaders also endorsed the development of a strategic plan to address health challenges and economic development goals. The strategic plan was to include identifying factors critical to success in each segment of the life sciences value chain. The resulting strategic

## APEC Members

Australia  
Brunei Darussalam  
Canada  
Chile  
People's Republic of China  
Hong Kong, China  
Indonesia  
Japan  
Republic of Korea  
Malaysia  
Mexico  
New Zealand  
Papua New Guinea  
Peru  
The Philippines  
Russia  
Singapore  
Chinese Taipei  
Thailand  
The United States  
Viet Nam

plan was endorsed in November 2004 and led to a focus on implementation projects in priority areas, including harmonization.

It was felt that regulators were a critical component of the life sciences innovation critical path and that the



effectiveness of a regulatory authority in fulfilling its mandate is critical to the achievement of desired life science outcomes. APEC leaders recognized the importance of good regulatory performances and harmonization in contributing to life sciences innovation.

This consideration is illustrated by elements of the LSIF Strategic Plan:

- Harmonization of standards... according to international best practices... will give the APEC region a competitive edge and expand opportunities for the rapid development of innovation
- To maximize the region's ability to address the region's health needs policies, standards and regulatory mechanisms should be reviewed against international best practices, in accordance with APEC principles on harmonization.

APEC's focus on harmonization emphasized that there should not be a duplication of efforts and that where international standards exist they should serve as the basis for harmonization throughout the region. Further, where appropriate organizations exist for developing international standards, APEC economies should promote the development of international standards through these bodies.

Despite these efforts, it was recognized that LSIF was not being used to its full potential in promoting a more strategic and effective approach to regulatory harmonization and cooperation throughout the APEC region. As a result, in August 2008, a series of strategic discussions took place during the LSIF VI meetings held in Lima, Peru, and a separate

regulatory session was held to examine the potential of LSIF to promote the achievement of regulatory harmonization in the region.

This session was attended by medical product regulatory authorities, industry, academia, and contract research organizations from the APEC region. Speakers helped frame the discussion by sharing views on the importance of international exchange and technical cooperation, internationally harmonized standards, the ICH Common Technical Document, and the WHO's regulatory assessment tool in promoting Good Regulatory Practices, and the possibility of leveraging regulatory resources.

Recommendations from this meeting to the APEC LSIF included:

- Establishment of the APEC Harmonization Center to address regional regulatory priorities
- Assessment by member economies of current regulatory capacity and resource levels as an important step in determining appropriate regulatory strategies and models, including the adoption of harmonized standards
- Working toward adoption of harmonized application and compatible review formats to promote a common regulatory language that supports sharing of information, good regulatory practices, and leveraging of resources
- The need to conduct a feasibility study on the confidential exchange and use of regulatory information

- The formation of a regulatory steering committee composed of interested economies.

These recommendations led to the establishment, with support from South Korea, of the APEC Harmonization Center (AHC) and the creation of a Regulatory Harmonization Steering Committee (RHSC)

### The APEC Harmonization Center

At the 20th APEC Ministerial meeting held in November 2008 in Lima, Peru, the AHC was endorsed by the APEC ministers.

"Recalling our commitment to promoting regulatory reform and harmonization, we welcomed and endorsed the establishment of the APEC LSIF Harmonization Center in Seoul as a key step forward."

With the establishment of the APEC Harmonization Center in March 2009, a formal mechanism was in place to enhance and sustain the implementation of harmonized standards and regulatory best practices throughout the APEC Region.

The AHC goals are to:

- Support access to the best practices and guidelines for regulatory harmonization
- Promote collaborative actions and information exchange
- Promote the conduct of clinical trials that meet international standards
- Enhance the quality, safety, and efficacy of therapeutic products.



The AHC serves as an APEC-wide resource for capacity-building efforts by conducting research and surveys, providing educational programs, publishing outcomes of meetings and trainings, and establishing networks and exchanges between participants and relevant international institutions.

### The Regulatory Harmonization Steering Committee

The Regulatory Harmonization Steering Committee (RHSC) was created to promote a more strategic, effective, and sustainable approach to harmonization by proactively identifying and prioritizing projects seen to be of greatest value and providing direction to the AHC on projects and activities that best meet these needs. The RHSC in partnership with the AHC will establish or strengthen linkages with other harmonization initiatives, training organizations, and key players in efforts to promote complementary actions and the most effective use of limited resources. These activities are to be conducted in accordance with an overall strategic plan and roadmaps focused on medical products (pharmaceuticals and medical devices).

The RHSC Work plan for 2010-2011 includes a series of workshops targeting the following priority areas:

- Multiregional Clinical Trials (MRCT)
  - MRCT/Tripartite Symposium (pharmaceuticals),
  - Medical Device Clinical Trials,
- Good Review Practices and the exchange and use of regulatory information
  - Pharmaceuticals,
  - Medical devices

- Global Harmonization Task Force Implementation,
- Pharmaceutical Quality
  - Integrity of the Supply Chain
  - ICH Quality by Design Workshop
- Pharmacovigilance
- Stem Cells ( prospective harmonization)
- 6th Pan-Asian Regulatory Conference (IFPMA/DIA/AHC)

An example of how AHC and RHSC work together to accomplish their objectives may be found in the MRCT Workshop held in Seoul, Korea in June 2009. This workshop served as a “diagnostic” of MRCT challenges, issues, and opportunities in the APEC region. The workshop provided a series of recommendations to address the challenges of conducting MRCT. These recommendations were considered in developing APEC project proposals that could lead to concrete directed in support of overall harmonization goals. As a result, the second workshop on MRCT was conducted in September 2010 to drill down into the issues and concerns delineated in the first program to get to their root cause and provide for possible pathways to successful MRCTs in the region. Many Ministers have endorsed the achievement of regulatory harmonization, thus demonstrating strong political support.

### Conclusion

Recent developments in the APEC have implications beyond the region in advancing regulatory harmonization in a more strategic, sustainable, and effective manner. APEC RHSC and AHC activities are being seen as playing a key role in

building a better global harmonization model.

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APEC:

<http://www.apec.org/>

APEC LSIF

<http://www.apec.org/Groups/Other-Groups/Life-Sciences-Innovation-Forum.aspx>

AHC

<http://www.apec-ahc.org/>

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*DIA, AHC, & IFPMA will co-sponsor the 1st Asian Regulatory Conference: Asia's role in Global Drug Development, April 26-28 in Seoul, Korea. See page 60 for more on this conference.*