Global Pharmaceutical Markets and the Influence of the International Organizations WHO and ICH

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Table of Content:

1 List of Abbreviations

ACCSQ	Asean Consultative Committee for Standards and Quality
ADR	Adverse Drug Reaction
APEC	Asia Pacific Economic Cooperation
API	Active Pharmaceutical Ingredient
ASEAN	Association of Southeast Asian Nations
ATC	Anatomical Therapeutic Chemical Classification System
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use
cGMP	current Good Manufacturing Practices
CPP	Certificate of Pharmaceutical Product
CTD	Common Technical Document
DDD	Defined Daily Dose
DRA	Drug Regulatory Affairs
DURG	Drug Utilization Research Group
EC	European Commission
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFTA	European Free Trade Association
EMEA	European Medicines Evaluation Agency
EPhMRA	European Pharmaceutical Marketing Research Association
EU	European Union
EWG	Expert Working Group
FDA	Food and Drug Administration
GCC	Gulf Cooperation Countries
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GRP	Good Regulatory Practice
ICD	International Classification of Diseases
ICH	International Conference on the Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
IMS	IMS Health GmbH, Frankfurt
INN	International Non-proprietary Name
IntPh	International Pharmacopoeia
IOCH	International Office for the Control of Medicines (Switzerland)
JPMA	Japan Pharmaceutical Manufacturers Association
MedDRA	Medical Dictionary for Drug Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
MRG	Mortality Reference Group
NCE	New Chemical Entity
OTC	Over-the-Counter
PAHO	Pan-American Health Organization
PANDRH	Pan-American Network on Drug Regulatory Harmonization
PhRMA	Pharmaceutical Research and Manufacturers of America
PIC	Pharmaceutical Inspection Convention
PMSB	Pharmaceutical and Medical Safety Bureau

RAS	Rapid Alert System
SADC	South African Development Community
SC	Steering Committee
SIAMED	WHO model system for computer assisted drug registration
TPP	Therapeutic Products Program (Health Canada)
TRIPS	Trade-Related Aspects of Intellectual Property Rights
UK	United Kingdom
UN	United Nations
UNHCR	United Nations High Commissioner for Refugees
UNICEF	United Nations Children`s Fund
URC	Updating and Revision Committee
USA	United States of America
WHA	World Health Assembly
WHO	World Health Organization
WTO	World Trade Organization

2 Introduction

The trade of pharmaceutical products on the global market is increasing from year to year. Pharmaceutical companies are often acting worldwide. For the pharmaceutical companies it is very time and resources consuming to fulfil the different requirements when they want to achieve marketing authorizations for drug products in different countries.

This thesis is to present the influence of the work of the organisations WHO and ICH to the process of globalisation of markets for pharmaceutical products.

International pharmaceutical organisations wanted to find out what is necessary to achieve a good medical care for the population in the whole world. To have a common and harmonised base for the registration of medicinal products global organisations like WHO and ICH developed guidelines, standards and systems.

Patients have the advantage that the common guidelines and standards assure that they get safe products and that new pharmaceutical products have a faster entry on many markets. The benefit of harmonized guidelines and standards for regulatory authorities in different countries is that they have a common basis for their work and that they have an easier communication with other regulatory authorities and with the pharmaceutical companies. Because pharmaceutical companies have common guidelines for the registration of medicinal products the work for achieving marketing authorizations in different countries is simplified.

The ICH is working with the three regions Europe, USA and Japan. The WHO has 193 Member States and 2 Associate Members. The WHO has its focus also on non-ICH countries and they support especially the developing countries. Developing countries are encouraged by guidelines and systems that help to implement a basic drug registration or to improve an existing system. A simple computer-assisted system supports efficient drug registration.

International standardized names of ingredients and codes for indications would encourage the international communication between the health agencies, the regulatory authorities, the pharmaceutical companies and the health experts. International accepted guidelines for development, studies and documentation and a defined structure of the technical documentation for the drug registration would be auxiliary for a fast registration of a medicinal product in different countries. This would lead to a better availability of drugs throughout the world.

For developing countries the access to medicines has an economic aspect. These countries need to have mainly essential medicines for health problems, which can be individual and different for each country. This thesis will also show how an international organisation can help these countries to find the most cost-effective medicinal products and how they can get patent protected medicines into their countries even when the patent holder does not want to supply this country. Will the incorporation of other international harmonisation organisations lead to an easier global trade of pharmaceutical products?

The main question is: How does the work of WHO and ICH influence the harmonisation of the regulatory work on the global market?

3 Global Markets for Pharmaceutical Products

Pharmaceutical Companies sell their products not only in the countries where the drug products are manufactured but all over the world. The pharmaceutical companies often are multinational groups that act worldwide.

The Pharma market is different in the countries, where the pharmaceutical companies want to sell. These differences are as well in the potential of sales (economic), in the population, the mentality of the patients, the medicinal system and also in the requirements for registration (regulatory).

Economic Situation

To have economic benefit, the pharmaceutical companies want to sell their products in the regions where the amount of sales can be high and good prices for the drug products can be achieved. The sales of pharmaceutical products on the different continents is listed in the following table for the time from August 2005 to August 2006 [1], [2].

Country/Continent	**Drug Sales (IMS) in US $ Millions**	**% Growth of Sales in US $**	**Population (July 2006)**
North America USA Canada	204,858 191,593 13,265	6 5 15	 298,444,215 44,098,932
Europe (leading 5 countries: Germany, France, Italy, Spain, United Kingdom)	93,026	1	729,270,329 (total Europe)
Japan	57,141	6	127,463,611
Latin America (leading 3 countries: Mexico, Brazil, Argentinia)	18,562	21	561,827,566 (Latin America & Carribean)
Australia/New Zealand	5,708	2	24,342,050
Africa	46,400	11	910,844,133 (total Africa)
China	11,700	20	1,313,973,713

Table 1: Global Drug Sales from 08/2005 to 08/2006 and Global Population in 2006

Generally a growth of 3% in drug sales was reported in the 12 month between August 2005 and August 2006 in the 13 key markets (USA, Canada, Germany, France, Italy, Spain, UK, Japan, Mexico, Brazile, Argentinia, Australia, New Zealand). The European market showed a 1% growth, North America posted a 6% growth and Japan`s overall growth was also 6%. Latin America had a growth of 21% in the last twelve month and Australia/New Zealand showed a 2% growth. Africa reached a growth of 11% and China had a growth of 20% as it had already in the last two years [3], [4].

The global Pharma market has noted a sale of 602,000 Million US $ in the year 2005 (from January until December 2005) and a total global growth of 7%. There are different reasons for these growth. One reason is that the life expectancy increases and with this the amount of medical products that were needed. Another reason is the growing prosperity which makes a higher amount of medicinal product consumption possible. Also new innovative products that show a bigger therapeutic progress have more influence.

40 % of the global market growth in the year 2005 depends on the introduction of new medicinal products. In the main markets (see table 1) 30 new active ingredients were introduced, which mostly were against severe or life-threatening diseases [4]. A growth in sales for innovative medicinal products for the treatment of severe and very common diseases is noted. The following therapy areas belong to these treatments:

- oncology
- central nervous system
- cardiovascular system
- rheumatic disease
- respiratory system

The amount of “blockbuster” medicinal products, that are products with a yearly sale of more than 1 billion Dollar, increased from 36 drug products in the year 2000 to 94 drug products in the year 2005 [4]. Some of these products will loose their patent in the next years, so that then the generic products will also come to the market and will replace the original products partly. This could bring an additional growth, because the generic products are cheaper and more patients can use these generics then. In some countries the patients have to pay (partly) for their medicinal products, so that the patients or the reimbursement systems are interested to use the cheapest possible medicinal product for the treatment. In the next five years a high increase of the sales of generic products is expected. Also new indications of existing products were established which will also bring more sales to existing medicinal products. This development will cause that in the next years the sales of these blockbusters will increase.

Nearly 50% of the global Pharma sales were made in North America. But the highest growth rates for the year 2005 were made in the “emerging markets” which is Latin America, Asia and Africa. China showed an enormous increase in the last years and it is expected that China will be one of the seven biggest Pharma markets in the world in the year 2009 [5]. In the next five years it is expected that the global pharmaceutical market will grow about 5-8% per year. For USA and Europe the growth will be about 5–8%, but the Asia-Pacific area and Africa will have a higher growth of about 9-12%. Latin America will have a growth of 7-10% and for Japan a growth between 3-6% is expected [6].

Regulatory Requirements

The regulatory requirements for the development and the registration of a medicinal product are different in the various countries. It is not always easy to ascertain the requirements for registration, especially in Arabian countries, Asian countries, African countries or Latin America. Because of the differences in language and mentality it is often necessary to find a native speaker who will act as a mediator between the pharmaceutical company and the regulatory authority of the country.

International Organizations e.g. ICH and WHO, which have the goal to find and implement common procedures, are helpful for the pharmaceutical companies, for the registration authorities and for the patients to get the opportunity to have the necessary medicinal products available. Countries outside the ICH regions can have highly divergent regulations. These countries differ not only in their regulatory systems, but often also in economic situation and in medicinal structure. Since the ICH has implemented guidelines for quality, safety and efficacy and since the WHO has established norms, standards, medicines nomenclature and GMP guidelines it had the effect that in the ICH region the pharmaceutical companies can register and sell new products easier and earlier than they could do before.

The amount of non-clinical and clinical studies were reduced, because many countries accept the studies, that are made according the ICH guidelines. Before these harmonized guidelines were established, many different national requirements existed, so that the pharmaceutical companies had to make several studies until they could sell their pharmaceutical products in different countries.

Today also non-ICH countries accept the ICH and WHO requirements and guidelines, that makes the global trade much easier. The harmonization brought, that the regulatory requirements are not the critical factor for the global trade of the pharmaceutical companies. The decision in which countries a medicinal product will be sold is more an economical issue.

4 World Health Organisation -WHO

4.1 WHO: History and Members

In 1945 the United Nations (UN) were founded and they discussed to set up a global health organization that is acting as a coordination office of the UN for the international health. On April 7th, 1948 the WHO constitution came into force with original 55 member states. The 7th April is now celebrated as the World Health Day [7].

At the first World Health Assembly in June 1948 delegates from 53 of the 55 member states met to discuss the priorities of the new organization. The WHO took over the responsibility for the International Classification of Diseases (ICD). The ICD exists already since 1850`s and is used to classify diseases and other health problems. It is the international standard for clinical and epidemical purposes.

1974 the WHO launched an expanded programme on immunization. In 1977 the WHO published the first Essential Medicines List. In 1978 at the International Conference on Primary Health Care in Kazakhstan the WHO set the goal for “Health for All”.

Today 193 countries and two associate members are WHO members (see Annex 1: List of WHO Member States). They meet every year in Geneva in Switzerland (headquarter) in the World Health Assembly to set the program and approve the budget [8],[9].

The WHO is the international agency within the United Nations system that is responsible for health. Every five years the Director-General of the WHO is appointed. The Health Assembly elects the 34 members of the Executive Board.

There also exist six regional committees which focus on health matters of a special region. At the moment almost 8.000 people work for WHO in 147 country offices, six regional offices and at the headquarter in Geneva, Switzerland. The people that work for the WHO are health experts e.g. doctors, epidemiologists, scientists, managers, administrators and other people. The coordination of the regional offices is done by the WHO headquarter in Geneva, Switzerland.

4.2 WHO: Goals and Visions

The WHO has a constitution that reports the principles that are basic to the happiness, harmonious relations and security of all people. In Article 1 of the WHO constitution it is stated that the objective of the WHO shall be the attainment by all people of the highest possible level of health. The WHO defines health as a state of complete physical, mental and social well-being and not simply the absence of disease or infirmity [10].

The WHO Medicines Strategy 2004-2007 (see also 2000-2003) defines the WHO visions and goals [11],[12].

The WHO vision is that people everywhere have access to the essential medicines they need; that the medicines are safe, effective and of good quality; and that the medicines are prescribed and used rationally [Medicines Strategy 2004-2007].

The WHO goal in medicines is to help save lives and improve health by ensuring the quality, efficacy, safety and rational use of medicines, including traditional medicines, and by promoting equitable and sustainable access to essential medicines, particularly for the poor and disadvantages [Medicines Strategy 2004-2007].

In the WHO Medicines Strategy 2004-2007 (and the former 2000-2003) the objectives are discussed, how these goals can be achieved.

One of the main goals of the WHO is to support the governments of the different countries to take the responsibility for the health of the people. The WHO wants that the development of the public health system of the different countries will be improved. The WHO collects and spreads information about the public health situation and helps to use the newest medicines of the medicinal research and development. WHO helps to improve access to essential medicines and assure their safety, quality and rational use. Over the years 2000-2003 more than 120 countries worldwide have been supported in this way. With the launch of the WHO Medicines Strategy 2004-2007, WHO is continuing to respond to the medicines challenges of the 21st century with many initiatives. The new Medicinal Strategy is based on 4 key objectives:

- National medicines policy: strengthening national medicines policy
- Access: improving access to essential medicines by supply strategies and financing models
- Quality and safety: improving the quality and safety of medicines due to effective registration of medicinal products
- Rational use: promoting the rational use of medicines by health care professionals, consumer organisations and health insurance systems

Improving the quality and safety of medicines has important influence to regulatory affairs systems. The quality, safety and efficacy of medicines will be assured by strengthening and implementation of regulatory and quality assurance standards by :

- Supporting the national drug regulatory authorities through assessment, information exchange and capacity building
- Promoting global norms, standards and guidelines for quality, safety and efficacy of medicines
- Promoting instruments for effective drug regulations and quality assurance systems.

4.3 WHO Activities

4.3.1 International Classification of Diseases (ICD)

The International Classification of Diseases (ICD) is of global interest, because the classification is important for many statistics and reports of health and vital problems. For many countries the statistical reports of national mortality and morbidity is based on the ICD. To obtain diagnostic information for clinical purposes it is necessary to have a common classification. A classification of diseases is the basic for the health system and for the health organisations.

Early History of the International Classification of Diseases

The statistical study of diseases began in the 17th century. It was very difficult to write statistics of diseases, because of the difficulties of classification. William Cullen published in 1785 a classification of diseases, which was the first one that was in most general use until the beginning of the 19th century [13].

William Farr developed 1855 a model classifying diseases by anatomical site, which was the basis of the International List of Causes of Death.

In 1893 Jacques Bertillon presented a revised classification of causes of death to the International Statistical Congress in Chicago, that was based on William Farr`s model of distinguishing between general diseases and those localised to a particular organ or anatomical site. This classification was adopted by several countries, e.g. USA, Canada, Europe and Mexico. The American Public Health Association decided that this classification should be revised every ten years to keep it up-to-date.

At the first International Conference for the Revision of the International List of Causes of Death in 1938 the need for a corresponding list of diseases was stated. The statistical requirements of different organisations, e.g. health insurance organisations, hospitals, military medical services and health administrations made it necessary to have an international accepted list of diseases.

In 1945 the United States Committee on Joint Causes of Death was appointed by the American Secretary of State to prepare a statistical classification of diseases, injuries and causes of death. This classification was adopted by various countries as Canada, United Kingdom and USA.

WHO: The adoption of the ICD

In the 1940`s the International Health Conference in New York gave the responsibility of the International List of Diseases to the World Health Organization (WHO). The interim Commission of the WHO appointed the Expert Committee to review the International Lists of Diseases and Causes of Death, that was prepared by the United States Committee on Joint Causes of Death for the Sixth Revision in 1948. The reviewed classification was circulated to national governments for comments [13].

The revised version was adopted by the International Health Conference. This was the Sixth Revision of the International Classification of Diseases in 1948. This Revision was the beginning of a new era in vital and health statistics. This Conference recommended international cooperation for the vital and health statistics and that National Committees should coordinate the health statistical activities for the national governments. The National Committees acts as links between the national statistical institutions and the WHO. Statistical problems of public health importance are investigated by the national committees and the information is transferred to the WHO.

In several revisions the ICD was optimised. Some countries needed a more detailed classification and they wanted, that the classification is more relevant for the evaluation of the medical care. The revised International Classification of Diseases retained the basic structure of the ICD with more details and more options. Users that need the ICD for statistics and indexes for medical care could find an additional method, that was installed at the ICD. Since the Ninth Revision the ICD had additional the possibility to classify diagnostic statements for general diseases and for information of a defined organ or site. Also other technical innovations were established for additional flexibility of the system.

Because of the great expansion of the use of the ICD it became necessary to think about the ICD structure and to reconsider the design of new or alternative structures for the Tenth Revision of the ICD. The WHO Collaborating Centres for Classification of Diseases were asked for developing new models of alternative structures for ICD-10 (Tenth Revision of the ICD). The process of revision of the ICD is a very long-lasting process, because many countries and organizations have to be consulted for their remarks. The ten-year interval between the revisions of the ICD was too short for fundamental changes in the ICD to achieve a classification, that can be stable for many years. Therefore the Tenth Revision Conferences was postponed from 1985 to 1989. This allowed the WHO to experiment with alternative models for the structure of the ICD.

The Tenth Revision Conference recommended that the WHO should develop an effective updating process between the revisions of the ICD. The updating process was managed by two different groups: the Mortality Reference Group (MRG) and the Updating and Revision Committee (URC). The ICD-10 came into use in the WHO member states in 1994. This is the latest revision of the ICD until today [14].

4.3.2 Norms, Standards and Guidelines for Pharmaceuticals

The WHO constitution in Article 2 says, that the WHO is required to:
"develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products" [15].

The WHO has developed a large number of pharmaceutical norms, standards and guidelines. The Member States look to WHO guidelines for the development of pharmaceutical legislation and regulations, they rely on WHO for guidance in regulation [16].

Due to increasing globalisation of trade and commerce pharmaceutical products get internationalised. Therefore international norms and standards are very important and they act as global tools to ensure safety and quality of medicines.

In different parts of the world there exist harmonization initiatives for drug regulation. In developed countries technical and administrative effort ensures that patients receive medicines of good quality. For other countries the WHO guidelines can help to improve their regulatory system and at the end to ensure the quality of medicines. Therefore many WHO guidelines have been adapted by many Member States or regional harmonization groups. WHO identifies areas where additional guidance is needed and they help countries implementing drug regulation standards. The WHO recommends a step by step procedure when a country has low capacity and resources for health activities. The task of the WHO is to continue the development of international norms and standards and to help countries to implement them [16].

The existing WHO norms, standards and guidelines have to be continually updated to keep them at the state-of–the-art. Therefore the WHO Expert committee on Specifications for Pharmaceutical Preparations meets on a regular base to discuss guidelines. They publish guidances on Good Manufacturing Practices, quality assurance for regulatory approval and guidance texts for quality control, testing and distribution of medicines to improve the quality, safety and efficacy of medicine worldwide. These guidelines should help national drug authorities for the process of drug approval. The WHO guidelines on Good Manufacturing Practices are used in many countries worldwide. The WHO has also designed guidelines for Good Laboratory Practice (GLP), Good Clinical Practice (GCP) and Good Regulatory Practice (GRP). Also the guidelines for active pharmaceutical ingredients, excipients and impurities give helpful recommendation for the pharmaceutical companies and to health agencies, especially to the regulatory agencies. The WHO helps to establish relevant harmonization agreements and they advice non-ICH member states to adapt existing guidelines to their special situation. ICH does actual not involve representatives from all developing countries. So WHO has an important role for non-ICH member states.

The increasing worldwide trade of pharmaceuticals has made it important to use harmonized guidelines that are of realistic and practical use.

4.3.3 Guidelines on Good Manufacturing Practices (GMP)

International accepted requirements for manufacturing and analysis of pharmaceutical products are necessary to achieve conformity in quality of drug products for global commerce. The Good Manufacturing Practices describes these norms for manufacturing operations and Quality Control of Drugs, that can be assured by independent inspections.

Good Manufacturing Practice is a set of guidelines for the manufacturing of medicinal products, medical devices, diagnostic products and active pharmaceutical ingredients (API`s). In USA they are called “current” Good Manufacturing Practices (cGMP) to show that the regulations are dynamic.

Different organizations have developed GMP guidelines. In 1963 the FDA published the cGMP in the Code of Federal Regulations. The WHO version of GMP`s is used by regulatory authorities and the pharmaceutical industry in more than 100 countries in the whole world, mainly in developing countries. The WHO GMP`s were published in 1968. These guidelines have been revised in 1975 and 1992. In 1972 the Pharmaceutical Inspection Convention (PIC) released their PIC-GMP and additional guidelines. In the EU the EU-GMP guidelines, which were published in 1989, were in use. They have more compliance requirements than those stated in the WHO GMP`s. In the USA, the FDA GMP versions, which include requirements over and above those in the WHO document, are enforced [17],[18],[19],[20].

The GMP guidelines take the approach of regulating the production and laboratory testing. Because only sampling and testing of pharmaceutical products does not ensure that the whole product is suitable for use. For the Good Manufacturing Practice it is very important to document every step of the process of production and testing. The testing of the raw materials, the process of production, the testing of the products and the storing of the products have to be evaluated and validated to be GMP conform. Only validated processes should be used. Persons that are responsible for the process have to be named. Standard operating procedures are necessary for the working processes. All this has to be documented and reviewed after a defined time. This allows traceability of the products. If a recall of the pharmaceutical product from the market is necessary when safety or quality problems occur, this is possible.

The national authorities can carry out routine inspections to ensure that the medicinal products are produced safe and correctly. The GMP guidelines are an important tool for the pharmaceutical industry to plan and realize a manufacturing concept, sampling and testing of the medicinal product. The regulatory authorities use the GMP guidelines for their inspections to see whether the pharmaceutical company produces according GMP and to certify that the production is according GMP.

GMP is an international accepted guidance for manufacturing of pharmaceutical products and active ingredients with a constant quality. For the international commerce it is important for the pharmaceutical companies that they work according GMP regulations. This is a requirement for many countries when they want to import pharmaceutical products.

4.3.4 WHO Certification Scheme

The WHO has developed a Certification Scheme on the Quality of Pharmaceutical Products moving in international commerce [21]. This Scheme is an administrative instrument for the participating countries. The GMP standard is the basis for this Scheme. One Member State attests to the competent authority of another Member State, that

- a specific product is authorized to be on the market
- the manufacturing plant is inspected in suitable intervals to proof, that it is conform to GMP as recommended by WHO
- the submitted product information (e.g. PIL, labelling) is authorized in the certifying country

The WHO Certification Scheme is applicable to finished dosage forms of pharmaceutical products. Certification of active ingredients will be subject of separate guidelines and certificates [22].

Member States that want to participate to the WHO Certification Scheme have to notify the Director-General of the WHO, that they want to attend, inform about any reservations to intend and communicate the name and address of their national drug regulatory authority. The WHO informs about the notifications in the monthly WHO Pharmaceutical Newsletter and in the annually Newsletter. It is possible, that a Member State can participate only to control the import of the pharmaceutical products and active substances. Member States, that participate to the WHO Certification Scheme to support the export of pharmaceutical products should have:

- an effective national licensing system for pharmaceutical products and for manufacturer and distributor
- GMP requirements to which all manufacturer of pharmaceutical products have to conform
- effective controls to monitor the quality of pharmaceutical products
- a national pharmaceutical inspection system organized by the national drug authority
- administrative capacity to issue the certificates, that are required.

The Member States can evaluate and determine themselves whether they fulfil all these above mentioned requirements. The WHO does not inspect the Member States.

Within the WHO Certification Scheme there are three different documents:

1) Certificate of a Pharmaceutical Product (Product Certificate)
2) Statement of Licensing Status of Pharmaceutical Product(s)
3) Batch Certificate of a Pharmaceutical Product

The WHO provides proposed formats of these three documents in the Annexes of the guideline for the WHO Certification Scheme.

The national authorities of the Member States should issue guidelines, that explain the responsibilities for importing pharmaceutical products, the contribution of certification to the drug regulatory process and when each of the three types of documents should be used.

The Certificate of a Pharmaceutical Product (CPP) is issued by the national authority of the exporting country for the use at the national authority of the importing country when a product licence is requested for the pharmaceutical product or when the licence is requested to be renewed, varied or reviewed. The applicant (e.g. the product licence holder) has to submit all requested information to the national authority of the exporting country, so that they can issue the certificate of a pharmaceutical product, which is a confidential document.

The Statement of Licensing Status of a Pharmaceutical Product attests that a license has been issued for a specified product for the use in the exporting country. This statement is important for international tender. It gives information about the regulatory status of the pharmaceutical product and is issued by the national authorities of the exporting country.

The Batch Certificate of a Pharmaceutical Product gives information about the individual batch of a pharmaceutical product concerning the quality and the expiry date of the specific batch. The Batch Certificate is issued by the manufacturer of the pharmaceutical product, but should be made available at request of the competent authority during inspection done by the competent authority.

For the trade of pharmaceutical products the WHO Certification Scheme is important. The Certification of a Pharmaceutical Product, the Statement of Licensing Status and the Batch Certificate give necessary information to the national authority of the importing country. It is a common system to simplify the trade of pharmaceutical products.

4.3.5 Medicines Nomenclature:

4.3.5.1 International Non-proprietary Names (INN)

The WHO provides the system of International Non-proprietary Names (INN). The INN-system gives a unique and universally accessible name to each active ingredient or pharmaceutical substance, so that a global communication about chemical substances is possible. This system provides a common nomenclature for health professionals and consumers. It helps to prevent confusion, which could result if several different names for one pharmaceutical ingredient would exist in different countries or at different pharmaceutical companies. The INN-system, that is provided by the WHO, is one of the oldest services that the WHO gives to the Member States. It was initiated in 1950 by a World Health Assembly resolution and the first list of INN for pharmaceutical substances was published in 1953 [23].

The International Non-proprietary Names are available in the following languages:

- Arabic
- Chinese
- English
- French
- Russian
- Spanish and
- Latin.

The INN is often referred to as a “generic” name. The names are called “non-proprietary” because the INN list was formerly in the public domain of the WHO website to make it available for the public use. The INN can be used without limitation. The INN is used for communication between scientists, pharmaceutical companies, regulatory offices, health organisations, governments and consumers to ensure a clear identification of a chemical substance.

This international nomenclature system for pharmaceutical substances is important for a clear identification, safe prescription and application of medicinal products to patients. The INN names show relationships between the pharmacological substances because of the use of a common “stem”. The persons who work with the pharmacological substances can identify to which group a substance belongs. This can give information about similarity in the pharmacological behaviour of a substance and a group.

The INN names are requested by the manufacturer or by the originator at the WHO with a request form. Mostly the requestor gives already a suggested name to the WHO. The WHO Secretariat evaluates the suggested name whether it is conform with the general INN rules. They check whether there are similarities with existing INN and whether there could be conflicts with trade-marks. The results of the examination is then sent to the INN experts for their comments. When the experts accept the suggested INN, the proposed INN is published in WHO Drug Information. This allows interested persons or companies to give comments within a four month objection period [24], [25],[26].

If within 4 month after publication of an INN an interested person considers that the proposed INN is in conflict with an existing trade-mark, the WHO experts will evaluate the objection. The WHO will then withdraw the objection or reconsider the proposed name. When the expert discussion is finished the name will get the status of “recommended INN”. The recommended INN will be published by the WHO. When the INN is published as a recommended INN it can be used for labelling, drug information and for publications. When the INN is available in the public domain of the WHO website, it can be used freely, but it can not be registered as a trade-mark [26].

The INN process should be started by the applicant during the period of investigation, so when the pharmaceutical substance is in the clinical study phase for human subjects.

INN are selected for single substances, that can be characterized by a chemical name. INN names are not given to mixtures of substances, to herbal substances or to homoeopathic products.

The importance of the INN-system is increasing due to increasing amount of generic names for medicinal products. For generic products the pharmaceutical companies often use the INN-name in combination with the company name as the name of the medicinal product.

The INN names are also used in pharmacopoeias, scientific literature and for regulatory affairs authorities for registration.

4.3.5.2 The Anatomical Therapeutic Chemical Classification System (ATC)

In 1969 at the Symposium “The Consumption of Drugs” in Oslo it was realized that an internationally accepted classification system for drug consumption studies was needed. Therefore the Drug Utilization Research Group (DURG) was founded to develop an internationally applicable system. On the base of the European Market Research Association (EPhMRA) classification system the Anatomical Therapeutic Chemical (ATC) classification was developed [27].

In 1982 the WHO Collaborating Centre for Drug Statistics Methodology was established in Oslo, Norway, to make the ATC/DDD (Anatomical Therapeutic Chemical/ Defined Daily Dose) methodology more widely used.

In 1996 the Centre was linked directly to the WHO Headquarters in Geneva, Switzerland, because the WHO realized the need to develop the use of the ATC/DDD (Anatomical Therapeutic Chemical/ Defined Daily Dose) system as an international standard.

The WHO Division of Drug Management and Policies founded the WHO International Working Group for Drug Statistics Methodology, which gives expert advice to the WHO Collaborating Centre for Drug Statistics Methodology. The WHO International Working Group for Drug Statistics Methodology comprises 12 members, which are selected by WHO Headquarters. They represent users of the ATC/DDD system from different nationalities [28].

With the ATC/DDD system it was easier to integrate international drug utilization studies and WHO`s initiative for developing countries to get access to needed drugs and to get rational use of drugs [29].

The ATC system makes standardised and validated information on drugs and drug use international available.

The ATC classification system divides medicinal products according to:

- the organ system, where they act (**A**natomical)
- their therapeutic properties (**T**herapeutical) and
- their chemical properties. (**C**hemical)

Drugs are classified in groups at five different levels. The first level is the main group. There are fourteen main groups for drugs. The second level is the pharmaceutical/therapeutical subgroup. The third and fourth levels are chemical/pharmaceutical/therapeutical subgroups. The fifth level is the chemical substance [27].

New entries in the ATC system are only made on request of researchers, pharmaceutical manufacturers and regulatory agencies. The registration is done by the WHO Collaborating Centre in Oslo. New medicinal products are not included in the ATC system before an application for marketing authorization is submitted [30].

The basic principle of ATC code is that only one ATC code is given for a pharmaceutical formulation. Drugs are classified to the main therapeutic use of the main active ingredient. If one medicinal product has several indications, and therefore alternative ATC codes could be possible, these medicinal products usually get one ATC code of the main indication. Changes in the ATC classification are only made when the main use of a drug has changed [27].

The use of the ATC code is increasing worldwide. In many countries the ATC code is used for drug regulatory affairs and is necessary for drug registration at the regulatory authorities.

The ATC system is of importance to classify the medicinal products. This classification gives a good overview about the chemical base and the functionality of the medicinal product. This system is also helpful for communication between pharmaceutical industry, regulatory authorities and health organisations worldwide. The ATC code is required for drug applications in many countries, e.g. in Europe.

4.3.5.3 The Defined Daily Dose (DDD)

The Defined Daily Dose is also developed by the WHO Collaborating Centre for Drug Statistics Methodology in Oslo, Norway, and the WHO International Working Group for Drug Statistics and Methodology gives expert advice as for the ATC classification [27], [28].

The Defined Daily Dose (DDD) is the average dose of the medicinal product that is used for the main indication in adults. It describes the result of the drug utilization studies for the medicinal product. A DDD is only given for drugs that have an ATC code already. A DDD is normally only assigned when a drug product is approved and marketed. To measure drug use, a unit of measurement and also a classification system is necessary.

Drug utilization statistics based on ATC and DDD`s can be used to improve drugs, when national health systems, universities and drug information centres identify over use, under use or misuse of individual drugs or therapeutic groups. This information can then be used for specific studies and also can be published in scientific journals.

The DDD is a unit of measurement and is not necessarily the recommended or prescribed daily dose. The prescribed daily dose differs from patient to patient and is based on individual characteristics (e.g. age and weight) and pharmacokinetic aspects [29].

The DDD gives information to the researcher about trends in drug consumption and comparisons between population groups.

DDD for plain substances and DDD for combination products are existing. The assigned DDD for plain substances is based on the average adult dose used for the main indication that is defined by the ATC code. When the DDD differs due to body weight, it is estimated that an adult person has the weight of 70 kg. Also special pharmaceutical forms (e.g. suppositories, mixtures) that are mainly used by children are assigned the DDD used for adults [27].

For combination products the combination is counted as one daily dose, regardless how many active ingredients are in the combination. The assigned DDD for combination products should be equal to the DDD for the main active ingredient, where the main ingredient is identified by the ATC code (exceptions are products used for treatment of hypertension) [27].

The ATC and DDD system is developed only to maintain a stable system of drug consumption measurement. This system can compare trends in the utilization of drugs in one group and across therapeutic groups.

Changes of the DDD may be necessary from time to time, because the dosages that are used may change. These changes of the DDD should be kept to a minimum, because the DDD`s are used also for long term studies on drug utilization. A change of the DDD would bring disadvantages to the study.

The International Working Group for Drug Statistics Methodology reviews the DDD when it is necessary. New DDD`s are reviewed during the third year after inclusion in the "ATC index with DDD`s" at the meeting of the WHO International Working Group for Drug Statistics Methodology. Then the DDD normally stays unchanged for five years. Sometimes new information makes a total revision of all assigned DDD`s in an ATC group necessary. This has to be decided by the WHO International Working Group for Drug Statistics Methodology [27].

The Centre for Drug Statistics Methodology has published "Guidelines for ATC classification and DDD assignment" and an "Index", which includes a list of all assigned DDD and ATC.

This information is helpful for the pharmaceutical companies during the process of making clinical studies and during the process of gaining a marketing authorization for a drug product. The ATC group makes standardised information available. It improves the communication between the pharmaceutical companies and the regulatory authorities. The DDD`s can be helpful for studies to improve drug products. It can give information about patient groups, about over use, under use and misuse. The pharmaceutical companies can improve the use of the drug products by including this information in their clinical studies.

4.3.6 Pharmaceutical Specifications, Reference Materials and the International Pharmacopoeia

The WHO has developed detailed pharmaceutical specifications for active ingredients, excipients, impurities and finished products for the use in quality control laboratories, for identification of the substance and for quality assurance. These specifications are also published in the International Pharmacopoeia, which is used in many countries worldwide [31].

In the WHO “Index of Pharmacopoeias” from 2006/2 the number of forty-five countries with their national pharmacopoeias, the European Pharmacopoeia, the African Pharmacopoeia and the International Pharmacopoeia from the WHO are described with the title of the pharmacopoeias, the pharmacopoeia commissions, the publisher, the web address, edition version, year of the publishing and the used languages [32]. The fact that so many pharmacopoeias exist worldwide shows that a harmonization is necessary and an internationally accepted pharmacopoeia would bring a simplification for the pharmaceutical industry and the regulatory authorities.

The tests that are described in the IntPh are developed to determine impurities, so that the limits of the tolerable impurities can be fixed and for the undesirable impurities the absence can be stated. Most of the recommended tests are based on simple chemical techniques, so that they also can be realized in developing countries. This is done to ensure a good quality of the pharmaceutical product without the need for expensive equipment in the laboratories.

The IntPh is written in cooperation with members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and specialists from industry and organisations. The information that is available in the IntPh is based on international experience [31].

In addition to the monographs that are published, the IntPh has also important general information, e.g. drug nomenclature and general specifications for dosage forms. In a special section anti malaria drug substances, that are newly developed, are described.

In special projects for “priority drugs” which were used in treatment of e.g. Malaria or HIV, the WHO developed specifications for the International Pharmacopoeia. This International Pharmacopoeia is the only Pharmacopoeia which has a set of “malaria treatment specifications”. These are specifications of active ingredients and finished products for the malaria treatment.

The IntPh gives high priority to drugs that are important to WHO programs and that can not be found in other pharmacopoeias, e.g. new anti malaria drugs. Additional priority is given to drugs that are used world wide.

This shows the importance of the work of the WHO, which develops specifications for substances against a special disease and can focus on special projects for e.g. diseases that are found more often in poor countries. This could lead to a close cooperation between WHO and national regulatory authorities e.g. in developing countries.

The specifications help to assure the quality of medicines that are traded internationally. Medicinal products produced in high-developed countries and exported to developing countries can be controlled regarding the same specifications of the WHO than pharmaceutical products produced in developing countries for the export to high-developed countries.

The International Pharmacopoeia has no legal status. WHO Member States can adopt parts or the whole pharmacopoeia into their national legislation.

The WHO has also developed International Chemical Reference Standards and Infrared Reference Spectra for the use of pharmaceutical companies and national regulatory authorities for investigations in quality control test laboratories. These standards can help the pharmaceutical companies worldwide to have a common base for analytical tests.

4.3.7 International Drug Monitoring (WHO Drug Alert System) against Counterfeit Medicines

About 10 per cent of all prescription drugs worldwide are counterfeits according to the World Health Organization. Counterfeit drugs are medicines that have been intentional mislabelled with respect to their identity or their producer. These medicinal products could be made of wrong ingredients or wrong amount of active ingredients. Sometimes the producer include correct ingredients but from poor quality and from different source than labelled [33].

The use of counterfeit medicine can lead to therapeutic failure, because the health expert gives a prescription for the original medicine which can have different activity or amount of the active ingredient. The patient takes less or too much of the active ingredients with the counterfeit medicine which can lead to drug resistance or to death. Not only the health of the patients is jeopardised but also the pharmaceutical manufacturers are damaged financially [34].

The governments have to regulate the manufacture, import, export, distribution and supply of medicinal products of good quality. Therefore the governments establish national regulatory authorities and an adequate legal basis for the medical care of the population. The regulatory authorities control the market by establishing mandatory licensing system for pharmaceutical companies and medicinal products. The regulatory authorities perform inspections of the pharmaceutical companies and they implement a post-marketing surveillance system.

The WHO estimates that about 30 % of their Member States do not have a well functionary national regulatory system or even have no regulatory system for pharmaceutical products. These member states are mainly low-income countries. In these countries about 20-30% of the medicinal products are counterfeit medicines [33]. The effort of the WHO to strengthen the medicine regulation will help to improve the regulatory requirement. At the end the number of counterfeit medicines will be reduced [35].

WHO has developed guidelines for combating counterfeit medicinal products [36]. The WHO has adopted a Rapid Alert System (RAS) for combating counterfeit medicine. The RAS is a web-based communications network involving WHO and partner organizations and representatives of countries and areas, where counterfeits are found very often. Many counterfeits are found in the Western Pacific Region. The counterfeit medicinal products are often distributed across national boundaries and are therefore not only a national problem. The problem of counterfeit has international dimensions. Therefore there is a need for international cooperation in the fight against counterfeiting. The RAS provides rapid communication [37], [38].

The purpose of the RAS system is to alert member countries and areas about cases of counterfeit medicines. Reports of counterfeit medicines will be reported in the RAS system by using an electronic reporting form. These reported cases will be incorporated into the WHO database. If necessary a moderator will inform all the members of the RAS. For the future the governments of the Member States need to identify weaknesses in the medicine regulation system and develop strategies to combat counterfeit medicines.

A good-working system against counterfeit medicines is important for the international trade of pharmaceutical products for the benefit of the patients and for the exporting companies.

4.3.8 SIAMED

In November 1985 a conference of Experts on the Rational Use of Drugs were held in Nairobi. The experts realised that ineffective drug regulation and control is the major cause of poor drug quality and irrational medicinal product use in many Member States. The experts of the conference gave recommendations to strengthen the national drug regulation authorities. Therefore the WHO prepared guidelines for a simple drug regulatory authority and to support governments in setting up or strengthening drug regulatory authorities [39].

The WHO and the Pan-American Health Organization (PAHO) have developed a Model System for Computer-assisted Drug Registration (SIAMED) to improve the efficiency of drug regulatory authorities. This shall assure that the marketing authorizations are consistent with the national drug policy. The SIAMED software was developed with support of many experts in regulatory authorities of several countries. A written guide “How to implement computer-assisted drug registration” was written with support of the Management Sciences for Health. SIAMED is a living system that is adapted to changes that occur in the medicinal product regulations and in the legislation [39].

The implementation of the computerization can mainly improve the regulatory information process. For a successful implementation the WHO describes eleven major steps:

1. Obtain management and policy support
2. Review Enabling Legislation and Regulations
3. Identify Needs, Define Enabling Objective, and Establish Priorities
4. Identify Funding and Support Requirements and Sources
5. Appoint Technical Coordinator and Define Time Schedule
6. Review Forms, Procedures, and Correspondence
7. Update Forms and Certificates, as Required
8. Prepare Data and Decide How to Handle Data Entry
9. Train Staff in Software System and New Procedures
10. Begin Computerization
11. Operate and Maintain “Computer-Assisted Drug Registration System”

Before the regulatory authorities begin with implementation of SIAMED the WHO requires a feasibility study to define local specifications. An appropriate organizational structure, reliable working procedures, competent staff and sufficient financial resources are necessary. SIAMED is a part of a programme of the WHO for improving the drug registration and make it more efficient in developing countries.

With this system also developing countries can start a registration system or improve their system. Pharmaceutical companies then have the opportunity to achieve a marketing authorization for their pharmaceutical products in these countries. This is the basis for the worldwide trade of pharmaceutical products.

4.3.9 Adverse Drug Reaction Monitoring System

The WHO wants to ensure that all medicinal products in all member states will be monitored for adverse drug reactions. The aim of an adverse drug reaction monitoring system is to promote patient safety when using medicinal products. Good information for the patient is important for more rational use of the medicinal products. The knowledge of the adverse drug reactions will lead to a good risk-benefit profile of the medicinal products. The aim is a safer and more effective use of medicinal products [40].

The WHO Programme for International Drug Monitoring consists of three parts which are linked:

- WHO Headquarter, Geneva
- National Centres
- WHO Collaborating Centre, Uppsala

The Adverse Drug Reaction Monitoring System has developed guidelines, e.g.

- "Guidelines for setting up and running a Pharmacovigilance Centre."
- "The Importance of Pharmacovigilance"
- "A guide to detecting and reporting adverse drug reactions."

A database for the adverse drug reactions was established by the WHO and the member states inform about the adverse drug reactions in their countries. The global database of the WHO has now more than 3 million reports of adverse drug reactions from the participating countries. 86 countries are included in the programme [41].

Many countries need to establish a national Adverse Drug Reaction (ADR) Centre. In other countries, where a Drug Reaction Centre is already existing, the ADR Centre has to improve their reporting in qualitative and in quantitative way. Health professionals all over the world have to be aware of the importance of the reporting of the adverse drug reactions. When new drugs were introduced into populations with little infrastructure to monitor the use of the medicinal products, the governments have to be aware that they have to improve the adverse drug monitoring system to get a better risk-benefit profile for their patients.

For the future the WHO will go on to promote Pharmacovigilance through different activities like: trainings, new guidelines and collaboration with existing Drug Reaction Centres. Safety and Effectiveness of drugs, that are on the global market, can be ensured by an ADR Monitoring System and regulatory actions are then stimulated by ADR reports.

4.3.10 WHO Model List of Essential Medicines

On October 21st, 1977 the first List of Essential Medicines was published by the WHO Expert Committee on the Selection of Essential Drugs [42]. They identified 208 individual medicines which were of utmost importance, and were basic indispensable and necessary for the health needs of the population [43]. These medicines should be available at all times in adequate amounts and in the appropriate dosage forms.

The selection criteria for the essential medicines are:

- the need to treat a priority health problem
- the effectiveness compared with other medicines
- the safety
- the cost-effectiveness compared to alternative medicines within the same therapeutic group

The Model List of Essential Medicines is updated every two years by the Expert Committee on the Use of Essential Drugs (the former name of the committee was: Expert Committee on the Selection of Essential Drugs).

The Director-General of the WHO selects the members of the Expert Committee, to have a group of eight to twelve members with a wide range of professional medical and geographical background.

The current Model List of Essential Medicines was published by the WHO Expert Committee in March 2005. This 14th Model List of Essential Medicines contains 312 individual medicines [44].

This WHO Model List is a guide for the development of national essential medicine lists. In 1999, 156 WHO Member States had developed their own national essential medicine lists, which are designed for the specific health problems of the individual nation. The WHO Model List of Essential Medicines was not designed as a global Standard List. But the Model List has got global acceptance to be a powerful tool for promoting the health systems of the nations. Lists of essential medicines guide the donation of medicines, the reimbursement of medicine costs and the local medicinal production. They are helpful for the nations to focus on the significant health problems.

Also international organizations, like UNICEF and UNHCR, have adopted the concept of essential medicines. The Essential Medicine List is the foundation of their medicine supply system.

The availability of pharmaceuticals has mainly economic aspects, especially in developing countries. In developed countries the spending on pharmaceuticals is less than one fifth of total public and private health spending. In transitional economies the spending on pharmaceuticals represents 15-30 % and in developing countries 25-66 % [45]. In most developing countries are the costs for pharmaceuticals the largest household health expenses [46].

The WHO wants to help that also in poor countries essential medicines will be available for all people at all times by using the cost-effectiveness analysis. Regarding the cost-effectiveness analysis the essential medicines are very economic.

The WHO Model List of Essential Medicines has a global impact and is forward-looking.

Although current patent protected medicines are relatively expensive and international trade legislation sometimes prevent the import of relative cheap generic products, the List of Essential Medicines has brought a guidance for health systems to improve the supply of patients in developing countries, because the health budget can be used in an effective way. The health systems can concentrate on the essential products of pharmaceutical therapies. The global availability of essential medicines is increasing for the benefit of the patients, because the cost-effective analysis makes the use of the health budget more effective. The pharmaceutical companies have the advantage that their products will be sold in many countries.

4.3.11 Access to Medicines and Impact of International Trade Agreements (WTO-TRIPS)

In May 1996 the World Health Assembly (WHA) adopted a resolution, requesting the World Health Organization to report on the impact of the agreements of the World Trade Organization (WTO) regarding drug policies and essential drugs. The WHA has forced the WHO to ensure, that the important issue of the international trade agreements on the access of medicines is considered in the WHO Medicines Strategy [47]. In the Constitution of the WHO the access to medicines is demanded. In 2001 the WTO members tried to clarify the discrepancy between the two aspects of global trade: on one hand the need for governments to have access to medicines for public health and on the other hand the need to fulfil the Trade-Related Aspects of Intellectual Property Rights (TRIPS). Especially in developing countries patent rules may restrict the access to essential medicines, e.g. against HIV, tuberculosis and malaria [48].

The WTO Member States have to fulfil the Patent Protection Agreement (TRIPS), to provide protection for a minimum term of 20 years from the filing date of a patent application of a pharmaceutical product or process. Before the TRIPS Agreement the patent duration was significantly shorter in many countries and some countries only had process patents and not product patents before [49]. Developing countries had transition periods for adopting the requirements into their national legislation. In most cases pharmaceutical companies have not patented their products in developing countries, because the market is too small and profit is too low. But also if no patents exist in developing countries, the patent system may have an effect on access to medicines. The pharmaceutical companies mainly patent their products in potential supplier countries and this prevents supplies being exported to another country, e.g. to a developing country.

Production of generic products is possible for most of the essential medicines, because they are not protected by patents in developing countries. But patented new medicinal products are protected, and may be not available in developing countries. In the Doha Declaration (Article 31) it is layed down that each Member State has the right to grant compulsory licenses and the freedom to determine the grounds upon which such licenses are granted [48]. Reasons for compulsory licenses can be national emergency or other circumstances of extreme urgency. Compulsory licenses gives the competent government authority the right to license the use of a patented medicinal product to a third party without the consent of the patent-holder. This gives developing countries the possibility to get access to medicines when the patent holding pharmaceutical companies do not supply this country.

The global access of medicines is possible due to the compulsory licences. Also developing countries can get affordable access to existing medicines to protect public health. WHO can provide help to find the right balance between trade of pharmaceutical products and the intellectual property protection of pharmaceutical products.

5 International Conference on Harmonisation - ICH

5.1 ICH: History and Members

The ICH was founded in April 1990 at a meeting of the European Federation of Pharmaceutical Industries Association (EFPIA) in Brussels. Representatives of the regulatory authorities and industry associations of Europe, Japan and USA met to discuss about the topics for harmonization of registration medicinal products. At this first meeting the ICH Steering Committee (SC), which meets twice a year now, was established [50].

Most of the new medicinal products are developed in the EU, Japan and the USA. That is the reason why the ICH has limited its scope to these three regions.

The ICH exists of six parties that are directly involved, additionally there are three observers and also the International Federation of Pharmaceutical Manufacturers Associations (IFPMA). These six parties, that represent the regulatory authorities and the pharmaceutical industry of the European Union, Japan and USA are the founding members of the ICH:

- EU
- EFPIA
- MHLW
- JPMA
- FDA
- PhRMA

The observers are WHO, EFTA and Canada. They act as a link between the ICH and non-ICH countries and regions.

The ICH operates via the ICH Steering Committee. The ICH Steering Committee consists of the six parties and an IFPMA representative. The ICH Secretariat, that is working from IFPMA in Geneva, Switzerland, supports the Steering Committee [51].

International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)

The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) is a federation of member associations which represent the research-based pharmaceutical industry and exist of manufacturers of prescription medicines in 56 countries in the whole world. The IFPMA is a non-profit, non-governmental organization representing national industry associations and companies from both developed and developing countries. The IFPMA is a non-voting member in the ICH Steering Committee.

European Union (EU)

The European Union (EU) represents the member states of the EU. The EU works on harmonization of the regulatory requirements for medicinal products to achieve an easier trade of the medicinal products in the EU. The European Agency for the Evaluation of Medicinal Products (EMEA) in London was founded for centralised registrations. The EMEA provides technical and scientific support for the ICH.

European Federation of Pharmaceutical Industries and Associations (EFPIA)

The European Federation of Pharmaceutical Industries and Associations (EFPIA) is located in Brussels. The member companies of EFPIA come from countries in Western Europe and they are manufacturers of prescription medicines. Thirty national pharmaceutical industry associations and forty-six leading pharmaceutical companies have the direct membership of EFPIA. The EFPIA represents the European pharmaceutical industry with 2.100 companies of different sizes. The experts of the EFPIA reflect the view of the European pharmaceutical industry in the ICH.

Ministry of Health, Labour and Welfare, Japan (MHLW)

The Ministry of Health, Labour and Welfare in Japan (MHLW) has the assignment to improve social welfare, social security and public health. The Pharmaceutical and Medicinal Safety Bureau of the MHLW is responsible for evaluation and licensing of medicinal products. MHLW regulatory expert groups give technical advice on ICH matters.

Japan Pharmaceutical Manufacturers Association (JPMA)

The Japan Pharmaceutical Manufacturers Association (JPMA) has seventy-four members (including twenty foreign affiliates), which are research-based pharmaceutical companies. Specialised committees of industry experts coordinate the ICH work. JPMA promotes the adoption of international standards by its member companies.

Food and Drug Administration, USA (FDA)

The Food and Drug Administration, USA (FDA) is the worlds largest drug regulatory agency. FDA is responsible for the registration of all medicinal products in the USA. The Centre of Drug Evaluation and Research (CDER) and the Centre for Biologics Evaluation and Research (CBER) give technical advice for ICH matters.

Pharmaceutical Research and Manufacturers of America (PhRMA)

The Pharmaceutical Research and Manufacturers of America (PhRMA) has seventy-two members of research-based pharmaceutical companies, which develop prescription medicines. The PhRMA represents the leading research-based pharmaceutical and biotechnology companies in the United States and is based in Washington, DC. The Scientific and Regulatory Affairs division gives technical input to ICH work.

Observers

The three Observers at the ICH act as a link with non-ICH countries and regions. The three observers are:

- The World Health Organisation (WHO)
- The European Free Trade Association (EFTA), represented at ICH by the International Office for the Control of Medicines (IOCH), located in Switzerland
- Canada, represented at ICH by the Therapeutic Products Programme (TPP), Health Canada.

The observers WHO, EFTA and Canada each have a seat on the ICH Steering Committee. The experts of the three observers work in expert working groups.

ICH Steering Committee (SC)

The Steering Committee has two members from each of the six ICH members and from the non-voting members from the IFPMA and the Observers.

The Steering Committee meets twice a year. The SC determines the procedures and polices for ICH and they select subjects for harmonization. The ICH Steering Committee monitors also the development of the harmonization process. The topics that are identified by the Steering Committee for harmonization are selected from Safety, Efficacy, Quality and Multidisciplinary matters.

The WHO is an Observer to the Steering Committee. The SC acts as a link between the ICH and the WHO member countries that are not ICH member countries.

ICH Coordinators

Each of the six ICH members have an ICH Coordinator, who acts as the main contact person with the ICH Secretariat. The ICH Coordinator distributes the ICH documents into their area of responsibility.

The ICH Secretariat

The ICH Secretariat, which is based in Geneva, Switzerland, at the IFPMA offices, prepares and documents the meetings of the Steering Committee, the EWG and the six-member groups. The technical documentation of the ICH conferences is made by the ICH Secretariat.

ICH Expert Working Groups (EWG`S)

The Expert Working Groups are appointed by the Steering Committee for each technical subject, that has been selected for harmonization. In the first phase of the harmonization the EWG reviews the differences of the requirements in the three regions Europe, USA and Japan. The members of the EWG discuss the technical and scientific aspects of the harmonization subject, because they write a draft of the harmonized guideline.
The EWG develops scientific consensus for the selected topic in the three areas. Members of the EWG can be the Observers to ICH, the pharmacopoeial authorities and representatives from the pharmaceutical industry.

A working principle of the EWG is that in each Expert Working Group is at least one expert from each of the six ICH members.

The EWG reports to the Steering Committee in their meetings.

5.2 ICH: Goals and Visions

The goal of ICH is the international harmonization of technical requirements of development and registration of medicinal products to ensure that safe, effective and high quality medicinal products are developed and that they are registered in a cost-effective manner.

To achieve this, the ICH brings representatives from the three ICH regions (Europe, USA and Japan) together to develop and maintain guidelines. With these activities the ICH will minimize the use of animal testing and prevent unnecessary duplication of clinical trials in humans, but will maintain safety and efficacy for the patients [51].

The harmonization of the technical requirements that are relevant in the three ICH regions will lead to well structured developments of medicinal products. The medicinal products will not have to pass three different kinds of animal testing or clinical trials for humans, because of possible different guidelines in the three regions, but will have clear requirements that are accepted in all three ICH regions [52].

This can lead to bring medicinal products earlier on all three markets, so that they are then earlier available for the patients. It can lead to minimize the costs of animal testing and clinical trials, because instead of three different studies only one study can be used for all three regions. For animal testing it can mean that less animals have to be taken for tests, because only one test is necessary for the three regions.

The ICH wants to maintain the dialogue between regulatory authorities and the pharmaceutical industry in the three ICH regions to ensure a more timely introduction of new medicinal products. The ICH wants to develop and maintain harmonized technical requirements that will be of acceptance in the ICH regions. The ICH wants to avoid that in future requirements are divergent in the three ICH regions. New improved technical developments were encouraged by the ICH to replace current practices. The harmonized guidelines and information about their use are communicated by the ICH.

The ICH harmonization subjects are mainly the four categories:

- Quality
- Safety
- Efficacy
- Multidisciplinary (including Regulatory Communications)

The quality subjects describe the chemistry, manufacturing and controls. The safety subjects relate to in vitro and in vivo pre-clinical studies. The efficacy subjects concern to the clinical studies in humans. Multidisciplinary subjects do not fit into one of those three a.m. subjects. An example is the development of electronic harmonized standards for adverse event reporting or the development of an international harmonized medical dictionary for regulatory activities (MedDRA).

5.3 ICH: Process

ICH harmonization processes are divided into major and minor subjects. Major subjects are proposals for new guidelines or changes of existing guidelines, which are of major nature. The handling of major subjects are based on a five step process. This ICH-process is very successful. Minor changes are handled in an abbreviated maintenance process [51].

The ICH party, that wants to propose a harmonization action has to prepare a concept paper, which includes a short summary of the subject that has to describe the following items:

- Type of Harmonization (e.g. new guideline or update of an existing guideline)
- Statement of the Problem
- Issues to be Resolved (issues that have to be harmonized)
- Background to the Proposal (further relevant information)
- Type of Expert Working Group – (is a six-party group enough or is an extended EWG necessary)
  (The maintenance of an existing guideline does not need an EWG)

The concept paper will be sent to the members of the Steering Committee, Observers and ICH Coordinators. A copy of the concept paper is also sent to the ICH Secretariat, so that they are informed and then they add this item to the agenda for the next meeting of the Steering Committee. Proposals for maintenance of existing guidelines only have to be sent to the ICH Secretariat. The maintenance will start when the sponsor mentions that the abbreviated process is appropriate [53].

5.3.1 5 Step Process

When an ICH party or Observer wants to bring a harmonization subject to the discussion at the Steering Committee, they have to present this issue in a concept paper. This concept paper has to be sent to the members of the Steering Committee, Observers, ICH Coordinators and the ICH Secretariat. Comments to the concept paper will be sent to the Steering Committee too. A decision has to be made whether the topic is of interest to all parties. When it is of interest to all parties, then this topic will occur on the agenda of the Steering Committee regular meeting under the item "Proposals for New Topics". When the topics are selected, all parties additional to the six ICH members and the three Observers that would be interested in these topics have to be identified and will be invited to the discussions [53].

The Steering Committee will then:

a) confirm the objectives and expected outcome of the harmonization action
b) confirm the composition of the EWG appointed to discuss the technical issues, and
c) set a timetable and action plan for the EWG

The concept paper will be updated to inform about these decisions.

In the Expert Working Group there will attend one designee of each of the six ICH parties and of the three Observers. These Topic Leaders for the new topic are participants of the EWG meetings and they are contact persons for their ICH group. Also a deputy Topic Leader has to be designated. The ICH Secretariat invites the EWG members and acts as a contact for receipt of documents [51].

The EWG meetings will also be held when not all parties attend to the meeting. To manage the number of attendees of the EWG meetings from interested parties, only one representative from each party is allowed in addition to their expert.

A timetable for the development of the scientific consensus in the EWG of each subject is made by the Steering Committee. The maximum time limit is two years (normally). All involved parties of one subject have to appoint their experts within a special time limit.

The Rapporteur is designated from one of the six ICH parties.

The 5-step process is very successful. It is divided into the following steps:

- Consensus Building
- Start of Regulatory Action
- Regulatory Consultation
- Adoption of a Tripartite Harmonized Text
- Implementation

Step 1: Consensus Building

Based on the concept paper and the discussions with the experts, a draft guideline is prepared by the Rapporteur. This draft version will be circulated for comments with fixed time lines. Meetings of the EWG are twice a year at the same time as the meetings of the Steering Committee. The EWG gives interim reports to the ICH Steering Committee meetings.

When consensus is reached within the timeline all parties of the EWG are invited to sign the document to show their consensus to this text. This signed document is then submitted to the Steering Committee for adoption as Step 2 of the ICH process.

When complete consensus has not been reached within the time line, a report with the information, which differences between the parties exist, is sent to the Steering Committee. All experts can explain their opinion to the Steering Committee. The Steering Committee then has to decide, whether :

- Additional time will be given to this topic, so that the possibility of a consensus is given within a specified time.
- To suspend or to abandon the harmonization project.
- To proceed with step 2, although not a complete consensus was found.

Step 2: Start of Regulatory Action

When the Steering Committee agrees on the report from the EWG, that there is scientific consensus on the technical issues for the draft guideline or recommendation, then the next step (step 2) the start of regulatory action will begin.

Step 2 is that the consensus text, that is approved by the Steering Committee, is signed off by the Steering Committee as Step 2 Final Document.

Step 3: Regulatory Consultation

In step 3 the guideline or recommendation leaves the ICH process and comes to external consultation. In this step the document is published in the three regions. In the EU it is published as a draft CHMP guideline, in the USA it is published as a draft guidance in the Federal Register and in Japan it is translated and issued by MHLW for consultation. Industry associates and regulatory authorities, also from non-ICH regions, can comment on this draft document. The comments can be implemented in the draft guideline. The final document is then written by the Regulatory Rapporteur and signed by experts which represent the other regulatory parties.

Step 4: Adoption of a Tripartite Harmonized Text

At step 4 the Regulatory Rapporteur sents a report to the Steering Committee. When regulatory and industry parties are content with the result of step 2 and the regulatory consultation of step 3 the text of the guideline or recommendation is adopted by the Steering Committee.

When the tree regulatory parties of the ICH regions have signed that they accept the guideline, then the guideline is recommended for adoption throughout the three regions.

If one or more parties, representing the industry, have strong objectives to the adoption of the guideline, because the revised draft guideline introduces new issues or departs from the original consensus in major parts, then the regulatory parties can decide that the revised draft guideline should be submitted to further consultation.

Step 5: Implementation

Step 5 is the final step of regulatory implementation. The implementation of the new guideline will be made according to the national procedures of the ICH regions.

Europe:

The CHMP establishes a timeframe for implementation of the guideline, which is usually six month. The guidelines are published by the European Commission on the EMEA homepage in the Internet.

USA:

The FDA publishes a notice with the full text of the guideline in the Federal Register. The guidelines are available for use on the date they are published in the Federal Register. The FDA guidelines are available on the Internet.

Japan:

The ICH texts are translated into Japanese. The Pharmaceutical and Medical Safety Bureau (PMSB) gives a notification about the implementation date for the finalised guidelines. The guidelines are available from PMSB and on the Internet by the National Institute of Health and Science.

5.3.2 Maintenance Process

Minor changes or revisions of existing ICH guidelines were handled in an abbreviated process. This maintenance process is a rapid and flexible procedure, which needs only a minimum of resources [51], [53].

The six ICH parties have to nominate experts for the maintenance of all ICH guidelines and of the implemented agreements. These maintenance experts work closely together with the ICH Coordinators. The Coordinators provide details of the maintenance for every ICH guideline to the ICH Secretariat. For all maintenance issues the first contact persons are the ICH Coordinators.

The party that wants the maintenance of an ICH guideline or an agreement has to provide a concept paper that explains in detail what has to be changed. The concept paper has to be sent to the ICH Secretariat and the Coordinators. The Coordinators decide whether the proposal is a major or a minor change. When it is a minor change than the maintenance process starts.

The maintenance proposal is registered by the ICH Secretariat. They fix a code number for the procedure and they prepare a draft sign-off sheet with the changes of the guideline. The concept paper and the draft of the ICH Secretariat is sent to the ICH Coordinators and to the maintenance network experts. The Observers and the Steering Committee members are informed about the proposed changes.

The maintenance contact from the party that provided the concept paper acts as coordinator of the topic. They are responsible for circulating documents, e.g. the comments and further proposals. Each of the maintenance contact have regional or international consultation to clarify whether they can agree or not to the proposal. It is possible that minor changes in wording were proposed.

In the case that no agreement can be reached, this issue will be discussed at the next Steering Committee to find a decision and establish an Expert Working Group. Then the full 5-step process has to be passed for the proposed changes.

When all experts agree to the changes, then the draft sign-off sheet will be signed and returned to the ICH Secretariat . The ICH Secretariat sents the signed proposal to the Steering Committee and informs that the proposal for maintenance has been agreed by the maintenance network. The Steering Committee has to give an answer within one month.

The Steering Committee asks every ICH party to give their opinion:

a) Whether the maintenance proposal can be implemented without further consultations. When the proposal is immediately accepted, then the text of the ICH guideline is updated and sent to the Steering Committee and to the maintenance contacts. The revised text of the guideline is then published.

b) Whether the proposal is accepted but needs additional consultation and has to be handled in a 5-step process. Then the ICH Secretariat needs a signed document from all six ICH parties, that the 5-step process is required.

c) Whether there are some additional issues that have to be discussed at the next Steering Committee. Then the ICH Secretariat informs the maintenance contact and put this item on the agenda of the next Steering Committee.

5.4 ICH Finalized Guidelines

The ICH guidelines are divided into four categories: Quality, Safety, Efficacy and Multidisciplinary [54].

The ICH guidelines for Quality (Q) are guidelines relating to chemical and pharmaceutical quality assurance. The ICH quality guidelines describe mainly stability testing, validation of analytical procedures, impurity testing, international pharmacopoeias and quality for biotech products.

The ICH guidelines for Safety (S) are guidelines relating to in vitro and in vivo pre-clinical studies. The ICH safety guidelines describe mainly carcinogenicity studies, genotoxicity testing, toxicokinetics, chronic toxicity testing to reproduction and preclinical safety for biotech products.

The ICH guidelines for Efficacy (E) are guidelines relating to clinical studies in human subjects. They describe mainly population in clinical studies, clinical safety data management, pharmacovigilance planning, clinical study reports and good clinical practice.

The ICH guidelines for Multidisciplinary (M) are the cross-cutting topics, which do not fit uniquely into one of the above mentioned categories. The ICH multidisciplinary guidelines describe for example the Common Technical Document (CTD) or the MedDRA (Medical Terminology).

The ICH guidelines are for pharmaceutical companies the basis for planning and coordination of the quality, safety, efficacy and multidisciplinary aspects during the development of pharmaceutical products.

5.5 The Common Technical Document (CTD)

The Common Technical Document is an international accepted format for the dossiers that have to be submitted to the regulatory authorities to achieve the marketing authorization approval for a drug product. The ICH guideline for The Common Technical Document reached Step 2 of the ICH process at the Steering Committee Meeting in July 2000. On November 8th, 2000 the CTD has reached Step 4 of the ICH process and was then implemented in all three ICH regions Europe, USA and Japan [55], [56].

In the CTD format the information is well structured presented to the regulatory authorities and this helps the authorities to save time and resources during the reviews. Also the exchange of information between regulatory authorities is easier with a common structured document.

Since July 1st, 2003 in Europe, USA and Japan all applications have to be made in CTD format. The ICH M4 CTD guideline informs about the CTD format, that is accepted in all three ICH regions.

Before the CTD format existed, the requirements for the technical reports for submissions were different in the three ICH regions. Applicants who wanted to achieve a marketing authorization in Japan had to prepare the GAIYO, that presented a summary of the technical information. In Europe the applicant had to prepare tabulated summaries, expert reports and summaries. The US- FDA had their own guidance for the format and content of the New Drug Application.

Now an applicant can use one format for the dossier of drug registration in the three ICH regions. This saves time and resources also for the applicant, who only has to prepare one dossier, instead of three different dossiers for the ICH countries.

The CTD does not inform about the content of the dossier and it also does not indicate which studies are required. It only indicates an appropriate format for the data that have to be submitted to the regulatory authorities. The CTD format is applicable for all types of products and for all types of marketing authorization applications independently which registration procedure is used (centralised, MRP, national, decentralized, full application, abridged application)

Also the terminology used in the CTD is harmonized. Therefore European specific terms like “active substance” and “medicinal product” are not used, but the international terms like “drug substance” and “drug product” are used instead. Requirements for readability and understanding of the text are made in the CTD guideline. The structure of text and tables should be prepared with margins, so that a print on EU and Japan sized A4 paper as well as on 8.5 x 11” US paper is possible. Even the font and the size of the signs are regulated, so that the text is easily readable. Times New Roman, 12 point font is recommended for the text in the CTD. All pages in the document have to be numbered. Abbreviations and Acronymes have to be explained in the document for a better understanding. All References that have been used have to be described. These recommendations are helping that an international understanding of the content is possible.

The Common Technical Documents exists of five modules. The first Module contains the information that is region specific. The regulatory authority of the region defines the necessary content and format of Module 1. In this module the administrative, regional or national information is described.

Module 2, 3, 4 and 5 are common for all three regions.

Module 2 contains the Tables of Contents, Introduction and the Overall Summaries and Overviews.

Module 3 describes the information of the Quality. The guideline M4 Q gives information about the structure of this module.

Module 4 presents the Non-clinical Study Reports. These Reports should be structured as described in the guideline M4S.

Module 5 presents the Clinical Study Reports. These Reports should be presented as described in the guideline M4E.

5.6 ICH Global Cooperation Group (GCG)

The ICH Global Cooperation Group (GCG) is a subcommittee of the ICH Steering Committee and was founded in March 1999 [57]. The members of the GCG are:

- one representative from each of the six parties of the ICH Steering Committee (EU, EFPIA, MHLW, JPMA, FDA and PhRMA)
- one representative from the ICH Secretariat at IFPMA.

Also two observers (WHO and Canada) are part of the Global Cooperation Group. The aim of the GCG is to make information about ICH activities and ICH guidelines available for regulatory authorities and pharmaceutical companies of non-ICH countries that are interested in these information. Therefore the GCG has developed information brochures and gives talks in public meetings. Since September 2001 the Global Cooperation Group collaborates with other harmonisation initiatives worldwide. The GCG has developed criteria that organisations have to fulfil to cooperate with the ICH Global Cooperation Group [58]. Harmonisation Initiatives have to meet the following criteria, when they want to be invited to work with the Global Cooperation Group:

1. International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH).
2. The initiative should be founded on the principle of harmonising drug regulation across a defined group of countries.
3. The initiative should be science-based, with clear scientific harmonisation objectives.
4. The initiative should be currently active with meetings/activities regularly scheduled.

In 2003 other harmonisation initiatives have been invited to the GCG to be partners [58]. The following organisations have been invited:

- Asian Pacific Economic Cooperation (APEC) Joint Research Project on Bridging Studies
- Association of Southeast Asian Nations (ASEAN) Consultative Committee for Standards and Quality (ACCSQ)
- Gulf Cooperation Countries (GCC)
- Pan American Network on Drug Regulatory Harmonization (PANDRH)
- South African Development Community (SADC)

The GCG has developed Terms of Reference for further expansion of their activities in future. The GCG will act as a forum for harmonisation topics and practices worldwide. The GCG meets regularly 2-3 times per year and invites the “Permanent Representatives” of non-ICH partner initiatives to discuss topics and process issues of harmonisation.

The GCG is an important committee for harmonisation of regulatory issues for a simplification of gaining marketing authorizations worldwide. The association of different harmonisation initiatives will help that the global trade of pharmaceutical products will be easier and more effective in future.

6 Results and Discussion

The benefit of the international organizations ICH and WHO for the global acting of pharmaceutical companies and for the regulatory authorities is impressive.

The establishment of WHO in 1948 and of ICH in 1990 led to an improvement of rational drug development with appropriate studies. New medicinal products could be brought sooner to the market in the three ICH regions and also in many other countries.
The WHO developed norms and standards, guidelines for good practices like GMP, GLP, GCP and GRP, the anatomical therapeutic chemical classification system (ATC) and the International Pharmacopoeia and other basics for pharmaceuticals. These fundamentals are the basis for drug development and drug registration in many countries worldwide.

One of the first activities of the WHO was to review and revise the existing International Classification of Diseases (ICD). The WHO has developed a new structure for the ICD to make the use of the ICD more comfortable. It is of global interest, because in many countries the ICD is the basis for statistical health reports.

For the increasing globalisation of trade and commerce, international norms and standards for pharmaceutical products get very important. The WHO developed a large number of pharmaceutical norms, standards and guidelines. The WHO guidelines can help to harmonize drug regulation. In developing countries the WHO guidelines can help to improve the regulatory system. This will then ensure the quality of the drug product for the patients to be of constant good quality in every Member State.

The WHO guideline for Good Manufacturing Practices is an important tool for the pharmaceutical industry to realize production, sampling and testing of drug products and to do the appropriate documentation. The regulatory authorities use the GMP guideline as a basis for their inspections at the pharmaceutical companies to see whether the drug products are produced according GMP. The GMP guideline ensures that the drug products are of safe and constant quality.

For the trade of pharmaceutical products the WHO Certification Scheme provides with the three existing documents: Certificate of a Pharmaceutical Product (Product Certificate), Statement of Licensing Status of Pharmaceutical Product(s) and Batch Certificate of a Pharmaceutical Product, necessary information to national authorities of the importing country. This Certification Scheme can simplify the trade of pharmaceutical products on the global markets.

The WHO provides the INN system, so that each drug substance gets a unique name. With this common nomenclature the communication between researchers, pharmaceutical companies, regulatory authorities and health organizations is very precise and avoids confusion. In different countries sometimes different names for one drug substance exists. With the use of the INN the substance is characterised. These universally accessible names for drug substances are helpful for the worldwide trade.

With the development of an internationally accepted classification system for drug application and drug consumption studies the ATC/DDD system gives validated information on drugs and drug use and is internationally available. A drug product is classified in groups with different levels. This ATC system gives information about the chemical base and the functionality of the drug product. In many countries the ATC code is required by the regulatory authorities for the drug registration. The DDD describes the result of the drug utilization studies for a drug product and gives information about the use of a drug product. This can be helpful for clinical studies. ATC and DDD are accepted systems in many countries and are the base for communication between pharmaceutical companies and regulatory authorities.

Pharmaceutical specifications for drug substances, excipients, impurities and drug products are published by the WHO. These specifications and the reference materials, that are available from the WHO, are helpful for identification of the substance and for quality assurance. For the laboratory work worldwide the same reference materials and specifications can be used.

In many countries there are national pharmacopoeias existing. When a pharmaceutical company wants to describe test methods according a pharmacopoeia for the drug registration, in many countries they may use various national pharmacopoeia. To have a common base the International Pharmacopoeia from the WHO can be used as the reference document worldwide. This saves time and resources at the pharmaceutical company.

Because the amount of counterfeit medicines is estimated about 10 per cent worldwide already, the WHO has developed a system to combat counterfeit medicines. The WHO has introduced the Rapid Alert System, which is a web-based communication system, that informs about counterfeit medicines. For the global trade it is important, that all medicinal products, that are on the market, are of good quality, so that the patients can rely on them. This is only possible when the national regulatory authorities control the pharmaceutical market with an established licensing system and when there exists a system that combats counterfeit drugs. The WHO supports also developing countries to improve their systems.

The WHO has developed the SIAMED Model System for computer-assisted Drug Registration. In many Member States of the WHO the drug registration needed an improvement. The SIAMED Model System can improve the efficiency of the drug regulatory authorities, mainly in developing countries. SIAMED shall assure that the marketing authorizations are consistent with the national drug policy. The SIAMED Model supports the regulatory authorities in developing countries, so that global acting pharmaceutical companies find a defined system and competent staff in the regulatory authorities in the countries where they want to gain marketing approval.

A global adverse drug reaction monitoring system shall promote the safety of the patients worldwide. Global acting pharmaceutical companies should note that in some developing countries the adverse drug reaction monitoring system is under improvement by the authorities.

The WHO Model List of Essential Medicines is a list of medicines which are necessary for the health needs of the population. This WHO List is a guide for countries to develop their own national essential medicines list to improve the supply of the patients in their country. Because of the cost-effectiveness analysis the essential medicines are very economic and also countries with a small health budget can import essential medicines. The Access to Medicine for public health can be supported by the possibility of compulsory licences when developing countries do not get pharmaceutical products because of Trade-Related Aspects of Intellectual Property Rights. In the Doha Declaration it is stated that the Member States have the right to grant compulsory licenses in cases of national emergency. The WHO can support countries to find the right balance between trade of pharmaceutical products and the intellectual property protection of pharmaceutical products.

The ICH project to bring regulatory authorities of Europe, Japan and the United States together with experts from the pharmaceutical industry of these three regions was a great progress to achieve harmonization in technical guidelines and requirements for drug registration. This brought a reduction of research duplication and a reduction of development time by removing duplication of studies for different countries.

The harmonization initiative of the ICH is specifically related to the EU, Japan and the USA. But because also other countries have an interest in the harmonization procedure the WHO, Health Canada and the EFTA are invited to nominate Observers to attend the Expert Working Groups (EWG`S) and the ICH Steering Committee Meetings. Also the Generic industry, OTC industry and pharmacopoeial authorities can sent representatives to EWG`s.

Efficacy:

Clinical trials are the most costly, time consuming and resource intensive part of the development of a medicinal product. The pharmaceutical industry feels that the ICH harmonization has the most significant impact in the area of clinical trials. The most important efficacy guideline for the pharmaceutical industry is “Ethnic Factors in the Acceptability of Foreign Clinical Data” (E5). Before the introduction of the E5 guideline the pharmaceutical industry had to repeat clinical trials Phase III when they wanted to market a drug in more than one region. If the E5 guideline on the influence of ethnic factors is followed and the clinical trials are run under the principles of GCP according the guideline E6 “Good Clinical Practice”, these data can be submitted in all three ICH regions for a marketing authorization application. The guideline E8 “General Consideration of Clinical Trials” gives internationally accepted principles to be applied to trial design, which will then lead to data that are accepted in the ICH region. The guideline E3 “Structure and Content of Clinical Study Reports” established a common format for clinical study reports. This guideline was the basic framework for the Efficacy section of the CTD.

Although these harmonized guidelines did not only lead to reduction in time and resources during the drug development, they brought harmonised operating practices in the clinical trial process that increases the safety of the patients in the clinical trial.

Quality:

ICH Quality guidelines focus on the two areas of stability data and impurities. This led to a reduction of duplicate testing. The ICH guidelines reduced the testing that was necessary when a registration should be made in different climate regions. Before the ICH guidelines existed, it was typical to test at “room temperature”, which was different from company to company and dependent on climatic zones. There was also no standardised humidity control done before ICH guidelines were implemented. The quality guidelines provided standard sets of conditions taking account to the climatic zones of the ICH region. Stability tests that were made in one ICH region according the Q1 guidelines about stability are accepted in all three ICH regions. Duplication of stability tests is reduced for the ICH regions.

The impurity guidelines (Q3) provide scientific agreement on the recording and reporting of impurity levels. Threshold limits for impurity qualification and impurity identification are defined in the Q3 guidelines. These guidelines make it possible that a single specification for a drug substance or a drug product is acceptable in the ICH regions. To have only one specification for three markets makes the supply chain easier and supply errors are reduced.

Safety:

The ICH Safety guidelines cover all major types of pre-clinical toxicity testing which are necessary for the registration of a New Chemical Entity (NCE). With the safety guidelines a harmonization of pre-clinical testing was made to agree on study length, study content, species requirement, dose selection and exposure levels. This did not only bring a reduction in time and resources, but also a reduction in animals needed for the tests, which is also an ethical aspect. The international acceptability of studies with the study design according ICH safety guidelines led to savings in animal resources. A standard battery of tests was defined that covers the carcinogenicity testing, genotoxicity testing, reprotoxicity testing, chronic toxicity testing and toxico-kinetics. It is stated that the safety data have to be available before the clinical trials with human volunteers or patients start with the new drug. For the safety testing a continual development is necessary to improve evaluating the safety of new drugs.

The Common Technical Document (CTD):

The harmonized structure of the dossier for marketing authorization application, that is described in the ICH guideline M4, leads to a time and resource saving dossier preparation. The CTD structure is the single format for all technical data in the three ICH regions. It is also an advantage for the regulatory authorities, because the review of the data will be faster. That results to a faster time to market within the three ICH regions. Also non-ICH countries accept the CTD dossier format.

Non-ICH countries:

The ICH guidelines also affect non-ICH countries, because pharmaceutical companies want to bring their products worldwide on the market. The ICH process could help the developing countries to make the registration process easier. To inform also non-ICH countries about the ICH activities, the ICH Steering Committee has established a Global Cooperation Group. They will make the ICH guidelines available to non-ICH countries to improve the understanding and the acceptance of ICH in these countries. The GCG has also developed activities to expand their work together with other harmonisation initiatives worldwide. These organisations want to harmonise the regulatory issues together with the GCG to find a common base for gaining marketing authorizations in their Member States.

Global Pharmaceutical Markets:

The harmonization of the three ICH regions Europe, USA and Japan has reached a high level already. These three regions have a high market share of pharmaceutical products. But a high increase of pharmaceutical sale is expected in countries in the next years that are non-ICH countries, like China, Latin America and Africa. Not all of these countries have a well-established regulatory system already. For improvement of their regulatory system the tools that are developed by WHO and ICH can help these countries to get a more effective regulatory system. The international pharmaceutical organizations WHO and ICH have layed the foundation for a global harmonized trade of pharmaceutical products.

7 Conclusion and outlook

The global trade of drug products will increase in the future. For the next five years a growth of the global pharmaceutical market of about 5-8 % per year is expected.

The highest growth rates for the next years will have the “emerging markets” which are Latin America (7-10 %), Asia (9-12 %) and Africa (9-12 %). For USA and Europe the growth will be about 5-8 % and for Japan 3-6 %.

Because the worldwide trade of pharmaceutical products will increase, the pharmaceutical companies are interested to have common regulations for drug registration all over the world.

ICH and WHO regulations and standards give the basis for this simplification of drug registration. The ICH countries which have the highest grade of harmonization worldwide will in future have drug sales on a high level. But the emerging markets will have the highest growth rate of drug sales. So, if Latin-America, Asia and Africa, which are non-ICH countries, will accept also the ICH guidelines, the CTD structure for their dossier and the WHO standards and norms, the drug registration - also in emerging markets countries- will be faster and easier. The population in the emerging markets countries will then have the advantage of early availability of drug products. The WHO guidelines, norms and standards, nomenclature and other tools will be able to help these countries of the emerging markets, which have to improve the efficiency of their drug regulatory system. The implementation of WHO`s SIAMED system, for example, would make the drug registration more efficient and global acting pharmaceutical companies would have an easier entry with their drug products on these markets.

But the economical aspect should not be forgotten. Pharmaceutical companies will only bring their products on the local markets in different countries, when they will have a profit from this. Not only the regulatory aspects, but also the economical aspect are important for the global trade.

If countries are developing in that way that pharmaceutical companies see a benefit for them when they get marketing authorization for their products on these markets, the regulatory system should not be the hurdle.

When developing countries wants to improve their health system on that way, that they will have a good portfolio of drug products available on their market, they should think about their regulatory system. The adaptation of norms and structures and working procedures as described in WHO and ICH guidelines would help to get a common base with other countries worldwide. The work of the GCG shows that worldwide different harmonisation initiatives are existing and they are willing to work together to improve the harmonisation of regulatory issues for pharmaceutical products.

Hopefully in the not too distant future a global common regulatory system would make all pharmaceutical products in every possible country easier available for the benefit of the patients. WHO and ICH have layed the foundation for this development.

8 Summary

The international commerce of pharmaceutical products is increasing worldwide. Today the key markets are USA, Canada, some EU-countries, Japan, Australia and New Zealand. It is expected, that the increase of drug sales in China, Africa and Latin America will get higher in the next years. These emerging markets will get an important part in the global trade of pharmaceutical products. How can a country be prepared to have an effective regulatory system or how can it improve the existing system?

The international organizations WHO and ICH developed tools for a harmonized common regulatory system. Global acting pharmaceutical companies will find harmonized regulations for drug registration in many countries already. And the harmonization is improving due to the support of the WHO in many countries. The ICH work brings additional new and improved existing guidelines to the three ICH regions USA, Europe and Japan. But also non-ICH countries use the guidelines for their national registration system.

The benefit of the work of the international organizations WHO and ICH on regulatory harmonization is impressive. Global WHO databases for adverse drug reactions and for counterfeit medicines are helpful for the patients, pharmaceutical companies and regulatory authorities.

The ICH project to bring regulatory authorities and pharmaceutical associations of Europe, Japan and USA together to achieve harmonization in technical guidelines and requirements for drug registration was a great progress. The requirements for clinical trials, which are the most costly and time and resource consuming aspect in the development of a medicinal product were harmonized by ICH guidelines. These harmonized guidelines did also bring unified operating practices in the clinical trial process that increases the safety of the patients in the clinical trial. The ICH safety guidelines harmonized the pre-clinical toxicity testing, which brought a reduction in time and resources, but also a reduction in animals needed for tests, which is also an ethical aspect. ICH Quality guidelines mainly recommend the two areas of stability data and impurities. The harmonization of quality testing leads to one specification of a pharmaceutical product for the ICH regions, which makes the supply chain easier. The harmonized structure of the dossier for marketing authorization application leads to a time and resource saving dossier preparation and an easier review of the data by the authorities. The result is a faster time to market within the ICH regions.

Also if the economic aspect is important for a pharmaceutical company to bring their products on the market, the regulatory system in a country should not be the hurdle to gain marketing authorizations. The harmonization of the different regulatory systems will bring drug products faster on the markets for the benefit of the patients. And the pharmaceutical companies save time and resources with the harmonized registration systems.

The ICH Global Cooperation Group promotes the association of different harmonization initiatives to improve the worldwide harmonization of regulatory aspects, so that the global registration of pharmaceutical products will be even more easier and more effective in future.

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10 Annex

Annex 1: List of WHO Member States

Afghanistan
Albania
Algeria
Andorra
Angola
Antigua and Barbuda
Argentina
Armenia
Australia
Austria
Azerbaijan

Bahamas
Bahrain
Bangladesh
Barbados
Belarus
Belgium
Belize
Benin
Bhutan
Bolivia
Bosnia and Herzegovina
Botswana
Brazil
Brunei Darussalam
Bulgaria
Burkina Faso
Burundi

Cambodia
Cameroon
Canada
Cape Verde
Central African Republic
Chad
Chile
China
Colombia
Comoros
Congo
Cook Islands
Costa Rica
Cote d`Ìvoire
Croatia
Cuba
Cyprus
Czech Republic

Democratic People`s Republic of Korea
Democratic Republic of the Congo
Denmark
Djibouti
Dominica
Dominican Republic

Ecuador
Egypt
El Salvador
Equatorial Guinea
Eritrea
Estonia
Ethiopia

Fiji
Finland
France

Gabon
Gambia
Georgia
Germany
Ghana
Greece
Grenada
Guatemala
Guinea
Guinea-Bissau
Guyana

Haiti
Honduras
Hungary

Iceland
India
Indonesia
Iran (Isalmic Republic of)
Iraq
Ireland

Israel
Italy

Jamaica
Japan
Jordan

Kazakhstan
Kenya
Kiribati
Kuwait
Kyrgyzstan

Lao People`s Democratic Republic
Latvia
Lebanon
Lesotho
Liberia
Libyan Arab Jamahiriya
Lithuania
Luxembourg

Madagascar
Malawi
Malaysia
Maldives
Mali
Malta
Marshall Islands
Mauritania
Mauritius
Mexico
Micronesia (Federated States of)
Monaco
Mongolia
Montenegro
Morocco
Mozambique
Myanmar

Namibia
Nauru
Nepal
Netherlands
New Zealand
Nicaragua
Niger
Nigeria
Niue
Norway

Oman

Pakistan
Palau
Panama
Papua New Guinea
Paraguay
Peru
Philippines
Poland
Portugal

Qatar

Republic of Korea
Republic of Moldova
Romania
Russian Federation
Rwanda

Saint Kitts and Nevis
Saint Lucia
Saint Vincent and the Grenadines
Samoa
San Marino
Sao Tome and Principe
Saudi Arabia
Senegal
Serbia
Seychelles
Sierra Leone
Singapore
Slovakia
Slovenia
Solomon Islands
Somalia
South Africa
Spain
Sri Lanka
Sudan
Suriname
Swaziland
Sweden
Switzerland
Syrian Arab Republic

Tajikistan
Thailand
The former Yugoslav Republic of Macedonia
Timor-Leste

Togo
Tonga
Trinidad and Tobago
Tunisia
Turkey
Turkmenistan
Tuvalu

Uganda
Ukraine
United Arab Emirates
United Kingdom
United Republic of Tanzania
United States of America
Uruguay
Uzbekistan

Vanuatu
Venezuela (Bolivarian Republic of)
Viet Nam

Yemen

Zambia
Zimbabwe

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

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