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OVERVIEW OF REGULATION OF MUTUAL RECOGNITION PROCESS AS PER UNITED STATES, EUROPE, JAPAN AND SWITZERLAND

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ABSTRACT

The Mutual Recognition is an effective way to ensure equivalency of "Good Manufacturing Practice" compliance Programme between different courtiers. The recognition process pre suppose the joint exercises to determine high standards of product safety and quality in order to increase communication between regulatory systems. This provision is applicable for all medicinal products manufactured in with GMP compliance, imported and exported to any regulatory authorized country. This paper high lights the regulatory requirements of United States, Europe, Japan and Switzerland for mutual recognition of medicinal products to establish working collaborative and strategical working to help ensure that patients have access to safe, effective and high-quality and more affordable medicines by minimizing duplication of inspection with better compliance activity.

KEYWORDS: Mutual Recognition, Agreement, Regulation, GMP, Medicine

INTRODUCTION[1][2]

Brief overview of Marketing Authorization

An official document issued by the competent drug regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality

which includes the name of the product, the pharmaceutical dosage form, the quantitative formula (including excipients) per unit dose (using INNs or national generic names where they exist), the shelf-life and storage conditions, and packaging characteristics. This process is performed with a legislative framework which defines the requirements necessary for application to the concerned regulatory authority and assessment procedure is based on quality, Safety, Efficacy criteria and grounds the approval or rejection of application.

Types of marketing authorization Procedure

There are four ways in which a medicinal product can obtain marketing authorization Procedure.

- Centralized procedure.
- National procedure.
- Decentralized procedure.
- Mutual recognition procedure.

The centralized procedure

The centralized procedure, which is set out in Regulation (EC) 726/2004, allows applicants to obtain wide marketing authorization that is binding on all Member States. Applications are made directly to the European Medicines Agency and are scientifically evaluated by the appropriate EMA is the Committee for Medicines for Human Use. It is compulsory for medicines such as those developed by biotechnological processes.

The National procedure

It can be used if applicant wants to marketing authorization to market a product in individual Europe member state.

There are many reasons where applicant can go for national procedure.

If Applicant wants to,

- Launch in one market only (Smaller/Local Company)
- Sort out continuous issue that might come up during assessment.
- Promote an overseas site inspection. (e.g.: GMP inspection of manufacturing site)

The decentralized procedure

It was introduced with newly revised Europe pharmaceutical directive 2004/27/EC in November 2005.This procedure is applicable in cases where marketing authorization does not

still exist in other member state of Europe at the time of application. It is similar to mutual recognition procedure and relies on the recognition by national authorities of a first assessment performed in one member state. Identical dossiers are submitted in all member state where a marketing authorization is wanted.

The mutual recognition procedure[3]

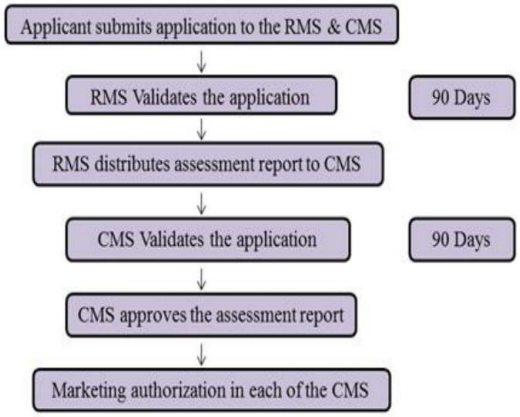
Mutual recognition is the principle of European Union law under which member states must allow goods which are legally sold in another member state also to be sold in their own territory. The procedure is followed by mutual recognition agreement by which two or more countries agree to recognize one another's conformity assessments. The traditional approach to product legislation in the Europe, known as the Old Approach, was simply to write detailed regulations containing all the necessary technical and administrative requirements for each type of product. This reflected the existing national approach to product legislation. This approach is for foodstuff, Biocides, motor vehicles, chemicals, cosmetics, detergent and pharmaceutical products.

The Convention for the Mutual Recognition of Inspections for the Manufacture of Pharmaceutical Products was founded in 1995 and which was founded in October 1970 by EFTA (European Free Trade Association) to improve the operation of the Mutual Recognition Procedure and the work in the SmPC harmonization field.

MUTUAL RECOGNITION PROCESS[4]

The procedure is applicable when applicant has already received marketing authorization in any member state at the time of application for the intended medicinal product and applying for more than one member state. One member state is consider as “Reference member state” and they will decide to evaluate medicinal product at that time other member state which are known as “Concerned member state” suspend their own evaluation and wait for reference member state’s decision on the medicinal product. If RMS’s decision is favorable, then a report is communicated to CMS, who recognize the RMS’s decision. In this process national licenses are issued through CMS and approved by RMS to establish mutually recognized in other countries for the determination of evaluation criteria are sufficiently harmonized with same standard.

Flow chart of Mutual Recognition Procedure



REGULATIONS AS PER UNITED STATES[5][7]

The International Partnership Agreements for Compliance Activities establishes Policy regarding USFDA, Foreign Government Agencies, Domestic Trade Associations and Other Organizations.

To represents the agency's current thinking on establishing its partnership agreements which satisfies the requirements of applicable status and regulation. The committee will monitor the implementation of the Good Manufacturing Practice through mutual recognition agreement to determine technical and administrative arrangements for effective implementation.

It impacts the following principal areas

- ✓ Exchange of information between the FDA and other regulatory authorities.
- ✓ Trade of medicinal products and their constituent ingredients between the regions.
- ✓ GMP inspections.

The regulations that most directly affect Mutual Recognition are contained

- ➢ 21 U.S.C. §301-The Federal Food, Drug, and Cosmetic Act (2002) and The Food Quality Protection Act: Public Law (1996)
- ➢ 21 U.S. Code § 351 - Adulterated drugs
- ➢ 21 U.S Code § 355-New drugs- approval of Human Drug
- ➢ 21 U.S Code § 360-New drugs- approval of Animal Drug
- ➢ 21 U.S.C. 374 Inspection authority
- ➢ 21 U.S.C. 384 Recognition of foreign government inspections
- ➢ 42 U.S.C. 262. Regulation of Biologic Products

- 21 CFR Part 210 Current Good Manufacturing Practice in Manufacturing, Processing, Packing or Holding Drugs
- 21 CFR Part 211 Current Good Manufacturing Practice for Finished Pharmaceuticals
- 21 CFR Part 600 Subpart B (Establishment Standards)
  Subpart C (Establishment Inspection)

REGULATIONS AS PER EUROPE[6][7]

Mutual Recognition Agreements is an international regulatory co-operation (IRC) identified by the Organization of Economic co-operation Development (OECD). The aim of this Regulation is to strengthen the functioning of the internal market by improving the free movement of goods which includes specific conditions relates to the protection of public safety, health, or the environment.

For any country that need Mutual Recognition of its product in European Country has to fulfill following regulation

- **Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use**.

❖ In the European Union a medicinal product needs a marketing authorization to be placed on the market. This application is subjected to Committee for **Medicinal Products for Human Use (CHMP)** So, this guideline are based on good manufacturing practice for investigational medicinal products for human use and arrangements of inspection which addresses specific issue and provide flexibility of any changes as knowledge to determine stages of development of products in order to promote harmonization of authorizations for medicinal products to enhance summary of product characteristics.

Classifications of Medicinal Products subjected to mutual recognition process

- ✓ A medicinal product subject to medical prescription.
- ✓ A medicinal product not subject to medical prescription.
- ✓ Medicinal products on medical prescription for renewable or non- renewable delivery.
- ✓ Medicinal products subject to special medical prescription.
- ✓ Medicinal products on restricted' medical prescription, reserved for use in certain specialized areas.

Other Regulations that most directly affect Mutual Recognition for Europe

- Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products.
- Directive 2001/20/EC of European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.
- Regulation (EU) 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.
- Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
- Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.
- Commission Directive 91/412/EEC of 23 July 1991 laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products.
- Commission delegated Regulation (EU) 1252/2014 of 28 May 2014 of the European Parliament and of the Council with regard to principles and guidelines of good manufacturing practice for active substances for medicinal products for human use.
- Current version of the Guide to good manufacturing practices contained in volume IV of Rules governing medicinal products.
- in the European Union and compilation of the community procedures on inspections and exchange of information.

PROVISIONS OF REGULATION FOR MEDICINAL PRODUCTS BETWEEN UNITED STATES AND EUROPE[8]

The European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services have a program to provide parallel scientific advice (PSA) to sponsors.

Parallel Scientific Advice (PSA)

The goal of PSA program is to provide a mechanism for EMA assessors and FDA reviewers to concurrently exchange with sponsors their views on scientific issues during the development of new medicinal products (i.e., new human drugs and biologics). The agencies conduct PSA procedures under the auspices of the confidentiality arrangement between European Commission and FDA.

"Sponsor" refers to

- The "sponsor" of an Investigation New Drug Application in the United States
- The "applicant" that submits a New Drug Application or Biologics License Application in the United States
- A potential marketing authorization application under the marketing authorization process in the European Union.

PSA requests focus primarily on specific questions or issues involving the development of a medicinal product for which the sponsor desires to have further scientific from both FDA and EMA and procedures should focus on sharing information and have a clear understanding of the agencies' respective requirements regarding the development.

PSA include important Medicinal Products

- Biosimilars
- Product with clinical Safety
- Animal toxicology
- Medicinal Products for oncology, anti-infective, rare disease, cardiovascular Disease

The sponsor participates in joint PSA activities and conducts pre-sponsor meeting by videoconference to discuss the sponsor's questions and specially focus on product development lifecycle of phase 2 trials.

The sponsor provides the following information

- The product in development
- Discussion with the assessors (reviews) of EMA and FDA would be beneficial to the products' development
- Specific questions requiring clarification
- The desired goals for the meeting

If both agencies grant the PSA request, the sponsor will receive an electronic mail message (email) from each agency acknowledging such agreement and indicating the primary contact person at each agency. The PSA process corresponds to the 70 day timeline of EMA Scientific Advice Working Party (SAWP).

The Scientific Advice Working Party (SAWP) is a standing working party and provides scientific advice and protocol assistance.

Following Areas of expertise is ensured

- Non-clinical safety
- Pharmacokinetics
- Methodology and Statistics
- Therapeutics fields for which there are frequent requests such as neurodegenerative disorders and infectious disease including human immunodeficiency-virus infection.

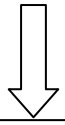
It brings integrated review on

- Quality relating to the development of medicinal products
- Non-clinical and clinical safety and efficacy relating to the development of medicinal products
- The significant benefit of orphan medicinal products

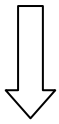
Each party enhance cooperative activities with its appropriate law-enforcement and regulatory authorities to actively investigate and prosecute individuals that manufacture, sell, distribute, test or export and also actively participate in the WHO'S International Medical Products Anti-Counterfeiting Taskforce (IMPACT) and the Permanent Forum on International Pharmaceutical Crime (PFIPC).

Agreement Process

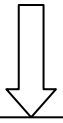
Within 15 days from the date of antry into force of agreement, each authority notify to other party in writing of its primary points of contact for coordinating all bilateral activities including meetings, exchanging information, sending and receiving notifications.



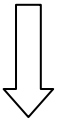
The Parties establish a working group within 30 days and within 60 days working group holds its first meeting to develop work plan to evaluate success of each activity.



Within 120 days, the working Group finalize Work plan and their conclusion for the 12 months period to evaluate the success of every activities on its respective websites.



Within 180 days, high-level representatives of the Parties discuss and review implementation and covers technical level meetings on mutually agreeable location.



Within 24 hours of determining it will be meet an agreed-upon deadline and provides the reason for the delay. The Parties agree to modify the timelines and establish new delivery date.

Elements to be consider in developing two way alert systems

- ❖ Documentation
- ➢ Emergency Alertness
- ➢ Standard Operating Procedure
- ➢ Mechanism of health hazards evaluation and classification
- ➢ Language of communication and transmission of information

- ❖ Management System
- ➢ Establishment of contact point
- ➢ Reporting mechanisms

- ❖ Enforcement Procedure
- ➢ Follow-up mechanisms
- ➢ Corrective action procedure

- ❖ Quality Assurance System
- ➢ Pharmacovigilance Programme
- ➢ Surveillance/monitoring of implementation of corrective action

REGULATIONS AS PER JAPAN[9]

The European Medicines Agency and the European Commission have a confidentiality arrangement with the Japanese Ministry of Health, Labour and Welfare (MHLW) and Pharmaceutical Medical Devices Agency (PMDA). The operation was carried out in may 2004 with discussion are ongoing to broaden scope to include sterile and biological products and active pharmaceutical Ingredients. The agreement was first signed in 2007 and was last extended in 2013 for future five years. The confidentiality agreement allows exchange of information between the parties as part of their regulatory and scientific processes, both before and after medicine has been approved.

The common interest in enhancing product quality with a view to ensuring the health and safety of the public and protecting the environment which recognizing the principles of

- ➢ Good Laboratory Practice
- ➢ Good Manufacturing Practice for medicinal Products

Europe and Japan accepts certificates of conformity issued by the conformity assessment bodies (CAB) of other part according to the requirements of importing party. This means that a manufacturer wherever located can have its product tested and certified according to a Japanese requirement by a CAB located in the Europe. This results of the evaluation without delays as stipulated by the applicable ministerial ordinance.

The following indicative Guidance Documents have been adopted to ease the application of the Regulations:

- ➢ Mutual Recognition Agreement between Europe and Japan
- ➢ Good Laboratory Practice for Chemicals
- ➢ Good Manufacturing Practice for Medicinal Products
- ➢ Conformity Assessment Procedure

- Statement by Mr. Yohei Kono, Minister for Foreign Affairs, on the Signing of the Agreement on Mutual Recognition between Japan and the European Community (EC)
- Entry into Force of the Agreement on Mutual Recognition between Japan and the European Community
- International Pharmaceutical Regulatory Harmonization, Ministry of Health, Labour and Welfare.

REGULATIONS AS PER SWITZERLAND[10-12]

The Activities in the area of quality and manufacturing under the mutual recognition agreement between Europe and Switzerland signed in 2002. The agreement builds on a previous cooperation during H1N1 influenza pandemic, initially placed in 2010 and then extended twice for a year in 2011 and in 2012. The agreement place between the European Medicine Agency (EMA) and Swiss Agency for Therapeutic Products (Swiss Medic) and the Swiss Federal Department of Home Affairs (FDHA) since July 2015.

The agreement covers non-public information on the Safety, Quality and Efficacy of medicines in order to enhance public health protection by improve the oversight of medicines for human and animal health. It is valid for five years. Medicines and vaccines used against the H1N1 virus remain authorized in the European Union and Switzerland. Product annex is divided into following sector.

- Agriculture and Forestry
- Good Laboratory Practice
- Medicinal Products GMP Inspection and Batch Certification
- Biocidal Products

Conformity Assessment Reports includes certification, Testing and Inspection and are frequently required by government regulators to ensure that product and process meet minimum health and safety standards.

The following indicative Guidance Documents have been adopted to ease the application of the Regulations.

- Mutual Recognition Agreement between Europe and Switzerland.
- EC – Switzerland MRA Sectoral Annex on GMP medicinal products GMP inspection and batch certification.
- Medical Devices: Regulation in the EU and in Switzerland.

- Mutual Recognition Agreement for Biocides.
- Agreement between the Swiss Confederation and the European Union on the mutual recognition of conformity assessments.

CONCLUSION

In this study, Mutual Recognition promotes trade between different countries and thus facilitates market access. The studied particulars of the regulatory bodies of the United States, Europe, Japan and Switzerland come out with rigorous regulations for the recognition of pharmaceuticals products in their country. Thus this article furnishes with information required to have faster access to new drugs already approved in one country with facts of potential risk-benefit associated with patients, in context of GMP compliance and other quality standards. More over this article brief that, all four countries addresses regulatory compliance with greater sustainability and capability of achieving world class product quality standards by generating single inspection environment.

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