AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Drug Regulatory Bodies: Key Role Players in Different Regions

Kamaljit Singh Sandhe[1, 2], Vikas Kumar Bhambhu[2], Saahil Arora[2], RSR Murthy[2]

1. Global Institute of Regulatory Affairs, Pune.

2. ISF college of Pharmacy, Moga (PUNJAB), India

ABSTRACT

Drug regulation is totality of all measures- Legal, administrative and technical- which the governments take to assure the quality, efficacy and safety of drugs. With reports of number of tragic adverse events caused by use of drugs, more stringent controls have been imposed upon the procedures for marketing authorization of drugs. The research and development, manufacture, import and export of pharmaceuticals is regulated by different regulatory bodies in different countries with varying levels of regulation stickiness. This review article provides useful information regarding the regulatory framework and Pharmaceutical key role players in many countries which are actively engaged in licensing and approval activities.

Key Words: Drug regulation, Drug registration, Drug Approval, EMEA, Pharmaceuticals, USFDA.

*Corresponding Author Email: kamal751@gmail.com

Received 14 March 2012, Accepted 26 April 2012

Please cite this article in press as: Sandhe KS *et al.*, Drug Regulatory Bodies: Key Role Players in Different Regions. American Journal of PharmTech Research 2012.

INTRODUCTION

The field of Drug regulatory science, both pharmaceutical and biopharmaceutical is emerging rapidly. The drug regulatory authorities as well as evaluation agencies either governmental or private are widening their vision emphasizing more and more on delivering the public with drug products of high quality, efficacy and safety. A range of regulatory agency and industry initiatives, including better quality dossiers, has contributed to improving the licensing dossier review process both for biopharmaceuticals and for pharmaceuticals[1]**.** Regulations and derived procedures have increased globally and this can be partly explained by the great progress of science in the last 10 years[2]**.** Before a drug product is marketed, drug reviewers in regulatory agencies need to apply review science to thoroughly evaluate whether the research results support the safety, effectiveness and quality control of the new drug product. Apart from this, as science is progressing, the existing regulations are also being constantly adapted as well as updated. They aim to contribute an environment where decisions about the benefits and risks of medicines are made in a scientifically robust and transparent way to serve patients. Evaluating the safety of prescription drugs prior to approval and monitoring their safety once they have been marketed is a major priority in any drug regulatory system.

The level of regulations varies significantly in different countries. The developed countries have set up stringent laws and regulations governing the flow of pharmaceuticals within their territories while developing countries offer a level of relaxation to back their domestic market and encourage pharmaceutical growth. In poorer countries regulatory capture is prevalent as government has little capacity[3] No doubt such countries also keep their vision open for moving parallel to the way by updating their existing system of evaluation and approvals. Same thing is true with reference to type of medicinal products too. The nonprescription products do not need to be subject to the same extent of regulation as new prescription medicines at the point of registration (marketing authorization) or in ongoing usage. The regulatory philosophy for biopharmaceuticals has differed from that for synthetic organic drugs, because of special concerns over biological contaminants, process variability, biological assays and preclinical testing limitations. But with the advancement in analytical and purification technology have now started to challenge this difference**[4].** In case of cancer vaccine (CaVs) no guidance document or regulation exists that specifically covers CaVs[5]. CHMP and WHO guidelines on vaccines emphasis that cancer vaccines that are not intended for the treatment of infectious diseases and monoclonal antibodies (mAbs) used as immunogens are not considered within the vaccine

guidance. The recommendations laid down in these documents may nevertheless be considered as relevant for the development of CaVs[6].

Reporting of ADRs and responding to the same for the safety of patients is one of the most concerned duties of regulatory bodies. Such drugs usually need to be thoroughly reinvestigation or withdrawn from market. New Zealand has the highest rate of reporting of ADRs in the world, due to a variety of methods, including the feedback that it provides to individuals filing reports and outreach strategies to emphasize the importance of reporting ADRs[7]. Internet is one of the best players in drug safety issues. Web sites are the most active media for drug label changes and warnings, and are used as well for conducting nationwide questionnaire surveys on drug safety surveillance. The Ryan Haight Online Pharmacy Consumer Protection Act passed by Congress in 2008, amends the Controlled Substances Act to prohibit the delivery, distribution, or dispensing of a controlled substance that is a prescription drug over the Internet without a valid prescription.

The regulations to control the purchases by internet are also an area of consideration. The harmonization of regulation is emerging area providing more encouragement for industries. International harmonization such as ICH as well as regional harmonization such as ASEAN regulations demonstrates the cooperation and willingness of new world for providing the public best medical care. Many countries regulate the price that consumers pay for pharmaceuticals. The regulated price is normally well below the market price[8]. Even it has been observed that countries with strict price regulation (France, Italy, and Japan) have lower prices than the less regulated markets of the United States and the United Kingdom[9].

International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) is a collaborative initiative between the EU, Japan and the United States with observers from WHO, EFTA (European free trade area) 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) supports harmonization on national, regional, inter-regional and international levels[10]. WHO's role in drug regulation is fourfold. First, issuing the necessary norms and standards through its Expert Committees. Second, supporting regulatory capacity building leading to implementation of drug regulation on national level and its harmonization on regional and Global level. Third, in selected areas of essential products, ensuring the quality,

safety and efficacy of limited high public health value essential medicines and vaccines through "prequalification. Fourth, WHO plays a very important role in facilitating exchange of regulatory information [11].

1. US-FDA:

The year 2006 marked the 100th anniversary of FDA which is regarded as world's most influential regulatory agency in the world. In the US, drugs are regulated by the Food and Drug Administration (FDA). Every new drug must receive marketing approval from the FDA prior to commercialization. The US drug approval process is considered to be one of the most stringent in the world. From the perspective of all consumers, the U.S. constitutes about 40 percent of the world pharmaceutical market. As a result, its pricing and regulatory policies materially influence world demand and hence the incentives of pharmaceutical firms to innovate[12]. The development and evolution of US-FDA was not smooth, rather various public health crisis and tragedies which took place in past century forced the governments to built strong laws and respective amendments in FDA regulations and setting stringent criteria as well as requirements for moving products in market.

In 1862 Abraham Lincoln appointed a chemist Charles M. Wetherill to the Department of Agriculture for detection of food adulterants. Other agricultural chemists also hired to form division of chemistry. In 1901 the Division of Chemistry was renamed as Bureau of Chemistry. The administration of Pure Food and Drug Act was charged to Bureau of Chemistry which was reorganized in two entities in 1927 and the regulatory function became the responsibility of Food, Drug and Insecticide Administration (FDIA). In 1930 this name was shortened to Food and Drug administration (FDA). Walter G. Campbell was the first commissioner of agency under the name FDIA and FDA[13]. Food Drug and Cosmetic Act was passed in 1938 after the occurrence of "Elixir sulfonamide" crisis[14]. Until this point FDA had been under Department of Agriculture. It was in 1940 when the agency was moved to new federal security agency. In 1953 it was transferred to Department of Health Education and Welfare (HEW). It became part of Public Health Services within the HEW. In 1980 the education functions from HEW and rename it as Department of Health and Human Resources. FDA was officially established in 1988 as agency of US Department of Health and Human Services[15].

FDA needs to establish rules and guidance to fulfill its mission. Rules implement the statute and are enforceable. The final rule is published in the federal register and becomes the part of the Code of Federal Regulations (CFR). Guidance is the less formal document that explains the FDA's current interpretation of policies as well as various issues.

FDA is organized into 8 centers each having assigned responsibilities and functions[15]:

1: CDER (Center for Drugs Evaluation and Research) is mainly concerned with safety and effectiveness of prescription and OTC drugs.

2: CBER (Center for Biologics Evaluation and Research) evaluates the biotechnological and biologics including Blood products, vaccines, Protein based products, Xeno-transplantation, transgenic plants and animals, genomics, proteomics and bioinformatics. 1986 Childhood Vaccine Act was result of CBER work.

3: Center for food safety and applied nutrition (CFSAN) have the responsibility to evaluate safety of food consumed within US. It Enforces the 1994 Dietary and Supplemental Health and Education Act. The Regulations are not as close as Food, Drug, and Cosmetic Act.

4: Center for Devices and Radiological Health.

5: Center for veterinary medicines is engaged in evaluating the safety of food as well as drugs used for animals.

6: National center for toxicological research keep check on toxicity and contamination of drugs, pharmaceuticals and food. It also keeps an account on terrorism biomarkers.

7: Office of Commissioner.

8: Office of Regulatory Affair.

The FDA has jurisdiction over administration of regulation and approval of drug products. For evaluation and approval of drugs, sponsors are required to submit the FDA substantial evidence of effectiveness and safety accumulated from adequate and well controlled clinical trials[16]. The process starts with preclinical testing. First drug sponsor submits an IND containing data from animal studies to the agency. Then FDA decides whether it is reasonably safe to move forward with testing the drug on humans. Unless otherwise notified, the sponsor may begin to investigate the drug 30 days after the FDA has received the application. If IND proves successful, the sponsor ordinarily submits an NDA. If an IND is withdrawn because of a safety reason, the sponsor shall promptly inform the FDA, all investigators, and all reviewing IRBs with the reasons for the withdrawal. A terminated IND is subject to reinstatement based on additional submissions that eliminate such risk. The pre-NDA period, just before a new drug application (NDA) is submitted there is a common time for the FDA and drug sponsors to meet. Phase 3 is the final step before submitting a new drug application (NDA) to the FDA. If a drug survives the clinical trials, an NDA is submitted to the FDA. An NDA contains all the preclinical and clinical information obtained during the testing phase. The application contains information on the chemical makeup and manufacturing process, pharmacology and toxicity of the compound,

human pharmacokinetics, results of the clinical trials, and proposed labeling[15, 16, 17]. When an NDA comes in, the FDA has 60 days to decide whether to file it so that it can be reviewed. In accordance with the Prescription Drug User Fee Act (PDUFA), the FDA's Center for Drug Evaluation and Research (CDER) expects to review and act on at least 90 percent of NDAs for standard drugs no later than 10 months after the applications were received. From analyses of the data, CDER reviewers assess the benefit to risk relationship. The review division and office director may decide to convene an advisory committee meeting to seek the advice of external experts. The FDA reviews information that goes on a drug's professional labeling, guidance on how to use the drug. The FDA inspects the facilities where the drug will be manufactured as part of the approval process. Overall, this entire process, on average, takes between 8 to 12 years[17]**.** Phase 4 studies, or post-marketing studies, are conducted after a product is approved.

Hatch-Waxman Drug Price Competition and Patent Term Restoration Act of 1984 established the Abbreviated New Drug Application (ANDA) pathway that required only establishing bioequivalence with the reference drug (eliminating the need to establish safety and efficacy anew) and compliance with Good Manufacturing Practices[15,18]**.** The FDA has two other mechanisms to facilitate the development of treatments for serious and life-threatening conditions: accelerated approval, implemented in 1993 and codified in the FDA Modernization Act of 1997, and fast track, which is a provision of the Act. A treatment with a significant benefit over existing therapies may receive accelerated approval based on its effect on a surrogate endpoint or an endpoint other than survival or morbidity, or it can be approved with restrictions to promote safe use. Therapies that receive fast track approval are those with the potential to treat patients with serious or life-threatening disorders whose needs are not presently being met[19,27].

FDA approved rofecoxib which was withdrawn from the market in 2004 after the reports of Heart attack and strokes. It was estimated that it was linked with about 88,000 such cases[22]**.**

2. EUROPEAN UNION:

In the EU, due to the Single European Market legislation, the European Medicines Evaluation Agency (EMEA) has the power to centrally approve medicines, with one single license [28]**.**

The European medicines evaluation agency is purely concerned for scientific evaluation of medicines intended to be used in EU[29]. The Agency gives scientific advice and other assistance to companies for the development of new medicines. It publishes guidelines on quality-, safety- and efficacy-testing requirements. The medicines that fall within the scope of the centralised procedure are evaluated by agency but in case of any kind of disagreement between member states regarding authorization of medicine, they can refer those medicines to EMEA for

evaluation. Another fact is very much true that agency is not involved in any kind of research, medicine development or in establishing ethical codes.

The eligibility and requirements are set in the commission regulation (EC) No 726/2004 and defined in the Article 8 and 10 are of the Directive 2001/83/EC. The article 8(3) is for full applications whereas Article 10 is for other kind of applications as listed follow [29]:

Article 10(1)	Generic
Article 10(a)	Bibliographic
Article 10(b)	Fixed combo
Article 10(3)	Hybrid
Article 10(4)	Biosimilars

The scientific committees are responsible for the **scientific evaluation** of marketing-authorisation application dossiers submitted by pharmaceutical companies. There are 6 scientific committees the professionals of which are nominated from member states[30]. The committees are as follow:

- Committee for Medicinal Products for Human Use (CHMP)
- Committee for Medicinal Products for Veterinary Use (CVMP)
- Committee for Orphan Medicinal Products (COMP)
- Committee on Herbal Medicinal Products (HMPC)
- Paediatric Committee (PDCO)
- Committee for Advanced Therapies (CAT)

Procedures for conducting environmental risk assessment (ERA) on pharmaceuticals are in effect in both Europe and United States. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Evaluation Agency (EMEA) has published guidelines for ERA, which came into effect on the 1st December 2006. An ERA is required for all new marketing authorization applications for medicinal products. An evaluation of the environmental impact should also be made if there is an increase in the environmental exposure[31,32].

CHMP was first known as CPMP (Committee for Proprietary Medicinal Products) which after 2004 was given the present form. It deals in the marketing procedures for medicines for human use in the European Union. Assessments conducted by the CHMP are based on purely scientific criteria and determine whether or not the medicines concerned meet the necessary quality, safety and efficacy requirements in accordance to Directive 2001/83/EC. The CHMP can issue an 'Urgent Safety Restriction' (USR) to inform healthcare professionals about changes as to how or in what circumstances the medication may be used. The agency aids in the preparation of scientific and regulatory guidelines for the pharmaceuticals industry. Another important task

performed by agency is close cooperation with international partners on the harmonisation of regulatory requirements for medicines.

CVMP (Committee for Medicinal Products for Veterinary Use) was established by Regulation (EC) No 726/2004. The prime act of CVMP is in the marketing procedures for veterinary medicines in the European Union. A core activity of the CVMP is the establishment of MRLs: the 'Maximum Residue Limits' of veterinary medicines permissible in food produced by or from animals for human consumption, including dairy products, meat, honey etc. These limits must be established for all pharmacologically active substances contained in a medicine before it can be granted a marketing authorisation. CVMP also involves itself in the preparation of scientific and regulatory guidelines for the veterinary pharmaceuticals industry.

COMP (The Committee for Orphan Medicinal Products) advises the European Commission on the establishment and development of a policy on orphan medicinal products in the EU, and assists the Commission in drawing up detailed guidelines on matters relating to orphan medicinal products**.** The committee reviews the applications for 'Orphan Medicinal Product Designation' for products. The Orphan drugs are those which are used for the diagnosis, prevention or treatment of life-threatening or very serious conditions that affect not more than 5 in 10,000 persons in the European Union.

HMPC (The Committee on Herbal Medicinal Products) is engaged in assisting the harmonisation of procedures and provisions concerning herbal medicinal products laid down in EU Member States. Another main task performed by HMPC is establishment of Community herbal monographs. Prior to 2004 this task was responsibility of CPMP Working Party on Herbal Medicinal Products. But in September 2004 HMPC was established in accordance with Regulation (EC) No 726/2004 and Directive 2004/24/EC, which introduced a simplified registration procedure for traditional herbal medicinal products in EU Member States.

PDCO (Paediatric Committee) was established in accordance with the 'Paediatric Regulation' (Regulation (EC) 1901/2006 as amended). The committee assesses the content of paediatric investigation plans (PIPs) and adopts opinions on them that the data have been generated in accordance with an agreed PIP or not [30]**.** This includes assessing applications for full or partial waivers and assessing applications for deferrals. It is also notable that PDCO is not responsible for marketing-authorisation applications for medicines for use in children[33]. This remains within the remit of the CHMP.

CAT (Committee for Advanced Therapies) performs the task of preparing the draft opinion on each ATMP (advanced-therapy medicinal products) application submitted to the European

Medicines Agency, before the Committee for Medicinal Products for Human Use (CHMP) adopts a final opinion on the granting, variation, suspension or revocation of a marketing authorisation for the medicine concerned. The committee also advises the CHMP on any medicinal product which may require, for the evaluation of its quality, safety or efficacy, expertise in ATMPs. CAT actively participates in Agency procedures for the certification of quality and non-clinical data for small and medium-sized enterprises developing advanced-therapy medicinal products.

TYPES OF PROCEDURES:

Centralized Procedure: European Council lays down a centralized procedure for the authorization of medicinal products, for which there is a single application, a single evaluation and a single authorization allowing direct access to the single market of the Community of 27 countries.

Decentralized Procedure: If no marketing authorization has been granted in the Community, the applicant may make use of a decentralized procedure and submit an application to all the Member States where it intends to obtain a marketing authorization at the same time, and choose one of them as reference Member State (RMS).

Mutual Recognition Procedure (MRP): If the applicant has marketing authorization in one Member state and wishes to obtain the same in other Member states; MRP is followed [29].In 2006, the EMEA published the "Template for the EU Risk Management Plan (EU-RMP)." The template directs drug developers and license holders to provide risk management plans in four sections, Safety Specifications, Pharmacovigilance Plan, Evaluation of the Need for Risk Minimization Activities and Risk Minimization Plan [34].

Within Europe, even with the implementation of the Single European Market, there remains significant variation in price formation and the reimbursement of medicinal products across member states, and thus, the single market remains distorted in pharmaceuticals[28].

The European Directive 2001/83/EC, as amended by Directive 2003/63/EC and Directive 2004/27/EC, defines the regulatory process for biosimilars and lays down specific guidelines. A Biosimilar drug is a medicine that is similar but not identical to a biological medicine that has already been authorised[35]. EU currently has the most advanced regulatory pathways for biosimilars, there is no harmonised worldwide regulatory system for these products[36, 37]. Comparable regulatory oversight is currently under discussion in the United States, Canada and Japan[38].

To ensure that there were no delays in the development of products that are important for developing countries and that there is no disincentive for the timely discovery and development of these products, a consultation and collaboration between EMEA and WHO led to the Article 58 in the new Regulation. This provision establishes a mechanism whereby the EMEA may give a Scientific Opinion, in the context of cooperation with the WHO, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community. In doing so, EMEA reviews the application with the same evaluation standards being applied with other products and hence provide an opinion.

3. JAPAN:

Japan is the world's second largest pharmaceutical market next to the US occupying about 11% of global sales and generates 67% of Asia-Pacific market [29]. The Ministry of Health, Labour, and Welfare (MHLW) is in charge of pharmaceutical regulatory affairs in Japan. Pharmaceutical and Medical Devices Agency (PMDA) undertakes main duties and functions of the Ministry and performs the task of approvals and licensing. PMDA is Japanese counterpart to the FDA and is involved in operational aspects of drug development. PMDA consists of 22 offices and 2 groups. It has primary responsibility for administering the approval of new pharmaceutical products and medical devices in Japan, although final authority to issue approvals still rests with the Ministry of Health, Labour and Welfare (MHLW)[45]. The Pharmaceuticals and Medical Devices Evaluation Center in the National Institute of Health Sciences was established to strengthen approval reviews. The Pharmaceutical Affairs and Food Sanitation Council (PAFSC) serves as an advisory body to the MHLW, and reviews and discusses important pharmaceutical and food sanitation-related matters.

A company wishing to import a pharmaceutical product into Japan or manufacture and sell a pharmaceutical in Japan must conduct clinical trials in Japan and apply for approval from the PMDA. This applies even if the drug has already been authorized and is being sold in one or more foreign countries. In some cases, the PMDA permits applicants to submit clinical data from overseas, but this depends on the specific drug. Due to the activity of the International Conference on Harmonization (ICH), data from clinical trials conducted in foreign countries can be used as a part of clinical data packages for new drug applications in Japan [46,49]. Average duration of a clinical trial in Japan is approximately four years, much longer than U.S, France and U.K. Application forms from both Japanese New Drug Application (J-NDA) and Japanese Abbreviated New Drug Application (J-ANDA) for approval to market drugs are usually submitted to the PMDA. When application forms for new drugs are received by the PMDA, an

approval review of the application data is done in consultation with experts from the PAFSC. PMDA also does the compliance review of GCP/GMP on-site inspection, and the team prepares a review report. This report then refers to MHLW which evaluates the application for medical needs, social issues in addition to scientific review and issues the final decision for approval. In reviews of new drugs prepared from vaccine or blood, the specifications and test methods are examined by the National Institute of Health Sciences or by the Infectious Disease Surveillance Center (IDSC) prior to approval. Applications using the ICH-CTD became obligatory for new products in applications filed on or after July 1, 2003. In Japan, submission of eCTD is not obligatory but it is recommended. If the data is being submitted in the form of eCTD as original then it is no longer necessary to submit a copy of the paper data for approval applications. For manufacturing facilities located in Japan, the manufacturing license is generally issued by the governor of the prefecture in which the manufacturing facility is located. For overseas manufacturing facilities, applications are made directly to the MHLW. Licensed manufacturing facilities are required to satisfy criteria established by the MHLW.

Pharmaceutical Affairs Law (PAL) enacted in 1943 and has been revised several times since then. Pharmaceutical Affairs Law (PAL) as revised in 2002 include the revisions such as a new risk-based classification system for products, adoption of internationally consistent pre-market submission documents, and a third-party certification system for low-risk medical devices. The Pharmaceutical Affairs Law has 11 chapters and 91 articles. The Pharmaceutical Affairs Law specifies that the data submitted to obtain approvals must be obtained and compiled according to the standards specified in its Article 14, Paragraph 3. Pharmaceutical Affairs Law (Article 77-(4)-2-1), requires the reporting of adverse drug reactions and infections by pharmaceutical companies to the PMDA for information processing[47,48].

Approval times differ among the US, the EU, and Japan, but the interpretations of such comparison results always entail some difficulty because of the differences in the review systems. According to the classification of therapeutic categories commonly used in Japan, peripheral nervous system drugs (e.g., anesthetics ;), cardiovascular drugs, gastric drugs except for peptic ulcer were associated with relatively shorter approval times. Anti-HIV drugs were approved in exceptionally short periods, showing that the Japanese government as well as the US FDA handled them differently from other priority drugs[56]. The Japanese Pharmacopoeia, Japanese Pharmaceutical Codex, Japanese Pharmaceutical Excipients, and other similar standards have been specified as quality standards. Laws and regulations related to pediatric field does not exist in Japan.

4. CANADA:

Health Canada is the Federal department of Canada which keeps eye on health issues within the country by encouraging research and fostering partnerships with researchers across the country and the world. Under Canada's Food and Drugs Act, the Therapeutic Products Programme (TPP) of the Federal Department of Health (Health Canada) is responsible, on behalf of the Ministry of Health, to ensure that "new drugs" meet health and safety requirements[57, 58] .Therapeutic Products Directorate (TPD) is the Canadian federal authority that regulates pharmaceutical drugs and medical devices for human use. Prior to being given market authorization, a manufacturer must present substantive scientific evidence of a product's safety, efficacy and quality as required by the Food and Drugs Act and Regulations. Pharmaceutical products, which are small molecules (e.g. Chemical Entities), are regulated in Canada under the Part C, Division 8 of the Food and Drug Regulations. The Therapeutic Products Directorate (TPD) receives and evaluates submissions, while inspections of pharmaceutical manufacturers are performed by the Health Products and Food Branch Inspectorate. Biological products are evaluated by the Biologics and Genetic Therapeutic Products Directorate, which also evaluates submissions for radiopharmaceuticals**.** TPD consists of 12 offices and bureaux which are listed as follow.

- Director General's Office
- Medical Devices Bureau
- Submission and Information Policy Division
- Office of Business Transformation
- Office of Clinical Trials
- Office of Patented Medicines and Liaison
- Office of Risk Management
- Bureau of Policy, Science and International Programs
- Bureau of Cardiology, Allergy and Neurological Sciences
- Bureau of Gastroenterology, Infection and Viral Diseases
- Bureau of Metabolism, Oncology and Reproductive Sciences
- Bureau of Pharmaceutical Sciences

The Health Products and Food Branch (HPFB) of Health Canada is responsible for review and approval of clinical trials in humans. Trials involving drugs and medical devices are the responsibility of the Therapeutic Product Directorate (TPD) while human trials with biological and radiopharmaceutical drugs, including blood and blood products, viral and bacterial vaccines,

genetic therapeutic products, tissues, organs and xenografts are the responsibility of the Biologics and Genetic Therapies Directorate (BGTD)[59]. HPFB also created a new organization, the HPFB Inspectorate. The Inspectorate has the mandate to manage, inspect, investigate, monitor activities and enforce strategies related to the fabrication, packaging, labelling, testing, importation, and distribution and wholesaling of regulated health products. The Natural Health Products Directorate (NHPD) is responsible for the review and approval of products such as vitamins, minerals, herbal remedies, homeopathic medicines, traditional Chinese medicines, probiotics and other products such as amino acids and fatty acids. In 2003, the Canadian Parliament published new regulations for Natural Health Products and Homeopathic Preparations. The Marketed Health Products Directorate (MHPD) is the part of Health Canada that collects adverse drug reaction reports through a network of 5 regional reporting centres, analyzes them, and issues warnings about safety concerns through a variety of means.

On September 1st, 2001, Canada amended its regulations on Clinical Trial Applications (CTA) for the protection and safety of participants[59]. The CTA regulation impacts the application, authorization, notification, amendment and cancellation processes and also defines the sponsor's obligations such as Good Clinical Practices, drug labelling and clinical record keeping.

Canada has been an observer on the International Conference on Harmonization (ICH) committee since 1990 and hence ICH guidelines are adopted in Canada once they reach Stage-4. Canada applies the principles contained within the ICH guidelines to both New and Existing Drugs. All current guidance is formatted according to the ICH M4 "Common Technical Document" (CTD) guidelines and data submitted to Health Canada for review is to be provided in the CTD format. Canada accepts information on the drug substance either as part of a submission, or in a separate Drug Master File (DMF). A DMF can be provided in one of three formats such as 1) Canadian format 2) European format 3) ICH CTD-Quality format, out of these the CTD format is most preferable. The DMF holder ensures that the drug substance manufacturer is able to manufacture material that meets the approved specifications at release and is acceptable for use up to the retest date. The DMF holder has to update the DMF every two years, regardless of whether any changes are made. A letter confirming that no changes have been made is acceptable. In general Canadian approval times are greater than other countries. It is also observed that the regulations in Canada are more stringent than European countries but less than America. When an NDS is submitted to TPD, it first undergoes an administrative screening procedure which does not include any technical review of the information. If the screening process identifies deficiencies in the NDS, the sponsor will receive a screening

deficiency notice, and has 45 calendar days to respond and resolve any identified deficiencies. Once an NDS for a new active substance passes the screening process and is accepted for review[60].

Table: 1 NDS for a new active substance

Submission type	Screening	Review
New drug submission	45 days	300 days
Priority new drug submission	25 days	180 days
NOC/c new drug submission	25 days	200 days

The TPD maintains a Drug Product Database on its Web site that lists both active and discontinued products (www.hc-sc.gc.ca/hpfb-dgpsa/tpd/dpt/dpd_index_e.html). Health Canada also has a priority review system, which began in 1996. The Canadian criteria are close to those of the FDA and the performance standard for priority-status medications (225 calendar days) is also shorter than the standard review target (355 calendar days). In Canada, priority-status products have longer approval times than those in the US[19,60].

The role of regulatory bodies in public health is evident from the actions taken against approved drugs. Aprotinin which was sold under the brand name TRASYLOL after approval in 1995 was withdrawn in 2005 due to increase in all-cause mortality. Gatifloxacin (TEQUIN) approved in 2001 was removed from market due to serious disorders of glucose metabolism. Lumiracoxib (PREXIGE) approved in 2006 was withdrawn in 2007 for Risk of serious hepatotoxicity which cannot be safely and effectively managed. Pergolide (PERMAX) entered market in 1991 but was withdrawn in 2007 due to Valvulopathy. Rofecoxib (VIOXX) approved in 1999 was found to be responsible for cardiovascular events, such as heart attack and stroke, so withdrawn in 2004[61].

4. ASEAN COUNTRIES:

ASEAN stands for Association of South East Asian Nations. This association includes 10 member countries such as Singapore, Thailand, Malaysia, Indonesia, Myanmar, Cambodia, Vietnam, Philippines, Brunei Darussalam and Lao PDR. ASEAN was established in 1967 by 5 member states only. In 1992 The ASEAN Consultative Committee for Standards and Quality (ACCSQ) formed to facilitate and complement the ASEAN Free Trade Area (AFTA). Efforts to harmonize regulatory requirements amongst ASEAN were initiated through the (ACCSQ) in 1998 when it initiated the PPWG (Pharmaceutical Product Working Group). For import these countries Accept WHO Certificate of Pharmaceutical Product (CPP) with statement on GMP compliance issued by Drug regulatory Agencies. Locally manufactured products require evidence of GMP conformance through inspections of local manufacturers by GMP auditors in their respective member states. Singapore attained membership to PIC/S in 2000 followed by

Malaysia in 2002 and they Implemented PIC/S (Pharmaceutical Inspection Co-operation Scheme) Guide to GMP for local manufacturers of medicinal products. The ASEAN Economic Ministers signed the ASEAN Sectoral Mutual Recognition Arrangement (MRA) for Good Manufacturing Practice (GMP). The efforts of PPWG led to the development of ACTR (ASEAN Common technical Requirements), ACTD (ASEAN Common Technical Dossier) and ASEAN guidelines.

Due to limited human resources the agencies traditionally performs mainly administrative work and simply endorse approvals of new drugs which are previously approved by developed countries. So these countries relay heavily on the Free Sales Certificate or Certificate of Pharmaceutical Product (CPP). Because of cultural and religious reasons, Indonesia, Malaysia and Philippines authorities require information on sources of all ingredients of animal origin. The Indonesian authority will not approve products containing any ingredient of porcine source Singapore, Philippine and Thailand are only three countries in this region which employ universal health insurance approach for managing health system.

For New Drug Registration in these countries ASEAN Harmonized ASEAN Common Technical Dossiers (ACTD) is used which is submitted in 4 parts as follow:

Part 1: Administrative Data and Product Information

Part 2: Quality Document

Part 3: Nonclinical Document

Part 4: Clinical Document

Table 2: ASEAN Quality guidelines

ASEAN Quality guidelines	Safety guidelines	Efficacy guidelines
(1)Analytical Validation guidelines. (2) BA/BE Studies guideline. (3) Process Validation guideline. (4) Stability Study guideline.	adopted ICH-Safety guideline (15 GLs)	Adopted 11 GLs

Because the majority of local Pharmaceutical industries in this region are generic industries, Greater emphasis is given on registration of generic drugs with respect to ASEAN technical requirements and dossiers. Blood services are usually run by the government (Malaysia, Myanmar and the Philippines) or the Red Cross (Thailand, Laos and Indonesia). In Singapore, the government-run blood service outsources the blood donor recruitment program to the Red Cross in a unique partnership model[63].

Singapore: Manufacturers located within Singapore are subjected to licensing and periodic inspections by Health Sciences Authority (HSA). Center for Drug administration (CDA) is

responsible for the formulation of drug regulatory policies and guidelines. Drug registration Branch (DRB) and Innovative therapeutics Group (ITG) are responsible for registration of medicines and continual review of approved medicines. Dossier submitted can be either in ASEAN CTD format (ACTD) or The ICH-CTD format. Once approved product is valid for one year. Among Traditional medicines mainly Chinese medicines are used which are regulated by Centre's Chinese Proprietary Medicine Unit. Among ASEAN countries Singapore has best and systematic infrastructures and policies for R&D. The investment in pharmaceutics is also highest among all ASEAN member states. The Health Products Act introduced in Singapore in 2007, is an example of a modular and flexible system based on smart regulation [Health Products Act, <http://statutes.agc.gov.sg>; 2007]. It allows incremental inclusion of different categories of health products in phases and modular application of different parts of the Act to different categories based on assessed risk profile of that category[64, 65].

Thailand: The regulation of medicinal drugs in Thailand is overseen by the Ministry of Public Health (MOPH). The Drug Control Division of the Food and Drug Administration (THAI FDA), a department of the MOPH, has the responsibility for Licensing and Drug registration as well as Post-marketing monitoring and surveillance. The Medical Sciences Department under the MOPH is the main authority responsible for ensuring the quality and safety of drugs on the market in Thailand. The legislative basis of this system is the Drug Act BE 2510 (1967) and amendments. According to the Drug Act 1987 (B.E. 2530), a Drug Committee has been appointed every two years to advise the Minister of Public Health on both regulatory and technical aspects concerning administration of the drug control. The Drug Board meets monthly and may give recommendations or opinions on licensing and registration decisions such as approval withdraw or suspend the licenses. For the process of New Drug Registration standard review takes 210 - 280 working days while Accelerated or priority review is completed in 100-130 working days. For the process of new generic drug registration standard review is completed within110 working days while Accelerated or priority review is completed in 70 working days. Once the review has been passed, the new drugs must undergo a two-year safety monitoring period. A foreign applicant must be a resident in Thailand to obtain a licence to manufacture, sell or import drugs. Prices of medicinal products are regulated when they are listed on the National List of Essential Drugs (NLED). This list is only available to government hospitals. There is no centralized regulation for clinical trials. To obtain approval for clinical trials in Thailand The sponsor must then obtain approval to conduct a study in humans from the Ethical Review

Committee for Research in Human Subjects of the MOPH (ERC) and/or the ethics committee of the research institute or university that will conduct the trial.

Malaysia: All Pharmaceutical products whether locally manufactured or imported, must be registered with Drug Control Authority (DCA) prior to being manufactured, imported or sold. The legislative basis for the registration and marketing authorization of pharmaceuticals including biopharmaceuticals in Malaysia is the Control of Drugs and Cosmetics Regulations (CDCR 1984) promulgated under the Sale of Drugs Act 1952 (act 368). The National Regulatory Authority (NRA) for medicinal products is the National Pharmaceutical Control Bureau (NPCB), Ministry of Health Malaysia[66,67]**.** Quality control is handled by Drug analysis Division based at NPCB. Medical Research Ethics Committee (MREC) reviews the ethical aspects of the study to safeguard the rights, safety and well-being of all trial subjects. Any trial conducted in a government health facility requires the approval of the Director-General of Health, Malaysia. Malaysia employs the combination of health insurance and public assistance model. There is no specific regulatory control in matter of price control.

Vietnam: Ministry of Health is responsible for drug regulation. The charge of regulation is in 3 departments, The Pharmacy Department, The Pharmaceutical Inspection department and The National institute of Drug Quality Control. These departments report directly to Vice-Minister for Pharmaceuticals[68]**.** The production, trafficking and use of illicit drugs are important social issues for contemporary Vietnam. Vietnam's response to drug use has historically focused on deterrence through punishment and supply-side measures[69]

Philippines: The Food, Drug and Cosmetic Act provide the legal environment for drug regulation. The agency within the Philippine Department of Health which is responsible for activities is the Bureau of Food and Drugs. For the distribution and sale, the pharmaceutical product must be registered with Bureau of Food and Drugs[70].

Cambodia: Department of Drugs and Food is the regulatory agency under the ministry of Health. Only products registered by DDF are authorized to be imported, manufactured and sold in market. It does not yet have social health insurance program and almost no private health insurance at present[71, 72].

Myanmar: The central body is Myanmar Food and Drug Board Authority (MFDBA) within the MOH, which oversees the enforcement of law[73]. Central Food and Drug Supervisory Committee has the responsibility for licensing drug manufacturers. The evaluation is carried out by Drug advisory committee. According to Law, for a product to be registered the clinical trials have to

be performed in Myanmar. The registration is valid for 5 years. State Food and Drug advisory committees license the drug wholesalers.

Indonesia: The Drug and Food control agency is the regulatory body in Indonesia. The applications for product registration can be submitted only by local manufacturers. The Indonesian authority will not approve products containing any ingredient of porcine source [75].

Laos: The Food and Drug Department (FDD) is the authority for pharmaceutical regulations. Drug manufacturers need to obtain license from FDD for production, import or distribution. Drug Quality Control Center performs the tests.

Brunei: Department of pharmaceutical services is under the Ministry of Health. Drugs are not manufactured locally. It is the only country in ASEAN which does not require registration of medicines sold in the country. Brunei has participated in the effort to harmonize the drug registration for ASEAN even though it does not yet have drug registration system in country. The Narcotics Control Bureau (NCB) is the main agency to combat drug abuse activities in Brunei Darussalam.

5. AUSTRALIA:

In Australia, The sale of medicines is governed by legislation at both Commonwealth and State levels. The Therapeutic Goods Administration (TGA) is responsible for regulating therapeutic goods in Australia including medicines, medical devices, blood and blood products. TGA is a division of the Australian Government Department of Health and Ageing which evaluates the therapeutic goods before they are marketed and then monitors products once they are on the market. The manufacturers of therapeutic goods are also regulated by TGA to ensure they meet acceptable standards of manufacturing quality. Medicines must be entered as either 'Registered' or 'Listed' medicines and medical devices must be 'included' on the Australian Register of Therapeutic Goods (ARTG) before they may be supplied in or exported from Australia, unless exempted. The TGA has six statutory expert committees members of which are appointed by the Ministry. These committees include Advisory Committee on Complementary Medicines (ACCM), Advisory Committee on Medical Devices (ACMD), Advisory Committee on Non-prescription Medicines (ACNM), Advisory Committee on Prescription Medicines, (ACPM), Advisory Committee on the Safety of Medicines (ACSOM), and Therapeutic Goods Committee (TGC). The Therapeutic Goods Act 1989 sets out the legal requirements for the import, export, manufacture and supply of therapeutic goods in Australia. The Standard is maintained by the TGA but takes force in legislation at the State level[76]**.** Australian Pharmaceutical Advisory Council – which is comprised of representatives of key health professions, the pharmaceutical

industry, and members of government meets twice yearly to discuss important issues and needs in relation to the NMP and to advise the minister on priority issues[77].

The extent to which companies can supply medicines to Australian pharmaceutical markets is governed by the operations of two government agencies. One is Therapeutic Goods Administration (TGA) which is compared to the equivalent organisations in the USA and Europe. The other government agency is the PBS (Pharmaceutical Benefits Scheme). Most prescription medicines in Australia are made available to patients under the Pharmaceutical Benefits Scheme[78, 79, 80]. Public hospitals are funded by State Governments in the main and they provide medicines to patients free. State Governments are reimbursed for the cost of those medicines listed on the PBS. On average patients pay only 19per cent of the cost of their prescriptions[8]. Responsibility for reviewing data regarding the clinical- and cost-effectiveness of medicines that manufacturers seek to have listed on the Schedule falls with the Pharmaceutical Benefits Advisory Committee (PBAC). Following a review, the PBAC advises the Minister on whether a medicine should be listed on the Schedule and under what conditions. The Minister cannot list a medicine without a positive PBAC recommendation; evidence suggests it is rare for the Minister to reject positive recommendations[81,8]. The TGA requirements for data from companies making applications are based on the European Union (EU) requirements and the TGA accepts data dossiers in the European Union format. The guidelines for submissions are also very similar to those of the EU. In general the TGA follows the EMEA approvals process quite closely. Australian Drug Evaluation Committee (ADEC) assesses all applications for new chemical entities, as well as for products which have already been approved but are seeking to have their indications varied. The average evaluation time for a new chemical entity is about 300 working days or about 420 elapsed days.

6. CHINA:

The drug registration process in China is centrally managed by the State Food and Drug Administration (SFDA). Sub-organizations which assist SFDA are Center for Drug Evaluation (CDE) and National Institute for the Control of Pharmaceutical and Biological Products (NICPBP) [83, 84]. Initially SFDA was an independent authority, but was incorporated into the Ministry of Health (MoH) in early 2008. There are seven major centers in SFDA which are listed below[85]. The fundamental legal document governing the administration of the pharmaceutical industry in China is the "Drug Administration Law of the People's Republic of China" ("The Law") issued in February 2001[86, 88].

- National institute of the control of pharmaceutical and biological products (NICPBP)

- Chinese pharmacopoeia commission (CPC)
- Center for drug evaluation (CDE)
- Center for certification of drugs (CCD)
- Center for drug reevaluation (CDR)
- National committee on the assessment of the protected traditional Chinese medicinal products (NCAPTCMP)
- Center for medical device evaluation (CMDE)

It typically takes four to five years to register a drug in China[87]. Currently, there are five types of drug registration application in China: New drug application, generic drug application, imported drug application, supplemental application and renewal application. Application for drug license are submitted to Office for Drug Registration (ODR), which checks the dossier content / format of the application documents then forward submissions to the NICPBP. No strict CTD format required currently. Different from the Good Review Practice (GRP) implemented in CDER (The Centre for Drug Evaluation and Research) at US FDA, the review practice in CDE only requires key points, instead of all submitted information, be reviewed in details[85]. After the testing results are verified by the NICPBP they are then returned to the ODR which forwards the application documents and testing results to the CDE for technical evaluation. SFDA reviews the document and decides whether to issue the license for clinical trial. Applicants conduct the clinical trial (CT) and send the clinical data to ODR which organizes a CT on-site inspection and forwards them to CDE. Technical evaluation by CDE and positive / negative recommendations are given to SFDA. After comprehensive review by SFDA it decides whether to issue the drug license[88]. For new molecular entities that are developed for serious or life-threatening diseases or diseases for which there is no available treatment, there exists fast track evaluation to accelerate the evaluation process[89]**.** Drugs cannot be imported into China without a Registration Certificate for Imported Drugs ("RCID"). For a RCID to be issued, prospective importers generally must satisfy the SFDA criteria for safety and efficacy, but they may be exempt if the drug is for emergency hospital use or individual use[90].

There are two types of drug reimbursement lists in China known as the A List and the B List. Both lists are compiled by Central Government authorities. The A List receives 100% reimbursement while 50% for list B[91]. The process for approving drugs for the reimbursement lists is dominated by the Ministry of Human Resources and Social Security (MoHRSS). For public safety and to keep eye on adverse effects of approved drug, a law "Regulation for the

Administration of ADR Reporting and Monitoring" was issued in March 2004. National Center for ADR Monitoring houses the Center for Drug Reevaluation (CDR) joined the SFDA and reports to both the SFDA and the MOH. Hospitals, drug distributors, pharmacies, and pharmaceutical companies submit ADR/ADE reports to regional centers [91,92,93]. The regional center reports all new ADRs/ADEs and all serious ADRs/ADEs within three days to the National Center. Both western medicines and TCMs (Traditional Chinese Medicines) are covered by the ADR/ADE reporting system and are regulated by the SFDA [94]. For renewal application, each approved drug should be re-evaluated after 5 years and the renewal approval will depend on whether the post-marketing data suggest serious drug safety issues or not during the last 5 years[85]. Center for Drug Re-evaluation (CDR) is responsible for the post-marketing evaluation while CDE is in charge of pre-marketing evaluation. The SFDA issued a total of 11 regulations, guidelines and notices in 2010 covering areas including drug quality, controlled substances, drug registration, R&D, electronic regulation and pharmaceutical export. In particular, the agency issued three documents on electronic regulation of drug products in 2010. In 2011, SFDA introduced a new GMP regulation for pharmaceutical products with effect from March 1, 2011[91,95].

7. AFRICAN COUNTRIES:

In most parts of Africa, the regulatory frameworks for medicines and clinical trials are not well established. Currently, many regulatory authorities in Africa have not attained a comprehensive legal framework suitable to meet the state of art operations expected for RAs. Most RAs are commonly characterized by inadequate legislation/regulations, severe lack of skilled human resources, poor logistical capabilities and a general apathy to their functions (WHO surveys 2006/2007). Most countries have marketing authorization offices that make a brief review of applications and grant authorizations to import and sell specific products on their markets. African medicine regulatory agencies have traditionally focused on generics relied on western regulatory agencies for review of innovator products. The WHO standards are taken as minimum requirement on quality of pharmaceuticals.

Pharmaco-vigilance or post marketing safety surveillance and reporting by the manufactures or sponsors is still evolving in Africa and hence no sufficient systems are in place to inform the RAs. Many products which are already approved and marketed in Africa, continued monitoring for safety and efficacy are greatly compromised. A number of countries in the continent largely rely on India and China for imports of affordable generics and raw materials[74].

RAs in different countries operate in different forms as per the mandates given by the laws of that particular country. For instance, in Tanzania the Tanzania Food and Drug Authority (TFDA) operates as per the mandate given under Tanzania Food, Drugs and Cosmetics Act No. 1 of 2003. Subsequent WHO surveys (2006/2007) on the status of RAs providing oversight to vaccine research in Africa revealed that: In Africa, only the South African RA was found to have capacity to adequately regulate vaccines. Six countries, namely, Nigeria, Senegal, Morocco, Tunisia, Algeria and Zimbabwe where found to have functional national RAs, but these needed to be strengthened; other countries including Ghana, Uganda, Ethiopia, Egypt, had potential to quickly become functional, meanwhile the rest of the surveyed countries had limited or weak RAs or no information at all[97].

Progress is being made at national levels across the continent, The WHO have done and continue to do a commendable job in supporting African RA's to be able to handle the prevailing regulatory challenges. A number of initiatives have been formulated to serve as expert resources supporting countries with minimal or none regulatory capacity. A good example of is African Vaccine Regulatory Forum (AVAREF) which is platform for African countries to discuss with peers and maximizing the use of resources available in the continent [98]. In January of 1996, the Health Ministry published a National Drug Policy (NDP). The various studies carried out on the existence and the capacities of ethics committees reveal a disparity between countries[99, 100]. A study led by the WHO Regional Office for Africa (WHO/AFRO) highlighted the absence of national ECs for medical research in 36% of its member states[101].

SADC (Southern African Development Community): The SADC was formally launched on 17th August 2002 under a Treaty was originated from the Southern African Development Coordination Conference (SADCC), which was formed in 1980. It consists of 14 Member States such as Angola; Botswana; Democratic Republic of Congo; Lesotho; Madagascar; Malawi; Mauritius; Mozambique; Namibia; Swaziland; United Republic of Tanzania; South Africa; Zambia; and Zimbabwe. The SADC Pharmaceutical Program was approved by the Integrated Committee of Ministers (ICM) at its meeting in June, 2004. All SADC Member States have a national medicines policy, Regulations, Regulatory Shared Network, and are members of the World Trade Organization (WTO), which automatically makes them signatory to the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS). But fact is also true that weak regulatory systems lead to concerns on quality, safety and efficacy of medicines with many unregistered products on the market. Inadequate national and regional medicine quality control laboratories are another barrier. There is one WHO Pharmaceutical Reference Quality Control

Laboratory in Zimbabwe and one WHO Collaboration Quality Control Laboratory in South Africa. About 85% of the generic ARV (Antiretroviral) medicines used in the region are imported from India and 15% are manufactured within the SADC region. COMESA: (Common Market for Eastern and Southern Africa): It Comprises 19 member states, 7 of which are in SADC and 4 in EAC. In March 2003, the Council of Ministers that met in Khartoum, Soudan noted the variations in legislation and regulations in DRAs and emphasized the need of harmonization of the regulatory environment. Member States improved the standard of facilities within national regulatory Authorities, to WHO recommended standards. COMESA GMP guidelines for industries have been established and efforts have been made on MRA. **EAC:** Kenya has the largest economy among the EAC countries. Kenya Medical Supplies Agency (KEMSA) is the public agency for the procurement and distribution of EMMS.

DISCUSSIONS:

Health is one of the basic rights for human being. In the past decade more than a dozen high-profile drugs,including rofecoxib (Vioxx), cisapride (Propulsid), troglization (Rezulin), terfenadine (Seldane), and cerivastatin (Baycol), were withdrawn from the market. In response to so many withdrawals, pressure has been building to reform drug safety regulations[94]. It should be noted that most regulatory authorities in different countries have similar but slightly different requirements for approval of drug products. The necessity to standardize regulatory requirements has been recognized by both regulatory authorities and the pharmaceutical industry. As a result, the International Conference on Harmonization (ICH) which consists of the European Community, the United States, and Japan was formed to evaluate and develop technical requirements for the registration of pharmaceuticals for human use. A number of guidance and draft guidelines for good pharmaceutical practices have been developed to assist pharmaceutical companies in drug research and development.

It is also clear that the developing world lagged behind and was not involved in the articulation of the international guidelines and standards for RAs. it is also a fact that in the developed countries the regulatory environment has become bureaucratic, expensive and complex, placing a greater burden on investigators in terms of compliance, documentation, and training[103]**.** Unnecessary bureaucratic rules and standard operating procedures produce inefficiencies that delays product evaluation process. Recent statistics show that pharmaceutical companies are changing their strategies by moving their sites of clinical trials to developing countries. For example, out of all clinical trials sponsored by American companies, the proportion of the

clinical trials sites within the United States regressed from90% in 1999 to 47% in 2007[104]. Throughout the world, medical regulation is a key healthcare issue. However, in many developing countries it is not satisfactorily addressed. While there has been some research on health sector regulation in industrialized countries, little has been written about developing countries[105].

REFERENCES:

1. Lumley C, Walker S: improving the Regulatory Review Process -Industry and Regulatory Initiatives. Dordrecht: Kluwer Academic Publishers; 1996.
2. Baeyens AJ, Lacombe D. Regulatory issues for clinical trials at EORTC: The way forward. European Journal of Cancer 2002; 38:S142–S146.
3. Soderlund N, and Tangcharoensathien V. Health Sector Regulation – Understanding the Range of Responses from Government. Health Policy and Planning 2000; 154: 347-348.
4. Lambert K. Regulatory affairs Biopharmaceuticals regulation-progress and challenges. Current Opinion in Biotechnology 1997; 8:347-349.
5. Chabicovskya M, Ryle P. Non-clinical development of cancer vaccines: Regulatory considerations. Regulatory Toxicology and Pharmacology 2006;44:226–237.
6. E4: World Health Organization. Guidelines on Nonclinical Evaluation of Vaccines 2003. <http://www.who.int/biologicals/publications/nonclinical_evaluation_vaccines_nov_2003. pdf>.
7. Lexchin, J. Drug makers and drug regulators: Too close for comfort. A study of The Canadian situation. Social Science & Medicine 1990;31(11):1257–1263.
8. Donald J. Wright DJ. The Drug Bargaining Game: Pharmaceutical Regulation In Australia. Journal of Health Economics 23 (2004) 785–813.
9. Danzon, P, Chao L. Does regulation drive out competition in pharmaceutical markets? Journal of Law and Economics 2000; 43:311–357.
10. WHO. Effective medicines regulation: ensuring safety, efficacy and quality. Geneva: World Health Organization; 2003. Available from:URL: http://whqlibdoc.who.int/hq/2003/WHO_EDM_2003.2.pdf
11. Santoso B. Drug Benefits and Risks: International Textbook of Clinical Pharmacology revised 2nd edition, Chapter-6 “Drug Regulation: History, Present and Future”. 2008; edition-2:66-76.

12. Danzon et al. Cross-National Price Differences for Pharmaceuticals: How Large and Why? Journal of Health Economics 2000;19(2):159-95.
13. Andrea T et al. The History and Contemporary Challenges of US-FDA. Clinical Therapeutics 2007; 29(1):1-16.
14. Routledge P. 150 years of pharmacovigilance. Lancet 1998; 351:1200–1201.
15. Pisano DJ, Mantus DS. FDA Regulatory Affairs: A Guide for Prescription drugs, medical devices and biologics. Edition 2nd Published 2008.
16. Rawat S, Gupta A. Regulatory Requirements for Drug Development and Approval in United States: A Review. Asian J. Pharm. Res. 2011;1(1):01-06.
17. Heilman RD. Drug development history, "overview," and what are GCPs? Quality Assur 1995; 4:75–79.
18. Mossingh off, Gerald J. Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process. Food and Drug Law Journal 1999; 54(2):187-194.
19. Nigel S.B. Assessing Prescription Medications for Priority Regulatory Review. Regulatory Toxicology and Pharmacology 2005; 42:70–76.
20. Kertz R. FDA: Evidentiary Standards for Drug Development and Approval. NeuroRx. 2004; 1:307-316.
21. Seiguer E, Smith J. Perception and Process at Food and Drug Administration: Obligations and Trade-Offs In Rules and Guidance. Food drug law j 2005; 60:17-32.
22. Burstein PD. A Sad Day for Science at FDA. N Eng J Med. 2005; 353:2619-2621.
23. Kennedy D. chess game at the FDA. Science 2005; 310:589.
24. Berndt et al. Authorized Generic Drugs, Price Competition and Consumers "Welfare". Health Affairs 2007; 26(3):790-799.
25. Frank, Richard G. New Estimates of Drug Development Costs. Journal of Health Economics 2003; 22(2):325-330.
26. Kyle, Margaret K. Pharmaceutical Price Controls and Entry Strategies. Review of Economics and Statistics 2007; 89(1):88-99.
27. Steven F. et al. Chapter 37- Product registration and drug approval process In United States. Developing Solid Oral Dosage Forms. 2009;861-863.
28. Casper S, Matraves C. Institutional Frameworks and Innovation in the German and UK Pharmaceutical Industry. Research Policy 2003; 32:1865–1879.
29. Ramesh T et al. Regulatory Perspective for Entering Global Pharma Markets. Pharma Times 2011;43(09):15-19.

30. Ceci A, FelisiM, CatapanoM, Baiardi P, Cipollina L, Ravera S et al. Medicines for Children Licensed by the European Agency for the Evaluation of Medicinal Products. Eur J Clin Pharmaco 2002; 58:495-500.
31. Committee for Medicinal Products for Human Use (CHMP), 2006. European Medicines Agency Pre-Authorization Evaluation of Medicines for Human Use (Doc. Ref. EMEA/CHMP/SWP/4447/00) Guideline on the environmental risk assessment of medicinal products for human use. 12pp.
32. Grung M et al. Environmental assessment of Norwegian priority pharmaceuticals based on the EMEA guidelines. Ecotoxicology and Environmental Safety 2008; 71:328–340.
33. European Medicines Agency. Better medicines for children. EMEA 2008. Available at http://www.emea.europa.eu/htms/human/paediatrics/regulation.htm
34. European Medicines Agency. Post-authorization evaluation of medicines for human use. Annex C: Template for EU risk management plan (EU-RMP). Available at http://www.emea.eurpa.eu/pdfs/human/euleg/19263206en.
35. Mellstedt, H. et al. The challenge of biosimilars. Ann. Oncol. 2008; 19:411–419.
36. Gottlieb, S. Biosimilars: Policy, Clinical, and Regulatory Considerations. Am J Health Syst. Pharm. 2008; 65: S2–S8.
37. Moran, N. Fractured European market Undermines Biosimilar Launches. Nat. Biotechnol. 2008; 26:5–6.
38. Joung, J et al. WHO informal consultation on regulatory evaluation of therapeutic biological medicinal products held at WHO Headquarters, Geneva, 2007. Biologicals 2008; 36:269–276.
39. Griffin JP, Shah RR. History of drug regulation in the UK. The regulation of medical products. London: Blackwell BMJ Books; 2003:3-12.
40. Permanand G, Mossialos E, McKee M. Regulating medicines in Europe: The European Medicines Agency, Marketing Authorisation, Transparency and Pharmacovigilance. Clin Med 2006;6(1):87-90.
41. Marty M. Drug Evaluation and Approval in the European Community. Eur J Cancer 1996; 32A:574-575.
42. European Medicines Agency Committee for Medicinal Products for Human Use. Guideline on risk management systems for medicinal products for human use. Available at http://www.emea/chmp/96268/2005.

43. European Medicines Agency road map to 2010: preparing the ground for the future. March 2006. Available at http://www.emea.europa.eu/htms/general/direct/roadmap
44. Hartford CE, Petchel KS, et al. Pharmacovigilance during the pre-approval phases. Drug Safety 2006; 29(8):657-673.
45. Hayakawa T. New drug approval process in Japan. Current opinion in biotechnology 1999; 10:307-311.
46. Uyama, Y et al. Successful bridging strategy based on ICH E5 guideline for drugs approval in Japan. Clin. Pharmacol. Ther. 2005; 78:102–113.
47. Bareilles M et al. Chapter 5- Japanese regulations. Global Clinical trials 2011;63-85.
48. Ono S et al. New drug approval times and clinical evidence in Japan. Contemporary Clinical Trials 2005;26:660 – 672.
49. Ono S, Kato O, Tsutani K, et al. Utilization of Foreign Clinical Data in Japanese New Drug Approval Review. Int J Pharm Med 2004; 18:159 – 165.
50. Tsuji K, Tsutani K. Approval of new biopharmaceuticals 1999–2006: Comparison of the US, EU and Japan situations. European Journal of Pharmaceutics and Biopharmaceutics.2008; 68:96-502.
51. Milsted R. Cancer drug approval in the United States, Europe, and Japan. Advances in Cancer Research. 2006; 96:371-391.
52. Wen-Hua Kuo. Techno-politics of genomic nationalism: Tracing genomics and its use in drug regulation in Japan and Taiwan. Social Science & Medicine 2011;73(8):1200-1207.
53. Horikawa, H et al. Industry Views of Biosimilar Development in Japan. Health Policy 2009;91(2):189-194.
54. Hirai Y et al. Analysis of the Success Rates of New Drug Development in Japan and the Lag behind the US. Health Policy 2012;104(3):241-246.
55. Yamaguch T, Arato T. Quality, safety and efficacy of follow-on biologics in Japan. Biologics 2011; 39(5):328-332.
56. DiMasi JA, Manocchia M. Initiatives to Speed New Drug Development and Regulatory Review: The Impact of FDA-Sponsor Conferences. Drug Inf J 1997; 31:771 – 88.
57. Health Canada. Health protective legislative renewal: detailed legislative proposal. Ottawa; 2003.
58. Health Canada. Improving Canada's regulatory process for therapeutic products: building the action plan: multi stakeholder consultation: Public Policy Forum; 2003 November 2–3.

59. Boisvert J. The Canadian Clinical Trial Regulation –Overview and Update. GOR 2003;5(2):35-39.
60. Rawson NSB. The Timeliness of New Drug Approvals in Canada. Int J Health Serv. 1995; 25:153–165.
61. Lexchin J. Drug Withdrawals from the Canadian Market for Safety Reasons, 1963–2004. CMAJ 2005; 172:765–67.
62. Lexchin J, Mintzes B. Transparency in Drug Regulation: Mirage or Oasis? CMAJ 2004; 171:1363–65.
63. Epstein J et al. Role of Regulatory Agencies. Biologicals 2009; 37:94-102.
64. Lim HH. The Pharmaceutical industry and ASEAN Free Trade Area- Initiatives on Tariff Reduction and Intellectual Property Protection. Australian Prescriber 1997; 20:217-21.
65. Lim MK. Shifting the Burden of Health Care Finance: A Case Study of Public-Private Partnership in Singapore. Health Policy 2004; 69:83-92.
66. Abas A. Regulatory Guidelines for Bio-similar In Malaysia. Biologicals 2011; 39:339-42.
67. Ministry of Health Malaysia. National Pharmaceutical Control Bureau, guidance document and guidelines for registration of bio-similar in Malaysia, portal.bpfk.gov.my/view_file.cfm?fileid¼302; 2008 [accessed on 25.10.11].
68. Vuong T et al. Drug Policy in Vietnam: A Decade of Change? International Journal of Drug Policy 2011,doi:10.1016/j.drugpo.2011.11.005.(article in press)
69. Reid G. Higgs P. Vietnam moves forward with harm reduction: An assessment of progress. Global Public Health: An International Journal for Research, Policy and Practice, 2011; 6(2):168–80.
70. Madulid DA. Guidelines and Policies on Collection of Biological Specimens in the Philippines. J Ethnopharmacology 1996; 51:205-208.
71. Noirhomme M, Meessen B et al. Improving Access to Hospital Care for the Poor: Comparative Analysis of Four Health Equity Funds in Cambodia. Health Policy and Planning 2007; 22:246–62.
72. Grundy J et al. Health System Strengthening In Cambodia—A Case Study Of Health Policy Response To Social Transition. Health Policy 2009; 92:107–115.
73. Tin N. An Approach to Health System Strengthening In the Union of Myanmar. Health Policy 2010; 95:95–102.
74. Guise JW, Carson BM. Biogeneric Regulatory Policies in China and India: A Comparison Study. Drug Information Journal 2010; 44:55-67.

75. Kristiansen S, Santoso P. Surviving De-centralization. Impacts of Regional Autonomy on Health Service Provision in Indonesia. Health Policy 2006; 77:247–259.
76. Lofgren H, Boer R. Pharmaceuticals in Australia: Developments in Regulation and Governance. Social Science & Medicine 2004; 58:2397–2407.
77. Morgan S et al. Balancing Health and Industrial Policy Objectives in the Pharmaceutical Sector: Lessons from Australia. Health Policy 2008; 87:133–145.
78. Doran E, Henry D. Pharmaceutical Benefits Scheme Policy: Confused and Tough On Patients. Internal Medicine Journal 2006; 36:211–213.
79. Duckett SJ. Drug Policy Down Under: Australia's Pharmaceutical Benefits Scheme. Health Care Financing Review.2004; 25:55–67.
80. Donovan, J. The benefits of the Pharmaceutical Benefits Scheme to the Australian community and the impact of increased copayments. Health Issues. 2002; 71:17–20.
81. Wonder MJ, Neville AM, Parsons R. Are Australians able to access new medicines on the Pharmaceutical Benefits Scheme in a more or less timely manner? An analysis of Pharmaceutical Benefits Advisory Committee recommendations, 1999–2003.Value in Health 2006; 9:205–212.
82. Roughead EE, Lopert R, Sansom LN. Prices for Innovative Pharmaceutical Products That Provide Health Gain: A Comparison between Australia and the US. Value in Health 2007; 10(6):514–520.
83. Li HZ. The Drug Registration Application. J. Pharm. Pharma Sci. 2003; 6:211-214.
84. Li HZ. Drug Control Authorities in China. Ann. Pharmacother. 2004; 38:346-350.
85. Lu D, Huang W. Overview of Drug Evaluation System in China. Scientific Research and Essays 2010; 5(6): 514-518.
86. State Food and Drug Administration of China (SFDA). Drug administration law of the People's Republic of China. Available from: http://www.sfda.gov.cn/cmsweb/webportal [Accessed December 3, 2011].
87. Sun Q et al. Pharmaceutical Policy in China. Health Affairs 2008; 27(4):1042-1050.
88. Deng R and Kaitin K. The Regulation and Approval of New Drugs in China. Drug Information Journal 2004; 37:29–39.
89. Yin H. Regulations and Procedures for New Drug Evaluation and Approval in China. Hum. Gene. Ther. 2006; 17:970-974.

90. Zhang Q. The Chinese Regulatory Licensing Regime for Pharmaceutical Products: A Law and Economics Analysis. Michigan Telecommunications and Technology Law Review 2009; 15:417-452.
91. James J. Shen. Drug Regulatory Framework in China" in China Pharmaceutical Guide. Published by WiCON International Group. 2011 (6th Edition), 346-449.
92. Cheng RL. Needs for Post-Marketing Evaluations in China. Chin J Pharmacovigilance 2005; 2:220–5.
93. Wang Y, Tang Z. The Analysis of ADRs Related To Houttuynia Herb Injections. Chin J New Drugs 2006; 15:739–741.
94. Du et al. Drug Safety Surveillance in China and Other Countries: A Review and Comparison. Value in Health 2008; 11(1):130-136.
95. LIANG H, Ding J, & Xue, Y. China's Drug Innovation and Policy Environment. Drug Discovery Today. 2011; 16:1-3.
96. Ding J et al. From Imitation to Innovation: A Study of China's Drug R&D and Relevant National Policies. J. Technol. Manag Innov. 2011 ;(6):1-13.
97. Belgharbi, L.Vaccine regulatory issues in African countries—building and sustaining national capacity. World Health Organization HTP/IVB/ATT, EDCTP Consultative Meeting, 11th June 2007.
98. Noor RA. Health Research Oversight in Africa. Acta Tropica 2009; 112:S63–S70.
99. Wassenaar DR, Slack CM. Perceived Capacity Of Selected African Research Ethics Committees to Review HIV Vaccine Trial Protocols. IRB 2006; 28(2):1–9.
100. Van Rensburg HCJ, Fourie A. Inequalities in South African health care: part I. The problem manifestations and origins. S Afr Med J 1993; 84:95–99.
101. Kirigia JM, Wambebe C, Baba-Moussa A. Status of National Research Bioethics Committees in the WHO African Region. BMC Medical Ethics 2005; 6:10.
102. Chima, S. Regulation of Biomedical Research in Africa. BMJ 2006; 332:848–851.
103. Glickman et al. Ethical and Scientific Implications of The Globalization Of Clinical Research. NEJM 2009; 360:816–823.
104. Karlberg JP .Sponsored Clinical Trial Globalization Trends. Clinical Trial Magnifier 2008;1.
105. Kumaranayake, L. The Role of Regulation: Influencing Private Sector Activity within Health Sector Reform. J Int Dev 1997; 94:641-649.