

Understanding Worldwide Regulatory Requirements

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**Understanding Worldwide
Regulatory Requirements**

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International Conference on Harmonization (ICH): The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together experts from the regulatory authorities and the pharmaceutical industry of Europe, Japan and the United States to discuss scientific and technical aspects of product registration. ICH strives to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines.

International Federation of Pharmaceutical Manufacturer's Associations (IFPMA): Represents the research-based pharmaceutical industry and other manufacturers of prescription medicines, worldwide channel of communication between this sector of the industry and the World Health Organization as well as other international organizations. The Federation has a central role in the exchange of information within the international industry and in the development of position statements on matters of policy.

Japan Pharmaceutical Manufacturers Association (JPMA): A voluntary organization of research-based pharmaceutical manufacturers that contribute to society by developing new pharmaceuticals. The JPMA works in close cooperation with the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

Pharmaceutical Inspection Convention (PIC), Pharmaceutical Inspection Cooperation Scheme (PIC/S): PIC is a legal treaty, founded in October 1970 by EFTA (European Free Trade Association) with the objective to exchange such information as is necessary for the mutual recognition of inspections relating to GMP compliance of pharmaceutical products. PIC/S is a less formal and more flexible cooperation scheme was developed to continue and enhance the work of PIC. Instead of being a legal treaty between countries PIC/S is a cooperative arrangement between Health authorities. It commenced operating on 2 November 1995. PIC and the PIC/S operate together as PIC/S and provide an active and constructive cooperation in the field of GMP (Good Manufacturing Practice). The purpose of PIC/S is to facilitate the networking between participating authorities and the maintenance of mutual confidence, the exchange of information and experience in the field of GMP and related areas, and the mutual training of GMP inspectors.

The Pharmaceutical Research and Manufacturers of America (PhRMA): An association of US based pharmaceutical companies.

Qualified Person (QP): EU requirement, a person who is held legally accountable for ensuring that all Quality conditions are met before releasing each batch of drug product.

Recall: A Major Quality Incident that leads to the removal of the entire affected batch or batches of material from the market or if clinical trials, from a study.

Seizure: An action by authorities, taken to remove a product from commerce because it is in violation of the law.

Violative product: A drug product produced or manufactured in violation of the Federal Food, Drug, and Cosmetic Act.

Warning Letter: An official advisory notice to a firm communicating the FDA's position on a matter but does not commit FDA to taking enforcement action. The agency's policy is that Warning Letters should be issued for violations which are of regulatory significance in that failure to adequately and promptly take corrections may be expected to result in enforcement action should the violation(s) continue.

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- Ensure that from a regulatory perspective that the interchange ability is based on sound science.
- Facilitate regulatory and industry access to the "benchmarked" harmonized text, ensuring that all are aware of exactly what text has been reviewed and given a status for interchange ability. This is deemed as essential for the regulatory acceptance of interchange ability.
- Working with the Pharmacopoeial Discussion Group, expedite the implementation for the interchange ability.

Worldwide Regulatory Agencies

Regulatory agencies play a very important role in the pharmaceutical business by assuring the public that the products on the market are safe and effective. Quality and Compliance Manual are to be developed to assure conformance to all major regulatory authorities

The expectation of a quality product is the same and the requirements are similar for these agencies. The achievement of quality is managed through different mechanisms. Quality is determined by whether the firm complies with GMP requirements and makes scientifically justified decisions.

Pharmaceutical companies are now taking a proactive stance with the new GMP Systems approach, more effective internal auditing and increased regulatory awareness throughout the company. Quality can only be achieved when everyone works together to meet the challenge.

In the global environment, it becomes even more evident that individuals must understand the major multiple regulations and regulatory authorities that any pharmaceutical company must abide by. There are still other regulations and regulatory authorities of smaller magnitude throughout the world that need to be considered.

On the following pages of this training unit you will see a general overview of the major worldwide regulatory agencies and the regulations they enforce,

Responsibilities of Regulatory Authorities

Regulatory Authorities have a wide range of responsibilities for medicinal products. The extent may vary but in the most common responsibilities will be describe here.

New Product Review

A regulatory authority will review applications for new medicinal products including the results of laboratory, animal and human clinical testing conducted by companies. Data and GMP compliance are verified through inspections by the inspectors employed by the regulatory authority. If the regulatory authority determines the product is safe and effective the company will get an approval to sell the product.

Acting as a " Watchdog"

Once products are on the market, the regulatory authority monitors their manufacture and responds to reports of problems or newly identified risks. This monitoring normally includes laboratory testing of samples.

Because initial testing of products is based on a relatively small number of users, the regulatory authority will monitor reports of adverse events with products after they are marketed. If this monitoring turns up a problem that needs to be corrected, the regulatory authority can, 1.) Ask the manufacturer to recall the product, 2.) Withdraw approval (of a drug, for example), 3.) Require labeling changes, or 4.) Send warnings to physicians or other health practitioners.

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governments to encourage the safety and quality of imported products by ensuring that foreign standards are equivalent to those enforced by FDA.

Research

FDA's research activities provide the scientific basis for its regulatory decisions and the tools needed to identify and assess risks. The agency uses its research results to establish standards, evaluate new products, develop test methods and other support for product monitoring, and to study emerging risks.

Enforcement - Correcting Problems

When a problem arises, FDA can take a number of actions to protect the public health. Initially, the agency works with the manufacturer to correct the problem voluntarily. If that fails, legal actions can be taken which include asking the manufacturer to recall a product, having federal marshals seize products if a voluntary recall is not done and detaining imports at the port of entry until problems are corrected. If warranted, the FDA can ask the courts to issue injunctions or prosecute those who deliberately violate the law.

Current Challenges for the FDA

Today, more than ever, the FDA needs to respond to a rapidly changing world. There are many obstacles to overcome if the FDA is to continue its high standards of consumer protection. The most important of these challenges are:

- Ø Keeping informed about scientific breakthroughs. FDA scientists will need to keep up with rapidly advancing technologies in all product areas.
- Ø Understanding more sophisticated products. These "cutting edge" technologies will translate into products with new complexities and risks.
- Ø Planning for new public health threats. The FDA needs to be prepared to respond rapidly to unexpected health risks, such as tougher strains of antibiotic-resistant bacteria or more dangerous food borne illnesses.
- Ø Predicting the impact of international commerce. Monitoring of imports and cooperation with foreign regulators will become more important as international commerce continues to grow.
- Ø Providing consumers with the information they need. Today's sophisticated consumers and the wide availability of information about FDA-regulated products will challenge the FDA to ensure consumers are getting the information they need from the right sources.
- Ø Reducing risks to the public health. The FDA will continue to effectively manage product risks throughout their life cycle- from research and development through use/ consumption. Risk management decisions will be supported by rigorous scientific analysis that weighs, when appropriate, not only the risk-to-benefit profile of the product itself but also the risk versus the benefit associated with Agency actions.

The FDA/ORA Guide to International Inspections and Travel, is intended to assist in fulfilling FDA's overall mission of assuring that drug, medical device, biological and food products manufactured in foreign countries and intended for U.S. distribution are in compliance with the law and regulations; that non-compliance is identified and corrected; and that any unsafe or unlawful products are removed from the marketplace.

This guide provides FDA personnel with standard operation, inspection and investigation procedures to assure uniformity in the program. It contains instructions and references to assist investigators and analysts who conduct international inspections. It also provides information regarding authorities, objectives, responsibilities, policies and guides applicable to inspectional operations, administrative procedures, and the basic guidance necessary for FDA personnel who travel to foreign countries. This guide is not designed to be all-inclusive, nor unduly restrictive. The procedures and guides are designed to supplement the experience, skill and proficiency of investigators and analysts and serve as a reference.

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The Parliament, the Commission and the Council govern EU. The decision process in EU starts with the Commission making a proposal. Laws/decisions can be passed/taken by the parliament and sometimes the council. Within the European Union the following commission has been developed to ensure the safety, efficacy and quality of the drug products.

European Commission (EC)- Enterprise DG - Pharmaceutical and Cosmetics

This commission initiates new proposals, whether new legislation or new authorization procedures, monitors implementation by national authorities and refers infringements to the European Court of Justice. The Commission's Directorate General includes a unit responsible for pharmaceuticals and cosmetics. The Commission is responsible for the EU GMP, which is published on the website of the Commission. The GMP is continuously updated.

European Medicines Agency (EMA)

The EU has established a joint regulatory agency in London originally named the European Agency for the Evaluation of Medicinal Products, now named the European Medicines Agency (EMA).

The tasks of EMA are to

- Protect and promote public and animal health
- Coordinate the evaluation and supervision of medicinal products throughout the European Union using the resources existing in the Member States

All member states in EU have their own regulatory agencies that provide the inspections necessary under the EU regulations. In EU companies are required to have Manufacturing Authorizations in order to manufacture Medicinal Products.

Manufacturing Authorizations are issued by the Regulatory Agency of the Member State, who also supervises all manufacturing authorizations within their territory. A listing can be found at the Heads of agencies website.

· Mutual Recognition Agreements between EU and other countries

In EU the Commission has the authority to negotiate Mutual Recognition Agreements with other countries. The European Community (EC) and MRA Partner Countries have established the MRAs to:

- a) Reduce technical barriers to trade by facilitating market access while safeguarding consumer interests in health,
- b) Grant mutual acceptance of inspection reports, certificates, authorizations, conformity marks issued by the regulated authorities of the Parties and manufacturers' declarations of conformity certifying conformity to the requirements of the other Party,
- c) Exchange information concerning procedures used to ensure that the conformity assessment bodies comply with the general principles of designation and
- d) Encourage greater international harmonization

Comparison of FDA and EU Practices

Some of the differences between the FDA and the EU's business practices are shown in enforcement actions listed below.

FDA and EU enforcement actions compared relative to increasing seriousness :

FDA

Inspection

C observations"/EIR

EU

Inspection

Post-inspection deficiency letter/report/ manufacturing authorization suspended/revoked

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The Therapeutic Goods Act, Regulations and Orders establish the requirements for inclusion of therapeutic goods in the ARTG, including advertising, labeling, product appearance and appeal guidelines. Some provisions such as the scheduling of substances and the safe storage of therapeutic goods are included by the relevant State or Territory legislation.

Cooperative Arrangement between the FDA and the TGA

On October 11, 2000, the TGA signed a cooperative arrangement with the Food and Drug Administration (FDA), USA, regarding the exchange of information on current Good Manufacturing Practice (GMP) inspections of human pharmaceutical manufacturing facilities. Under this agreement the FDA and TGA expressed their intent to:

- Ø Provide copies of pharmaceutical establishment inspection reports (confidential information purged) and product sample results to one another, upon request, within certain specified time frames.
- Ø Notify one another when one authority plans to conduct inspections in the other authority's territory and be receptive to permitting joint inspections for the purpose of promoting better understanding of one another's inspectional programs and techniques.
- Ø Provide other GMP-related information such as recall information, adverse product trends, health hazard evaluations, and alert system information.

Both authorities agree to exchange appropriate information about manufacturers when shortage situations occur which involve medically necessary human pharmaceuticals. The information in the inspection report allows the FDA and TGA to make their own decisions concerning the compliance of manufacturers and appropriate follow up. Each agency may carry its own inspections in the other's territory if it deems necessary.

The agreement applies to GMP inspections of pharmaceutical facilities where the inspections have been conducted using the current FDA GMP requirements for drugs or the current TGA GMP Code for medicinal products.

TGA and EU

Australia has an MRA with EU, which means that the legislation and the way TGA works with regards to pharmaceuticals has been assessed and is considered equivalent to the EU system.

Australian Code of Good Manufacturing Practice for Medicinal Products

The Australian Code of Good Manufacturing Practice for Medicinal Products (16 August 2002), replaces the Australian Code of Good Manufacturing Practice for Therapeutic Goods - Medicinal Products (August 1990), the Australian Code of Good Manufacturing Practice for Therapeutic Goods - Medicinal Gases (July 1992) and the Investigational Medicinal Products Code of GMP (Annex 13, EC GMP Guide, 1997).

The new Code is based entirely on the international standard entitled Guide to Good Manufacturing Practices for Medicinal Products, PE 009-2, 1 July 2004, published by the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/S). The modifications to that Guide and its adoption as the Australian Code of Good Manufacturing Practice, is done so with the expressed permission of the PIC/S. It was enacted in August 2003 as the basis for the licensing of all Australian manufacturers of medicinal products.

Canadian Health Products and Food Branch Inspectorate (HPFBI)

When a product is offered for sale in Canada to treat or prevent diseases or symptoms, it

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WHO

Many countries in particular in Asia and Africa have adopted the WHO GMP, which is available from the WHO website. Generally the requirements are similar but less stringent than for example the EU GMP. WHO is focused on Essential medicines e.g. those that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety and comparative cost-effectiveness.

Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remains a national responsibility.

International Conference on Harmonization (ICH)

Harmonization of regulatory requirements was pioneered by the European Community, in the 1980s as the EC (now the European Union) moved toward the development of a single market for medicinal products. The success achieved in Europe demonstrated that harmonization was feasible. At the same time there were bilateral discussions between Europe, Japan and the USA on possibilities for harmonization. It was at the WHO Conference of Drug Regulatory Authorities (ICDRA) in Paris in 1989 that specific plans for action began to materialize. Soon afterwards, the authorities approached the International Federation of Pharmaceutical Manufacturer's Associations (IFPMA) to discuss a joint regulatory-industry initiative on international harmonization and ICH was conceived.

The birth of ICH took place at a meeting in April 1990, hosted by the European Federation of Pharmaceutical Industries' Associations (EFPIA) in Brussels. Representatives of the regulatory authorities and industry associations of Europe, Japan and the USA met primarily to plan an international conference but the meeting also discussed the wider implications and terms of reference of ICH. The ICH Steering Committee (SC), which was established at that meeting, has since met at least twice a year with the location rotating between the three regions.

ICH Parties

ICH is comprised of six parties who are directly involved, as well as three observers and IFPMA. The six parties are the founding members of ICH and represent the regulatory bodies and research-based industry in the European Union, Japan and the USA. These parties include the EU, EFPIA, MHLW, JPMA, FDA and PhRMA. The observers are WHO, EFTA, and Canada, represented by Health Canada. This important group of non-voting members acts as a link between the ICH and non-ICH countries and regions.

ICH is operated via the ICH Steering Committee, made up of the six parties plus an IFPMA representative. Technical and scientific support from the EU for ICH activities is provided by the EMEA through the Committee for Proprietary Medicinal Products (CPMP). The Steering Committee is supported by the ICH Secretariat, which operates from IFPMA in Geneva.

Early in the ICH Process it was agreed that there was adequate international agreement on the technical aspects of Good Manufacturing Practices (GMP) for Pharmaceutical Products and that further harmonization action through ICH was not needed. Recently, however, attention has focused on the need to formalize GMP requirements for the components of pharmaceutical products - both active and inactive. In November 2000 ICH published Q7a for implementation 'GMP for Active Pharmaceutical Ingredients'