

Comparison Review of Two Regulatory Agencies Regulation: Therapeutic Goods Administration (TGA) and the European Medicine Agency (EMA) in Relation to Good Manufacturing Practice (GMP) Guideline

Farida Nur Aziza

Graduate School of Health, University of Technology Sydney

Corresponding author: Farida Nur Aziza; Email: farida.aziza@gmail.com

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ABSTRACT

There are some regulatory bodies in the world that impacting the pharmaceutical industry to operate and perform Good Manufacturing Practice (GMP) principles. These regulatory bodies exist to ensure that the pharmaceutical product and other human supporting products have a high standard of quality, safety, and efficacy from product registration to product distribution to the patient. This article reviews some aspects which is regulated by two of regulatory entities including Therapeutic Goods Administration (TGA) and European Medicines Agency (EMA) in relation with Good Manufacturing Practice (GMP) principles. The GMP principles which is structured by these regulatory agencies may be originally created by the agencies or influenced by other regulatory body concepts. The guidance can be a primary source or second reference for the pharmaceutical industry in impacting countries depending on the guideline's legal status. It is noticeable that both regulatory bodies have some similar concepts to support GMP implementation and some different practices which may be considered by the pharmaceutical industry when it is aimed to market their product in the regulated countries.

Keywords: Good Manufacturing Practice; regulatory agencies; pharmaceutical industry; guideline

INTRODUCTION

A pharmaceutical industry should ensure that its pharmaceutical product has a high standard of safety, quality, and efficacy. These standards should be built and designed from the beginning of the process until it is distributed to the patient or consumer based on the regulation required in Good Manufacturing Practice (GMP) guidelines. To ensure this guideline is implemented adequately by manufacturers, every country in the world has its own GMP guideline derived from their national authority guideline or by adopting from other national regulatory authorities and international guidelines (Gouveia *et al.*, 2015). Besides, some regulatory entities and pharmaceutical stakeholders in the world agree for a harmonization of pharmaceutical guidelines which can be applied in some agreed countries. The agreed harmonization which available in the world such as the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Pharmaceutical Inspection Co-Operation Scheme (PIC/S), and Eudralex by the European Commission.

There are some significant regulatory agencies in the world that influence pharmaceutical company operation or process in the world such as US Food and Drug

Administration (FDA), EU European Medicines Agency (EMA), and the Australian Therapeutic Goods Administration (TGA). The US Food and Drug Administration (FDA) is the regulatory authority of the United States responsible for ensuring the quality, safety and efficacy of human and veterinary drugs, medical devices, biological products, food supply, cosmetic, and radiation products (FDA, 2018). FDA laws are followed and referred by some countries worldwide for their national guidance for food and drug regulation. Therapeutic Goods Administration (TGA) is a regulatory entity of Australia which regulates therapeutic goods related activity including research, production, and distribution of the product in Australia. TGA regulates some product areas such as prescription medicine, over-the-counter medicines, complementary medicines, sunscreens, medical devices, biologicals products, blood and blood components, and other therapeutic goods (TGA, n.d.). At the same time, European Medicines Agency (EMA) is a decentralised authority which responsible for human and animal medicine product lifecycle in the European Union (EU) (EMA, n.d.). This article will compare some aspects between two regulatory agencies: Australian Therapeutic Goods Administration (TGA) and European Medicines Agency (EMA), concerning with Good

Table I. Comparison of Product Regulated by TGA and EMA

TGA	EMA
<ul style="list-style-type: none"> - medicines - complementary medicines including herbal, vitamins and traditional medicines - vaccines, blood products and other biologics - medical devices - products used to test for various illness or conditions 	<ul style="list-style-type: none"> - medicines for human and veterinary use
<p>Do not :</p> <ul style="list-style-type: none"> - veterinary medicine - food - cosmetics - chemicals 	<p>Do not :</p> <ul style="list-style-type: none"> - medical devices - food supplement - cosmetics

Manufacturing Practice which is applied in related countries.

METHODOLOGY

This article will review the information from two regulatory authorities (Therapeutic Goods Administration and European Medicines Agency) information such as the main website and some supporting publications which discuss good manufacturing practice (GMP) guidelines implementation in Australia and European countries.

RESULT AND DISCUSSION

Type of Regulated Products

Therapeutic Goods Administration (TGA) and the European Medicines Agency (EMA) imply that they may have a different scope of regulated products. Related to regulation scope, TGA regulates medicines, complementary medicines including herbal, vitamins, and traditional medicines, vaccines, blood products and other biologics, medical devices, and products used to test for various illnesses or conditions (TGA, n.d.). It is similar to EMA which regulates medicines for humans, although EMA also regulated medicine products for veterinary use (EMA, n.d). Besides, TGA also covers medical devices in its guidelines. At the same time, EMA only involves in specific medical device categories as it is handled explicitly by a specific Australian national authority for the medical devices. In addition, it is likely that both regulatory bodies have different treatment for vitamin product where TGA classify vitamins as complementary medicines, while EMA classifies

it into food supplement. Furthermore, both TGA and EMA do not regulate cosmetics and chemicals, which their other national agency handled in Australia and the national level in European countries.

The legal status of GMP Requirement in Impacting Countries

Implementation of Good Manufacturing Practice (GMP) principles by the pharmaceutical industry is imperative to ensure the product quality while the guideline which should be followed may differ in each country based on the legal status of GMP guidelines applied in a related area. It is likely because some countries implement their national GMP guidelines as a mandatory regulation to be followed by the pharmaceutical industry and all pharmaceutical sectors related. However, this GMP guideline from their national regulatory body, in some countries, it is applied as a second option after a primary reference such as union guideline. For example, in Australia, the implementation of GMP guidelines regulating GMP activity such as manufacture, supply, export, and import are regulated in the Therapeutic Goods Act 1989 (TGA, n.d.). This law is implemented in Australia as a legal requirement which should be applied on therapeutics goods (medicines, biological products, and medical devices) from listing, registering including product appearance, advertising and labelling on the Australian Register of Therapeutic Goods (ARTG). Besides that, this Act is also maintained by the Regulations and many Order and Determination which is included in the Act.

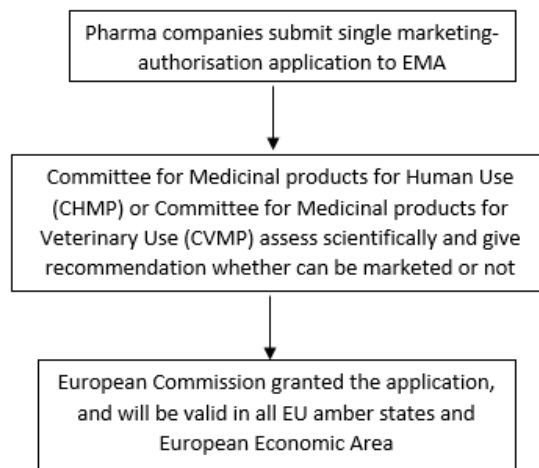


Figure 1. Flowchart of EMA Centralised Route for Medicine Registration

On the other hand, based on European Commission website in 'EU Legislation' (European Commission, n.d), European Union (EU) regulates pharmaceutical sector with Eudralex as Directives and Regulations. Eudralex volume 1 (one) until 10 (ten) as EU legislation is categorized as guideline and legislation, with Eudralex volume 1 and 5 as legislation, and another volume as a guideline. From this implementation, it seems that the EU Commission provides GMP basic guideline for each member country then stretch the opportunity to its member to implement the GMP principles in their responsibility. This concept is likely suitable for EU countries with their national authority guideline in each area, such as Medical Products Agency in Sweden, Spanish Agency for Medicines and Health Products in Spain and National Authority of Medicines and Health Products in Portugal.

From the comparison above, it can be seen that TGA applies GMP requirements as 'must-do' rather than 'may to do' as EMA applies for some requirements in their member states. EMA likely implements a decentralised system for registration which allows national authorities in each country to define their procedures for their internal process, while TGA implements a centralised system of GMP implementation across the country and impacts countries which export their pharmaceutical product to Australia.

Product registration and evaluation process

Australian TGA implements registration and evaluation process based on the Therapeutic Goods Regulations 1990 which will proceed the product registration depend on the product type (TGA, n.d). It can be categorized as prescription medicines, complementary, or over the counter (OTC) medicine. The registration and evaluation process for each product type has its specific guideline. TGA classifies guidelines for pharmaceutical product into three including Australian Regulatory Guidelines for Prescription Medicines (ARGPM), Australian Regulatory Guidelines for Over the counter (OTC) Medicines (ARGOM), and Australian Regulatory Guidelines for Complementary Medicines (ARGCM) which is divided into listed and registered complementary medicine.

In addition, the TGA registration process needs to be supported by nonclinical, clinical, and/or bioequivalence data (category 1 and category 2). Medical product exported from, imported into and supplied in Australia should be included in ARTG (Australian Register of Therapeutic Goods) which registered and listed pharmaceutical products. Australian TGA implements the main element for the registration process including management by milestones, preparation of dossiers and common technical document (CTD) format and other TGA requirements, pre-submission

planning phase, submission phase, and request for information at the end of initial evaluation phase (TGA, n.d).

On the other hand, European Union with its EMA regulatory body applies two pathways to register medicine (European Medicines Agency, n.d.)

Centralised Route

This procedure is mandatory for new substance for HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune or other immune diseases, viral disease, biotechnology processed medicine, orphan medicine, advance-therapy medicine, and veterinary medicine for growth.

National Route

This route authorises medicine at member country national level and is applicable for products which authorised before EMA creation or not in the scope of the centralised procedure.

For pharma company which expands their product in other EU company and not in centralised scope, they may use one of this procedure: Decentralised procedure which is a simultaneous process for gaining authorisation from one of EU member with other EU member states; Mutual-recognition procedure where marketing authorisation from one EU member can be accepted in other or several EU member state

The differences between TGA and EMA implementation for their registration process may likely because the authorisation scope of the regulatory body is different. EMA regulates some countries where every country has their national regulation so that it may impact on decentralised system and mutual recognition mechanism, while TGA only covers Australia and impacting country which aim to export their product to Australia. Thus, it can be concluded that the authority for all medicine in Australia is controlled and centralised by TGA, while in Europe, it is handled by EMA and national authorities depend on the product type and the certain condition such above.

Qualification Process of Manufacturer

A pharmaceutical product can be manufactured if the manufacturer is registered in the impacting country where the manufacturer is located then it can be

distributed after the product and manufacturer is licensed in the marketed area. TGA and EMA may implement different stages of the manufacturer qualification process before the manufacturer is legitimately produced a pharmaceutical product which will be distributed to the area. Australian TGA requires an Australian manufacturing site should have a manufacturing license for their manufacturing operation and inspect by TGA. However, it has a different requirement for overseas manufacturers aiming to distribute their product to Australia. This manufacturer should have GMP certification or clearance by a sponsor which is followed by on-site TGA inspection. The sponsor may be an Australian company which has a legal entity in Australia. This sponsor should also be registered by TGA (TGA, n.d).

On the other hand, manufacturing authorisation in European Union can be initiated by the national competent authority in each country which issues an authorisation for manufacturers or importers to allow their activities in the European Economic Area (EEA). The manufacturer should follow EU GMP guidelines. National competent authorities conduct inspection process for manufacturing sites in the location of manufacturing sites unless MRA is in place between the country issued and the EU (EMA, n.d.).

Thus, it can be seen that TGA differentiates the licensing process for the manufacturer from Australia and overseas manufacturing, while EMA applies the same procedure for both parties. Besides, TGA requires the overseas manufacturer to apply the license by the Australian sponsor or agent acting on the Australian sponsor's behalf.

The Role of Mutual Recognition Agreement (MRA) and Memorandum of Understanding (MOU)

Mutual Recognition Agreement (MRA) can be described as an agreement of two regulatory authorities to recognise each other's regulatory inspection, review or assessment (EMA, n.d). Australian TGA implements MRA which may eliminate replication testing and recertification of traded product from overseas countries. MRA pathway can also be one mechanism to gain GMP clearance for overseas manufacturing sites to verify that they comply with Australian GMP principles. The countries which have MRA with Australia are Austria,

Belgium, Canada, Cyprus, and some other countries.

EMA likely implements the similar practice. EMA utilises MRA to ease the regulation proses. If a MRA is applied, national competent authorities in Europe mutually rely on each other's inspections. The European Commission is responsible for negotiating MRAs with partner countries on behalf of the EU where EU commission consults with EMA on the scientific and regulatory part during the process (EMA, n.d.). EU has MRAs such as with Australia, Canada, Israel, Japan, New Zealand, Switzerland, and the United States. This MRA may bring advantage to the pharmaceutical sector since it may reduce cost by minimizing the inspection number taking place in their plant and waiving re-test of the products upon importation.

For Memorandum of Understanding (MOU) implementation, MOU may bring an effective collaboration of regulatory bodies with other parties. It is because it enables TGA with other parties to share and co-operate information which agreed together (TGA, n.d.). For example, MOU with NATA (National Association of Testing Authorities) for In House In Vitro Diagnostic Medical Devices testing in relation to laboratory accreditation in the manufacture of IVD medical devices. It is similarly implemented in the European Union where EMA utilises MOU to avoid duplication and enhance the cooperation between two parties such as by exchange information, specific joint work implementation (EMA, n.d.). For example, MOU between EMA with the European Food Safety Authority. Thus, it is likely that both TGA and EMA have similar mechanisms of implementing and utilising MRA and MOU to improve their effectiveness in the regulatory process. By implementing those agreements, they may minimise activities and resources for evaluating, assessing, and inspecting certain filed which already performed by other parties or organisation.

CONCLUSION

It is noticeable that Good Manufacturing Practice (GMP) guideline is a foremost guideline which should be implemented by pharmaceutical manufacturing. The guideline can be referred to the local regulatory agencies where the pharmaceutical manufacturer is located. Two regulatory entities in the world including the Therapeutic Goods Administration

(TGA) and the European Medicines Agency (EMA), have some similar concepts to support GMP implementation such as in product types regulated, and also in MRA and MOU utilisation. TGA and EMA may have some differences in the registration process, the legal status of guideline, and authorisation process of the manufacturer. Thus, it is necessary for pharmaceutical manufacturer who wants to operate in related countries to analyse the GMP requirement which is applied in the marketed countries

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