

Introducing the International Conference on Harmonization  
Guidelines Into the World Trade Organization:  
A Strategy to Remove Technical Trade Barriers for  
Pharmaceutical Products

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\* Appendices II and IV were collected from PDFs and could not be entered into the electronic version of this paper, therefore they are not part of the numbered pages. Appendix III is 1 page and Appendix IV is 11 pages.

### List of Abbreviations

<b>API</b>	Active Pharmaceutical Ingredients
<b>CBER</b>	Center for Biologics Evaluation and Research (within FDA)
<b>CDER</b>	Center for Drug Evaluation and Research (within FDA)
<b>CTD</b>	Common Technical Document (ICH)
<b>DSB</b>	Dispute Settlement Body (within the WTO)
<b>EC</b>	European Commission
<b>EFTA</b>	European Free Trade Area
<b>EFPIA</b>	European Federation of Pharmaceutical Industries and Associations
<b>EMA</b>	European Agency for the Evaluation of Medicinal Products
<b>ESTRI</b>	Electronic Standards for the Transfer of Regulatory Information and Data
<b>EU</b>	European Union
<b>EWGs</b>	Expert Working Groups (ICH)
<b>FDA</b>	United States Food and Drug Administration
<b>GATT</b>	General Agreement of Tariffs and Trade (WTO)
<b>GCG</b>	Global Cooperation Group (ICH)
<b>GMP</b>	Good Manufacturing Practices
<b>ICH</b>	International Conference on Harmonization
<b>IFPMA</b>	International Federation of Pharmaceutical Manufacturers Association
<b>IND</b>	Investigational New Drug Application
<b>IOCM</b>	International Office for the Control of Medicine (within EFTA)
<b>JPMA</b>	Japan Pharmaceutical Manufacturers Association
<b>MHLW</b>	Ministry of Health, Labor and Welfare, Japan
<b>MSSO</b>	Maintenance and Support Services Organization (for ICH's MedDRA)
<b>MOFA</b>	Ministry of Foreign Affairs, Japan
<b>NDA</b>	New Drug Application
<b>NIHS</b>	National Institute of Health Sciences, Japan
<b>PhRMA</b>	Pharmaceutical Research and Manufacturers of America
<b>PMSB</b>	Pharmaceutical and Medical Safety Bureau (within MHLW)
<b>PMDEC</b>	Pharmaceuticals and Medical Devices Evaluation Center (within NIHS)
<b>SC</b>	Steering Committees (ICH)
<b>TBT</b>	Agreement on Technical Barriers to Trade (WTO)
<b>TTP</b>	Therapeutic Products Programme (Canada)
<b>US</b>	United States
<b>USTR</b>	United States Trade Representative
<b>WHO</b>	World Health Organization
<b>WTO</b>	World Trade Organization

**DC Producers**            Developing countries within the WTO with pharmaceutical production.

**DC Non-Producers**    Developing countries within the WTO with no pharmaceutical production.

**Preface**

The pharmaceutical industry is one of most complex business in the global economy. There are a multitude of ethical and economic issues surrounding the business from safety assurances to profit margins to patent rights and protection. Each of these issues affects the trade of pharmaceutical products. This project will focus on one specific facet that greatly affects the trade of pharmaceutical products: testing requirements used to establish the safety of pharmaceutical products for human use. Testing requirements are set by national regulatory agencies and they vary from country to country. The differences in requirements can sometimes act as trade barriers, greatly delaying foreign market access. This type of delay is a disadvantage for both the exporting manufacturer and the importing consumer. Over ten years ago the European Union, Japan and the United States decided harmonize their regulations for pharmaceutical market approval. In this project I lay out the steps and challenges involved in extending the International Conference on Harmonization (ICH) guidelines to the members of World Trade Organization (WTO).

The goal of ICH is to harmonize testing requirements of pharmaceutical products intended human use; therefore, it does not address pharmaceutical products for animal use, nor does it address patent rights, price controls or medical equipment.

**Scenario**

For the purpose of this project I will assume the role of a staff member on the ICH Secretariat. The ICH board members would like to extend their testing guidelines to the World Trade Organization (WTO). I have been asked to research the issues surrounding this potential project.

**Issue:**

The pharmaceutical industry is one of the largest sectors of international trade. Global sales of pharmaceutical products are currently estimated to be over \$300 billion dollars<sup>1</sup>. Despite the magnitude of trade activity for this sector, the WTO does not currently have an agreement that addresses testing requirements for pharmaceutical products. Most nations require pharmaceutical products to be tested for safety. The tests are mandated by regulatory agencies of each specific nation, so they vary from country to country. WTO members can currently refuse market access for pharmaceutical products based on these testing requirements. Country A, the importing country, can ban the entry of a pharmaceutical product if it has not been tested according to Country A's specific requirements even if the product has passed all safety tests in Country B, the exporting country. Exporting countries cannot contest this action within the WTO Dispute Settlement Body (DSB) because there are no guidelines in WTO agreements that address testing requirements for pharmaceutical products. Until guidelines are set importing nations can continue to refuse market access based on Article XX (General Exceptions) of the *General Agreement on Tariffs and Trade*, which allows members to disregard other trade rules in order to protect human safety.

Recognizing the problems cause by varying testing requirements the EU, Japan and the US decided to harmonized their testing requirements. Manufacturers and regulatory authorities from all three parties joined together to design a set of testing guidelines that would ensure consumer safety without creating trade barriers. They called the initiative the International Conference on Harmonization.

The ICH initiative addresses the problem of duplicate testing between the three parties, but challenges remain for many other countries. ICH membership covers only eighteen of the 144 member nations of the WTO; introducing ICH guidelines into the WTO would expand that membership to an additional 126 countries.

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<sup>1</sup> United States. Department of Commerce. US Industry and Trade Outlook 2000 Washington 2000

## **Executive Summary**

### **Issue:**

Technical barriers currently obstruct the trade of pharmaceutical medication. Each nation has its own testing requirements. In order to export their products, manufacturers are often required to repeat similar tests containing slight variations. Duplicate testing results in extraneous costs for manufacturers, wasted resources (animals and human volunteers) and delayed market access. Delayed market access poses great disadvantages for exporting manufacturers and importing consumers. This problem can be solved by having trade partners agree to harmonize testing requirements. Recognizing the benefits of harmonized testing standards, the European Union, Japan and the United States formed a joint initiative between the industry and regulators called the International Conference on Harmonization, but barriers still remain for non-ICH member nations. The ICH members would like to solve the trade problems caused by duplicate testing on a larger scale, not just among themselves. ICH members have opened their doors to any country interested in adopting their guidelines, but there is no enforcement mechanism. ICH and WTO members alike are powerless to contest pharmaceutical testing standards as a trade barrier because the WTO agreements do not currently contain any set testing guidelines. WTO adoption of ICH guidelines would remove technical trade barriers for pharmaceutical products.

### **Potential Obstacles to Consider:**

Introducing ICH standards into the WTO is a complex process with a multitude of issues to consider. In proposing this project to the WTO, ICH members will first have to consider where in the WTO agreements these guidelines should be placed. Next ICH members will have to consider how to gain support from regulatory authorities. ICH members should be prepared to convince regulatory agencies that the pharmaceutical products are completely safe; this involves not only guaranteeing the safety of the actual ICH guidelines, but also assuring the agencies that all WTO members follow good manufacturing processes. ICH members should also expect potential resistance from developing countries concerned that ICH guidelines (considered the most stringent in the world) may stifle the development of their own industries by enforcing standards they are not financially or technologically capable of following. Before ICH members attempt to introduce their guidelines into the WTO they should first be prepared to address and solve each of these potential issues.

### **Key Recommendations:**

- ❖ Convince WTO member countries to adopt ICH guidelines for market approval requirements of pharmaceutical products. The guidelines can be adopted into an annex of the Agreement on Technical Barriers to Trade. The process can take place during the next WTO Ministerial Round.
- ❖ Address developing nations concerns by providing technical and financial assistance. Allow a longer time frame for developing countries to adopt ICH guidelines.
- ❖ Address the safety concerns of regulatory agencies by ensuring that all participating parties operate on the same level. ICH currently has an Expert

Working Group developing Good Manufacturing Practices (GMP). The World Health Organization also has a code for GMP. All participating parties will be required to adhere not only to ICH guidelines, but also the GMP in order to ensure the highest level of consumer safety.

**Background:**

The current provisions of the WTO agreements allow importing countries to impose technical barriers to trade for pharmaceutical products. The technical barriers are applied in the form of testing requirements mandated to evaluate the safety, efficacy and quality of a product. Testing requirements are typically mandated by the regulatory agency of the importing country, so they vary from nation to nation. Many nations have similar testing requirements with only slight variations. Manufacturers find themselves repeating similar tests for each market they export their products to.

As stated earlier testing requirements vary from nation to nation. Developed nations with greater resources to devote to regulatory agencies tend to have the most stringent testing standards; these nations also tend to have the largest consumer share. European Union member nations, Japan and the United States alone represent 85% of worldwide consumption. Typically testing procedures for pharmaceutical products are extremely time consuming and costly. The testing requirements for most developed nations take twelve to fifteen years to complete.

For the past ten years the EU, Japan and the US, the three industry leaders for drug development, have been working towards harmonized testing requirements for the safety evaluation process of pharmaceutical products. The three parties formed an initiative called the International Conference on Harmonization. The ultimate goal of the ICH is to eliminate duplicate testing for pharmaceutical products. Over the past twelve years ICH members have harmonized over fifty guidelines to ensure the quality, safety and efficacy of their pharmaceutical products. ICH members entered into the initiative with the understanding that they would work together to eliminate duplicate testing, but there are no legal provisions mandating the agreement. Introducing ICH guidelines into the WTO would not only enforce the ICH initiative, it would also harmonize all WTO members, thereby removing technical barriers to trade on a much larger scale.

In order to ensure successful adoption of ICH guidelines into the WTO agreements members will have to address the potential obstacles listed above. Following is a strategy outlining recommended actions for handling these potential obstacles.

**Strategy:**

The overall strategy to introduce ICH guidelines into the WTO involves three phases:

- A strategy to introduce ICH guidelines into the WTO
- A strategy to gain support from regulatory agencies for this project
- A strategy to gain support from developing countries for this project

*Strategy to Introduce ICH guidelines into the WTO:*

In order to introduce ICH guidelines into the WTO, ICH members will have to act through their trade representatives. This will involve lobbying their trade representatives and convincing them to introduce this topic for negotiations in the WTO. ICH members should provide their trade representatives with the suggestion that the guidelines be adopted as an annex to the TBT agreement. ICH members should form a coalition with the World Health Organization to gain their support for the project. WHO support may help advance acceptance of this proposal.

*Strategy to Gain Support from Regulatory Agencies:*

Regulatory agencies of both the ICH member regions and the other WTO member nations may resist the idea of facilitated market access because they may mistake it as increased safety risks. The ICH guidelines on testing requirements only address drug approval. Regulatory agencies need to feel secure that imported pharmaceutical products will not pose any safety risks once they are released on the market. Continued safety of pharmaceutical products involves the manufacturing process, including storage and sealing. The WHO has issued universal guidelines on good manufacturing practices. In order to ensure that regulatory agencies feel secure with the provisions of this project, ICH members should suggest that the WHO guidelines on GMPs accompany the ICH testing guidelines in the annex to the TBT.

*Strategy to Gain Support from Developing Countries:*

In order to gain support from the developing countries within the WTO we will have to convince them that they will benefit from WTO adoption of ICH guidelines. The key to gaining support from developing countries is to target developing countries with pharmaceutical production. Show those countries the potential harmonized testing requirements provide to develop their own industries. Developing countries may argue that the short-term sacrifices of adjusting their current procedures to a much more costly and stringent procedure will hamper their industries to the point that they may not be able to reach the long-term benefits we suggest. ICH members should answer these concerns by providing financial and technical assistance to developing countries in order to ensure a smooth transition from their current procedures to the ICH and WHO guidelines. ICH members will also have to consider the concerns of developing nations that do not have any pharmaceutical production. These developing countries may be concerned that compliance with ICH guidelines will lead to higher prices, due to more expensive testing procedures. Once again, technical and financial assistance to developing countries with pharmaceutical production is the answer. Financial and technical assistance will help contain the costs of compliance to more stringent testing procedures, thereby avoiding increasing costs for consumers.

ICH members should work with the World Health Organization, the World Bank and the Group of 77 on this project. Support from the three organizations could help convince developing countries to support the project.

## **Background**

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### **The International Conference on Harmonization:**

#### **Overview:**

The International Conference on Harmonization (ICH) is an agreement between the European Union (EU), Japan and the United States (US) to harmonize regulatory requirements for the testing, application and approval process of pharmaceutical medications. The official name is the “International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.” ICH is a joint initiative between government regulators and industry manufacturers. ICH strives to deliver medications to consumers in the EU, Japan and the US in the most efficient, timely and cost effective manner<sup>2</sup>.

#### **Historical Overview:**

The first attempt to harmonize pharmaceutical regulatory requirements was undertaken by the European Commission (EC) member nations during the 1980’s<sup>3</sup>. Recognizing the mutual benefits to both industry and consumers, the EC decided to facilitate the trade of pharmaceutical products through the development of a single market. The undertaking was a success and demonstrated that multilateral harmonization for pharmaceutical products could be accomplished without jeopardizing consumer safety. Concurrently, the EC began bilateral discussions on possible pharmaceutical harmonization with both Japan and the United States. It was not until 1989 that all three parties joined together and considered a trilateral harmonization<sup>4</sup>. Specific plans began to materialize at the World Health Organization’s (WHO) Conference on Drug Regulatory Authorities held that year in Paris. One year later ICH was formed to oversee and carry out harmonization plans. The European Federation of Pharmaceutical Industries and Associations (EFPIA) hosted the original meeting, which took place in Brussels. ICH headquarters would later be set up in Geneva, Switzerland and the International Federation of Pharmaceutical Manufacturers Association (IFPMA) would take over administrative duties for ICH<sup>5</sup>.

#### **Members:**

Each of the three founding members has two active parties in ICH, one representing the government regulators and one representing industry manufacturers. Government and industry representatives work together closely to ensure a smooth

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<sup>2</sup> “Questions & Answers About ICH” International Conference on Harmonization 5 September 2001 <<http://www.ifpma.org/ich.html>>

<sup>3</sup> The various sources I checked did not provide an exact year.

<sup>4</sup> For the purpose of this paper the member nations of the European Commission, later to become the European Union will be considered as one party, making it the ICH a trilateral as opposed to multilateral agreement. I will use the term multilateral for my proposal to adopt ICH standards into the WTO.

<sup>5</sup> ICH does not have “offices” per se because it is a voluntary cooperative effort between regulators and industry of the three regions, but because IFPMA runs ICH headquarters can be considered to be in Geneva, Switzerland, where IFPMA is located. The address for contacting ICH is in Geneva.

development of ICH guidelines that address industry concerns while maintaining the most prudent standards for consumer safety.

European Union: The European Commission and European Federation of Pharmaceutical Industries' Associations are the two representatives for the EU.

- The EC represents the fifteen member countries of the EU. ICH activities are handled by the European Agency for the Evaluation of Medicinal Products, which was established by the EC specifically for this purpose (EMA)<sup>6</sup>. EMA is located in London.
- EFPIA represents pharmaceutical companies from sixteen countries in Western Europe, including all of Europe's major research based pharmaceutical companies. The association works closely with the EC and EMA to ensure that ICH activities are representative of the entire European industry, not just the EU member nations<sup>7</sup>.

Japan: Ministry of Health, Labor and Welfare (MHLW) and Japan Pharmaceutical Manufacturers Association (JPMA) are the representatives from Japan.

- MHLW oversees social welfare, social security and public health in Japan. The Pharmaceutical and Medical Safety Bureau (PMSB), a division of MHLW manages ICH activities. MHLW and PMSB work closely with Japan's National Institute of Health Sciences (NIHS), which carries out research and testing on drugs and vaccines. The agencies also work with the Pharmaceuticals and Medical Devices Evaluation Center (PMDEC), a division within NIHS, which focuses on the development of new drugs.
- JPMA represents ninety Japanese pharmaceutical companies, including all the major research-based pharmaceutical manufacturers in Japan. One of JPMA's primary goals is to improve the industry's understanding of international issues.

United States: The US Food and Drug Administration (FDA) and Pharmaceutical Research and Manufacturers of America (PhRMA) are the two parties representing the US in ICH.

- The FDA staff includes administrative, scientific and regulatory specialists organized under the Office of the Commissioner. The FDA deals with safety evaluations for a wide range of products including drugs, biologicals, medical devices, cosmetics and radiological goods. ICH activities are handled by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER).

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<sup>6</sup> "Structure" International Conference on Harmonization 27 November 2001  
<<http://www.ifpma.org/ich2.html>>

<sup>7</sup> "Structure"

- PhRMA represents seventy-two research based pharmaceutical companies in the US. The association also represents twenty-four affiliates that conduct biological research related to drug and vaccine development. PhRMA's Scientific and Regulatory Affairs division handles ICH activities.

In addition to the six participating parties, ICH also includes three observers who act as a liaison between ICH and non-ICH countries and regions. The three observers are the WHO, the European Free Trade Area (EFTA), and Canada. The International Office for the Control of Medicines (IOCM) represents EFTA at ICH. Switzerland has observer status through EFTA. IOCM, like ICH is located in Switzerland. The Therapeutic Products Programme (TTP) is the group representing Canada at ICH. TPP is affiliated with Health Canada. Each of the observers has a seat in ICH.

### **Structure:**

The structure of ICH contains four main groups: the Steering Committee, the Expert Working Groups (EWGs), the Secretariat and the Coordinators. The SC and EWGs develop the work and process of ICH. The Secretariat and the Coordinators carry out the administrative duties of ICH.

#### The Steering Committee

The Steering Committee is comprised of two representatives from each of the six member parties and one representative from each of the three observing parties. The Steering Committee is responsible for determining ICH policies and procedures and selects topics for harmonization; the committee also monitors the progress of harmonization initiatives. All Steering Committee work is done according to ICH Terms of Reference<sup>8</sup>.

#### Expert Working Groups

The Steering Committee assigns an EWG to each of the technical topics selected for harmonization. EWG represent each of the six members, the observers and any other relevant parties (such as the generic drug industry, pharmacopoeias etc.)<sup>9</sup>. The groups are comprised of industry specialists on the topics discussed; the members are nominated by each of the six parties. EWGs do not have a fixed membership, they participate for the timeframe in which their relevant topic is being discussed and/or reviewed.

#### The Secretariat

The primary duties of the Secretariat involve preparations for and documentation of all ICH meetings (both Steering Committee and EWGs meetings) and liaisons with any speakers who attend those meetings. The Secretariat is provided by IFPMA in Geneva, Switzerland.

#### The Coordinators

ICH coordinators act as the main contact between the six member parties and the Secretariat. The coordinators also ensure that ICH documents are distributed properly.

<sup>8</sup> Please see Appendix 1 for ICH Terms of Reference.

<sup>9</sup> "Questions and Answers About ICH"

### Meeting Structure

The ICH meeting structure is similar to the meeting structure of the World Trade Organization (WTO) in that there is an umbrella timeframe in which various topics are addressed and a set meetings within that timeframe to handle the details of the topics discussed; in the WTO the timeframe is referred to as a “Round” in the ICH it is referred to as a “Conference.” Conference sessions take place roughly every two to three years<sup>10</sup>. Within each conference session there is a series of meetings that take place twice a year; the location of meetings rotates between the three member regions. During these meetings, the Steering Committee reviews proposals for new topics and guidelines; the Steering Committee also reviews previously established guidelines to ensure that the harmonization process is carried out smoothly.

ICH also offers occasional workshops on the implementation and use of ICH guidelines. Traditionally the workshops have been offered simultaneously with the biennial meetings in order to benefit from the presence of the Steering Committee members. ICH would like to continue to offer workshops in the future, even though no official schedule or plans have been finalized as of yet<sup>11</sup>.

### **Topics:**

When the ICH initiative first started in 1990, its creators introduced eleven possible topics to address; twelve years later, fifty guidelines have been harmonized between the three regions<sup>12</sup>. ICH guidelines are divided into four main categories: quality, safety, efficacy and multidisciplinary<sup>13</sup>.

### Quality

Sixteen different guidelines fall under the category of quality. The guidelines cover various issues including stability, temperature, trial duration, light sensitivity, residual solvents, and impurities. The Quality section also evaluates viral safety for medications created using biotechnological engineering.

### Safety

There are thirteen guidelines covered in the Safety section. This section deals with detailed scientific issues including: carcinogenicity, genotoxicity, toxicokinetics (including reproductive toxicity testing), and pharmacokinetics. The guidelines in this section also look at toxicity issues during the testing phases and pre-clinical safety evaluations.

### Efficacy

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<sup>10</sup> From 1990 to 1997 Conferences were held every two years, from 1997 to 2003 conferences are scheduled every three years. See Appendix 2 for the exact schedule of meetings.

<sup>11</sup> “ICH Information Brochure” International Conference on Harmonization 10 January, 2002 <<http://www.ifpma.org/ich.html>> 10

<sup>12</sup> Chew, Nancy J. “ICH Now: Harmony at the End of the Century.” Biopharm 12 (1999): 24-32

<sup>13</sup> See Appendix 3 for a detailed description of ICH guidelines.

The Efficacy section covers fourteen guidelines. The guidelines addressed in this section are a combination of technical and administrative issues. Technical issues include: the effectiveness of long-term treatment for non-life threatening conditions and dose response information. Administrative issues include: clinical safety data management and standards for successful expedited reporting, maintenance of ICH guidelines, structure and content of clinical safety reports and ethnic factors in the acceptability of foreign clinical data.

### Multidisciplinary

The Multidisciplinary section covers topics that do not traditionally fit into one of the three sections discussed above. Many of the subjects in this section are actually tools that ICH helped create such as a medical terminology dictionary and a common marketing application for new pharmaceutical products<sup>14</sup>.

### **Products and Services:**

In addition to the guidelines ICH has developed, they have also created various products and services to facilitate the harmonization process. Over the twelve years member parties have been working on the ICH initiative, they have learned that their initial goal of tripartite pharmaceutical harmonization is a constantly evolving process, particularly considering the fast paced R&D nature of the medical industry. As the ICH SC and EWGs move further along the development of harmonization and the creation of new guidelines they may create new products and services. To date, they have developed four main products and services: MedDRA, the Electronic Standards for the Transfer of Regulatory Information and Data (ESTRI), the Common Technical Document (CTD) and the Global Cooperation Group (GCG). These tools aid member parties' manufacturers adhere to ICH guidelines and increase transparency of those guidelines and other ICH activities for non-members.

### MedDRA:

Pharmaceutical R&D teams in the EU, Japan and the US all used different terminologies to record drug development materials. Early in the ICH process the Steering Committee and EWGs realized true harmonization would not be feasible as long as regulatory communication barriers existed, and so they decided to create a medical terminology vocabulary that would allow all three parties to use one medical language; they named this dictionary MedDRA.

MedDRA is modeled after MEDDRA, a similar version of common medical terminology used by the EU<sup>15</sup>. The ICH Steering Committee and EWGs began the creation of MedDRA in 1994; it took four years to reach a point where the industry could actually use the dictionary. The MedDRA process will never actually be completed; it is an ever-evolving dictionary that will change in response to the future needs of the

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<sup>14</sup> These tools will be covered in greater detail in the next section of the ICH background: ICH Products and Services.

<sup>15</sup> Burley, Joanna and Nancy J. Chew. "ICH Regulatory Communications." Biopharm Sep 1999: 12, pg. 20-24

pharmaceutical industry<sup>16</sup>. IFPMA was granted the rights to MedDRA. Pharmaceutical regulators, researchers and manufacturers can access MedDRA on the Internet. MedDRA is available to regulators free of charge. Industry pays for the publication fees<sup>17</sup>.

The nature of MedDRA requires active maintenance of the dictionary. Updated terminology and online availability of MedDRA both require the continuous attention of specialized experts. ICH and IFPMA decided to contract such duties to separate companies able to carry out each specific task. The result is an intricate system involving five different companies that work to ensure that MedDRA successfully serves the needs of both regulators and industry. The main company that leads the MedDRA workgroup is BDM International, based in Virginia. BDM handles the maintenance and support services for MedDRA terminology. The group that works on MedDRA is called MSSO (Maintenance and Support Services Organization). MSSO implements updates to MedDRA, it also provides customer support services for MedDRA subscribers such as training, quarterly updates and a twenty-four hour help desk. Lead by BDM, the MSSO team is aided in the complete maintenance by four other companies: Quintiles Transnational Corporation in North Carolina, Stellar Systems in Virginia, Cyntergy in Maryland and Ernst & Young in New York. Quintiles handles medical review and translation of all MedDRA terminology. Stellar Systems operates the engineering services for development of the information systems and the standard operating procedures. Cyntergy runs the international help desk. Ernst & Young supports the user groups. The multiple dictionaries that were used prior to the creation of MedDRA were often incompatible with one another and lead to communication problems when manufacturers reported their information to multiple regulatory agencies<sup>18</sup>. The creation of MedDRA helps ensure a certain level of public safety when dealing with the development and production of pharmaceutical medications through one harmonized terminology.

#### Electronic Standards for the Transfer of Regulatory Information and Data (ESTRI):

The ICH initiative took place during the height of the technology and Internet boom. The founding parties of ICH spread across three different continents, making the use of high-speed technology and the Internet the most efficient means for information exchange and application processing. The ICH Steering Committee assigned an EWG to oversee the development of an electronic system for informational exchange between manufacturers and authorities. ESTRI covers the evaluation of encryption technologies, physical media (floppy disks and CD-ROMs), network messaging, message formats and electronic document transfers<sup>19</sup>. In 1996 the EWG selected the appropriate software to handle ICH needs for electronic information transfer; they selected Templar Software, based in Virginia<sup>20</sup>. By 1997 ICH members had successfully used the software to transfer drug reports.

<sup>16</sup> "ICH Regulatory Communications" p. 21

<sup>17</sup> "Questions and Answers about ICH" p. 11

<sup>18</sup> "ICH Regulatory Communications" p.21

<sup>19</sup> "Synopsis of ICH Guidelines and Topics" International Conference on Harmonization 10 November, 2001 <<http://www.ifpma.org/ich.html>>

<sup>20</sup> Wechsler, Jill. "Biologics, CTD and BSE." Biopharm May 2001: p.60-64

### The Common Technical Document (CTD)

ICH members initially worked to harmonize the technical requirements for the registration of pharmaceutical medications. The goal of harmonization was to improve and expedite access to foreign markets in a cost-effective manner; while harmonization of technical requirements helped reach this goal, the submission process continued to slow exportation of pharmaceutical products. Each of the three regions had their own requirements for the organization of marketing applications. The EU *Expert Dossier* required expert reports and tabulated summaries, while the Japanese *Gaiyo* required written summaries<sup>21</sup>. Another problem for manufacturers was the significant disparities in the timeframe for approval; the *Gaiyo* ran hundreds of pages and could in some cases take a few years to produce, greatly delaying market access in Japan<sup>22</sup>. ICH members addressed this problem by harmonizing the application for market approval. They created the Common Technical Document, an application for all three regions that follows the same guidelines for submission of new products.

Five modules divide the CTD<sup>23</sup>. Module 1, *Administrative and Prescribing Information*, includes product name, manufacturer, and dose indication information. Some of the information in this module is region specific, for example the type of labeling used in the particular country. Module 2, *Common Technical Document Summaries*, addresses pharmacologic class, proposed clinical use, toxicology studies, and other topics assessing the quality, safety and efficacy of the medication. This module contains seven sections, and three separate documents. The seven sections are:

- Table of Contents
- Introduction
- Quality Overall Summary
- Nonclinical Overview
- Clinical Overview
- Nonclinical Written and Tabulated Summaries
- Clinical Summary

The seven sections should be presented as one document. Following that document are three individual reports. The three individual reports are *M4Q Quality*, *M4E Efficacy* and *M4S Safety*. M4Q, M4E and M4S of Module 2 provide overall summaries of their respective topics. More detailed information follows in modules 3, 4 and 5. Module 3, *Quality*, provides detailed information on development of dosage form, formulation, container closure system and additional manufacturing information. Module 4, *Clinical Study Reports*, provides a critical assessment of clinical data on the effectiveness of the

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<sup>21</sup> United States. Food and Drug Administration. Guidance for Industry M4S: The CTD-Safety. Washington, DC: August 2001.

<sup>22</sup> Wechsler, Jill. "Risks and Rewards in the Global Marketplace." Pharmaceutical Technology May 2001: 16-24

<sup>23</sup> See Appendix 4 for an outline of the CTD. This outline states that Module 1 is not technically part of the CTD, but every CTD application must include module 1, so for the purpose of this section module 1 is considered to be a part of the CTD.

medication. Module 5, *Nonclinical Study Reports*, provide extensive summaries and discussions of nonclinical information on pharmacology, pharmacokinetics and toxicology.

Manufacturers have already used the CTD successfully. In August of 2001, Biogen, a US pharmaceutical company, used the CTD to simultaneously file a marketing application in the US and EU. The CTD allowed the US manufacture to file in a foreign market less than one hundred days after Phase III clinical results<sup>24</sup>. Currently the use of the CTD is optional in all three regions. The EU and Japan plan to mandate the use of the CTD sometime within the next two years; the US does not have plans to require use of the CTD, it will however provide guidance to manufacturers who choose to file using the CTD<sup>25</sup>. Global use of the CTD has already been discussed. Canada, an ICH observer plans to use the CTD in order to allow its manufacturers the benefit of concurrently filing in the ICH member countries. The World Health Organization is considering recommendations to 190 countries to adopt use of the CTD<sup>26</sup>. Although the CTD primarily harmonizes application format, it may eventually lead to a standardized registration process.

#### The Global Cooperation Group (GCG):

The members of ICH have made an effort from the onset of the initiative process to maintain a transparent code of practice that would keep all ICH guidelines and documents open to authorities and manufacturers of all countries, not just ICH member nations. Representatives from non-member nations are able to attend ICH plenary sessions as observers and the ICH information is available on the websites of all member parties, the ICH and IFPMA. In an effort to ensure smooth communication with non-member parties, the ICH created a specific group to serve as an information liaison between ICH participants and non-member parties. This panel, the Global Cooperation Group was formed in 1999 as a subcommittee of the Steering Committee. The GCG is comprised of one representative from each of the six parties on the Steering Committee, the Secretariat, and one observer from the WHO and Canada<sup>27</sup>. The GCG created a set of principles to follow when handling requests from outside parties<sup>28</sup>:

- ICH will not seek to impose its views on any country, region or company, but will serve as a resource for information and data
- ICH will provide non-ICH member countries or companies with any document related to the GCG initiative without charge
- This subcommittee will not cause or require any change to the current ICH structure or procedures of operation

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<sup>24</sup> "Biogen Completes International Registration Filing." Cambridge, MA. August 6, 2001  
<[http://www.biogen.com/site/content/releases/pressrelease\\_subpage\\_131.asp](http://www.biogen.com/site/content/releases/pressrelease_subpage_131.asp)>

<sup>25</sup> "Risk and Rewards in the Global Marketplace" p.18

<sup>26</sup> "Risk and Rewards in the Global Marketplace" p. 18

<sup>27</sup> "Global Cooperation Group" International Conference on Harmonization 10 November, 2001  
<<http://www.ifmpa.org/ichGCG.html>>

<sup>28</sup> Principles taken from "Global Cooperation Group"

- While some non-ICH countries are not in a position to utilize ICH guidelines at present, these guidelines will be used as the basis of ICH's response whenever information is requested
- The Global Cooperation Group will provide information upon request from non-ICH countries and will make information available about the existence of the ICH website, the address for communications and related information.

The ICH welcomes non-members to adopt its guidelines and the GCG works to address the needs of those parties<sup>29</sup>. The ICH has also published various informational brochures on the ICH.

### **Policy Background:**

#### **The Need for Testing<sup>30</sup>:**

Pharmaceutical practices dates back over thousands of years. It began with the use of herbs, minerals and other compounds to treatment ailments of the human body. The first official guide on the preparation of medicinal products can be traced as early as the 16<sup>th</sup> century (published in Germany) and by 1617 the first pharmaceutical association, *The Society of Apothecaries*, was established in London<sup>31</sup>. Overtime the nascent production of medications through the use of natural resources evolved to the development of chemical based treatments. By the nineteenth century the mass production of potent medicinal compounds were already a common practice in several European nations and the United States. Modern day industry leaders such as Bayer, Hoechst, Parke Davis and Eli Lilly were already established businesses in the two regions and the majority of their products were chemical based<sup>32</sup>.

With the growth spur of new medicinal products came new dangers in consumption of these goods. The first realization that the products taken to improve human ailments could result in detrimental health consequences occurred in the early 1900's. Opiates such as morphine, cocaine, opium and heroin were commonly used in medicinal products. Because there were no laws regulating the industry, the danger of using opiates in pharmaceutical products was not realized until patients started to develop addictions to their medications. Currently, a journalist named John Sinclair wrote a book called, *The Jungle*, which revealed the unsanitary practices of the Chicago meat packing industry. The two incidents propelled the U.S. Congress to pass the 1906 *Pure Food and Drug Act*. For the first time regulators were granted the authority to ban dangerous drugs. The law also mandated accurate labeling practices. All ingredients had to appear on the label and manufacturers could not make unsupported or misleading claims about the targeted treatment.

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<sup>29</sup> "Global Cooperation Group"

<sup>30</sup> I chose to focus on the United States because the US is currently the industry leader for research and development and the US represents the some of the most stringent guidelines. I have included minimal information on Europe and Japan because their laws are incorporated into the current ICH guidelines.

<sup>31</sup> Heil, Scott, ed. *Gale Encyclopedia of Global Industries* Detroit: Gale Research, 1999 p. 126

<sup>32</sup> This information was gathered from two sources *Gale Encyclopedia of Global Industries* p.126 and Carson, Thomas, ed. *Gale Encyclopedia of U.S. Economic History, Volume 2, L-Z* Detroit: Gale Research, 1999 p.788

The 1906 law was an initial step to protect consumers of pharmaceutical products, but as the industry grew, so did evidence of the need to more prudent guidelines. The 1930's marked an unprecedented situation illustrating the dire need for improved regulations. In 1935, The Massengill Company marketed a sore throat remedy containing diethylene glycol, now the main ingredient in antifreeze. One hundred and seven people died from using this cough syrup before the problem ingredient was discovered<sup>33</sup>. In response to the tragedy, Congress passed *The Food and Drug Cosmetic Act of 1938*, which required that all medicinal products pass tests for safety before they are put on the market. This was the first time pharmaceutical products tested for toxicity in the US.

Pharmaceutical testing procedures were extended to cover indirect side effects during the 1960's when a popular European sleeping pill was identified as the cause of over ten thousand birth defects in Europe. Infants whose mothers took the sleeping pill during the first trimester suffered severe deformities in their arms and legs. The realization propelled more stringent guidelines for market approval in both Europe and the US<sup>34</sup>. Japan mandated government regulations for the sale of pharmaceutical products during the 1950's<sup>35</sup>. As the use of synthetic chemicals in pharmaceutical products has increased, all three regions have adapted their regulatory guidelines in order to ensure consumer safety.

### **Understanding the Market Approval Process<sup>36</sup>:**

Rigorous pharmaceutical testing procedures geared to protect consumer safety has resulted in a thorough and extended market approval process. Once a new pharmaceutical product is discovered it usually takes an additional ten to fifteen years before it is released for public consumption. There are five stages to pharmaceutical testing: pre-clinical testing, phase I, phase II, phase III and phase IV<sup>37</sup>. The manufacturer typically does the pre-clinical testing. Clinical trials are carried out either by the manufacturer, a regulatory agency or a clinic, university or other research facility.

<sup>33</sup> Marlow-Ferguson, Rebecca, ed. Encyclopedia of American Industries Detroit: Gale Research, 2001 p. 491

<sup>34</sup> Immel, Barbara "A Brief History of GMPs for Pharmaceuticals" Pharmaceutical Technology vol. 25 July 2001 p.44-52

<sup>35</sup> "A Brief History of the ICH" International Conference on Harmonization <<http://www.ifpma.org/ich8.html>> 9 October, 2001

<sup>36</sup> This is a generalization of the market approval process in countries with stringent regulatory policies. The EU, Japan, the US and Australia are all examples of countries that fall under this category.

<sup>37</sup> This information has been gathered from four different sources:

"Phases of Product Development" Alliance Pharmaceutical Corporation December 18, 2001 <[http://www.allp.com/drug\\_dev.htm](http://www.allp.com/drug_dev.htm)>

United States. National Library of Medicines. "What is a Clinical Trial?" December 18, 2001 <[http://www.clinicaltrials.gov/ct/gui/c/wlb/info/whatis?JservSessionIdzone\\_ct=fqp5yqaz21](http://www.clinicaltrials.gov/ct/gui/c/wlb/info/whatis?JservSessionIdzone_ct=fqp5yqaz21)>

European Federation of Pharmaceutical Industries and Associations. "The Pharmaceutical Industry in Figures" 1999 Update. <[http://www.efpia.org/6\\_publ/default.htm](http://www.efpia.org/6_publ/default.htm)>

Australian Pharmaceutical Manufacturers Association, Inc. "Pharmaceutical Fact Sheet, Research and Development" March 18, 2002 <<http://www.apma.com.au>>

- **Pre-Clinical Testing:** The purpose of pre-clinical testing is to evaluate the biological activity of a compound against the targeted disease of aliment. Once this has been determined the compound is evaluated for safety. This is commonly done in animals, however scientists are working on alternative methods such as *In Vitro and In Vivo Diagnostic Testing*. Scientists predict that these types of testing will produce more accurate results than animal testing<sup>38</sup>.
- **Clinical Trials, Phase I:** The overall goal of this phase is to determine safety and dosage. The tests during this phase evaluate how the drug is absorbed, distributed, metabolized and excreted. The tests also evaluate the duration of the drug's activity in the body.
- **Clinical Trials, Phase II and III:** The main purpose of tests done during these phases is to determine the drug's effectiveness, efficiency and identify any long-term adverse reactions.
- **Post-marketing, Phase IV:** Phase IV tests are done once the regulatory agency has approved the drug for market release. This allows the regulatory agency and the manufacturer to extend safety and efficacy evaluations to a wider population and over a longer period of time. This also provides the opportunity to evaluate the drug's performance with other diseases/aliments and other medications.

	<b>Pre-clinical Testing</b>	<b>Phase I</b>	<b>Phase II</b>	<b>Phase III</b>	<b>Phase IV</b>
<b>Years</b>	3-4 years	1-2	2-3	3-4	Varies according to medication
<b>Test Population</b>	Laboratory and animal studies	20 to 80 healthy human volunteers	100 to 300 patient volunteers	1,000 to 3,000 patient volunteers	Varies according to medication
<b>Purpose</b>	Asses safety and biological activity	Determine safety and dosage	Evaluate effectiveness and look for side effects	Verify effectiveness and monitor adverse reactions from long-term use	
<b>Success Rate</b>	5,000 Compounds evaluated	Only 250 in 5,000 make it to phase I	Only 5 in 250 make it to phase II		Only 1 in 5 make it to phase IV

<sup>38</sup> Encyclopedia of American Industries p. 498

In addition to the testing phases, the manufacturer also has to account for the time it takes to apply for the testing, review the application and officially approve the product. This varies from nation to nation. In the United States the manufacturer must enter two separate application processes: the *Investigational New Drug Application* and the *New Drug Application*. The manufacturer must file for an IND after completing the pre-clinical testing phase. The FDA has thirty days to approve or reject the drug for clinical trials. The manufacturer files for the NDA after the completion of phase III. The NDA must contain all the scientific information that the company has gathered. The document typically runs roughly over 100,000 pages. The expected time limit for the FDA to review the NDA is six months, but in the majority of the cases the review process takes longer than the estimated time<sup>39</sup>. The Japanese version, *The Gaiyo*, can in some cases take years to review<sup>40</sup>. The ICH's CTD is the harmonized version of the market approval application.

### **Good Manufacturing Practices:**

GMPs cover a wide array of variables in the fabrication process of a pharmaceutical product. GMPs go beyond just factory inspections; the most stringent guidelines for GMPs address the entire manufacturing and post-manufacturing period from production, packaging and storage of a medication. GMPs set rules for equipment cleaning and validation, water quality, hygienic practices of personnel, sanitary upkeep of factories, packaging materials and tamper resistant lids and seals just to name a few<sup>41</sup>. Adequate GMPs and adherence to those guidelines are essential to ensuring the quality and safety of a pharmaceutical product.

GMPs have evolved overtime just as testing standards have. In the United States, the first federal law regarding sanitary production practices of medicinal treatments was passed in 1902. The law required inspection and licensing of all biologicals products<sup>42</sup>. The 1902 law was a first step in designing hygienic practices to protect consumer safety, but it contained many loopholes and it did not address the actual manufacturing process. Like testing standards, the need for detailed GMP guidelines gained attention as a result of tragedies related to the consumption of tainted pharmaceutical products. In many ways, GMPs and testing standards are closely connected. The ultimate goal of both policies is to prevent adverse health reactions injuries from medicinal products. *The 1938 Food, Drug and Cosmetic Act*, on testing regulations also included a small section on GMPs: manufacturing plants became subject to both registration and inspection<sup>43</sup>. Manufacturing and quality control requirements were further enhanced in 1944 when Congress passed *The Public Health and Services Act*. The law was passed in response to a catastrophic disaster involving sulfathiazole tablets; nearly three hundred people died when the drug was tainted with the sedative phenobarbital<sup>44</sup>. *The Public Health and*

<sup>39</sup> "Phases of Product Development"

<sup>40</sup> Wechsler, Jill "Taking Steps Toward Harmonization with Europe and Japan" Pharmaceutical Technology March 1999 p.16-19

<sup>41</sup> Mirasol, Feliza "FDA, ICH Face Challenges in Development of GMPs" Chemical Market Reporter 29 March 1999: 4-10

<sup>42</sup> Encyclopedia of American Industries p.492

<sup>43</sup> Encyclopedia of American Industries p.493

<sup>44</sup> "A Brief History of GMPs for Pharmaceuticals" p.46.

*Services Act* updated the 1902 law on the regulation of biological products; it also included regulation on the control of communicable diseases.

The 1970's and 1980's marked a watershed period for GMP regulation in the United States. In 1978 the Food and Drug Administration revised GMP regulations. The updated version specified that GMPs cover "the facilities or controls used for the manufacturer, processing, packing or holding of a drug"<sup>45</sup>. The law states the purpose of such guidelines as "to assure that such drug meets the requirements of the act as to safety and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess."<sup>46</sup> In 1983 GMPs in the United States was extended to cover packaging of medicinal products in the *Federal Anti-Tampering Act*. The law was passed after the discovery in 1982 that roughly thirty-one million bottles of Tylenol aspirin had been laced with cyanide post-production. The 1983 law mandated that tamper resistant sealing<sup>47</sup>.

GMPs are internationally recognized as crucial to ensuring quality pharmaceutical products. It is in the WHO's belief that any attempts governments make to advance health needs of their societies may be compromised without the assurance that their medical products meet acceptable standards of quality, safety and efficacy<sup>48</sup>. The WHO believes so strongly in GMPs that they have designed their own set of guidelines on GMPs. The WHO guidelines are meant as a frame of reference for any government looking for guidance of GMPs. WHO's first steps to determine GMPs were presented in a draft text written for the Twentieth World Health Assembly in 1967<sup>49</sup>. The initial draft has evolved into a two-volume compendium on guidelines for quality assurance of pharmaceutical products. The guidelines have been composed through the aid of various technical experts, including expert committees on biological standardization and pharmaceutical preparations.

GMPs play a vital role in the regulatory guidelines of all three regions of ICH members. ICH addresses GMPs throughout their guidelines and topics, but ICH takes GMPs one-step further by specifically addressing GMPs for active pharmaceutical ingredients (APIs) in guideline *Q7A Good Manufacturing Process for Active Pharmaceutical Ingredients*. APIs are often traded between nations, and do not necessarily undergo the same type of rigorous inspections mandated for finished pharmaceutical products<sup>50</sup>. The ICH Steering Committee and EWG are still in the process of drafting and finalizing the specifics for this guideline. ICH members anticipate that finalization of the guideline will take a considerable amount of time because no

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<sup>45</sup> "A Brief History of GMPs for Pharmaceuticals" p.47

<sup>46</sup> "A Brief History of GMPs for Pharmaceuticals" p.47

<sup>47</sup> "A Brief History of GMPs for Pharmaceuticals" p.48

<sup>48</sup> "WHO Quality Assurance of Pharmaceuticals, Vol.2" World Health Organization January 9, 2002, Introduction <<http://www.who.int/medicines/organizations/qsm/activities/qualityassurance/gmp.htm>>

<sup>49</sup> "WHO Good Manufacturing Practices: Main Principles for Pharmaceutical Products" World Health Organization January 9, 2002

<[www.who.int/medicines/organization/qsm/activities/qualityassurance/gmp.htm](http://www.who.int/medicines/organization/qsm/activities/qualityassurance/gmp.htm)>

<sup>50</sup> Fabian, Arthur "Global Harmonization of GMPs for APIs: A Panel Discussion" Pharmaceutical Technology June 1999 p.90-101

country to date has developed GMPs specifically for APIs. Other ICH guidelines have been modeled after the policies of the EU, Japan and the US. Guideline Q7A is the first to be drafted completely from scratch.

### **Commercial Background:**

Research and development drives many of the world's leading pharmaceutical companies, including the majority of companies in the three ICH member regions. The entire process of producing a new drug, from creation to market access is referred to as R&D. The term research refers to the actual creation of the drug in the laboratory; the term development refers to the testing requirements the drug must pass in order to gain market access. R&D is a crucial part of the pharmaceutical business for both manufacturers and consumers alike. For manufacturers new drug discoveries lead to increased business; for consumers it means new choices for treatments and improved versions of the treatments that already exist. R&D provides countless benefits to the industry and consumers, but it is a long, risky and expensive procedure. Scientists will experiment with thousands of chemical compounds before discovering a successful mix. Of five thousand chemical compounds tested only 250 will make it to the pre-clinical testing phase. Of those 250 potential developments only one will reach consumers on the market. It takes an average of fifteen years from the time a drug is created in the laboratory to the time it reaches consumers on the market and an average of \$800 million US dollars spent on the R&D of just one medication<sup>51</sup>.

Much of the time and money involved in R&D is spent on the testing phases. The testing phases alone take an average of twelve years to complete. Aside from the time and money, testing phases also result in the use of thousands of animals, roughly 80 healthy volunteers and as many as 5,300 patient volunteers. The financial, animal and human costs involved in testing are often exacerbated when manufacturers prepare to export the medication. Each country has individual standards for market approval. In order to export their pharmaceutical products manufacturers must often repeat similar tests to gain market access. This is particularly true for safety tests. Regulatory agencies are often testing for the exact same results, but the tests must be repeated because of slight variations of specifics such as study length, content, species requirements, dose selection and exposure levels<sup>52</sup>.

### **Political and Stakeholder Background:**

The following stakeholders have a vested interest in pharmaceutical trade and any agreements affecting the trade of pharmaceutical products. Many of the organizations listed share member nations.

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<sup>51</sup> "PhRMA Industry Profile 2002" Pharmaceutical Manufacturers Association of America January 25, 2002 <<http://www.pharma.org/publications/profile02/index.html>>

<sup>52</sup> Nutley, Caroline, Dr. "The Value and Benefits of ICH to Industry" International Federation of Pharmaceutical Manufacturers Association October 1, 2001 <<http://www.ifpma.org/pdfifpma/valuebenefits.pdf>>

### **The International Conference on Harmonization:**

ICH is comprised of both industry and regulatory agencies of the EU, Japan and the US, the three global leaders for research and development and consumption of pharmaceutical products. The three regions are responsible for 92% of research and development and 83% of consumption of pharmaceutical products<sup>53</sup>. Canada, Switzerland and the WHO are official observers to the ICH. ICH administrative services are provided by IFPMA, including the staffing of the ICH Secretariat. The main goal of ICH is to eliminate the waste of financial and material resources and the delayed market access caused by duplicate testing.

### **World Trade Organization:**

The primary purpose of the WTO is to facilitate trade between nations; the organization deals with every aspect of trade. This is done in large part through the various multilateral trade agreements of the WTO. New topics for trade agreements are typically decided upon by consensus among members. There are 144 member nations in the WTO. Over three-quarters of WTO members are developing or least developed nations. Consensus on WTO agreements often involves finding an adequate balance between the needs of developed and developing nations. All three members of the ICH are parties to the WTO.

### **World Health Organization:**

The WHO, a sub-organization of the United Nations was established in 1948. The goal of the WHO is to promote the highest possible levels of public health worldwide. The WHO recognizes the attainment of the highest health standards possible as a fundamental human right<sup>54</sup>. WHO work falls into three basic categories:

- Provides information and guidance on developments of diseases and healthcare, established international sanitary standards and quarantine measures
- Sponsors measures for the control of epidemics and eradication of diseases (immunization campaigns, clean water assistance etc)
- Strives to strengthen public health programs in member nations.

The WHO has several projects involving the issues surrounding the pharmaceutical industry. These projects include guidelines for good manufacturing processes and programs to ensure the access of safe, affordable pharmaceutical medications worldwide. As mentioned earlier WHO is an official observer to the ICH and all three ICH member regions are also members of the WHO. The WHO shares many of its members with the WTO.

### **World Bank:**

The World Bank is comprised of 180 member nations, many of which are also members of the WTO. The main purpose of the World Bank is to provide development assistance to third world nations; it is one of the largest financial organizations devoted to

<sup>53</sup> Encyclopedia of Global Industries p. 123

<sup>54</sup> "Health as a Human Right" World Health Organization January 9, 2002  
<<http://www.who.int/archives/who50/en/human.htm>>

development assistance. The World Bank funds several development programs working to improve public health in developing countries. These programs recognize the importance of pharmaceuticals and strive to improve access of safe and affordable pharmaceutical products for the poor.

### **The Group of G77:**

The Group of G77 (G-77) is comprised of 133 developing nations. G-77 is a coalition within the United Nations. G-77 member nations work together to ensure policies that will advance and promote the economic interests of developing nations. G-77 member nations recognize that trade is essential to their economic development. The group has specific agreements devoted to issues surrounding trade. Many of the group's projects involve mobilizing financial and technical support from developed countries. Promoting investment, trade and technology in developing countries is a primary goal of G-77. Many G-77 members are also members of the WTO.

### **Developing Countries Within the WTO:**

Over three quarters of WTO members are developing countries. The levels of socio-economic development among these nations vary greatly, as do their specific needs. For the purpose of this project, the WTO developing member nations will be separated into two categories: developing nations with pharmaceutical production and developing nations with no pharmaceutical production; they will be referred to as DC producers and DC non-producers.

### DC Producers:

Although developed countries lead the R&D side of the pharmaceutical industry, they do not completely dominate global pharmaceutical development and production. Some developing countries have very successful pharmaceutical industries. Brazil, India, Egypt, Mexico, and Thailand are all examples of developing countries with strong pharmaceutical industries. Many of these countries have developed their pharmaceutical industries by providing affordable generic medications both domestically and globally. For example, Brazil and India were responsible for providing many Sub-Saharan African nations with affordable generic versions HIV/AIDS drugs before patent-holders offered discounted versions of the medications<sup>55</sup>.

Although DC producers typically have a lower R&D rate than developed nations their industries do include drug discoveries not just production of existing drugs. Many DC producers have sophisticated pharmaceutical industries that produce a wide array of pharmaceutical medications. A review of India's pharmaceutical industry illustrates this point. The pharmaceutical industry is the leading science based sector in India. Pharmaceutical production in India covers almost every type of existing medication, including antibiotics and cardiac drugs<sup>56</sup>. The Indian pharmaceutical sector is comprised of a knowledgeable workforce and well-equipped production facilities, many of which are approved by EU and US regulatory authorities for good manufacturing practices. Both production and exports of pharmaceutical products have risen steadily over the last

<sup>55</sup> Chirac P. "AIDS: Patent Rights Over Patient's Rights" *The Lancet* August 2000

<sup>56</sup> "The Pharmaceutical Industry in India" Organization of Pharmaceutical Producers of India. March 1, 2002 <<http://www.indiaoppi.com/pharmindia.htm>>

ten years. R&D expenditure in India is relatively low (1.9% compared with the 10 to 16% of industry leaders) due to a lack of patent protection laws; India is in the process of adopting patent right policies and expects the new patent rights protection will spur R&D growth<sup>57</sup>.

#### DC Non-Producers:

Many least developed WTO member nations fall into the category of DC non-producers. These countries have either have no pharmaceutical production or extremely limited pharmaceutical production. Due to the lack of a domestic industry they are dependant on other nations for their pharmaceutical products. Many of these countries also lack the resources (mainly regulatory agencies) to evaluate the safety of imported pharmaceuticals so they become dependant on the evaluations of the exporting nations. Many DC non-producers lack the adequate institutional capacity to regulate pharmaceutical activities. They do not have strict testing requirements (if they mandate testing requirements at all) and therefore do not generally impose technical trade barriers to pharmaceutical products. These nations also lack adequate funding for national healthcare; they have a vested interest in ensuring that pharmaceutical producers, particularly producers of generic versions can continue to provide affordable pharmaceutical products. Many of the WHO and World Bank health programs are geared towards improving access to medicines in these countries.

#### **Regulatory Agencies:**

The specific interests of regulatory agencies vary from nation to nation depending on the country's socio-economic situation. The abilities and duties of these agencies vary greatly from country to country. Typically the main interest of the regulatory agencies is the assurance of safe, quality products for consumers. In most developed nations agencies are generally responsible for creating and reviewing safety tests for pharmaceutical products before they are released on the market. Developing nations may set their own standards or adopt the standards of the importing country and simply review the results depending on the resources of the agencies.

#### **Commercial Analysis**

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The EU, Japan and the US had three primary objectives they hoped to address by forming ICH<sup>58</sup>:

- A more efficient use of human, animal and material resources
- The elimination of unnecessary delay in the global development and availability of new medications
- Maintain the highest levels of safety, quality and efficacy regulatory obligations to protect public health

The fifty ICH guidelines created to date show the great success ICH members have had in working towards each of those objectives in the three regions, but the problem of

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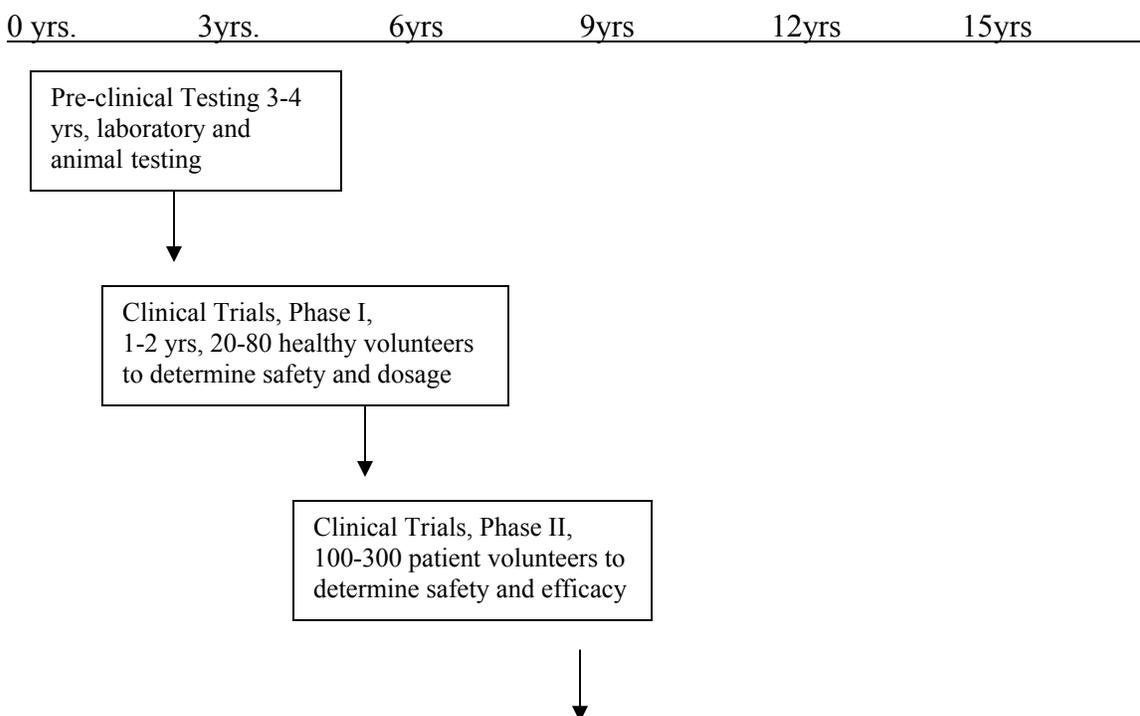
<sup>57</sup> "Research & Development" Organization of Pharmaceutical Producers of India. March 1, 2002  
<<http://www.indiaoppi.com/research&dev.htm>>

<sup>58</sup> "The Value and Benefits of ICH to Industry" p.2

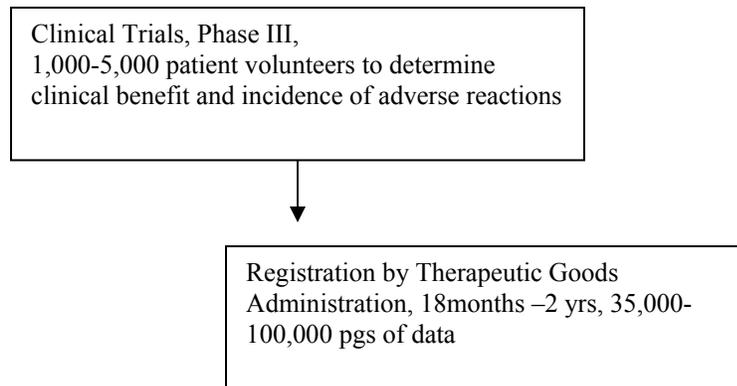
duplicate testing remains for the rest of the global market, particularly within the largest trade regime, the WTO. The lack of testing guidelines in the WTO acts as a technical trade barrier for pharmaceutical products. Exporters are often required to repeat the testing phases for each importing country in order to satisfy the exact requirements for the specific importer. Often the testing requirements are similar with only slight variations such as dosage selection and species requirements. The ICH members recognized the similarity of their testing requirements. They realized the slight variations in testing requirements did not actually alter the testing outcomes; they were testing for the same results, they simply used slightly different procedures, which resulted in extraneous expenses for manufacturers without actually benefiting consumers. Harmonization of testing requirements among ICH members provides a solution but only among eighteen of the 144 members of the WTO.

Australia is a good example of a WTO member not included in the ICH initiative with arduous testing requirements that closely resembles those of the ICH member nations. Australia's testing requirements take an average of fifteen years to complete, costs an average of \$500 million US dollars and produce roughly 100,000 pages of data for review<sup>59</sup>. The tests required for market access in Australia closely resemble the tests performed in the ICH regions. The pre-clinical and clinical trials require roughly the same number of tests subjects and examine the same data. The approval application, which the ICH CTD would replace, runs from 35,000 to 100,000 pages depending on the medication and takes from eighteen months to two years to complete.

### Australia's Drug Approval Process



<sup>59</sup>Australian Pharmaceutical Manufacturers Association. "APMA Facts Book 1999-2000, Pharmaceutical and Health Industry Information" March 20, 2002 <<http://www.apma.com.au/facts.pdf>>



There is enough activity in pharmaceutical trade between Australia and ICH member nations to merit attempts to facilitate trade interactions for pharmaceutical products; over 90% of Australia's imports of pharmaceutical products are from the ICH members and roughly 33% of Australia's exports are to ICH member nations<sup>60</sup>. Due to the significant pharmaceutical trade interactions between Australia and ICH members, Australia's adoption of ICH guidelines offers great potential for more efficient drug development, both in terms of financial resources and animal and human test subjects.

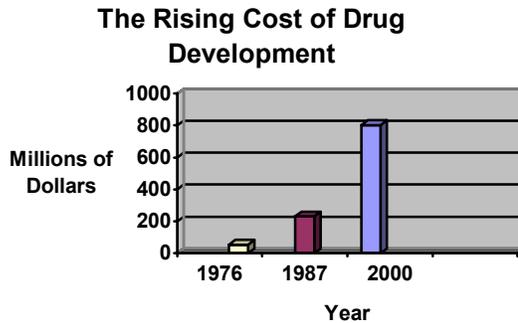
Manufacturers export their products in order to increase profits, not costs. Duplicate testing greatly increases export costs for pharmaceutical manufacturers. Pharmaceutical R&D companies, most of which are profit driven, can spend as much as \$800 million developing just one medication<sup>61</sup>. As stated earlier development refers to the testing requirements for market approval; therefore, much of the R&D cost is spent on rigorous testing to ensure safety, quality and efficiency of the products. It is difficult to provide an exact dollar amount for testing requirements because the pharmaceutical industries typically release expenditure costs for the entire R&D process without breaking it down between the creation of the drug and the testing process. Each country has individual standards for testing requirements. In order to export their pharmaceutical products manufacturers must often repeat similar tests to gain market access. Manufacturers depend on market access to recover the exorbitant costs of drug development. Exporting offers the chance to enlarge their market access. Duplicate testing often negates the potential benefits of foreign market access. Pharmaceutical companies typically pass the added costs to consumers. Harmonization of testing standards offers the potential of savings for consumers as well<sup>62</sup>.

<sup>60</sup> "APMA Facts Books 1999-2000, Pharmaceutical and Health Industry Information" p. 12

<sup>61</sup> "PhRMA Industry Profile 2002" p. 12

<sup>62</sup> The author realizes there is no guarantee pharmaceutical companies will actually pass the savings on to consumers, but savings could be realized in the absence of added costs that would most likely be passed onto the consumers.

The cost of R&D has consistently soared over the past twenty years, from \$54 million US dollars in 1976 to \$231 million in 1987 to \$800 million in 2000. Much of the increase can be attributed to the need for more detailed and stringent testing requirements as new drugs become more complex and the marketplace (including health insurers) become more demanding<sup>63</sup>. Pharmaceutical manufacturers are under increasing pressure to develop new drugs that can improve health outcomes, not just treat symptoms. More complex drugs results in more expensive testing requirements. Another factor that attributed to the rising cost of testing requirements is difficulty recruiting human test subjects for clinical trials<sup>64</sup>.



The cost of testing requirements is expected to continue to show dramatic increases in the future and many pharmaceutical companies have faced increasing pressure from shareholders to contain expenses for the entire R&D process<sup>65</sup>. Harmonized testing standards between a greater number of countries offers an avenue to eliminate the expense of duplicate testing, thereby containing a portion of drug development expenses.

It is difficult to predict exactly how much pharmaceutical manufacturers spend on duplicate testing because the industries release costs for the entire R&D process without specifying how much of those costs are spent on the testing phases. The drug creation is a fairly short process, roughly two years compared with the testing requirements that can last from twelve to fifteen years. Drug creation involves mixing chemicals where the testing phases involve animal and human test subjects. For this reason assume that drug creation is only 25% of the total R&D costs, making testing requirements 75%. As stated above, the current cost of R&D is roughly \$800; therefore testing requirements would be roughly \$600 million per new drug. The pharmaceutical industry does not release the exact costs of duplicate testing because it varies from country to country and for countries to with similar standards, the manufacturer would only have to repeat the testing phases with differences between the exporting and importing nations. Choosing a conservative estimate would still demonstrates that duplicate testing is a costly procedure. Assuming manufacturers must spend roughly 40% of the total testing costs on duplicate testing, it would cost roughly \$240 million just for the testing requirements to export a pharmaceutical product.

<sup>63</sup> "PhRMA Industry Profile 2002" p.23

<sup>64</sup> Cookson, Clive "Still No End to the Slowdown" *Financial Times* 30 April, 2002: II

<sup>65</sup> *Encyclopedia of Global Industries* p.123

## **Policy Analysis**

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WTO adoption of ICH guidelines will depend, in part upon the support of regulatory agencies. The regulatory agencies will have to feel confident that this WTO mandated testing requirements would not jeopardize consumer safety. The issue is not the ICH testing requirements that would be used to initially approve the medications, but the manufacturing process those products would follow once they have gained market access.

Good manufacturing processes are essential to assurance safe pharmaceutical products. The absence of GMPs in the production of pharmaceutical practices can lead to tragic consequences: in 1955 sixty individuals (in the US) inoculated with the polio vaccine developed the disease because the vaccines had not been completely inactivated due to poor manufacturing<sup>66</sup>. Instances such as this has made policy makers and regulatory agencies realize the importance good manufacturing practices and guidelines.

GMPs for pharmaceutical testing are present throughout the ICH guidelines, but GMPs are not just a part of the testing phases. GMPs typically address the entire life of a pharmaceutical production from research in the laboratory through the time it reaches a consumer. GMPs address various facility operations such as equipment cleaning, water temperature and worker hygiene. ICH members all operate under similar manufacturing processes. WTO adoption of ICH guidelines could potentially harmonize testing standards for 144 different countries. Typically, the market approval process does not address post market issues that still affect safety such as storage and sealing of the product. Those are issues that fall under manufacturing of the product and are to some extent beyond the current ICH guidelines.

The WHO has long believed that GMPs of pharmaceutical products are crucial to maintaining a high level of public health. The introduction of the WHO's publication of GMPs states without assurance that drugs "meet acceptable standards of quality, safety and efficacy, any health service is evidently compromised."<sup>67</sup> The WHO guidelines on GMPs offer thorough and comprehensive steps to ensure that the entire production process for medications will result in a safe, quality product.

ICH guidelines offer comprehensive standards for the entire testing period, but do not specifically address production. In order to assure regulatory agencies that WTO adoption of a harmonized market approval system will not result in jeopardized safety the WTO should also adopt the WHO guidelines on GMPs

## **Legal Analysis**

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The current legal agreements of the WTO contain a loophole that allows members to apply a technical barrier for pharmaceutical products. That technical barrier is applied

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<sup>66</sup> "A Brief History of GMPs for Pharmaceuticals" p. 46

<sup>67</sup> "Quality Assurance of Pharmaceuticals"

in the form of testing requirements for safety evaluations. As stated previously, testing requirements are set by the regulatory agencies of each specific nation; therefore they vary from country to country. Because WTO agreements do not contain guidelines for testing requirements importing nations can refuse market access of a pharmaceutical product until it has passed the exact testing requirements of that specific country. Exporting nations have no legal basis on which to oppose the actions of the importing nations. Furthermore, importing nations may defend their actions based on Article XX of the GATT. Article XX, *General Exceptions*, allows WTO members to disregard all trade obligations in order to protect human health. Importing countries may impose protectionist measures by claiming that the testing requirements of the exporting nation do not fully meet the safety standards of the importing nations. With respect to pharmaceutical products, Article XX allows importing nations circumvent the obligations set forth in the *Agreement on Technical Barriers to Trade* (TBT).

The TBT strives to prevent deceptive trade practices disguised as technical requirements by encouraging harmonization of conformity assessments, testing and certification procedures. The TBT calls for the preparation and application of international standards for these procedures. Section 1.3 of the TBT states “all products shall be subject to the provisions of this Agreement<sup>68</sup>” Despite the provisions of Section 1.3 the WTO has not identified testing requirements for pharmaceutical products. For this reason, coupled with GATT Article XX, importing countries have the right to refuse a pharmaceutical product that has not been tested according to the importing countries requirements.

ICH members have attempted to address this problem by agreeing to a harmonized set of testing requirements, but even the ICH does not guarantee complete removal of technical barriers to trade for pharmaceutical products because there is no legal framework within ICH that binds members to fully adopt ICH testing standards. When the three member regions agreed to the initiative it was understood that the ICH standards would be used as guidelines, no party is under legal obligation to either follow or adopt the guidelines. The US takes, for example, takes ICH guidelines and then formats them to ensure they are compliant with the FDA’s Good Guidance Practices<sup>69</sup>.

The TBT agreement contains provisions consistent with the goals of the ICH initiative. The TBT strives to remove technical barriers to trade through harmonization and recognition of testing standards. It addresses each of the facets that must be considered for the harmonization of pharmaceutical products: the removal of duplicate testing, good codes of practice and mutual recognition. WTO adoption of ICH guidelines would provide ICH members the legal provisions lacking in their initiative, while also extending the goal of harmonized testing requirements to the larger scale of WTO member nations. Section 1.6 of the TBT allows for annexes to the agreement. Introducing ICH guidelines as an annex to the TBT would be a natural addition, uniting the ICH

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<sup>68</sup> World Trade Organization. The Legal Texts, The Results of the Uruguay Round of the Multilateral Trade Negotiations Cambridge: Cambridge University Press 1999 p. 121

<sup>69</sup> Anquez, Christelle, Office of International Programs FDA. “Re:ICH” E-mail to author. 15 April, 2002.

initiative with the goals of the TBT. WTO adoption of ICH standards would eliminate the use of testing requirements as a technical barrier to pharmaceutical products.

Article 6 of the TBT agreement specifically addresses mutual recognition of conformity assessment procedures. Section 3 encourages members to enter into negotiations for mutual recognition. This section could be applied to the good manufacturing practices policies discussed in the Policy Analysis section. Members can use compliance with WHO guidelines on GMPs to negotiate mutual recognition of pharmaceutical facilities. Pursuant to Section 2.6 of the TBT, an international standardizing body must set the guidelines WTO members are required to follow. Both the ICH and the WHO fit this category, further supporting adoption of the guidelines.

Adoption of ICH guidelines into the WTO would also provide ICH members another benefit: it would eliminate the possibility that a WTO participant could take advantage of the ICH agreement under “unconditional Most Favored Nation” clause. Under MFN, Article I of GATT, WTO members must apply the same trade policies to all WTO participants. All three ICH member regions are parties to the WTO. Customs Unions and Free Trade Agreements are the general exceptions to the MFN clause; ICH is neither a Customs Union nor a Free Trade Agreement; if ICH members agree in the future to fully adopt ICH guidelines, they will be obligated under their WTO membership to extend those benefits to all WTO participants. However, under the “unconditional MFN clause” reciprocity is not required; ICH members would be required extend their benefits to all WTO members, but they would not have the right to demand the same treatment.

ICH members have already ensured that their guidelines and practices are available to non-ICH members; ICH even set up the Global Cooperation Group in part to assist non-ICH members. The invitation from ICH is open, but the provisions under ICH are not enough the guarantee reciprocity; WTO adoption of ICH guidelines would close any loopholes not addressed by simply conforming to ICH guidelines

If ICH guidelines are adopted into the WTO special provisions will have to be included for developing nations pursuant to the agreements of the WTO. Article 12 of the TBT, *Special and Differential Treatment of Developing Country Members*, includes special exceptions designed to allow developing countries the ability to comply with the provisions of the TBT without jeopardizing their production potential. Section 12.3 mandates that “technical regulations, standards, and conformity assessment procedures do not create unnecessary obstacles to exports from developing country members.”<sup>70</sup> One way to prevent unfair trade obstacles for developing countries is to allow them a longer timeframe to apply the ICH guidelines. Section 12.8 mandates that special time considerations in the form of extensions are granted to developing countries.

According to GATT Article XXXVI, *Principles and Objectives* and Article XXXVIII, *Joint Action*, contracting parties, in this case ICH members and other developed nations are requested to provide technical and if necessary financial assistance

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<sup>70</sup> Legal Text, The Results of the Uruguay Round of the Multilateral Trade Negotiations p.134

so that developing nations may comply with newly mandated WTO trade rules. In order to introduce their testing guidelines into the WTO, ICH members should be prepared to provide assistance to developing nations. Section 6 of Article XXXVI allows contracting parties to request the aid of international lending institutions so developed nations would not have to take the full financial burden of assisting developing nations, they could enlist the help of international institutions that have an interest in development in global health. The WHO and the World Bank would both be good choices for this potential project. As long as ICH members ensure that developing nations would be granted the financial, technical and schedule assistance they need to comply to with ICH standards, developing nations do not have a legal basis to refuse WTO adoption of ICH standards.

### **Political Analysis**

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Introducing ICH guidelines into the WTO will be a complex process because the interests of all members will have to be considered. The WTO must address the political, economic and social concerns of 144 divergent members in their agreements. Developed and developing countries are not always able to operate according to the same trade and production rules. Policies that are crucial for developed economies can sometimes hinder the progression of developing economies. The varying levels of socio-economic development in developed and developing countries leads to varying political concerns. For example, developed countries with high levels of education, public health and employment typically address concerns such as environmental protection and animal rights. Developing countries on the other hand often views such issues as luxurious concerns. Their primary concern is often economic growth and development, a goal attainable through the development of their industries. Developing countries have consistently struggled to advance their domestic industries and promote economic growth. Developing countries often cannot afford to operate with the same regulations imposed in developed nations. Regulations imposed by developed nations often hinder industry advancement in developing nations and therefore, are often viewed as unfair and met with resistance.

The varying political concerns of developed and developing WTO members will no doubt play a role in WTO adoption of ICH testing guidelines. Developed countries will have ensure that any guidelines adopted guarantee the highest levels of protection in order to satisfy safety concerns of regulatory agencies. The EU, Japan and the US have the world's most stringent guidelines for pharmaceutical products; therefore, ICH guidelines are among the most prudent and rigorous testing standards in the global market<sup>71</sup>. Regulatory agencies and consumers should feel confident that ICH guidelines for testing requirements are the most appropriate choice for ensuring safe and accurate tests. However, as discussed earlier in the Commercial Analysis section, stringent testing requirements are costly and expenditures are expected to rise over the next few years. WTO adoption of ICH guidelines might appear to be a protectionist measure by certain developing nations with less expensive testing requirements. Such member nations, striving to develop their own pharmaceutical industries may not want to agree to abide to stricter, more expensive guidelines.

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<sup>71</sup> "PhRMA Industry Profile" p. 12 and "The Value and Benefits of ICH to Industry" p.7

While safety assurances will be a leading factor for acceptance among developed nations, the primary concerns of developing nations will defer. Safety assurances are a concern for any nation whether developed or developing, but developing countries will have to give economic factors equal consideration. Developing countries with pharmaceutical production (DC producers) will have to ensure that enforcement of ICH guidelines will not jeopardize their industry growth and developing countries with no pharmaceutical production (DC non-producers) that are completely dependant on trade partners for their pharmaceutical products will have to ensure that access to affordable medications will not be interrupted.

Many DC producers have developed their markets through lower expenditure costs. US manufacturers typically spent roughly \$191 million annually compared with \$3 million spent by manufacturers in India<sup>72</sup>. Much of the manufacturers costs are spent on rigorous testing standards. As stated earlier, many DC producers such as India and Brazil are responsible for exporting affordable medications to DC non-producers. Because many least developed nations lack the funds to regulate pharmaceutical imports, they often accept the testing standards of the exporting country, saving the exporter the cost of duplicate testing, specifically the lengthy rigorous tests mandated by developed countries such as the ICH member regions. Being forced to operate by ICH guidelines, as opposed to the guidelines DC producers and DC non-producers have already accepted as adequate may raise production costs for DC producers, thereby raising costs for consumers in developing nations.

The WHO, the World Bank and G-77 all share the concerns of the developing member nations of the WTO. The WHO and the World Bank have invested considerable time, money and efforts to improving public health in developing nations. Pharmaceutical products are a key tool in combating disease and improving overall public health. The WHO and World Bank continue to combat the third world diseases that are virtually absent from developed nations such as malaria and leprosy. Because manufacturers of developed nations are under increasing pressure to increase profits they have largely ceased production of unprofitable third world drugs. Many medications that treat diseases of LDCs such as malaria and leprosy now come from DC producers such as Brazil and India<sup>73</sup>. The WHO and World Bank have a vested interest in ensuring the production of these products are not abandoned by DC producers. The two organizations will need assurances that adoption of strict ICH guidelines within the WTO will not result in more expensive pharmaceutical medications. The primary purpose of G-77 is to foster economic growth and development in developing nations; the key to this is through industry development. Like the WHO and the World Bank, G-77 will want to ensure that WTO adoption of ICH guidelines will not negatively affect DC producers and stifle their industry potential. G-77 has focused its efforts to advance economic growth of developing nations by gaining financial and technical support from developed nations.

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<sup>72</sup> Organization of Pharmaceutical Manufacturers of India.

<sup>73</sup> Jordan, Miriam. "Brazil Makes A Name for Itself Pumping Out AIDS Drugs" The Wall Street Journal 27 April 2001

Overtime, WTO members have come to realize that not all trade agreements are suitable for each of its members. WTO members have learned that the varying political interests of developed and developing nations often makes consensus on trade agreements difficult. The WTO has addressed this problem by creating special exceptions for developing nations, often in the form of technical and financial assistance and extended schedules for compliance to new trade rules. Provisions for development assistance are laid out in WTO trade agreements (as discussed in the Legal Analysis section). Developmental assistance for DC producers could quell concerns that ICH guidelines will stifle DC producers' industries and interrupt the flow of affordable medicines to developing nations in general.

Although WTO adoption of ICH guidelines initially seems threatening to developing countries and the goals of the WHO, the World Bank and G-77, it actually presents great potential benefits. If the correct provisions are made to ensure successful compliance by DC producers WTO conformity for pharmaceutical testing requirements could actually benefit DC producers in the long run. Due to higher standards of living profits for pharmaceutical companies tend to be higher in developed nations<sup>74</sup>. ICH member regions alone account for 83% of total global consumption even though they include only eighteen countries<sup>75</sup>. If DC producers gain facilitated market access to developed countries, they will be given the potential to advance their domestic industries and potentially advance their economic growth. Industry advancement for DC producers also helps meet the development goals of G77 and the World Bank.

Agreeing to provide financial and technical assistance for developing nations also aids the ICH members and other developed nations in the WTO. The adoption of guidelines created by the three global leaders for both pharmaceutical trade and trade in general could be misconstrued by opponents to global trade as an effort to dominate pharmaceutical trade by the largest trading partners. By demonstrating a wiliness to help developing nations advance their own industries, ICH member regions also address political opposition to their trade practices.

Ensuring that all WTO members follow ICH guidelines will also help meet the goals of the WHO and World Bank global health programs. The WHO's primary goal is to attain the highest level of global public health. Pharmaceutical medications is the primary choice of medical treatment worldwide<sup>76</sup>. Pharmaceutical products are not only used to save lives, they are used to prevent infections and illness and they can improve the quality of life for those with chronic conditions. Pharmaceutical products are a primary avenue to achieve high levels of public health. The WHO is currently working with pharmaceutical companies to find ways to remove trade barriers for pharmaceutical products<sup>77</sup>. ICH offers the highest level of safety, quality and efficacy standards to ensure consumer protection. WTO adoption of ICH guidelines is the best available option to remove trade barriers without sacrificing consumer safety.

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<sup>74</sup> [Encyclopedia of Global Industries](#) p. 123

<sup>75</sup> [Encyclopedia of Global Industries](#) p. 123

<sup>76</sup> "US Industry and Trade Outlook" p.11-14

<sup>77</sup> "US Industry and Trade Outlook" p.11-14

Showing developing nations the benefits they stand to gain by supporting WTO adoption of ICH guidelines is the key to gaining their support, but why would ICH members want to facilitate trade for their competition and potentially threaten their (ICH members) market share? Through the Global Cooperation Group (GCG) ICH members have opened their doors to non-members. All ICH guidelines are made available to outside parties and representatives are able to observe ICH plenary sessions. The ICH members welcome any interested outside party to use their guidelines. As stated earlier, the ICH does not have any legal authority; if and when ICH member regions fully implement ICH guidelines, outside parties may use ICH guidelines to export their pharmaceutical products to ICH member regions and then refuse to offer reciprocity. If that were to occur ICH members could close their guidelines to outside parties, but they would then be in violation of GATT Article I, the MFN clause discussed earlier in the Legal Analysis section. Even the MFN clause does not provide ICH members protection from this potential loophole because of unconditional MFN, which does not require the outside party to grant reciprocity. By introducing their standards into the WTO, ICH members are not truly enhancing their competition; they are preventing the potential abuse of efforts to assistance outside parties.

## **Strategy**

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### **Recommendations:**

There are various issues that need to be addressed in this project. The first issue is that the current provisions of the WTO agreements allow member nations to use testing requirements as a technical barrier to trade. My recommendation for this issue is to introduce ICH guidelines as an annex to the TBT agreement of the WTO.

WTO adoption of the ICH guidelines presents two primary obstacles that will have to be dealt with in order to achieve successful removal of technical trade barriers: how to get support from regulatory agencies and developing countries.

My recommendation for the first obstacle, gaining support from regulatory agencies, is to include the WHO guidelines on good manufacturing practices along with the ICH guidelines in the annex to the TBT. ICH guidelines address the testing requirements mandated to introduce a new drug to the market, but they do not necessarily ensure the safety of that medication after it has been approved. GMPs do address drug safety for the entire lifetime of the product because they address manufacturing process, including storage and sealing. Article 6 of the TBT addresses mutual recognition and conformity assessment procedures so WHO guidelines would fit well into the provisions of the agreement.

My recommendation for the second obstacle, gaining support from developing countries, is to provide financial and technical assistance and allow developing countries an extended timeframe for compliance. The details on all three provisions (the exact dollar amount of assistance and the timeframe for compliance) can be worked out during negotiations; my estimated recommendations for figures to enter in negotiations with are included in the strategy below. I also recommend building a coalition between G-77, the World Bank and the WHO to assist developing countries lay out their requests could ensure that the correct provisions are agreed upon. The three organizations have an interest in assisting developing countries; their support with this project may help persuade developing countries to accept the WTO adoption of ICH guidelines. ICH members can also request that the World Bank share the costs of the financial assistance that will be provided for developing countries.

### **Comprehensive Strategy:**

The overall strategy to introduce ICH guidelines into the WTO involves a three part strategy:

- A strategy to introduce ICH guidelines into the WTO
- A strategy to gain support from regulatory agencies for this project
- A strategy to gain support from developing countries for this project

Strategy to Introduce ICH guidelines into the WTO:

As stated earlier ICH is a joint initiative between manufacturers and regulatory agencies. The benefits of introducing ICH guidelines into the WTO no doubt benefit manufacturers much more than it will benefit regulatory agencies. The push for this project should come from ICH manufacturers. Each of the three regions has a manufacturer's association (EFPIA, JPMA and PhRMA). These three associations should work together on this project. The pharmaceutical associations cannot introduce this project as a topic for negotiations in the WTO themselves; their respective trade representatives must do that. The first step the pharmaceutical associations must take is to lobby their trade representatives and request that they introduce this as a trade topic in the next WTO Round. ICH members should request that their trade representatives submit a joint proposal (from the EU, Japan and the US) in order to give a united appearance. Support from the WHO will also help strengthen this request. The WHO promotes facilitated access to medicines worldwide, so they should approve a project that will speed market access through the removal of trade barriers. As stated earlier, this ICH guidelines best fit into the TBT agreement. ICH members should make this suggestion to trade representatives upfront so that trade representatives can include this suggestion in their request to the WTO. Once ICH guidelines have been introduced into the TBT agreement, members (with the exception of developing countries) should be granted 5 years for complete compliance. WTO members should adopt new ICH guidelines as they are completed by the ICH Expert Working Groups.

Strategy to Gain Support from Regulatory Agencies:

Regulatory agencies of both the ICH member regions and the other WTO member nations may resist the idea of facilitated market access because they may mistake it as increased safety risks. The ICH guidelines on testing requirements only address drug approval. Regulatory agencies need to feel secure that the pharmaceutical product will not pose any safety risks once it released on the market. Continued safety of pharmaceutical products involves the manufacturing process, including storage and sealing. The WHO has issued universal guidelines on good manufacturing practices. In order to ensure that regulatory agencies feel secure with the provisions of this project, ICH members should suggest that the WHO guidelines accompany the ICH guidelines in the annex to the TBT.

Strategy to Gain Support from Developing Countries:

In order to gain support from the developing countries within the WTO we will have to convince them that they will benefit from WTO adoption of ICH guidelines (as discussed in the Political Analysis section). Developing countries with pharmaceutical production stand to gain from facilitated market access. The status quo requires that they conduct individual tests for each country they wish to export to. As discussed in the Commercial Analysis section, testing is a long and costly procedure. Conducting one set of tests that will be accepted by each importing country can save their manufacturer's

considerable costs. Developing countries may argue that the short-term sacrifices of adjusting their current procedures to a much more costly and stringent procedure will hamper their industries to the point that they may not be able to reach the long-term benefits discussed above, or they may simply say they do not have the capacity to adjust their current procedures to the ICH testing guidelines and the WHO GMPs guidelines. ICH members should answer these concerns by providing financial and technical assistance to developing countries in order to ensure a smooth transition from their current procedures to the ICH and WHO guidelines. The exact numbers for financial assistance should be determined based on further research and negotiations with developing nations. Developing countries should be granted a timetable of fifteen years to comply with ICH guidelines, once developing nations are in full compliance with ICH guidelines, they should adopt new ICH guidelines as they are completed by the ICH Expert Working Groups.

Actual discussions with developing countries will not need to start until the topic is adopted for negotiations within the WTO. As mentioned earlier it will be beneficial to have the support of the WHO, the World Bank and G-77. These groups can help persuade developing countries that in the long term harmonization of pharmaceutical testing requirements will be beneficial. All three groups have a vested interest in the socio-economic development of developing nations and so they would be alliance.

### **Negotiation Strategy Steps:**

#### **Strategy To Introduce ICH Guidelines Into The WTO's TBT:**

The member companies of the ICH will not be able to approach the WTO themselves because they do not have trade negotiating authority. They will have to depend on their trade representatives to head the initiative within the WTO. ICH members should request that their respective trade representatives submit a joint request (all three regions together) to introduce negotiations to write an annex to the TBT that basically states that WTO members agree to recognize ICH guidelines for market approval of pharmaceutical products for human use. ICH members should work together with WHO, one of their official observers to publicly support the adoption of harmonized standards in the WTO. WHO should also support ICH standards as the best choice in order to ensure safe, effective pharmaceutical products of the highest quality. WHO has witnessed and at times given options on the creation of ICH guidelines so gaining their support to promote these guidelines as the top choice for safety, quality and efficacy should not be difficult. Representatives from ICH's Global Cooperation Group should head this initiative and should be the main contact/liaison with WHO.

#### **Lobby Respective trade representatives to accept this as a trade topic for the WTO:**

Each ICH member should approach their respective trade representative and request that they adopt this topic on their trade agenda. The pharmaceutical manufacturer's association for each member region can head the initiative and guide member companies on the course of action needed to accomplish this goal. Each association should begin with the following:

- Set up informational sessions with the business-government affairs representative from each pharmaceutical manufacturers association's (EFPIA, JPMA and PhRMA) respective member companies and map-out the needed actions. If certain members cannot attend because of distance set up a telephone/videophone conference call.
- Provide member companies with a sample letter to write to their trade representatives. For this EU this will be Trade Commissioner Pascal Lamy, for Japan it will be Takeo Hiranuma and for the US Ambassador Robert Zoellick. Please see attached sample letter for an example.
- Where possible set up meetings with staff members of the respective trade representatives and explain to them in person why this is an important trade topic and why you feel they should adopt it into their trade agendas. Provide concrete evidence and facts to support your arguments.
- Offer an assistant/liaison who can provide information to the trade official working on this case. The assistant can do the trade official's research tasks and any leg work i.e. draft letters, stuff envelopes, send faxes, answer e-mails (especially from public and NGO's). Basically the assistant can relieve the trade representative of any administrative work this initiative will create for him/her. If the budget does not allow for a full-time assistant we can hire student interns eager for the experience. If the position is filled by the intern write up fact-sheets to assist the intern in answering questions from the public and NGOs. The trade representative, not the assistant, should handle all press relations.
- Make it clear to trade representatives that the pharmaceutical associations will provide full assistance with this initiative throughout the entire process. If and when this topic makes it to WTO meetings offer to have someone from each of the pharmaceutical manufacturer's association accompany the trade negotiator(s) to the WTO meetings site. Even though the association's employee will not be able to attend the meeting, they should attend to assist the trade representative with last minute questions that may come up during negotiations.

Establish a coalition with the WHO to support this initiative:

- Send letters to Gro Harlem Brundtland ,WHO Director General and Dr. Yasuhiro Suzuki, Executive Director of Health Technology and Pharmaceuticals to request that WHO join ICH in this initiative. Please see attached sample letter for an example.
- Set up meetings with appropriate WHO staff (particularly Dr. Suzuki) and work out details for the cooperation initiative.
- Arrange to post information about the initiative on both ICH and WHO web sites.

Strategy to Gain Support from Regulatory Agencies:

Many of the steps listed for the strategy to lobby trade representatives should be repeated to lobby regulatory agencies to accept this project. For this strategy ICH members will have to extend their lobbying efforts outside their nations to other developing countries whose regulatory agencies also have strong safety concerns. Extending lobby effort outside the ICH regions does not need to take place until after we have entered negotiations in the WTO. Begin lobby efforts with the regulatory agencies of the ICH member regions first. For this part of the strategy ICH members should form a coalition with the WHO.

Establish a Coalition with the WHO:

We will need to contact the same people listed above. This can be done concurrently when we lobby them for support to adopt ICH guidelines into the WTO.

Lobby Regulatory Agencies:

Once the coalition with WHO is started send out joint letters to the appropriate person at the regulatory agencies of all three ICH members.

- Provide member companies (same as above for first strategy) with a sample letter to write to their regulatory agencies. For this EU this will be Mr. Phillippe Brunet and Dr. Eric Abadie at the EMEA, for Japan it will be Mr. Souichi Ikegaya and Dr. Satoshi Toyoshima at the MHLW and for the US it will be Dr. Justina Molzon and Dr. Kathryn Zoon at the FDA. Please see attached sample letter for an example.
- Where possible set up meetings with staff the appropriate contact people and explain to them in person why this is an important trade topic and why you feel they should support their respective trade agencies in this initiative. Provide concrete evidence and facts to support your arguments.

Strategy To Gain Developing Country Acceptance:

Establish a coalition with the WHO, the World Bank and G-77:

- Identify the appropriate contact people for each of these organizations and send letters to request their support. Please see sample letter attached.
- Where possible set up meetings the contact people and explain why this is an important initiative and why they should support it.

Media Strategy:

Due to the complexity of this issue, the media strategy should be geared towards an audience of healthcare, pharmaceutical and trade professionals and policy makers, instead of the general public. All media pieces should clearly map out the following information:

- What exactly is the ICH, who are their members, what are their goals, how do they alter current pharmaceutical market approval processes, what does not change about the process

- Why it is a good idea to extend ICH guidelines to the WTO, how will industry and consumers benefit
- Why does WHO support this initiative
- How consumer safety will remain the number one priority and will unequivocally be guaranteed

Media coverage can take place in the following forms:

- Informational essays and articles in trade journals (i.e. World Trade)
- Op-eds and articles in newspapers widely read by policy makers and trade professionals i.e. The Washington Post, The New York Times, The International Herald Tribune, The Financial Times, etc.
- Informational essays and articles in pharmaceutical magazines and journals, particularly peer review journals
- Informational essays and articles in healthcare magazines
- Information on relevant websites: WTO, WHO, ICH, EFPIA, JPMA, PhRMA, pharmaceutical companies, USTR, FDA, EU Commission, EMEA, MHLW, MOFA, etc.

#### Research Strategy:

In order to strength coalition support and negotiating strategies research in the following areas is necessary:

- Determine the exact costs of duplicate testing. Make a list of key countries for pharmaceutical trade and gather the numbers on those countries. Present numbers for both ICH industries and the key countries so you can show how much you could save on your exports and how much they can save on their exports. Remember that in a negotiation situation you want to show how this will benefit them
- Once the exact of duplicate testing and the potential savings have been demonstrated, calculate how this savings could be passed onto either their national health plans or their consumers. For each country, research per capita expenditure on pharmaceutical products (i.e. is theirs deficit in their health plan that could be adjusted through this savings?)
- Present numbers supporting the shortage of volunteers for human test subjects and show how duplicate testing exacerbates this problem.
- Present numbers on the animal test subjects that could be reduced through harmonized testing requirements. These numbers could later be presented to animal rights groups who could pressure their governments to agree to this trade initiative.
- Research the costs fro providing developing countries with technical assistance.

#### Estimated Timetable:

	<b>Phase I</b>	<b>Phase II</b>	<b>Phase III</b>
<b>Time Frame</b>	6 months to 1 year	6 months to 1 year	2 to 4 years
<b>Action</b>	Lobby trade representatives and WHO, World Bank and G-77	Submit proposal to WTO	WTO negotiations

Estimated Budget:

The ICH member companies should provide initial funding for this project. The total costs can be equally divided among the three manufacturer's associations and then they may determine how much each individual company will contribute. Costs to lobby trade representatives and regulatory agencies can be paid for by the pharmaceutical associations (from membership fees). All amount in the table are in US dollars. I have not included the cost of financial and technical assistance to developing countries because further research is required to determine that figure (see Research Strategy section). Costs for office support do not include rent for office space because operations can be headed from the ICH office provided by IFPMA and the offices EFPIA, JPMA, and PhRMA.

<b>Item</b>	<b>Phase I</b>	<b>Phase II</b>	<b>Phase III</b>	<b>Total</b>
<b>Administrative/ Office Support</b>				
Stipend for intern assistant	\$1000	\$1000	\$1000	\$3000
Office Space, staff, telephones, faxes, postage, and supplies (pens, computers, etc) provided for by IFPMA, EFPIA, JPMA and PhRMA all included in membership fees	N/A	N/A	N/A	N/A
Information brochures with statistics (this cost includes research, translation in languages for	\$20,000	N/A one time fee only	N/A one time fee only	\$20,000

each trade representative and coalition organization and printing).				
<b>Travel</b> to meet with personnel to build coalition, lobby and possibly be observe (or at least be present in the same city) WTO negotiations				
Airlines	\$20,000	\$5,000	\$30,000	\$55,000
Hotels	\$5,000	\$1,000	\$5,500	\$11,500
Food, Taxis etc.	\$1,000	\$500	\$2,000	\$3,500
Printing additional copies of the information brochure listed above	\$5,000	N/A one time fee	N/A one time fee	\$5,000
<b>Media</b>				
Paid advertising in publications listed in media strategy (this costs includes an ad agency to create the message)	\$100,000	\$50,000 (just reprint of ad won't have to pay additional ad agency fee)	\$50,000 (just reprint of ad won't have to pay additional ad agency fee)	\$200,000
Print additional copies of information brochures	\$5,000	N/A one time fee	N/A one time fee	\$5,000
<b>Total Expenses</b>	\$157,000	\$57,500	\$87,500	\$302,000

Sample Letter to Trade Representatives:

Date

Name of Person

Title

Agency Title

Address

Re: Introducing ICH Guidelines into the WTO

Dear (Name),

We, the members of the International Conference on Harmonization are writing to you in order to bring to your attention a trade problem we feel needs to be addressed. The current provisions of the World Trade Organization allows for technical barriers to trade in the form of testing requirements. Each time a manufacturer exports a new pharmaceutical product we must repeat the entire testing progress even if the product has passed domestic safety tests.

Overtime we have found that many of these tests are very similar, negating the need for duplicate testing. Duplicate testing is not only extremely expensive; it is also a waste of resources (animal and human volunteers). In our experience we have also found that duplicate testing delays market access of critical pharmaceutical treatment for patients.

The ICH members recognized this issue long ago and we have attempted to address by designing guidelines for testing requirements. We would like to offer our guidelines to the World Trade Organization so that they may extend their goal of facilitated trade to the pharmaceutical industry. In order to extend our benefits to all WTO member nations we need your assistance in bringing this crucial topic to WTO negotiations.

We would be happy to meet with you to discuss the details of this potential project. We will contact you next week to set up a meeting time. We look forward to meeting with you soon.

Sincerely,

Name of representative from pharmaceutical manufacturer's association.

Sample Letter to Regulatory Agency:

Date

Name of Person

Title

Agency Title

Address

Re: Introducing ICH Guidelines into the WTO

Dear (Name),

We, the members of the International Conference on Harmonization are writing to you in order to bring to your attention a trade problem we feel needs to be addressed. The current provisions of the World Trade Organization allows for technical barriers to trade in the form of testing requirements. Each time a manufacturer exports a new pharmaceutical product we must repeat the entire testing progress even if the product has passed domestic safety tests.

Overtime we have found that many of these tests are very similar, negating the need for duplicate testing. Duplicate testing is not only extremely expensive; it is also a waste of resources (animal and human volunteers). In our experience we have also found that duplicate testing delays market access of critical pharmaceutical treatment for patients.

The ICH members recognized this issue long ago and we have attempted to address by designing guidelines for testing requirements. We would like to offer our guidelines to the World Trade Organization so that they may extend their goal of facilitated trade to the pharmaceutical industry. We are currently in negotiations with our trade representatives to have them introduce this topic into the WTO trade agenda. We would be honored to have your support in this project.

We would be happy to meet with you to discuss the details of this potential project and answer any questions you may have. We will contact you next week to set up a meeting time. We look forward to meeting with you soon.

Sincerely,

Name of representative from pharmaceutical manufacturer's association.

Sample Letter to WHO:

Date

Name of Person

Title

Agency Title

Address

Re: Introducing ICH Guidelines into the WTO

Dear (Name),

We, the members of the International Conference on Harmonization are writing to you in order to bring to your attention a trade problem we feel needs to be addressed. The current provisions of the World Trade Organization allows for technical barriers to trade in the form of testing requirements. Each time a manufacturer exports a new pharmaceutical product we must repeat the entire testing progress even if the product has passed domestic safety tests.

Overtime we have found that many of these tests are very similar, negating the need for duplicate testing. Duplicate testing is not only extremely expensive; it is also a waste of resources (animal and human volunteers). In our experience we have also found that duplicate testing delays market access of critical pharmaceutical treatment for patients.

The ICH members recognized this issue long ago and we have attempted to address by designing guidelines for testing requirements. We would like to offer our guidelines to the World Trade Organization so that they may extend their goal of facilitated trade to the pharmaceutical industry. We are currently in negotiations with our trade representatives to have them introduce this topic into the WTO trade agenda. We would be honored to have your support in this project.

We know that a priority of the World Health Organization is worldwide access to affordable pharmaceutical products; we believe this project would help you realize that goal. As an official observer to the ICH initiative you are aware that our guidelines are of the most prudent and include every measure to protect consumer health. We also believe this project will help find a solution to the current project you are working on with the WTO to facilitate access to pharmaceutical products.

We would be happy to meet with you to discuss the details of this potential project and answer any questions you may have. We will contact you next week to set up a meeting time. We look forward to meeting with you soon.

Sincerely,

Name of representative from pharmaceutical manufacturer's association.

## **Appendix I**

### **ICH Terms of Reference (1997)**

- ❖ 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 monitor and update harmonized technical requirements leading to a greater mutual acceptance of research and development data;
- ❖ To avoid divergent future requirements through the harmonization 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 the information on harmonized guidelines and their use such as to encourage the implementation and integration of common standards.

## Appendix II

### Schedule of ICH Meetings

<b>November 2003 : ICH 6</b>	<b>Sixth International Conference on Harmonisation, Osaka, Japan</b>
July 2003	SC and EWGs, Brussels, Belgium
February 2003	SC and EWGs, Tokyo, Japan
September 2002	SC and EWGs, Washington, USA
February 2002	SC and EWGs, Brussels, Belgium
May 2001	SC and EWGs, Tokyo, Japan
<b>November 2000 : ICH 5</b>	<b>Fifth International Conference on Harmonisation, San Diego, USA</b>
July 2000	SC and EWGs, Brussels
March 2000	SC and EWGs, Tokyo, Japan
October 1999	SC and EWGs, Washington
March 1999	SC and EWGs, Brussels
September 1998	SC and EWGs, Tokyo, Japan
February 1998	SC and EWGs, Virginia, USA
<b>July 1997: ICH 4</b>	<b>Fourth International Conference on Harmonisation, Brussels, Belgium</b>
March 1997	SC and EWGs, Narita, Japan
November 1996	SC and EWGs, London
July 1996	SC (special planning meeting), Geneva
May 1996	SC and EWGs, Virginia, USA
<b>November 1995: ICH 3</b>	<b>Third International Conference on Harmonisation, Yokohama, Japan</b>
July 1995	SC and EWGs, Brussels
March 1995	SC and EWGs, Washington
October 1994	SC and EWGs, Brussels
March 1994	SC and EWGs, Tokyo
<b>October 1993: ICH 2</b>	<b>Second International Conference on Harmonisation, Orlando, USA</b>
June 1993	SC and EWGs, Washington
March 1993	SC and EWGs, Brussels
September 1992	SC and EWGs, Tokyo
March 1992	SC and EWGs, Washington

<b>November 1991: ICH 1</b>	<b>First International Conference on Harmonisation, Brussels, Belgium</b>
April 1991	SC and EWGs, Washington
January 1991	SC and EWGs, Washington
October 1990	SC and Expert Working Groups (EWGs), Tokyo
April 1990	ICH Steering Committee (SC), Inaugural Meeting, Brussels

**STAKEHOLDERS' INTEREST CHART**

<b>PEOPLE</b>	<b><u>INTEREST</u></b>	<b><u>OPTIONS</u></b>	<b><u>OBJECTIVE CRITERIA</u></b>	<b><u>BATNA</u></b>
<i><u>ICH Members</u></i>	<ul style="list-style-type: none"> <li>-Protect and advance industry</li> <li>-Ensure the future of ICH</li> <li>-Protect the authority of ICH Steering Committee, ensure the SC continues to make the decisions regarding pharmaceutical guidelines</li> <li>-Ensure consumer safety</li> <li>-Increase market access</li> <li>-Reduce/remove trade barriers</li> <li>-Reduce marketing costs for manufacturers</li> <li>-Eliminate high cost and waste of resources connected to duplicate testing</li> <li>-Accelerate foreign market entry for pharmaceuticals</li> <li>-Boost ICH standards and guidelines as the best option for any pharmaceutical manufacturer, promote ICH</li> </ul>	<ul style="list-style-type: none"> <li>-Negotiate with developing countries with pharmaceutical production-offer financial and technical assistance</li> <li>-Enlist the support of other developed nations within the WTO, request that they encourage developing countries to support WTO adoption of ICH testing guidelines</li> <li>-Convince regulators to support the initiative</li> </ul>	<ul style="list-style-type: none"> <li>-Data showing similarity of testing requirements between many WTO member nations</li> <li>-Data on wasted resources of duplicate testing (how many animals could be saved, the reduced number of human volunteers needed, how much money would be saved)</li> <li>-Data on the delayed access to consumers on foreign markets because lengthy duplicate tests are required</li> <li>-Data on how facilitated access to developed markets could help the pharmaceutical industries of developing countries</li> <li>-The WHO guidelines on GMPs and how adopting those guidelines along with ICH testing</li> </ul>	<ul style="list-style-type: none"> <li>-Extend membership on a country by country basis</li> </ul>

	standards as the most prudent for consumer safety, the best choice for manufacturers and regulators alike		standards would help ensure consumer safety	
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## STAKEHOLDERS' INTEREST CHART

<u>PEOPLE</u>	<u>INTERESTS</u>	<u>OPTIONS</u>	<u>OBJECTIVE CRITERIA</u>	<u>BATNA</u>
World Trade Organization	<ul style="list-style-type: none"> <li>-Facilitate global trade</li> <li>-Remove trade barriers</li> <li>-Address and meet the varying needs of the 144 member nations</li> <li>-Advance global economic growth and development through trade</li> <li>-Maintain and defend the legal text of the organization</li> <li>-Encourage members to resolve any trade issues within the organization instead of forming private agreements, if trade agreements resolving trade problems are formed within the WTO then all members benefit. Members will benefit not only through participation (which they would get</li> </ul>	<ul style="list-style-type: none"> <li>-Encourage members to adopt ICH standards in order facilitate trade of pharmaceutical products</li> <li>-Encourage developed nations to address the concerns of developing nations</li> <li>-Encourage developing nations to work with developed nations to ensure the agreement meets their needs, instead of just refusing the agreement altogether</li> <li>-Work with World Bank and G77 ensure that the correct provisions are included for developing nations are included in the agreement (make sure no leaf is left unturned)</li> </ul>	<ul style="list-style-type: none"> <li>-WTO agreements (TBT) that address technical barriers to trade</li> <li>-Data that supports the benefits of harmonized testing requirements (documenting that duplicate testing results in wasted resources, delays market access etc)</li> <li>-WTO agreements (GATT) that included special provisions for developing nations</li> </ul>	<ul style="list-style-type: none"> <li>-If members reach an impasse delay the project and reintroduce it in another Round.</li> </ul>

	<p>anyway through MFN) but also through input on the provisions of the agreement</p> <ul style="list-style-type: none"> <li>-Resolve trade disputes between member nations</li> </ul>			
World Health Organization	<ul style="list-style-type: none"> <li>-Promote world health</li> <li>-Eradicate infectious and parasitic diseases</li> <li>-Ensure that access of medications to the entire world population</li> <li>-Ensure access to affordable medications</li> <li>-Ensure the production of essential medications, not just profitable medications</li> <li>-Ensure development of new drugs and continued production of existing drugs that will treat and in some cases help prevent (i.e. vaccines) illness of the poor (malaria, tuberculosis, etc)</li> <li>-Treat, prevent</li> </ul>	<ul style="list-style-type: none"> <li>-Form a working group with ICH members, World Bank, WTO and G77 countries to design a plan that will ensure this project will not negatively affect the production (by developing nations such as Brazil and India) of affordable drugs (usually generic), i.e. ensure that the guidelines will not raise production costs for manufacturers of generic medications</li> <li>-Work with ICH and WTO to ensure that all members will follow GMPs, ensuring the production of safe, quality</li> </ul>	<ul style="list-style-type: none"> <li>-WHO guidelines on GMPs</li> <li>-Historical examples supporting the need for testing and GMPs to protect consumer safety</li> <li>-Documents from the United Nations, the World Bank, G77 nations and other organizations if applicable supporting the need for affordable medication worldwide, particularly in developing nations</li> </ul>	<ul style="list-style-type: none"> <li>-If protection of affordable medications is not granted then encourage and support developing nations refusal to accept the project</li> <li>-If protection of affordable medications is ensured by the project is rejected by WTO members support reintroduction in another Round</li> </ul>

	<p>and if possible completely eradicate fatal diseases and epidemics (i.e. HIV/AIDS)</p> <p>-Develop new drugs that will help nourishment and development of the poor (i.e. vitamin tablets for malnourished children, natal drugs for malnourished mothers, etc)</p>	medications		
World Bank	<p>-Foster economic growth and development for developing countries</p> <p>-Eradicate poverty</p> <p>-Support health and education programs that will foster development</p> <p>-Relief debt of developing countries</p> <p>-Increase investment in developing countries</p> <p>-Strengthen existing partnerships and develop new partnerships with other organizations</p>	<p>- Work with WTO and G77 ensure that the correct provisions are included for developing nations are included in the agreement (make sure no leaf is left unturned)</p> <p>-Form a working group with ICH members, WHO, WTO and G77 countries to design a plan that will ensure this project will not negatively affect the production (by developing</p>	<p>-Data on health programs (World Bank and WHO) in developing countries</p> <p>-Data on developmental assistance for third world nations</p> <p>- WTO Agreements that provide special support for developing nations- the entire Part IV of the GATT</p>	N/A

	that that support and aid development	nations such as Brazil and India) of affordable drugs (usually generic), i.e. ensure that the guidelines will not raise production costs for manufacturers of generic medications		
G77 Member Countries	<ul style="list-style-type: none"> <li>-Foster economic growth and development for developing countries</li> <li>-Advance “the voice of” and negotiation abilities of developing countries</li> <li>-Increase trade for developing countries</li> <li>-Increase fair trade regulations that assist not hinder developing nations</li> <li>-Obtain assistance from and support of developed nations to assist G77 members reach their development goals</li> <li>-Increase</li> </ul>	<ul style="list-style-type: none"> <li>-Negotiate with developed countries to ensure technical and financial assistance for developing nations so that ICH guidelines will not stifle the development of their industries</li> <li>-Meet with large pharmaceutical companies to promote FDI in member nations</li> <li>-Ensure that if the agreement does go through special provisions for developing countries will be included</li> <li>-One of those provisions should be a special timeframe that</li> </ul>	<ul style="list-style-type: none"> <li>-Previous G77 declarations and agreements that support assistance for developing nations</li> <li>-WTO Agreements that provide special support for developing nations- the entire Part IV of the GATT</li> <li>-World Bank documents supporting assistance for developing nations</li> </ul>	<ul style="list-style-type: none"> <li>-G77 members who are also WTO members can refuse to agree to the adoption of ICH guidelines in the WTO.</li> <li>-Stall negotiations—delaying the finalization of the agreement lets opposing parties (ICH members and perhaps other developed nations that support the initiative) know how serious you are-yet leaves the door open so they don’t think it is a hopeless case-this tactic may further motivate them agree to your requests</li> </ul>

	<p>employment in member nations</p> <ul style="list-style-type: none"> <li>-Increase investment in member nations</li> <li>-Eradicate poverty in developing nations</li> <li>-Relieve the debt of developing nations</li> <li>-Develop their own pharmaceutical industries</li> </ul>	<p>allows developing countries the appropriate amount of time to adopt ICH measures</p> <ul style="list-style-type: none"> <li>-Work with World Bank and WTO to ensure the correct provisions (to assist developing nations) are included, i.e. make sure no leaf is left unturned</li> </ul>		
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## STAKEHOLDERS' INTEREST CHART

<u>PEOPLE</u>	<u>INTERESTS</u>	<u>OPTIONS</u>	<u>OBJECTIVE CRITERIA</u>	<u>BATNA</u>
Developing Countries with pharmaceutical production	<ul style="list-style-type: none"> <li>-Advance and protect their economy</li> <li>-Advance and protect their pharmaceutical industries</li> <li>-Protect access to affordable pharmaceutical medications</li> </ul>	<ul style="list-style-type: none"> <li>-Work with World Bank and G-77 to ensure financial and technical assistance</li> <li>-Work with ICH members and the other developed nations in the WTO to ensure assistance for developing countries</li> <li>-Form coalition with developing countries with no pharmaceutical production</li> </ul>	<ul style="list-style-type: none"> <li>G77 declarations and agreements that support assistance for developing nations</li> <li>-WTO Agreements that provide special support for developing nations- the entire Part IV of the GATT</li> <li>-World Bank documents supporting assistance for developing nations</li> <li>-Documents from the United Nations, the World Bank, G77 nations and other organizations if applicable supporting the need for affordable medication worldwide, particularly in developing nations</li> </ul>	<ul style="list-style-type: none"> <li>-Refuse to support the adoption of ICH guidelines into the WTO</li> </ul>
Developing Countries with no pharmaceutical	<ul style="list-style-type: none"> <li>-Protect access to affordable pharmaceutical products</li> </ul>	<ul style="list-style-type: none"> <li>-Form coalition with developing countries with pharmaceutical</li> </ul>	<ul style="list-style-type: none"> <li>G77 declarations and agreements that support</li> </ul>	<ul style="list-style-type: none"> <li>-Refuse support the adoption of ICH</li> </ul>

production		<p>production</p> <ul style="list-style-type: none"> <li>-Negotiate with ICH member manufacturers to provide pharmaceutical products at discounted price in exchange for support for this project</li> <li>-Work with the World Bank and G-77 to assist developing countries with pharmaceutical production with technical and financial assistance</li> </ul>	<p>assistance for developing nations</p> <ul style="list-style-type: none"> <li>-WTO Agreements that provide special support for developing nations- the entire Part IV of the GATT</li> <li>-World Bank documents supporting assistance for developing nations</li> <li>-Documents from the United Nations, the World Bank, G77 nations and other organizations if applicable supporting the need for affordable medication worldwide, particularly in developing nations</li> </ul>	<p>guidelines into the WTO</p>
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