

Chapter 6

Drug Regulation: History, Present and Future¹

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I. HISTORY OF MEDICINES REGULATION

Medicines are perhaps as old as mankind and the concepts how their quality has to be ensured has evolved gradually over the time. For example, Mithridates VI (120 BC), King of Pontus, concocted a compound preparation called “Mithridatium” which included 41 individual components and was held as a panacea for almost all diseases until as late as 1780s. It took until 1540 when in England the manufacture of Mithridatium and other medicines was subjected to supervision under the Apothecaries Wares, Drugs and Stuffs Act. The Act was one of the earliest British statutes on the control of medicines and it established the appointment of four inspectors of “Apothecary Wares, Drugs and Stuffs”. This could be seen as the start of pharmaceutical inspections. History of Pharmacopoeias, the official books of drug quality standards, probably dates back to one of the proclamations of the Salerno Medical Edict issued by Fredrick II of Sicily (1240), and ordered apothecaries to prepare remedies always in the same way – *forma curiae*. The first Pharmacopoeias as we know them today started to appear in Europe from 16th century e.g. the first Spanish Pharmacopoeia

was issued in 1581. The standards for the manufacture of Mithridatum were established in England in *The London Pharmacopoeia* only in 1618.

The modern medicines regulation started only after breakthrough progress in the 19th century life sciences, especially in chemistry, physiology and pharmacology, which laid a solid foundation for the modern drug research and development and started to flourish after the second World War.

Unfortunate events have catalysed the development of medicines regulation more than the evolution of a knowledge base. In 1937 over 100 people in the United States died of diethylene glycol poisoning following the use of a sulfanilamide elixir, which used the chemical as a solvent without any safety testing. This facilitated introduction of The Federal Food, Drug and Cosmetic Act with the pre-market notification requirement for new drugs in 1938. However, in countries with poor regulatory environment even recently medicines contaminated with diethylene glycol have killed patients.

The second catastrophe that influenced the development of medicines regulation far more than any event in history was the thalidomide disaster. Thalidomide was a sedative and hypnotic that first went on sale in Western Germany in 1956. Between 1958 and 1960 it was introduced in 46 different countries worldwide resulting in an estimated 10,000 babies being born with phocomelia and other

¹ The views stated in this chapter reflect the views of the authors and not necessarily those of the World Health Organization.

deformities. The role of this disaster in shaping the medicines regulatory systems is not hard to underestimate.

As a result the whole regulatory system was reshaped in the UK where a Committee on the Safety of Drugs (CSD) was started in 1963 followed by a voluntary adverse drug reaction reporting system (Yellow Card Scheme) in 1964. In the United States, The Drug Amendments Act of 1962 was passed by Congress requiring the FDA to approve all new drug applications (NDA) and, for the first time, demanded that a new drug should be proven to be effective and safe. Of equal importance, the FDA was also given the authority to require compliance with current Good Manufacturing Practices (GMP), to officially register drug establishments and implement other requirements. The EEC Directive 65/65/EEC on the approximation of provisions laid down by law, regulation and administrative action relating to medicinal products was also induced by the thalidomide disaster.

It took almost ten years for the European Community (EC), since Council Directive 65/65/EEC was introduced, to further develop harmonization in the Community. In 1975 two Council Directives were introduced, the first on approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products (75/318/EEC), and the second on the approximation of provisions laid down by law, regulation and administrative action relating to medicinal products (75/319/EEC). The latter established an 'old' Committee on Proprietary Medicinal Products (CPMP) as an advisory committee to the EC and introduced the multistate procedure known now as the mutual recognition procedure. Directive 87/22/EEC introduced the concentration procedure which is now known as the centralized procedure. These directives, and following council regulation, were the landmarks for starting harmonization inside the European Union with the final longstanding aim of creating a 'common market' for medicines. The Council Regulation EEC/2309/93 established the European Medicines Evaluation Agency (EMA) in 1993 and re-established the CPMP as a 'new' CPMP to formulate the opinion of the Agency on questions relating to the submission of applications and granting marketing authorizations in accordance with the centralized procedure. The details of European marketing authorization procedure are described in detail in other publications.

Somewhat parallel with the ongoing harmonization and movement towards creating a common market for medicines inside the EU, the need for wider harmonization was after preliminary contacts between officials from Japan, EU and US discussed during the International Conference of Drug Regulatory Authorities (ICDRA – organized by WHO every second year) in Paris in 1989. The preliminary informal discussions had revealed a need for the harmonization of requirements relating to the new innovative drugs and the green light given in Paris led to the establishment in 1990 of the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH), a collaborative initiative between the EU, Japan and the United States with observers from WHO, EFTA and Canada. ICH harmonization focuses primarily on technical requirements for new, innovative medicines. However, countries with limited resources are mostly generic markets and may have difficulties of implementing numerous sophisticated ICH standards. Pharmaceutical regulatory harmonization facilitates the availability of safe, effective and good quality pharmaceuticals. World Health Organization (WHO)² supports harmonization on national, regional, inter-regional and international levels. International consensus on quality, safety and efficacy standards can accelerate the introduction of new medicines and increase availability of generic medicines through fair competition, thereby lowering prices.

II. WHY REGULATING DRUGS?

Drugs are not ordinary consumers' products. In most instances, consumers are not in a position to make decisions about when to use drugs, which drugs to use, how to use them and to weigh potential benefits against risks as no medicine is completely safe. Professional advice from either prescribers or dispensers are needed in making these decisions. However, even healthcare professionals (medical doctors, pharmacists) nowadays are not in capacity to

² WHO is the directing and coordinating technical agency for health within the United Nations system. It is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends.

take informed decisions about all aspects of medicines without special training and access to necessary information. The production of medicines, their distribution and dispensing also requires special knowledge and expertise. Among medical disciplines clinical pharmacology could be considered as a discipline that covers most comprehensively clinical aspects of medicines safety and efficacy. Among medical specialists clinical pharmacologists have the most comprehensive training to understand all the complexities of the clinical use of medicines. Due to sophisticated scientific issues related to medicines just any medical training may not be enough to take fair judgments about their safety and efficacy. Also only basic training in pharmacy may not enable to take proper judgments about medicines quality.

The use of ineffective, poor quality, harmful medicines can result in therapeutic failure, exacerbation of disease, resistance to medicines and sometimes death. It also undermines confidence in health systems, health professionals, pharmaceutical manufacturers and distributors. Money spent on ineffective, unsafe and poor quality medicines is wasted – whether by patients/consumers or insurance schemes/governments. Governments have the responsibility to protect their citizens in the areas where the citizens themselves are not able to do so. Thus, Governments need to establish strong national regulatory authorities (NRAs), to ensure that the manufacture, trade and use of medicines are regulated effectively. In broad terms the mission of NRAs is to *protect and promote public health*. Medicines regulation demands the application of sound scientific (including but not limited to medical, pharmaceutical, biological and chemical) knowledge and specific technical skills, and operates within a legal framework. The basic elements of effective drug regulation have been laid down in several WHO documents.

III. WHAT IS MEDICINES REGULATION?

Medicines regulation incorporates several mutually reinforcing activities all aimed at promoting and protecting public health. These activities vary from country to country in scope and implementation, but generally include the functions listed in Table 1.

What makes medicines regulation effective? Medicines regulation demands the application of sound medical, scientific and technical knowledge

Table 1. Principal medicines regulatory functions

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- Licensing of the manufacture, import, export, distribution, promotion and advertising of medicines
 - Assessing the safety, efficacy and quality of medicines, and issuing marketing authorization for individual products
 - Inspecting and surveillance of manufacturers, importers, wholesalers and dispensers of medicines
 - Controlling and monitoring the quality of medicines on the market
 - Controlling promotion and advertising of medicines
 - Monitoring safety of marketed medicines including collecting and analysing adverse reaction reports
 - Providing independent information on medicines to professionals and the public
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Source: WHO Policy Perspectives on Medicines no 7, 2003.

and skills, and operates within a legal framework. Regulatory functions involve interactions with various stakeholders (e.g. manufacturers, traders, consumers, health professionals, researchers and governments) whose economic, social and political motives may differ, making implementation of regulation both politically and technically challenging. Medicines regulation has administrative part but far more important is the scientific basis for it. *All medicines must meet three criteria: be of good quality, safe and effective.* The judgments about medicines quality, safety and efficacy should be based on solid science. There are several general and specific factors contributing to effective regulation by NRAs. General factors include political will and commitment to regulation, adequate availability of medicines that are accessible (to avoid smuggling and illegal use), strong public support for drug regulation, effective cooperation between the NRA and other government institutions including those dealing with law enforcement (e.g. customs and police), and sufficient qualified and experienced pharmaceutical, medical and other professionals. Political environment favouring independent science based decision-making and control of import/export and distribution (including e-commerce) of medicines is essential. The specific factors for NRA include clear mission statement, adequate medicines legislation and regulation, appropriate organizational structure and facilities, clearly defined NRA roles and responsibilities, adequate and sustainable financial resources, including resources to retain and develop staff and appropriate tools, such as standards, guidelines and procedures. International collaboration with other NRAs

Table 2. Minimum regulatory functions for a national regulatory authority (NRA)

As an absolute minimum NRAs should

- Ensure that all medicines manufacturing, importation, exportation, wholesale and distribution establishments are licensed. Activities and premises must comply with Good Manufacturing Practices (GMP) and Good Distribution Practice requirements
- Before medicines are marketed, assess their *safety, efficacy and quality*
- Monitor the quality and safety of medicines on the market to prevent harmful, substandard and counterfeit medicines from reaching the public
- Regularly inspect and control the informal market, including e-commerce, to prevent illegal trade of medicines
- Monitor advertising and promotion of medicines, and provide independent information on their rational use to the public and professionals
- Participate in sub-regional and regional regulatory networks and international meetings of drug regulatory authorities to discuss issues of mutual interest and concern, facilitate timely exchange of information and promote collaboration
- Monitor and evaluate performance to assess if perceived regulatory objectives have been met, to identify weaknesses and take corrective action

Source: WHO Policy Perspectives on Medicines no 7, 2003.

(for example, in the EU national regulators are required to collaborate in line with respective Community regulations) and internal collaboration with all stakeholders, transparency (making transparent how and based on which information decisions are made) and accountability combined with good management and effective internal quality system contribute to the success of a regulatory authority. Minimum functions that a NRA should be able to carry out are laid down in Table 2.

Excessive promotion of pharmaceuticals has been associated in many countries with serious problems of irrational drug use. Unethical medicines promotion activities often convey misleading information about drugs to the different target audiences. Misinformation can be in the form of an expansion of indications or an exaggeration of efficacy but can also present itself as downplaying the seriousness or the incidence of adverse reactions. Such misleading information will create a wrong perception of the efficacy and safety of medicinals among prescribers and consumers and it will lead to a significant increased demand for drugs. In many countries, relevant provisions regarding such control measures have been stipulated in legislation. For example, only product information approved during the registration process can be included in the package inserts, leaflets or promotional materials. Regulatory or legal provisions with respect to drugs usually appreciate the right of patients or consumers on proper information about the drugs they take. WHO has developed guidelines on Ethical Criteria for Medicinal Drug Promotion. These guidelines in line with European

regulations and regulations in many other countries do not allow direct to patient advertising of prescription only medicines (in US it is allowed and has increased sales of several medicines dramatically). These guidelines remain also useful today and provide ethical criteria for different promotional activities and cover, among others, advertisements to prescribers and to the general public, the availability of free samples of prescription drugs for prescribers or of non-prescription drugs to the general public, medical symposia and other scientific meetings, activities of medical representatives, packaging and labeling and the information for patients in the package inserts.

There are few in depth comparative studies of regulatory systems in different countries globally. The study by Ratanwijitrasin and Wondemagegnehu (2002) revealed that in spite of similarities there are still substantial differences existing in how regulatory systems in different countries carry out minimum functions required for effective medicines regulation. A huge variety in national regulatory capacity does exist and not all national regulators can effectively implement even minimum regulatory oversight of pharmaceutical market in their jurisdiction. Substandard and counterfeit medicines are still common in many parts of the world.

IV. DRUG REGISTRATION

Registration of drugs, also known as *product licensing* or *marketing authorization*, is an essential element of drug regulation. All drugs that are marketed,

distributed and used in the country should be registered by the national competent regulatory authority. Only the inspection of manufacturing plants and laboratory quality control analysis certainly does not guarantee product quality and safety. Drug regulation should therefore include the scientific evaluation of products before registration, to ensure that all marketed pharmaceutical products meet the criteria of *safety*, *efficacy* and *quality*. Although these criteria are applicable to all medicines including biological products (including vaccines, blood products, monoclonal antibodies, cell and tissue therapies) and herbal medicines (also other traditional and complementary medicines) there are substantial differences in the regulatory requirements for some groups of medicines. There should also be clear distinctions between medicines which can be dispensed without prescription (over the counter or OTC medicines) and those for which a prescription is needed. Usually new medicines are introduced as prescription only medicines and only after obtaining knowledge and experience about their safe use they may be considered being used as OTC for self-medication. This is valid only in case patients are expected to be able for adequate self-diagnosis as well. WHO has issued Guidelines for the Regulatory Assessment of Medicinal Products for Use in Self-Medication. In regulatory practice active pharmaceutical ingredients used in medicines are expressed using International Nonproprietary Names (INNs). INNs are assigned upon request to a molecular entity responsible for the pharmacological action by WHO. The INN system as it exists today was initiated in 1950 by a World Health Assembly resolution WHA3.11 and began operating in 1953. Chemical names and entire formulas are often difficult to remember and may be incomprehensible for a non specialist (for example, perhaps few medical doctors know that 4'-hydroxyacetanilide or *N*-(4-hydroxyphenyl) acetamide is paracetamol). The cumulative list of INN now stands at some 7500 plus names designated since that time, and this number is growing every year by some 120–150 new INN (INNs are proposed also for biological medicines such as monoclonal antibodies and gene therapy products). INNs are also widely used in scientific literature and in teaching basic and clinical pharmacology. The lists of International Nonproprietary Names are published in regular manner. Use of INNs in product labeling and information is nowadays in

most countries compulsory. As important as assessment of quality, safety and efficacy is ensuring appropriateness, accuracy and availability of approved by regulators product information. When marketing authorization is granted for medicines a set of clinical information including indications are approved. The use of medicines for indications that have not been approved by a regulator is called 'off-label' use. This means that the safety and efficacy of medicines for these indications has not been assessed and approved by a regulator. One of the most common off-label use areas is pediatric medicine.

In the next section we are concentrating on giving general overview of registration requirements for two major groups of medicines: *innovative* (originator) and *multisource* (generic) medicines.

IV.a. Innovative Medicines

Innovative medicines (originator products) are new medicines that have not been used in humans earlier and contain new active ingredients (usually expressed using INN system). Nowadays these medicines are usually first approved by regulators in well resourced countries using regulatory requirements harmonized in the framework of International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH – see also web site: www.ich.org). The terms of reference for ICH include to maintain a forum for constructive dialogue between regulatory authorities and the pharmaceutical industry on the real and perceived differences in the technical requirements in the EU, USA and Japan in order to ensure a more timely introduction of new medicinal products, and their availability to patients, to monitor and update harmonized technical requirements leading to a greater mutual acceptance of research and development data and to contribute to the protection of public health from international perspective.

The ICH technical Topics are divided into four major categories and specific ICH Topic Codes (such as Q1, E6, S1 and M4) are assigned according to these categories. Q means '*Quality*' Topics i.e., those relating to chemical and pharmaceutical Quality Assurance (examples: Q1 Stability Testing, Q3 Impurity Testing). S means '*Safety*' Topics, i.e., those relating to *in vitro* and *in vivo* pre-clinical studies (examples: S1 Carcinogenicity Testing, S2 Genotoxicity Testing). E means '*Efficacy*'

Topics, i.e., those relating to clinical studies in human subject (examples: E4 Dose Response Studies, Carcinogenicity Testing, E6 Good Clinical Practices; Clinical Safety Data Management is also classified as an 'Efficacy' Topic – E2). M designates '*Multidisciplinary Topics*', i.e., cross-cutting Topics which do not fit uniquely into one of the above categories (examples here are M1 Medical Terminology – MedDRA, M2 Electronic Standards for Transmission of Regulatory Information – ESTR1, M3 Timing of Pre-clinical Studies in Relation to Clinical Trials, M4 The Common Technical Document – CTD and M5 Data Elements and Standards for Drug Dictionaries). ICH guidelines are not mandatory for anybody per se but the strength of ICH process lies in the commitment for implementation by the ICH 'regions' (EU, USA and Japan) using appropriate national/regional tools. For example, in the EU all ICH guidelines are submitted to the Committee for Human Medicinal Products (CHMP) associated to European Medicines Agency (EMA, see web site: <http://www.emea.europa.eu/>) for endorsement once they have reached certain maturity phase ICH process. The CHMP, in consultation with the European Commission decides on the duration for consultation with interested parties (up to 6 months). The European Medicines Agency (EMA) publishes and distributes the *Step 2* guidelines for comments. At *Step 4* the guidelines are endorsed by the CHMP and a time frame for implementation is established (usually 6 months). The guidelines are subsequently published by the European Commission in the Rules Governing Medicinal Products in the European Union (<http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm>). *Step 2* and *Step 4* guidelines are also available from the EMA site on the Internet (<http://www.emea.europa.eu>).

As more than 95% of new medicines are worked out in the ICH "regions" the technical requirements for the safety, efficacy and quality of new medicines is determined at large by ICH technical guidelines. The application format for registration (marketing authorization) of new medicines in ICH and associated countries (such as Canada, Switzerland and Australia) has to follow The Common Technical Document (CTD) which provides harmonized structure and format for new product applications. This Common Technical Document is divided into four separate sections and 5 modules (see Fig. 1). The four sections address the application organization (M4: Organization), the Quality section (M4Q), the

Safety section (M4S) and the Efficacy section (M4E) of the harmonized application. Module 1 contains ICH region specific administrative data and prescribing information and is not part of CTD. Module 2 contains CTD summaries, Module 3 is dedicated to quality, Module 4 for non-clinical study reports and Module 5 on clinical study reports. The structure of Common Technical Document (CTD) is given in the Fig. 1. The content for CTD has to be compiled taking into consideration technical requirements in more than 56 ICH guidelines for Quality, Safety and Efficacy plus 5 multidisciplinary (M) topics. Registration of new medicines by less resourced regulatory agencies is often based on first approval either by US FDA or EMA from EU. Indirectly ICH guidelines used by these regulatory agencies have major impact on approval of new medicines beyond ICH regions. Many ICH guidelines, especially those concerning preclinical and clinical research, are of interest to the research community and can serve also as educational tools.

Clinical pharmacologists should be familiar with available ICH guidelines concerning medicines efficacy and safety. Those involved in clinical research have to know in depth Good Clinical Practice (GCP – ICH E6) guidelines as well the guidelines concerning the research ethics. WHO has its own GCP guidelines which do not contradict ICH guideline but which in addition describe the role of regulatory authorities. In addition, WHO has developed a tool for implementation of GCP which provides practical advice on the principles of GCP and has an interactive CD which incorporates many texts related to GCP and research ethics. In research ethics the fundamental principle that "*no one shall be subjected without his free consent to medical or scientific experimentation*" has found further interpretation in a set of principles laid down in the World Medical Association (WMA) *Declaration of Helsinki* (first edition 1964, current version from 2004 under revision). In case of research ethics and medicines safety the work of the Council for International Organizations of Medical Sciences (CIOMS) should be referred to. CIOMS was founded under the auspices of the World Health Organization (WHO) and the United Nations Educational, Scientific and Cultural Organization (UNESCO) in 1949. In the late 1970s, CIOMS set out, in cooperation with WHO, to prepare guidelines "to indicate how the ethical principles that should guide the conduct of biomedical research involving human subjects, as set forth in the *Declaration of Helsinki*,

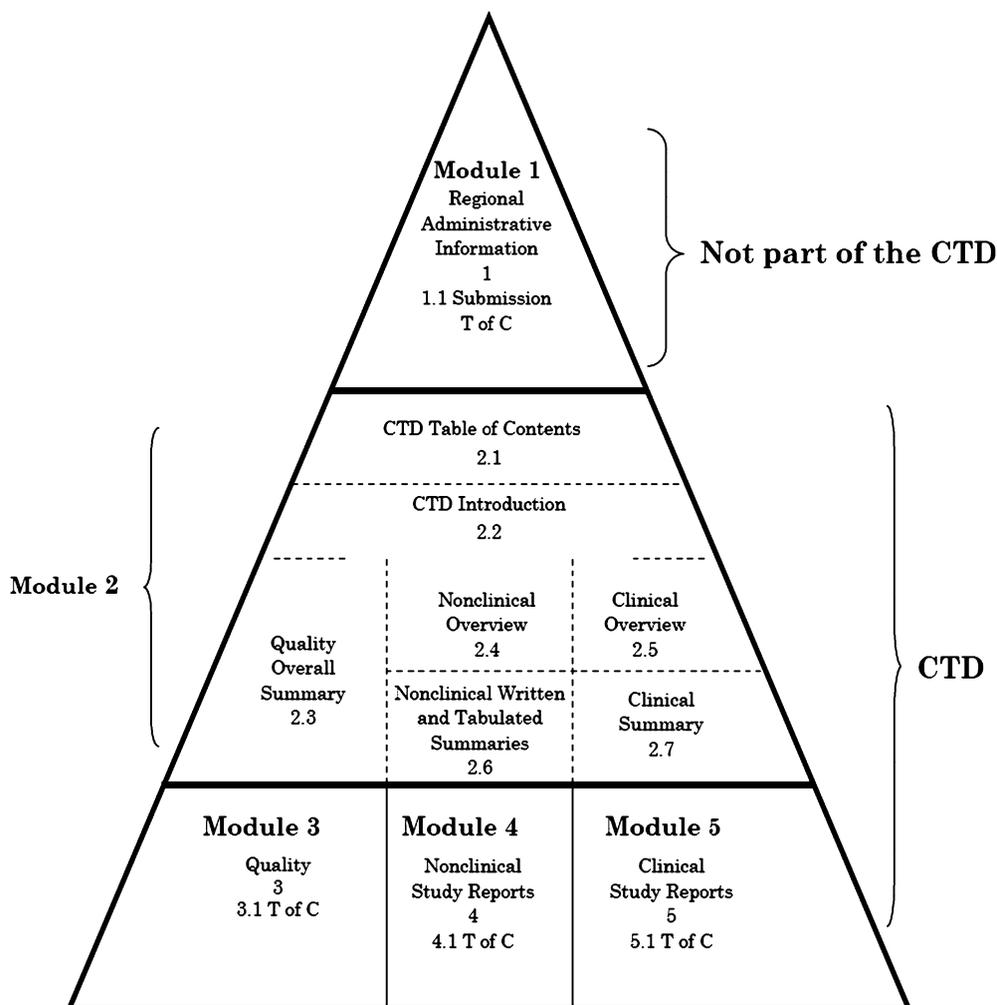


Fig. 1. Diagrammatic representation of the organization of the ICH Common Technical Document (CTD).

could be effectively applied, particularly in developing countries". In 1991, CIOMS published the International Guidelines for Ethical Review of Epidemiological Studies; and, in 1993, International Ethical Guidelines for Biomedical Research Involving Human Subjects. This guideline was updated and published in 2002 and is designed to be of use, particularly to low-resource countries, in defining the ethics of biomedical research, applying ethical standards in local circumstances, and establishing or redefining adequate mechanisms for ethical review of research involving human subjects. In addition, WHO has created several guidance documents how to establish and run Ethics Committees dealing with clinical research. Several CIOMS guidelines have also influenced regulatory approach to medicines safety.

Most important of them are International Reporting of Adverse Drug Reactions, which has been basis for ICH guideline E2A (pre-approval reporting) and ICH E2B (electronic case submission of individual case safety reports – ICSRs). CIOMS International Reporting of Periodic Drug-Safety Update Summaries has been basis for ICH E2C (periodic safety update report – PSUR). The latest CIOMS working group resulted in publishing The Development Safety Update Report (DSUR): Harmonizing the Format and Content for Periodic Safety Reporting During Clinical Trials. CIOMS has also been involved in discussing issues related to pharmacogenetics with regulators, industries and academia which resulted in publishing Pharmacogenetics: Towards Improving Treatment with Medicines.

IV.b. Multisource (Generic) Medicines

Multisource (generic) medicines are formulated when patent and other exclusivity rights expire. These medicines have an important role to play in public health as they are well known to medical community and usually more affordable due to competition. The key for generic medicines is their therapeutic interchangeability with originator products. To ensure the therapeutic interchangeability generic products must be pharmaceutically interchangeable (contain the same amount of active ingredient and have the same dosage form) and bioequivalent to the originator product. Bioequivalence is usually established using comparative *in vivo* pharmacokinetic studies with originator products. The detailed description how it is carried out is described in respective WHO document and national regulatory guidelines. Well resourced regulatory authorities require that a multisource (generic) medicine must meet certain regulatory criteria. These are presented in Table 3.

WHO has developed comprehensive set of guidelines for generic drug registration which are useful for drug authorities in developing countries: *Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products – A Manual for Drug Regulatory Authorities* (first edition 1999, updated version to be published in 2008).

In the context of generic medicines it is appropriate to ask what is a “pharmacopoeia” (word is derived from Greek *pharmako-poiros* “drug-maker”) and how it fits in nowadays regulatory systems? The answer to this question may seem obvious, but the term “pharmacopoeia” is used in a varied way

Table 3. Regulatory requirements for multisource (generic) medicines

A generic medicines must:

- (1) contain the same active ingredients as the innovator drug
- (2) be identical in strength, dosage form, and route of administration
- (3) have the same use indications
- (4) be bioequivalent (as a marker for therapeutic interchangeability)
- (5) meet the same batch requirements for identity, strength, purity and quality
- (6) be manufactured under the same strict standards of GMP required for innovator products

in different contexts. In the pharmaceutical sense, the pharmacopoeia is an official (legally binding) publication containing recommended quality specifications for the analysis and determinations of drug substances, specific dosage forms, excipients and finished drug products. A quality specification is composed of a set of appropriate tests which will confirm the identity and adequate purity of the product, ascertain the strength (or amount) of the active substance and, when possible, certain its performance characteristics. General requirements are also given in the pharmacopoeia on important subjects related to drug quality, such as microbiological purity, dissolution testing and stability.

The underlying principles of a pharmacopoeia are that pharmaceutical substances and products intended for human use should be manufactured in sites that are adequately equipped, dispose of appropriate professional and technical knowledge and that are operated by qualified staff. General rules of appropriate pharmaceutical manufacture are contained in the Good Manufacturing Practices (GMP) requirements recommended by WHO and/or those laid down by the competent national (or regional, such as European Commission) regulatory authority. In regulatory terms GMP could belong to ABC of regulatory requirements for medicines and compliance with it is vital for products quality. GMP is applicable for both innovator and generic products. It is applicable for manufacture of active pharmaceutical ingredients and finished dosage forms. Even manufacture of investigational drugs should follow GMP. Without GMP consistency of manufacture clinical performance of medicines cannot be assured.

There is a practical distinction between pharmacopoeial standards and manufacturers’ release specifications, although both comprise sets of tests to which a given product should conform. Release specifications are applied at the time of manufacture of a pharmaceutical product to confirm its appropriate quality but they also need to have a predictive value, to support the notion that the manufacturer is responsible for the product during its entire shelf-life. In many cases pharmacopoeial monographs are based on the specifications developed by the manufacturers of innovator (originator) products.

In order to launch innovator products pharmacopoeial specifications are not necessary as the manufacturers quality specifications have to pass rigor scientific assessment by the competent regulatory authorities in conjunction with pre-clinical and clinical safety and efficacy data. It is important to notice

that the focus in regulatory environment has been shifting from finished dosage form quality control to the control of the whole complex of processes and procedures involved in the manufacture of both active pharmaceutical ingredients (APIs) and finished dosage forms. The objective of a nowadays regulatory approval is to ensure that the manufacturer has built quality into the product from A to Z.

In case of multisource (generic) medicines (which are formulated after the patents and other exclusivity rights expire) pharmacopoeial monographs are more important as they enable manufacturers not to elaborate their own specifications but rather develop the products to meet the requirements of pharmacopoeial standards (both for APIs and finished dosage forms). It should be noted that not all pharmacopoeias present monographs (quality standards) for finished dosage forms. Pharmacopoeial standards have also certain limitations. For example, testing using pharmacopoeial methods is not necessarily identifying all possible dangerous impurities.

Pharmacopoeial methods are usually designed to catch the impurities that are likely to occur during the route of synthesis that has been utilized by the originator. In case of different route of synthesis or accidental contamination with other chemicals it may not necessarily pick up the impurities even if they pose danger to the health. This is why nowadays well resourced regulatory authorities never base their marketing authorizations of multisource (generic) products only on quality control testing based on pharmacopoeial monographs. In fact, the pre-marketing quality control testing has diminished constantly and more accent is put on market surveillance after the product is put on the market.

Pharmacopoeial monographs help to verify the quality and in case of multisource (generic) medicines they may indicate also on pharmaceutical interchangeability with the originator product. However, pharmacopoeial monographs even for finished dosage forms may have limitations in proving therapeutic interchangeability which is very important for clinical use of medicines (Box 1).

WHO hosts *The International Pharmacopoeia*. This pharmacopoeia is based on specifications validated internationally, through an independent international scientific process.

Unlike national (such as *British Pharmacopoeia*, *Indian Pharmacopoeia* or *US Pharmacopoeia*) and regional (such as *European Pharmacopoeia*) pharmacopoeias, *The International Pharmacopoeia* has, *a priori*, no determined legal status, but WHO Member States are free to adopt it and to incorporate it into national legislation, either in part or in whole. The first edition was published in two volumes (1951 and 1955). The latest fourth edition of *The International Pharmacopoeia* was published in 2006 and an update is to be published in 2008.

Most importantly, a new series of monographs has been added for antiretrovirals. These monographs have been developed as part of the WHO strategy to make quality antiretroviral medicines more widely available to HIV-positive patients. Such specifications support the joint United Nations – WHO Prequalification project, managed by WHO (web site: <http://mednet3.who.int/prequal/>). International Chemical Reference Substances (ICRS) are primary chemical reference standards used in conjunction with *International Pharmacopoeia* monographs. They are supplied primarily for use in physical and chemical tests and assays described in the specifications for quality control of drugs published in *The International Pharmacopoeia* or proposed in draft monographs.

WHO gives advice on the establishment and management of national quality control laboratories, prepares guidelines on their functioning, publishes guidance and gives advice on Good Manufacturing Practices (GMP) and other regulatory issues, following the underlying principle that *quality must be built into a product from the very beginning of the manufacturing process*. The whole area of work is overseen by the WHO Expert Committee on Specifications for Pharmaceutical Preparations. The WHO Expert Committee on Specifications for Pharmaceutical Preparations is the highest level advisory body

Box 1. Pharmacopoeial standards

Pharmacopoeial standards should be used in the framework of *all regulatory measures* such as Good Manufacturing Practice (GMP) inspection of active pharmaceutical ingredient and finished dosage form manufacturing, scientific assessment of all quality specifications, interchangeability data and labeling information provided by the manufacturer. The most of their value is in post-marketing surveillance of the quality of multisource (generic) medicine.

to WHO's Director-General and its Member States in the area of quality assurance. The advice and recommendations provided by this Expert Committee are intended to help national and regional authorities (in particular drug regulatory authorities), procurement agencies, as well as major international bodies and institutions to combat problems of substandard and counterfeit medicines.

The importance and role of WHO in the field of quality assurance of medicines, especially for those countries that have no or little means to develop their own quality control specifications, persists. WHO has numerous activities to support member states such as creating necessary nomenclatures, guidelines and guidance (WHO GMP being a good example) but also delivering training courses and workshops on various topics of regulatory sciences dedicated to assessment of safety, efficacy and quality of medicines in order to build national capacity to regulate medicines.

V. ROLE OF WHO IN DRUG REGULATION

WHO is the directing and coordinating authority for health within the United Nations system (see more on web site: <http://www.who.int/en/>). It is responsible for providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends. In the 21st century, health is a shared responsibility, involving equitable access to essential care and collective defence against transnational health threats.

WHO's role in drug regulation is fourfold. First, issuing necessary norms and standards (see examples above) through its Expert Committees (such as WHO Expert Committee on Specifications for Pharmaceutical Preparations and WHO Expert Committee on Biological Standardization) and Expert Committee like bodies (such as International Non-proprietary Names Expert Group and International Working Group for Drug Statistics Methodology – issuing Anatomical, Therapeutic and Chemical or ATC codes and Daily Defined Doses or DDDs for drug utilization research). Second, supporting regulatory capacity building leading to implementation of drug regulation on national level and its harmonization on regional and Global level. This

activity involves assessment of regulatory activities on country level and various technical training courses (such as GMP and GCP, how to assess generic medicines, bioequivalence, safety monitoring and pharmacovigilance, quality assurance and quality control) and customized technical assistance (in cooperation with numerous WHO collaborating centers and other partners) to the countries. Third, in selected areas of essential products, ensuring the quality, safety and efficacy of limited high public health value essential medicines (such as antiretrovirals to treat HIV/AIDS, or medicines to treat malaria) and vaccines (used in national vaccination programs) through “prequalification”. *De facto* prequalification, although primarily meant for UN procurement and international donors, is a regulatory activity mimicking medicines registration (marketing authorization) in its all elements to ensure that products prequalified meet all international standards for quality, safety and efficacy. Prequalification program has also a very strong capacity building element built into it. Fourth, WHO plays a very important role in facilitating exchange of regulatory information for which it has developed a number of tools. Since 1980 WHO convenes every second year International Conference of Drug Regulatory Authorities (ICDRA) and publishes their proceedings. These conferences provide drug regulatory authorities of WHO Member States with a forum to meet and discuss ways to strengthen collaboration. The ICDRAs have been instrumental in guiding through its recommendations regulatory authorities, WHO and interested stakeholders and in determining priorities for action in national and international regulation of medicines, vaccines, biomedicines and herbals.

WHO manages also a system for regular exchange of information between Member States on the safety and efficacy of pharmaceutical products, using a network of designated national drug information officers. WHO ensures the prompt transmission to national health authorities of new information on serious adverse effects of pharmaceutical products and it also responds to individual requests for information. These goals are achieved by the regular publication of regulatory information in the *WHO Pharmaceuticals Newsletter* (<http://www.who.int/medicines/publications/newsletter/en/index.html>) and by the dissemination of one-page *Drug Alerts* on an *ad hoc* basis. Relevant restrictive regulatory decisions are ultimately compiled in the United

Nations Consolidated List of Products Whose Consumption and/or Sale Have Been Banned, Withdrawn, Severely Restricted or not Approved by Governments. WHO publishes updates to this list: Pharmaceuticals: Restrictions in use and availability. WHO publishes also quarterly *WHO Drug Information* (<http://www.who.int/druginformation/>) journal which provides an overview of topics of current relevance relating to drug development, safety and regulation. Latest lists of proposed and recommended International Nonproprietary Names (INN) for Pharmaceutical Substances are also published in this journal.

WHO cooperates very actively with national regulatory authorities of all of its Member States. It tries to facilitate spreading best practices and experience. Through its observer role in the international Conference of Harmonization (ICH) WHO is liaising between ICH and non-ICH countries trying to ensure that information exchange between highly industrialized and less resourced countries is taking place.

VI. FUTURE OF MEDICINES REGULATION

Medicines regulation has been developing together with the sciences involved in developing new drugs. Also developments in health delivery systems have played a role as those involved in health service delivery are interested in safe and effective treatments which would be cost effective and affordable. Both costs of research and development and regulatory assessment of products is increasing. There is likely no alternative for more harmonization (international, regional and sub-regional) of regulatory requirements and work sharing (together with information sharing) between different national regulatory authorities. The cost of full regulatory assessment of a new drug is increasingly becoming not affordable (both in terms of financial and human resources) for less resourced smaller regulatory agencies. What are the new areas of development beyond better harmonization, information exchange and gradual building of trust in each others decisions leading to recognition instead of duplication?

Although even quality issues are still a problem (poor quality of starting materials including active pharmaceutical ingredients, quality problems with finished dosage forms, spreading of counterfeit medicines) it is likely that new technologies

and new products will create new regulatory challenges. For example, how will increasing public attention and expectations on medicines safety shape the regulations? How using new technologies such as nanotechnologies change the medicines regulation? Issues relating to the understanding of how the nanoparticles are presented to organs, cells and organelles are of the highest importance when trying to understand the different mechanisms for intracellular trafficking and use their full therapeutic potential. Those aspects cannot be established without improving appropriate basic knowledge of cell and molecular biology at the intracellular level. However, at the same time important quality problems can rise. In order to assure quality physical and chemical properties of nanopharmaceuticals, including residual solvents, processing variables, impurities and excipients, should all be well known. There will be a need for well-established standard tools to be used in the characterization of nanopharmaceuticals, including availability of validated assays to detect and quantify nanoparticles in tissues, medicinal products and processing equipment. Toxicological aspects of nanomedicines have been highlighted with focus on long-term toxicity. Carbon nanotubes, quantum dots and other nonbiodegradable and potentially harmful materials should be given closer attention whether associated with medicines or diagnostics. A special set of standards must be gradually established in the global regulatory environment. In fact, some elements already do exist. In Europe Directive 2004/27/EEC on medicines addresses directly the need for the study of environmental impact of medicines which will have major impact for new nanomaterials to be used in medicines. To examine and predict environment impact is a new task for regulators.

Using genetic information to create safe and effective medicines offers potential for more individualized therapies and patient benefits but will also have an impact on the use of healthcare resources. Pharmacogenetics has been viewed as something for the future, but real clinical examples now exist. Some pharmacogenetic tests, such as the thiopurine methyltransferase (TPMT) test that aims to predict the risk of severe neutropenia for the purine drugs azathioprine and 6-mercaptopurine, have already relatively low unit costs (approximately 50\$ US). However, even low unit cost tests may have a significant cost impact if they have a high volume of uptake in a healthcare system. There may be added value associated with introducing a pharmacogenetic test to

guide a prescribing decision, in terms of improved health-related quality of life resulting from fewer severe side effects and improved treatment response in the patient population taking the medicine. Pharmacogenetic tests broadly fall into one of two categories, those provided through clinical laboratories, such as the TPMT test, and those for which a product license has been granted in a similar way to new medicines, such as Third Wave Technologies' (WI, USA) Invader[®] UGT1A1 Molecular Assay, which was approved by the US FDA in 2005. The last option means that regulators are directly involved. Regulators are starting to regulate pharmacogenetics and some guidance already exists in Canada, EU and US. Recently also ICH started to deal with pharmacogenomics and pharmacogenetics. The E15 guideline Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories has been finalized.

Another area of challenges includes biological medicines including 'generic' biological medicines. New product groups are emerging and even with known product groups there are challenges ahead, especially from the point of view of safety. Other important areas for drug regulators remain pharmacovigilance, pediatric medicines, orphan medicines and medicines for diseases outside ICH regions. There are few financial incentives to create medicines for tropical and neglected diseases but recently due to public private partnerships for drug development and creation of specific regulatory pathways such EU Article 58 procedure that enables European Medicines Agency to assess these products and provide scientific advice for WHO has improved the situation. There are even calls for 'complete rethink' of the regulatory systems in order to prepare for the next 20–30 year.

The present short overview of medicines regulation is clearly not comprehensive but rather an attempt to give idea about the complexities of this important area of work that has many direct links with clinical pharmacology. Clinical pharmacologists as medical specialists equipped with unique knowledge about medicines have a role and responsibility to develop and contribute to medicines regulation.

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History of FDA drug regulation. The foundation of FDA's regulatory authorities was laid in the 1906 Pure Food and Drug Act, which focused on misbranding and adulteration. In keeping with other consumer product laws, it focused on postmarketing remedies only. The history of court challenges to restrictions on DTC advertising is lengthy and instructive. Attempts to ban DTC advertising have foundered due in part to uncertainty as to whether such a prohibition is constitutional. Drug advertising has been held to be commercial speech deserving First Amendment protection (*Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748, 762 [1976]).

A Short History of Digital Transformation. Digital transformation is an actively discussed topic these days, but this was also true in the late 1990s and again in the mid-2000s. We started to computerize processes almost 30 years ago, and we have already implemented digital activities in our organizations. First, digital channels, or websites, connected companies and their customers.