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Review Article

Bridging the Gap: Aligning GMP Requirements for Generic Manufacturing across the US, EU and Japan

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ABSTRACT

Medications that are no longer covered by a patent and that are made by companies other than the original inventor are known as generics. In recent years, the use of generic medications has grown, principally as a cost-cutting tool in the delivery of healthcare. The typical price difference between generic and brand-name medications is 20 to 90%. The principal objective of laws governing pharmaceuticals in the US, Europe, and Japan is to protect public health. Good Manufacturing Practice (GMP) requirements in the United States, European Union, and Japan are designed to ensure that products are consistently produced and controlled according to quality standards. In the US, GMP regulations are enforced by the Food and Drug Administration (FDA). The EU has GMP guidelines that are enforced by national authorities, and Japan has its own GMP regulations that are enforced by the Ministry of Health, Labor, and Welfare. These regulations cover a wide range of areas including facilities, equipment, production processes and record keeping, which are put in place to ensure product quality and safety. Adhering to GMP requirements is essential for ensuring that products are manufactured to the highest standards and meet the expectations of consumers and regulatory authorities. Overall, the GMP requirements in these regions play a vital role in maintaining the safety and quality of products and are crucial for the pharmaceutical and food industries.

Keywords: Generics, Good Manufacturing Practice, European Union, Japan, United States.

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INTRODUCTION

The government enforces a number of laws and regulations in the pharmaceutical sector to safeguard the public's health and welfare. This makes it one of the highly regulated industries. Since the health care system depends on drug regulatory affairs to make safe and effective medications available to patients, it is regulatory affairs' duty to ensure the safety, efficacy, and quality of medications throughout the entire lifecycle of the product and is predictable to carry out its duties impartially.[1]

The regulatory agencies' responsibilities extend to the manufacturing, distribution, and promotion of medications in addition to the regulation and oversight of their use. Making sure that pharmaceutical products are developed in accordance with that nation's regulatory requirements is one of the main challenges. Evaluation of crucial parameters during product development is a part of this regulatory procedure.[2]

A generic drug is characterized as a pharmaceutical product that is comparable to a reference (brand) listed pharmaceutical product in terms of dosage form, strength, administration route, quality and use intended.[3]

The manufacturer's name and the drug's adopted name (non-proprietary name) are both listed on the labels of generic medications.

The same active components from the original formulation must be present in generic medicine. The innovator drug's strict standards apply to the generic version as well. The same in terms of potency, dosage form, and method of administration of the innovator medicine; the same active components; the same use indications; and bioequivalence.[4]

There are microorganisms everywhere in the atmosphere, including bacteria, viruses, protozoans, fungi, and others. What if a few dangerous bacterial cells get into the production process for tablets or the packaging for devices? A chemical substance's

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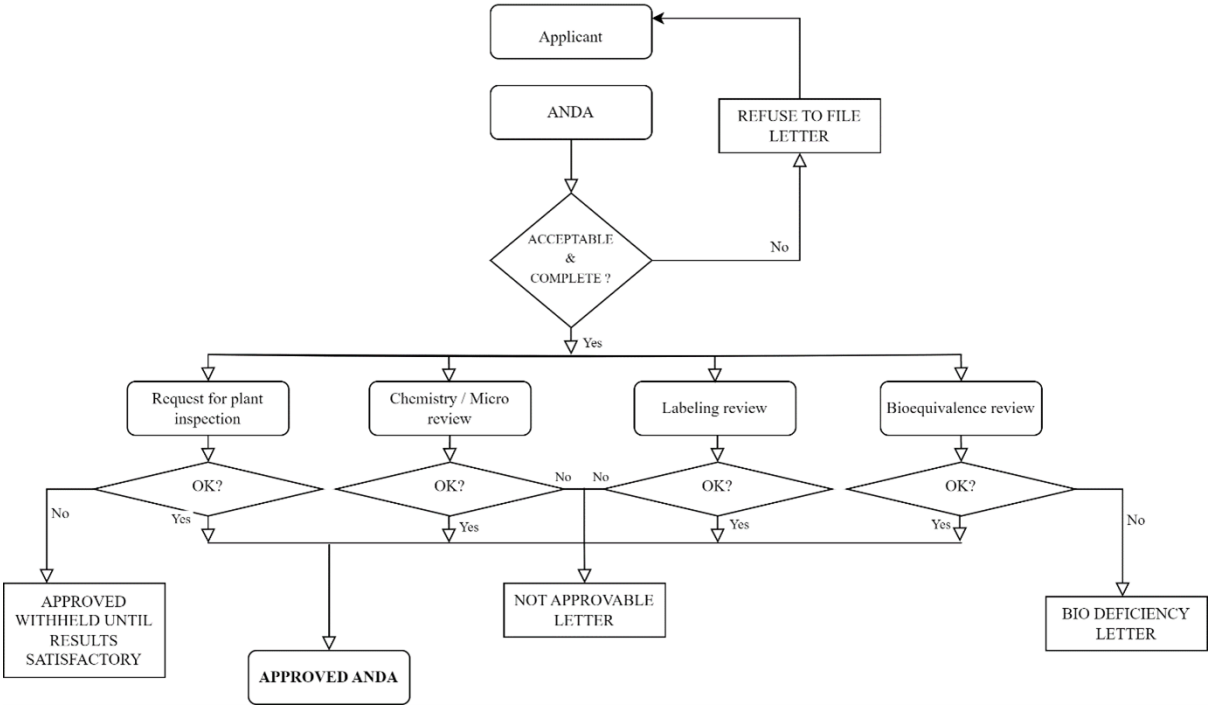

Figure 1: Generic Drug Review Process.

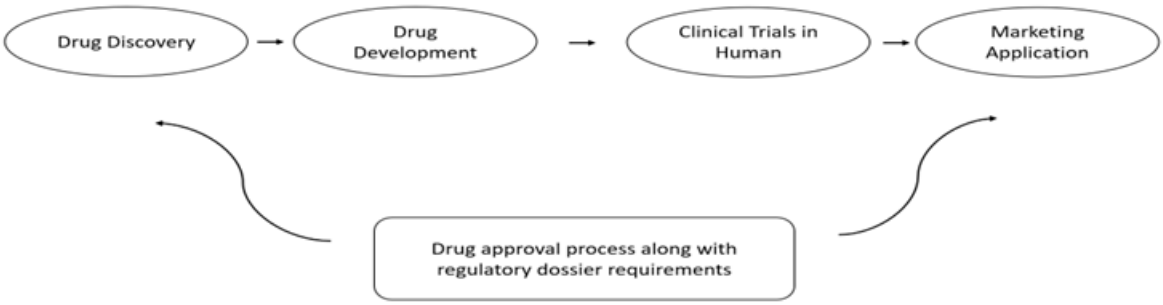

Figure 2: Drug approval process in EU.

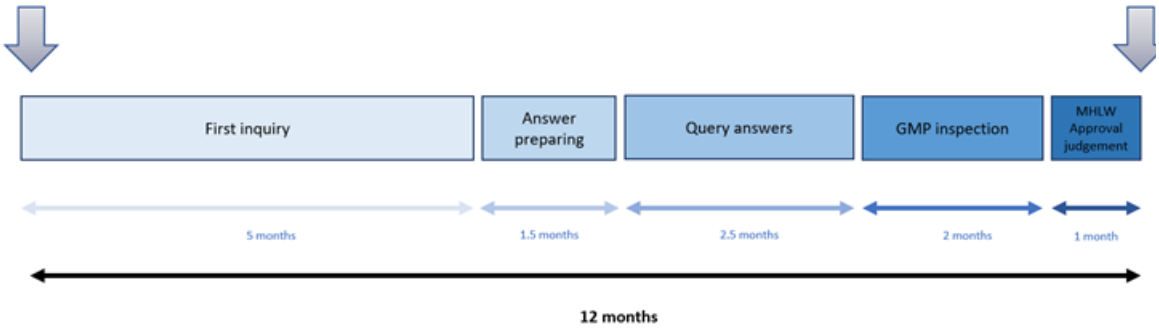

Figure 3: Generic drug application process.

concentration can vary slightly and cause a distinct reaction. What if that cough syrup included a few milliliters of a dangerous chemical? By giving contaminated medicine to thousands of unwitting people who believe it would treat their illnesses, one can endanger their lives. Such a mistaken action might force the government to close down production facilities. The FDA has implemented a rule known as GMP to ensure that a situation like this never happens. To ensure that the final consumer receives the product in the safest and purest form possible, The GMP rules and principles are a set of legal requirements for quality and purity that must be followed from the procurement of raw materials from production to packaging of API, devices, and other products. The pharmaceutical, food, and biotech industries are required by the laws of more than a hundred nations to abide with GMP standards and norms. They all still operate under the same basic principles.[5]

The quality of product manufactured is heavily regulated since it can have a severe impact on consumer and even environmental health. A product that does not adhere to GMP rules can have deadly effects on users because to issues with cleanliness, temperature control, cross-contamination, and adulteration at any stage of the production process.[6]

DISCUSSION

Many manufacturers all around the world adhere to GMP, which is required by their individual national governments, in order to control the manufacturing, verification, and validation of manufactured goods and guarantee its efficacy and safety for market distribution. For instance, the US FDA enforces GMP in the country through current Good Manufacturing Practices (cGMP), which applies to a wider range of industries, including those producing food, medical devices, cosmetics, and prescription medications. To determine if a manufacturing company complies with cGMP rules, the FDA performs facility inspections. FDA recalls all items if any severe breaches are discovered during the inspection, which is troublesome for manufacturers in terms of both revenue and operational efficiency.[7]

An effective manufacturing process may be implemented with the support of GMP guidelines, which are a set of principles that guarantee quality is ingrained throughout the business and the procedures involved. GMP regulations are typically forgiving, and each nation has its own legislation that must adhere to its own GMP principles and regulations. However, practically all rules are drawn from the fundamental idea and principles that are:[6]

1. Management of Quality.

2. Hygiene and Sanitation.

3. Building and facilities/premises.

4. Raw materials.

5. Equipment.

6. Validation and qualification.

7. Personnel.

8. Complaints.

9. Documentation and recordkeeping.

10. Inspections and quality audits.

GMP compliance rules have been established to improve the safety of manufactured items, particularly pharmaceutical products, and to guarantee that customers receive the best quality products. GMP compliance not only improves the standing of manufacturing firms but also lessens batch recalls and consumer complaints. You can take the following actions to maintain GMP compliance:[8]

1. Quality team.

2. Validation.

3. Surprise Audits.

4. Compliance Training.

The most effective strategy to guarantee GMP compliance is to provide workers with compliance training. Improve processes or systems to keep standards GMP-compliant while assisting personnel in better understanding GMP. To reduce errors and ensure compliance, all personnel should get training on recordkeeping, cleanliness, right equipment handling and labeling, and SOPs.[6]

GMP requirements for manufacturing of generics in US

GMP requirements for the manufacturing of generic drugs in the United States are set by the Food and Drug Administration (FDA). These requirements are outlined in the Code of Federal Regulations (CFR) Title 21, Part 210 and 211.[9]

The GMP requirements for generic drug manufacturers in the US include:

1. Proper design, construction, and maintenance of facilities and equipment.

2. Adequate controls for raw materials, packaging, and labeling materials.

3. Proper production and process controls.

4. Adequate laboratory controls to ensure the identity, strength, quality, and purity of the finished product.

5. Adequate complaint handling, record keeping, and documentation.

6. In charge of approving or rejecting all parts, drug product containers, closures, packaging material, labels, etc. is the quality control unit.

7. FDA conducts regular inspections of manufacturing facilities to ensure compliance with GMP regulations. Generic drug manufacturers in the US are also required to submit an Abbreviated New Drug Application (ANDA) to the FDA, which must demonstrate that the generic product is the same as the reference listed drug (brand-name drug) in terms of safety, efficacy, and quality.

It's important to note that the GMP regulations are subject to change, and companies are responsible for ensuring compliance with the most current version of the regulations.[4]

Regulatory process for manufacturing generics in US

The regulatory process for manufacturing generic drugs in the United States is governed by the Food and Drug Administration (FDA). The process involves the submission of an Abbreviated New Drug Application (ANDA) to the FDA, which must demonstrate that the generic product is the same as the reference listed drug (brand-name drug) in terms of efficacy, safety and quality.[10]

The ANDA process includes the following steps (Figure 1).

Step 1: File an ANDA: The generic drug manufacturer submits an ANDA to the FDA, which includes information on the proposed generic drug, including its chemical and biological properties, as well as its proposed labeling.

Step 2: Review by the FDA: The FDA reviews the ANDA to ensure that the proposed generic drug is the same as the reference listed drug in terms of efficacy, safety and quality. The FDA also conducts inspections to ensure compliance with GMPs of the manufacturing facilities.

Step 3: Approval: If the FDA determines that the proposed generic drug meets all requirements, it will approve the ANDA.

Step 4: Post-approval: After the ANDA is approved, the FDA may conduct additional inspections of the manufacturing facilities to ensure ongoing compliance with GMPs.

It's important to note that the ANDA process is subject to change, and companies are responsible for ensuring compliance with the most current version of the regulations.[6]

It's also important to point out that the ANDA holder must comply with the Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act) and must certify that their generic drug product does not infringe any validly held patents on the RLD.

In addition, FDA has the authority to require additional studies or testing for generic drugs, particularly for complex drug products or for products for which there are limited data available on safety and efficacy.[7]

Generic Drugs Dossier Submission Requirements in United States

Information from bioavailability and bioequivalence studies is essential for the approval of generic drugs. Generic drug manufacturers are mandatory to submit an Abbreviated New Drug Submission (ANDS), and they are also required to demonstrate that their product is bioequivalent to the "Canadian Reference Product" (CRP). These requirements cover both the drug filing and various aspects of obtaining United States Food and Drug Administration (USFDA) approval for a drug to obtain Marketing Authorization in the US and Canada, as well as their useful role in enhancing the standards set by them. The ANDA filling of the approval procedure requires sufficient information on the drug's safety and effectiveness in humans. All ICH nations adopt the Common Technical Document (CTD), which offers a uniform format for submissions.[11]

FDA regularly monitors medication manufacturers' compliance with its current Good Manufacturing Practice (cGMP) requirements to assure the quality of drug products. The minimal standards for the processes, settings, and controls utilized in the creation, processing, and packaging of a drug product are laid forth in the cGMP laws for pharmaceuticals. The rules ensure that a product is safe to use, that it has the components and strength it purports to have, and that it is labeled accurately.[12]

An examination of the manufacturer's adherence to the cGMPs is part of the approval process for new and generic drug marketing applications. Assessors and investigators from the FDA decide if the company has the facilities, tools, and capacity to produce the medication it proposes to market.[13]

The regulations outline the standards that drug producers, applicants, and the FDA must meet in order for the regulatory process to be understood by all parties such as 21 CFR Part 314, Part 210, Part 211, Part 212, Part 600.[14]

GMP requirements for manufacturing of generics in European Union

GMP requirements for the manufacturing of generic drugs in the European Union are set by the European Medicines Agency (EMA) and are outlined in the EU GMP Guidelines. These guidelines apply to all stages of the manufacturing process, including the quality control of active substances and finished products, as well as the control of facilities and equipment used in the manufacturing process.[15]

The EU GMP requirements for generic drug manufacturers include:

1. Proper design, construction, and maintenance of facilities and equipment.

2. Adequate controls for raw materials, packaging, and labeling materials.

3. Proper production and process controls.

4. Adequate laboratory controls to ensure the identity, strength, quality, and purity of the finished product.

5. Adequate complaint handling, record keeping, and documentation.

6. All parts, drug product containers, closures, packaging material, labels, etc. must be approved or rejected by the quality control unit.

7. Properly trained personnel and appropriate documentation.

8. Adequate self-inspection and self-auditing.

9. Compliance with the principles of Good Distribution Practice (GDP) if products are intended for wholesale distribution.

The EU GMP guidelines are regularly updated and are subject to change, and companies are responsible for ensuring compliance with the most current version of the guidelines. Compliance with EU GMP is verified through regular inspections by the national competent authorities of the member state where the manufacturer is located.[16]

It's important to note that EU GMP requirements are also applied to the API (Active Pharmaceutical Ingredient) manufacturers, which supply the raw materials for the finished products.

Regulatory process for manufacturing generics in Europe Union

European Medicinal Agency (EMA) is a decentralized European Union agency that was based in London before to the United Kingdom's vote to leave the EU but moved to Amsterdam in March 2019. The Agency's responsibilities include scientific review and assessment of pharmaceutical company-developed medicines as well as requests for European MA for both human and animal medications. Applicant submits a single MA application to the Agency under consolidated method. Centralized MA license is valid throughout all EU and EEA-EFTA states once it is given by the European Commission (Iceland, Liechtenstein and Norway).[17]

In EU, process for drug approval is referred to as regulatory procedure for obtaining authorization to sell a medical product on the market. This activity comprises many stages: submitting an application for review in order to perform clinical and conducting trials, and finally submitting a request for drug MA and post-observation research. Submits a dossier to the agency review in order to apply Marketing Authorization (MA). The file is completed using the appropriate regulatory method. Individually country has itself drug authority, that is in charge of implementing the laws, regulations, and standards that applicants must follow. The regulation of medication marketing is managed in this way. Figure 2 depicts the agency's regulatory procedure.[18]

Described MA as process of reviewing, analyzing a file supporting pharmaceutical product in light of marketing necessities, issuing a finished file. In European Union, the MA application referred to as MAA. For MA grant, agency supervises Efficacy, Quality and Safety. A pharmaceutical medicine sold in European Union after MA. It can be given by:

a) Member State's responsible authority or

b) Commission for entire EU.[19]

Manufacturers will want to release generic versions of their products onto the market whenever a new drug's patent expires, in order to sell their products. Preclinical and clinical data not required when applicant can establish bioequivalence with authorized RLD (generic).

The regulatory process involves the submission of a Marketing Authorization Application (MAA) to the EMA, which must demonstrate that the generic product is the same as the reference product in conditions of safety, efficacy, quality.[20]

The MAA process includes the following steps:

Step 1: File a MAA: The generic drug manufacturer submits a MAA to the EMA, which includes information on the proposed generic drug, including its chemical and biological properties, as well as its proposed labeling.

Step 2: Review by the EMA: The EMA reviews the MAA to ensure that proposed generic drug is the same as the reference in conditions of safety, efficacy, quality. The EMA also review the compliance with GMPs and Good Distribution Practice (GDP) guidelines.

Step 3: Approval: If the EMA determines that the proposed generic drug meets all requirements, it will issue a centralized marketing authorization for the EU.

Step 4: Post-approval: After the MAA is approved, the EMA and national competent authorities of the member states may conduct additional inspections of the manufacturing facilities and wholesale distributors to ensure ongoing compliance with GMPs and GDP.

It's important to note that the MAA process is subject to change, and companies are responsible for ensuring compliance with the most current version of the regulations.

It's also important to point out that the MAA holder must comply with the EU legislation on generic medicines, which include the Regulation 726/2004 and Directive 2001/83/EC. These legislations establish the requirement for a generic product to be bioequivalent to the reference product and for the generic product to have the same quality, safety and efficacy as the reference product.

In addition, the EMA has the authority to require additional studies or testing for generic drugs, particularly for complex drug

products or for products for which there are limited data available on safety and efficacy.[20]

GMP requirements for manufacturing of generics in Japan

Good Manufacturing Practice (GPM) requirements for the manufacturing of generic drugs in Japan are similar to those in the European Union and the United States. These requirements are set by the Japanese Ministry of Health, Labor and Welfare (MHLW) and also the Pharmaceuticals and Medical Devices Agency (PMDA). They include strict standards for facilities, equipment, production processes, and quality control, as well as regular inspections to ensure compliance. Generic drug manufacturers in Japan must also comply with the requirements of the Japan Pharmaceutical Manufacturers Association (JPMA).[21]

Regulatory process for manufacturing generics in Japan

The regulatory process involves the submission of a Generic Drug Application (GDA) to the PMDA, which must demonstrate that the generic product is the same as the reference product in terms of safety, efficacy, and quality.[21]

The GDA process includes the following steps:

Step 1: File a GDA: The generic drug manufacturer submits a GDA to the PMDA, which includes information on the proposed generic drug, including its chemical and biological properties, as well as its proposed labeling.

Step 2: Review by the PMDA: The PMDA reviews the GDA to ensure that the proposed generic drug is the same as the reference product in terms of safety, efficacy, and quality. The PMDA also review the compliance with Good Manufacturing Practices (GMPs) guidelines.

Step 3: Approval: If the PMDA determines that the proposed generic drug meets all requirements, it will approve the GDA and issue a manufacturing and sales authorization.

Step 4: Post-approval: After the GDA is approved, the PMDA may conduct additional inspections of the manufacturing facilities to ensure ongoing compliance with GMPs.[22]

It's important to note that the GDA process is subject to change, and companies are responsible for ensuring compliance with the most current version of the regulations.

It's also important to point out that the GDA holder must comply with the Japanese regulations on generic medicines, which include the "Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices" and the "Ordinance for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices". These regulations establish the requirement for a generic product to be bioequivalent to the reference product and for the generic product to have the same quality, safety and efficacy as the reference product.

In addition, the PMDA has the authority to require additional studies or testing for generic drugs, particularly for complex drug products or for products for which there are limited data available on safety and efficacy.[23]

Requirements for Generic Drugs Dossier Submission in Japan

The drug product may submit an application as a novel drug rather than a generic drug if it has an API that differs from the original medication's salts, esters, and ethers. At the time of approval, the original medications are granted an 8-year period for re-examination. After the term for original pharmaceuticals' re-examination, the applicant may submit an application for generic medications. The development costs of generic pharmaceuticals are lower than those of original drugs since they are approved following in Japan that the original drugs patent expiration and period of re-examination. As a result, the price of a generic drug is lower than that of an original drug. For instance, in Japan, the cost of a generic medication is typically 60% of the cost of the brand-name medication.[24] Recently, there has been an upsurge in desire for lower medical costs in various nations, including Japan, Europe and US.[25,26] In Japan, there are currently over 20% of people over the age of 65, and by 2050, that number is expected to rise to about 40%.[27] This is a significant contributor to Japan's rising healthcare costs. In order to save healthcare expenses, the MHLW suggested using generic medications in 2007. Particularly, the market share of generic pharmaceuticals in Japan was lower than that of other developed nations, coming in at 18.7% in 2007.[28] Comparatively, the market share of generic medications in the USA, England, and Germany was 72%, 65%, and 63%, respectively.[29]

There was no right of substitution for pharmacists, which may be one factor in the low market share of generic drugs in Japan. Prior to 2006, doctors had the authority to choose between using brand-name drugs or generic versions. One significant reform to public health insurance in 2006 was the grant of the pharmacists' ability to substitute generic medications for brand-name medications provided the doctors expressly permit substitution on their prescription format. Prior to 2008, the prescription structure was such that the pharmacists were unable to switch to generic medications unless the doctors signed in the "substitution" box on the prescription. In 2008, the format of the prescription was altered to read "No substitutes" rather than "Substitutions." Pharmacists have the right to substitute generic medications if there isn't a checkmark in the "No substitutions" box on the prescription. There is a space for a signature in this prescription format "in case all prescription pharmaceuticals cannot be changed to generic drug." All prescription medications required a doctor's signature and could not be substituted. The

prescription format was changed in 2012 to one that permitted generic substitution for each drug, making it simpler to switch to generic medications. To encourage the use of generic medications, Japan is taking a variety of steps, such as changing the prescription format.[28] In addition, the MHLW set a 5-year strategy in 2013 to increase the use of generic medications to above 60% by 2018.[28,30]Accelerated approval review for generic drugs is essential to promoting the use of those medications.

The approval review of generic medications in Japan is handled by the Office of Generic Drugs, a division of PMDA. Based on a document provided by generic drug applicants, the PMDA evaluates the quality, efficacy, and safety of generic and brand-name medications in comparison to one another.[31]

Contrarily, only documents pertaining to specifications, test procedures, accelerated testing, and Bioequivalence (BE) studies are needed when applying for a generic medicine. It may also be necessary to provide the results of long-term storage tests if the drug stability cannot be inferred merely from the initial medication. The way that is generally acknowledged to show therapeutic equivalence between brand-name and generic medicine is through BE studies. The Bioavailability (BA) of brand-name and generic drugs is compared in BE research. The rate and volume of an active ingredient's or metabolite's absorption from a drug product are referred to as BA.[32]

In Japan, the approval of new generic medications and partial changes requires two different forms of application. Applications for brand-new generic drugs are submitted first, followed by applications for post-approval alterations that are only partial changes. In Japan, the approval content contains the brand name, the formulation or manufacturing site, the manufacturing technique, the effects, the directions, the dose, the specifications, the test methods, the storage methods, the validity term, and the indication. For partial change approval, the PMDA review is required if the generic medicine applicant makes changes to these contents after approval, with the exception of minor adjustments. Numbers for applications and approvals include both newly developed generic medications as well as those with brand name changes for already approved generic medications. About 1000–1900 generic pharmaceuticals are proposed and authorized yearly, with specific figures varying by fiscal year. New generic medication approval peaked in the Fiscal Year (FY) 2011 and has since declined. However, the number of partial change requests and approvals has grown annually, with partial change requests made and 2066 partial change requests accepted in FY2013.[24]

The entire process, from application to approval, for new generic drugs typically takes 12 months (Figure 3).

The National Health Insurance Drug Price List is updated yearly twice, that is in June and December, which results in the approval of new generic medications in February and August. 9 months are allotted for the application review process, while the final 3 months are used for MHLW approval processes and GMP inspections. An application for drug authorization must first be made by the generic medication applicant. Within five months of receiving the application, the PMDA evaluates the submission dossier and notifies applicant of the results of the first inquiry. Within 1.5 months, the applicant must reply to the PMDA's enquiry. During the inquiry, there may be three to four exchanges of emails between the PMDA and the petitioner. As opposed to this, the length of time required to consider an application for approval of a partial change varies depending on its content.[28]

CONCLUSION

The global pharmaceutical market is expanding quickly, yet each country has a different regulatory profile. In the US, Europe, and Japan, laws governing drugs are primarily focused on safeguarding the public's health. The duty of ensuring that pharmaceutical companies adhere to the law falls on public regulatory organizations. Pharmaceuticals must be developed, tested, trialled, and manufactured in line with laws that are in place to guarantee patient safety and well-being. According to studies, there are significant differences between the GMP that regulatory agencies utilize. For this reason, it is crucial to harmonize GMP in accordance with contemporary, internationally acceptable quality standards founded on cutting-edge science, as doing so will be favorable for both enterprises and patients. Since pharmaceutical businesses wouldn't be obligated to follow the laws set by the State in which they intended to create a product, patients would benefit from high-quality pharmaceuticals regardless of where they were made.

Many of the time industry fails to comply with the lack of uniformity in international GMP for the product which results in the health risk of the people. To avoid this, industry should follow proper regulation and GMP requirement for the manufacture of the product which helps in the safety and efficacy.

GMP requirements in the United States, European Union, and Japan are designed in order to guarantee that goods are continually produced and controlled in accordance with quality standards. In the US, GMP regulations are enforced by the Food and Drug Administration (FDA). The EU has GMP guidelines that are enforced by national authorities, and Japan has its own GMP regulations that are enforced by the Ministry of Health, Labor, and Welfare. These regulations cover a wide range of areas including facilities, equipment, production processes and record keeping, which are put in place to ensure product quality and safety. Adhering to GMP requirements is essential for ensuring that products are manufactured to the highest standards and meet the expectations of consumers and regulatory authorities. Overall, the GMP requirements in these regions play a vital role in maintaining the safety and quality of products and are crucial for the pharmaceutical and food industries.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVATIONS

ANDA: Abbreviated New Drug Application; **ANDS:** Abbreviated New Drug Submission; **BA:** Bioavailability; **BE:** Bioequivalence; **CRP:** Canadian Reference Product; **CFR:** Code of Federal Regulations; **Cgmp:** Current Good Manufacturing Practices; **EEA-EFTA:** European Economic Area-European Free Trade Association; **EMA:** European Medicines Agency; **EU:** European Union; **FDA:** Food and Drug Administration; **GDP:** Good Distribution Practice; **GDA:** Generic Drug Application; **GMP:** Good Manufacturing Practice; **JPMA:** Japan Pharmaceutical Manufacturers Association; **MA:** Marketing Authorization; **MAA:** Marketing Authorization Application; **MHLW:** Ministry of Health, Labor and Welfare; **PMDA:** Pharmaceuticals and Medical Devices Agency; **RLD:** Reference Listed Drugs; **SOPs:** Standard Operating Procedures; **US:** United States; **USFDA:** United States Food and Drug Administration.

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