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Comparative Study of Regulatory Requirement for ANDA Submission in US and JAPAN

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ABSTRACT

Most developed nations require drug manufacturer to prove that their formulations are bioequivalent to their brand name counterparts. Bioequivalence does not mean generic drugs must be exactly the same as the brand name product, chemical differences may exist

Hatch Waxman act, standardized procedures for recognition of generic drugs. Before a company can market a generic drug, it needs to file an abbreviated new drug application (ANDA) with the food and drug administration. These products cannot be entirely identical because of batch-to-batch variability and their biological nature, and they are subject to extra rules. FDA also recognizes drugs that use the same ingredients with different bioavailability and divides them into therapeutic equivalence groups.

Each year, drug makers lose exclusivity for popular medicines, forcing them to constantly research and launch new drugs to stay afloat. The FDAs purpose is to promote international harmonization of technical and scientific standards for generic medicine development.

According to precedence research, the global generic drugs market was worth $390.57 billion in 2020 and is projected to reach approximately $574.63 billion by 2030, attaining a compound annual growth rate (CAGR) of 5.59 percent between 2021 and 2030. Generic cost around 40 to 60 percent less, and you get the same strength, dosage and quality of medication.

Generic drug approval review in Japan is conducted by the pharmaceuticals and medical devices agency (PMDA), which reviews the equivalence of the original drugs. The original drugs are given the reexamination period of 8 years at the time of approval. The applicant can apply for the generic drugs after the reexamination period of original drugs.

To manufacture and market generic drugs, unlike the original drug, there is no need to conduct clinical trials to verify efficacy and safety of the active ingredients.

Keywords: abbreviated new drug application, generic drug application, USFDA, PMDA, office of generic drug, CTD Modules.

Introduction:

A pharmaceutical medication product with the same chemical composition as branded pharmaceuticals. These are known as generic medications, and they are authorized to be sold once the patents on branded drugs have expired. The active component in a generic medicine must be the same as in the original brand name formulation.

The FDA does not allow generic pharmaceuticals to look exactly like brand-name drug already on the market in the United States. As a result, the generic drug's color and form may differ from the brand name.

The key regulatory basis for generic medicine approval in the European Union and the United States is bioequivalence. The Hatch Waxman Act of 1984 established a balance to assure generic medication market access in the United States and the world. (1)

According to the Hatch Waxman Act, generic medicine applicants must include certification for each patent mentioned in the orange book for innovator drugs in their application.

If a generic drug manufacturer confirms 1 and 2, the FDA will immediately begin processing the generic ANDA.

Paragraph 2: the patent has already passed its expiration date

Paragraph 3: The generic drug will not be available until the patent expires. If a generic drug producer verifies 3, the FDA will begin processing the ANDA and grant approval when the patent expires. (2)

ANDA files tell the patent proprietor within 20 days if the patent is not infringed or invalid. Within 45 days, the patent holder must sue for infringement. FDA must stop clearance for 30 months if the patent holder sues (one time only). FDA may approve ANDA at any moment if the patent holder does not sue.

Because they do not have to redo animal and clinical tests, generic medicines are less expensive than their brand-name counterparts. The cost of a generic drug might be up to 85% less than that of a brand-name drug.

Aim:

COMPARATIVE STUDY OF REGULATORY REQUIREMENT FOR ANDA SUBMISSION IN US AND JAPAN

Objective:

a) Comparison of generic drug approval process between US and JAPAN.
b) How ANDA helps to grant permission for manufacturing and exporting of generic drug in USA
c) PMDA application is used for the generic drug approval process in JAPAN
d) US and JAPAN both are regulated markets for the pharmaceutical sector this study help to understand market overview of generic drug and all the appropriate requirement.
e) This study provide clear vision to understand the whole submission process and maintain harmonization.

Need:

1. Generic drug accounted for more than 88% of prescriptions filled in the United States. India is also the largest provider of generic drugs globally. Japan represents the worlds eight biggest market for generic drugs in terms of value.

2. ANDA filing process is challenging procedure therefore there is need to conduct the comparative study of regulatory requirement for US and JAPAN.

3. The study will give you the detailed information regarding the application for generic drug, its regulation from different countries and how the application file with them.

4. The process of generic drug is vast process within itself. This study might clear all your aspect in relation with ANDA and PMDA study.

5. There was no study conducted so I have decided to work on this as these two are major countries for generic market.

Plan of Work;

1. Pharmaceutical companies must submit Abbreviated New Drug Applications (ANDA) to FDA's Office of Generic Drugs (OGD) and receive FDA's approval before marketing new generic drugs.
2. Collecting all data from the respective regulatory authority official website.
3. Do comprehensive study of generic drug submission process in US and Japan.
4. Going through the official guidelines for ANDA filling in US and Japan.
5. Summary of the project.
6. Doing comparative study of it.
7. Coming to the conclusion about the comparison of the ANDA study .
8. Lastly adding the references.

Literature Review:

1. **Department of Health and Human Services, Office of Inspector General- The Food and Drug Administration's Generic Drug Review Process by Daniel R. Levinson Inspector General. June 2008 OEI-04-07-00280**- A generic drug is the same as a reference-listed (i.e., brand name) drug with respect to conditions of use, active ingredient(s), route of administration, dosage form, strength, and labeling. In addition, the generic drug must be bioequivalent to (i.e., perform in the same manner as) the brand name drug. A generic drug that is therapeutically equivalent is expected to have the same clinical effect and safety profile as the brand name drug when administered under the conditions specified in the labeling. If generic drugs are determined to be therapeutically equivalent, physicians and pharmacists can substitute them for brand name drugs. Generic drug applications are referred to as Abbreviated New Drug Applications (ANDA). Pharmaceutical companies must submit ANDAs and receive FDA's approval before marketing new generic drugs.

2. **ANDA Submission- Content and format Guidance for Industry, US Department of Health Services Food and Drug Administration, (CDER), (CBER) September 2018, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm** This guidance is intended to assist applicants in preparing abbreviated new drug applications (ANDAs) for submission to FDA under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)).

3. **A Review on Drug Approval Process for US, Europe and India, Prajapati Vishal- International Journal of Drug Regulatory affairs, 2014, 2(1), 1-11. ISSN: 2321-6794. www.ijdra.com-** Developing a new drug requires great amount of research work in chemistry, manufacturing, controls, preclinical science and clinical trials. Drug reviewers in regulatory agencies around the world bear the responsibility of evaluating whether the research data support the safety, effectiveness and quality control of a new drug product to serve the public health. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs. This article focuses on drug approval process in different countries like USA, Europe and India.

4. **A comparative Study of the Drug Approval Process in US, INDIA, JAPAN AND EUROPE- Akhilesh Chandra, Department of Pharmaceutics, Delhi. World Journal of Pharmaceutical Research, vol 6, issue 1, ISSN: 2277-7105-** Safety and efficacy of a drug product for use in humans is essential before the drug product can be approved for import or manufacturing a new drug. For this every country has its regulatory authority that bears the responsibility of evaluating whether the research data of new drug/product supports the safety and efficacy to serve public health. Regulatory affair department of a company plays a vital role of working in accordance to the rules, regulations and guidelines established by the regulating agencies of different countries.

This article aims to compare different aspects of drug approval process in USA, Europe, India and Japan.

5. **Japan Drug Regulatory Overview 2014, Pacific Bridge Medical, 7315 Wisconsin Avenue, Suit 609E, Bethesda, MD 20814, www.pacificbridgemedical.com**

6. **Generic Drug in Global Market and Regulatory Environment- Pankaj Kumar, Department of Pharmaceutics, New Delhi. Indo American Journal of Pharmaceutical Sciences. ISSN: 2349-7750. http://www.iajps.com-** Different regulatory authorities regulate the drug development in various countries of the world. Various Regulatory authority for generic drug application Food and Drug Administration (FDA), European Medicines Agency (EMA), Pharmaceutical and Medical Devices Agency (PMDA), Health Product and Food Branch (HPFB) Central Drug Standard of Organization (CDSO). Generic manufacturers may file an abbreviated New Drug Application (ANDA) that incorporates the safety/effectiveness data submitted by original innovator drug manufacturer and adds only bioequivalence studies. Therefore, it is very difficult and challenging task to approve a drug by the manufacturing companies, simultaneously submitted in all the regulatory authorities. Regulatory authorities are responsible to ensure the quality, safety, and efficacy including manufacturing, distribution of the drug product. There is lot of challenges for the pharmaceutical industry to development and filling of generic drug application, which can be overcoming by the common format of submission. This is due to the different regulatory procedure of the various countries. Through the international conference on harmonization (ICH) process common technical documents (CTD) has been developed for USA, EU, JAPAN, INDIA AND CANADA. There are few differences in the dossier submission for among these five regions. To development of any generic drug product still we need strategic planning by these regulatory authorities.

7. **Comparison of Generic Drug Reviews for Marketing Authorization between Japan and Canada- Ryosuke Kuribayashi, Original Research Article, 2 June 2017**- Purpose Generic drugs are assuming an increasingly important role in sustaining modern healthcare systems, as the cost of healthcare, including drug usage, is gradually expanding around the world. To date, published articles comparing generic drug reviews between different countries are scarce.

8. **Comparison of Generic Drug Application and their Approval Process in US, Europe and Japan. Jawahar. N. Jawahar. N et al/J.Pharm. Sci & Res, Vol. 10(3), 2018, 523-527. Journal of Pharmaceutical Science and Research. ISSN: 0975-1459-** www.jpsr.pharmainfo.in. Abbreviated new drug application (ANDA) can be filed to the regulatory authorities, to get generic drug approval. Under section 505(j) of Hatch-Waxman act, an abbreviated new drug application

may be filed for any generic versions of the reference listed drug. This study was conducted with an objective to compare the regulatory framework of generic drug application and their approval process in various countries like USA, EUROPE, and JAPAN. This study mainly emphasizes on the application form, approval timelines and sequence of steps in the generic drug approval.

ANDA REGULATION IN US.

In dosage form, strength, mode of administration, quality and performance feature, and intended purpose, a drug product that is comparable to a brand or reference listed drug product.

The drug price competition and patent term restoration act of 1984 (the Waxman act) created the grounds for allowing generic copies of drug items. If a judge decides that the patent is not infringed or invalid, FDA may proceed.

If the first generic ANDA is filed, the FDA will provide 180 days of exclusivity (per product) for ANDA submissions under section 505(j) of the federal food, drug, and cosmetic act (FD&C).

ANDA guidelines were developed in collaboration with CBER by the office of generic drugs at the Center for Drug Evaluation and Research.

An abbreviated new drug application (ANDA) is a document that is submitted to the FDA which has the information of generic drug has to be submitted for assessment and approval of a generic drug product.

Once granted, an application can produce and market generic drug products as a safe, effective, and less expensive alternative to the brand-name drug it refers to.

In terms of dosage form, strength, method of administration, its quality, performance characteristic, and intended application, a generic medication product is comparable to an innovator drug product.

The FDA authorized drug products with therapeutic equivalence evaluation orange book lists all approved medications, including innovator and generic.

Generic drug applications do not have to provide preclinical and clinical data to prove their safety and effectiveness, hence they are referred to as “abridge”.

Generic applicants must demonstrate scientifically that their product works in the same way as the innovator drug.

This bioequivalence demonstration gives the information on the rate of absorption and bioavailability of generic drugs, which can be compared to FDA-approved innovator drugs. The generic version must deliver the same number of active components into the bloodstream as the innovator drug in the same length of time. [1] [2]

Resources for ANDA Submission:

CDER can assist you in meeting these criteria as well as internal ANDA review concepts, policies, and procedures. ANDA form and submission requirements include summary tables, application forms, and other submission materials.

ANDA FORMS:

To commercialize a new biologic or antibiotic medicine for human use, fill out FDA Form 356h.

ANDA is employed when the patent on the innovator medicine has expired or is about to expire and the generic drug has a similar impact in terms of rate and extent of absorption.

It takes about ten years for an NCE (new chemical entity) to pass through three rounds of clinical trials and receive final FDA approval after filing an IND with the FDA.

It's important to remember that the generic producer is reliant on the innovator's safety and efficacy data. And it simply needs to show the FDA that its product is comparable to the innovators.

ANDA contains all of the information necessary by the FD&C Act's section 505(j) (2) (A). 505(j) application: new drug application includes information to show that the proposed product is identical by active ingredient, dosage form, strength, method of administration, labeling, quality, performance, characteristic, and intended use, as it is the condensed version of the generic application. for example: (1)

21CFR part 314: application for a new drug market by FDA

21CFR part314: Abbreviated application i.e., subpart C

314.92: drug product for which abbreviated application may be submitted

314.94: content and format of ANDA

314.96: amendment to an unapproved ANDA

314.97: supplements and other changes to an approved ANDA

314.99: Applicant’s other responsibilities of an ANDA

SUBPART D: FDA action on application and abbreviated application

314.100: timeframe for reviewing application and abbreviated application

314.101: filing NDA and receiving ANDA

314.105: approval of NDA and ANDA

314.107: date of approval of 505(j) (b) (2) application or ANDA

314.122: submitting an abbreviated application or a 505 (j) (2) (C) petition that depends on a no longer marketed listed medication

314.127: refuse to approve an ANDA application.

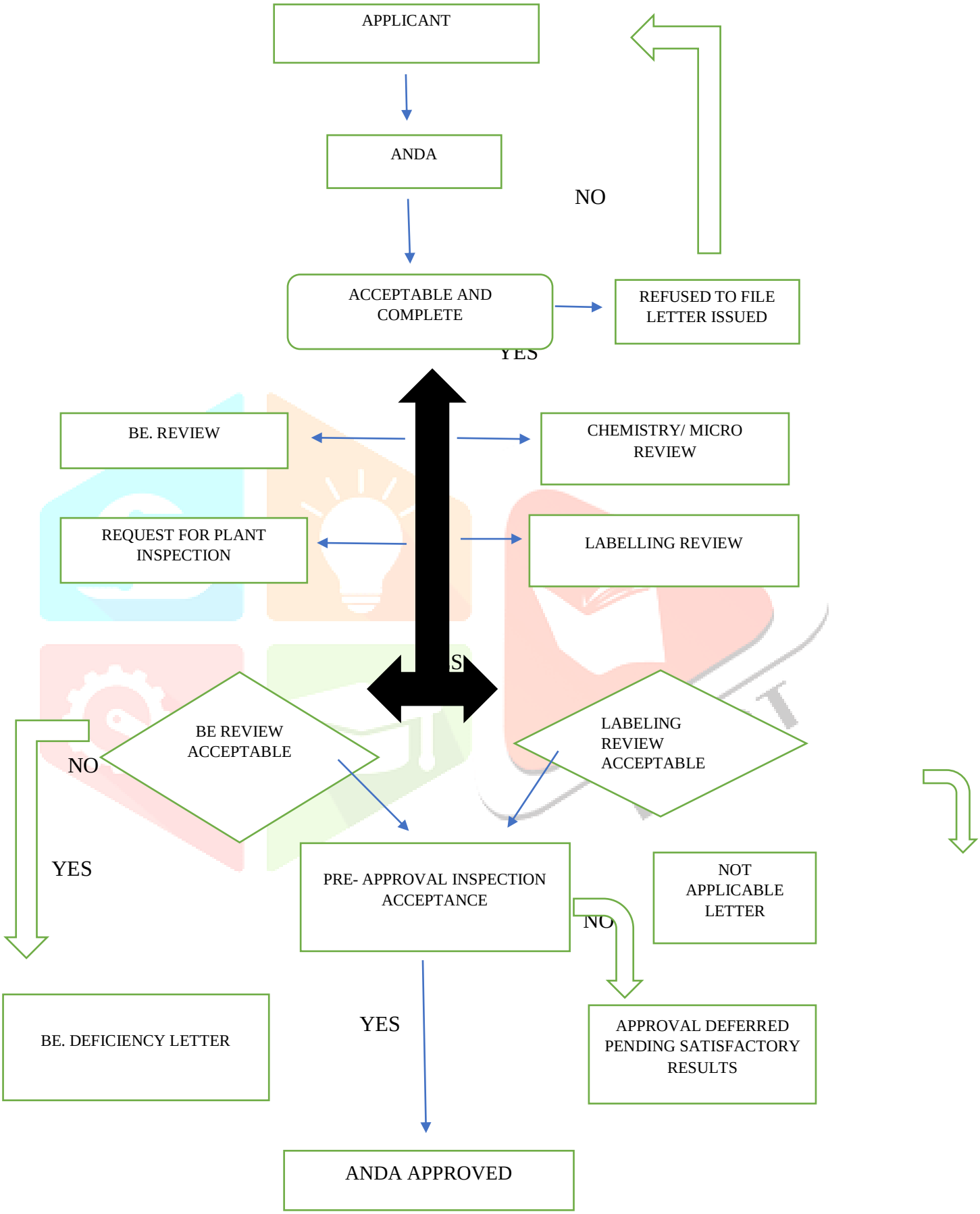
314.150: Removal of approval of an application or abbreviated application

314.151: Removal of approval of ANDA under section 505 (j) (5) of act

314.152: notice of withdrawal of approval of an application or abbreviated application for new drug

314.153: Approval of an abbreviated new drug application has been halted. 314.160: approval of an application or abbreviated application that had previously been denied, suspended, or withdrawn.

fig 1: ANDA Review Process



ANDA submission:

This guideline helps to assist applicants in preparing an abbreviated new drug application for submission to the FDA under section 505(j) of the Food and Drug Administration and Control Act (21 USC 355 j)

This information should be provided in each section of the CTD

- The guidance was developed by CDER's Office of Generic Drugs in collaboration with the Food and Drug Administration's CBER.
- In section 505(j) of the FD&C Act, the Drug Price Competition and Patent Term Restoration Act of 1948 established an abbreviated approval process for previously approved drug products.
- According to Section 505(j) of the FD&C Act and its implementing regulation, an ANDA must include information indicating that drug product and related RLD are identical in terms of active ingredients, dosage form, route of administration, strength, and labeling.
- The ANDA must contain enough evidence to show that the proposed product is bioequivalent to RLD.

  RLD is the FDA-designated drug product on which an applicant bases its ANDA 21CFR 314.3 submissions (b)

  “Listed drug” is an innovative drug product that is approved under section 505(C) or 505(j) of the food, drug, and cosmetic act. This listed drug should not have been withdrawn or suspended by section 505(e) (1) through (e) (5) or section 505(j) of the act. (1) (6)

CTD FORMAT:

- ICH has adopted the standard format like quality, safety, efficacy data which is collected by CTD. eCTD is the electronic regulatory submission format for ANDA. (1)

- CTD comprised of:

Module 1: administrative information and prescribing information
Module 2; summary data
Module 3: quality information
Module 4: nonclinical trails
Module 5: clinical trials

1 Module 1: Administrative Information

1. Forms and cover letter:

Section 1.1 –

- FDA Form 356(h)- application to market a new medicine, abbreviated new drug, or biologic for human use, which ANDA applicants must thoroughly complete and sign before submitting their application.
- Cover sheet for FDA Form 3794, generic medicine user fee
- Form 3674- certification of conformity with the requirements of the Clinical Trials Government Data Bank (42 USC section 282(j)) under 42 USC section 282(j) (5) (B).

Section 1.2

- Includes a cover letter. This guide includes a cover letter template. They make the following suggestions:

❖ A new strength of medication in solid oral dose form
❖ A change in concentration for a medicine in a parenteral dosage form
❖ To a parenteral dosage form drug product, a change in vial size, fill volume or package size (total drug content)
❖ An oral liquid, ophthalmic, otic, transdermal, or topical medicinal product's concentration changes.
❖ Any dosage form that has had its formulation changed.
❖ Section 1.2 contains copies of FDA restricted correspondence connected to meetings with applicants to discuss the development of generic drug products that are the subject of an ANDA, as well as (2) any copies of meeting minutes. [1]

2. Administrative information:

Section 1.3.1.2-

- Include a letter of appointment from a US agent. It is a distinct document that must be submitted in addition to the signatures of US agents on Form 356h if applicable.

Section 1.3.2-

- Certification of the field copy is included. The applicant should notify the appropriate office of regulatory affairs district office that their eCTD application will be sent to FDA in a letter. The medicine name, application number, FDA center, and FDA division that is reviewing the application should all be included in the letter.

Section 1.3.3-

- Includes the signed debarment certification mandated by the 1992 generic drug enforcement act.

- All convictions described in sections 306(k), 306(a), and 306(b) of the FD&C Act must be listed by the applicant.

Section 1.3.4-

- Includes a financial certification (FDA form 3454) for any clinical investigator who has no disclosable financial interest in any applicant for a covered clinical study, as well as a disclosure statement (FDA form 34550) for any clinical investigator who has or has had a disclosable financial interest in any sponsor of a covered clinical study, or whose spouse or dependent child has. (1)

Section 1.3.5-

- Contains information about patents and exclusivity.

Section 1.3.5.1-

- Applicants must produce an appropriate patent certification or statement for each patent issued by the United States Patent and Trademark Office and later listed in the orange book that claims

1. The drug's active ingredient
2. The pharmaceutical product
3. The use of RLD as cited in the ANDA

Section 1.3.5.2-

- If the orange book does not list a patent for RLD, include a patent certification. The ANDA applicant must confirm that the NDA holder has not submitted such patent information for inclusion in the orange book (para 1 certification)
- The patent information is no longer valid (para 2)
- Information about when the patent will expire (para 3)
- The patent is invalid, unenforceable, or will not be infringed upon by the manufacture, use, or sale of the drug (para 4)

3. References:

Section 1.4.2-

- For every drug master file, provide a statement of a right of reference. In the application, there is a reference that is identified on Form 356h.
- Applicant must include a letter of authorization from the DMF holder authorizing the applicant to rely on the information in the DMF.
- The process for this notice is outlined in 21 CFR 314.95, section 505(j) (2) (B) of the FD&C Act.
- An ANDA applicant must give notice of a para 4 certification within 20 days of receiving a para 4 acknowledgment letter from FDA declaring that the application is sufficiently complete to permit a substantive review. (1)

4. Other correspondence:

Section 1.12.4-

• ANDA applicants who want a proprietary name should request it at the time of submission to guarantee that a suitable name is available when the ANDA is approved. (1)

Section 1.12.11-

Contains the rationale for application; the applicant should include the following information:

- RLD's name; RLD's application number; RLD's address; RLD's address; RLD's address; RLD's address; The person who has applied for the RLD.
- When a generic medicine applicant seeks approval for a generic medication that is a duplication of a drug product in an authorized petitioned ANDA (but for which the identical drug has not been approved under section 505(c) of the FD&C Act),
- RLD must be the same as the listed medicine in the approved suitability petition, as well as the RLD application number.
- Reference to the docket number assigned by the FDA to the suitability petition.
- A copy of the FDA letter approving the suitability petition

Section 1.12.12-

- Applicants should supply the following information to indicate that their proposed generic medicine product meets this standard: a statement that the generic product's condition of use has been previously approved for RLD.
- The active ingredient in a generic drug product is the same as the active ingredient in an RLD drug product, according to the data.

- The route of administration, dosage form, and strength of the generic medicinal product are identical to those of RLD.
- Data to determine the strength of generic drug products utilized in in vivo bioequivalence testing to show generic drug product BE to RLD, if applicable.

Section 1.12.14-

- Include a declaration that the applicants have met the categorical exclusion criteria, as well as a statement that no unusual circumstances exist to their knowledge.

Section 1.12.15-

- If relevant, include a request to exclude applicants from submitting evidence measuring in vivo bioavailability or establishing in vivo bioequivalence of the generic product.

5. Labelling-

Section 1.14.1-

- The labelling of a generic medicine product is shown. If the application is for a sterile pharmacy bulk package product, the pharmacy bulk package sterility assurance table must be completed and submitted, which addresses sterility assurance components of the drug product relating to labelling and microbiological research data.

Section 1.14.1.1-

- Applicant should check that label and labeling design do not lead to medication error and validate whether container closure is child-resistant in a text-based PDF file for each strength and container, including package size.

Section 1.14.1.2-

- Include annotated draught labeling text for each container closure system, as well as a side-by-side labeling comparison of generic drug product container and carton to RLD container and carton.

Section 1.14.1.3-

- Text-based PDF contains prescription and patient information. Product labeling files in Microsoft Word format

Section 1.14.1.4-

- If applicable, include a pharmacy bulk package sterility assurance table.

Section 1.14.1.5-

- Have a history of labeling

Section 1.14.3-

- Include RLD labeling and a comparison of that labeling to the generic product's draught labeling. All differences must be annotated and explained in a side-by-side labeling comparison.
- If applicable, the applicant must additionally include the RLD package insert, medicine guide, one container label, and one outer carton.

Section 1.14.3.1-

- State that each package size will include a suitable quantity of drug guidelines.
- Confirm the distribution of medication guidelines in conformity with 21 CFR 208.24.

Section 1.14.3.3-

- RLD labeling, pharmaceutical guidance, and one RLD outer carton label per strength and the package size are all included.

Section 1.16.1-

- For products that require instruments to limit risk while keeping advantages, include a risk management plan (no REMS).

Section 1.16.2-

- Contains a REMS for generic medicine products, as well as any REMS supporting documentation, for applications relying on an RLD with a risk evaluation and mitigation strategy.
- The same drug guide and patient package insert must be included in the REMS for an ANDA as in the RLD. An ANDA REMS, on the other hand, does not include a timeline for submitting the REMS evaluation or a communication plan.

2 Module 2 – CTD summaries.

1. Quality overall summary:

Section 2.3-

- Include the quality overall summary (QoS), which gives a high-level overview of chemistry, production, and quality control.
- It summarizes information from sections 2.3.S and 2.3.P about drug substance and drug product, respectively.
- 2.3.S - the applicant must give information on each drug substance in the product separately.
- All information provided in QOS should be correct, and module 3 should also include it. When writing QOS, they must employ the QbR model. QbR is a tool for reviewing the CMC portion of an ANDA, which includes the drug substance and drug product quality sections. (5)

2. Clinical Summary:

Section 2.7-

- Contains summary data that is necessary for determining bioequivalence. The table provides a structure for applicants to summarize several components of their BE application, such as in vivo and in vitro BE studies, and in vitro dissolution testing data.

Section 2.7.1-

- Includes a summary of biopharmaceutical research and the analytical methods used in them, as well as summary tables.
- The identity and entire address of all sites used to create data submitted in support of BE decision are also included in this area.
- There are additional dissolution data tests for the entire and half tablets in this area.

3 Module 3: - Quality

Keep all CMC data in one place.

- In the CDER manual of rules and procedures, the particular placement of product quality microbiology information in module 3 is stated.
- Applicants should read the following three industry guidance documents to help them prepare for module 3.
- Drug product impurities
- Drug substance impurities
- Drug stability testing

i. Drug substance:

1. Section 3.2.S-

   Contain CMC information specific to drug substance

2. Section 3.2.S.1-

   Contain nomenclature, structure, general principle

3. Section 3.2.S.2-

   Contain information related to the manufacture of the drug substance.

   This section should include all manufacturing facilities listed on the form 356h

4. Section 3.2.S.2.1-

   Include information on each drug substance's maker, such as the manufacturer's name and full address, as well as contact information.

   - If appropriate, the name of a US agent
   - The manufacturer's role or responsibility
   - API Type 2 DMF number
   - Data universal numbering system numbers, central file number, facility establishment identification

5. Section 3.2.S.2.2-

   Include a detailed description of the production process as well as the sterile substance's sterilization method.

6. Section 3.2.S.2.3-

   Contain the control of materials used in the manufacture of the drug substance.

7. Section 3.2.S.2.4-

   Contain control of critical steps and intermediates.

8. Section 3.2.S.2.5-

   Contain process validation or evaluation, including the sterile drug substance's production and sterilization processes.

9. Section 3.2.S.2.6-

   Contain manufacturing process development.

10. Section 3.2.S.3-

    Contain characterization information for the API

11. 3.2.S.3.1-

    Contain an elucidation of API structure and another characteristic

12. Section 3.2.S.3.2-

    Contain all potential impurities

13. Section 3.2.S.4-

    Contain information regarding the drug substance's control, including the validation technique and, if relevant, the results of the microbiological analytical test. (1)

14. Section 3.2.S.4.1-

The drug substance specification must be included. The test, acceptance criteria, a tabular reference to techniques, and any microbiological properties for the drug substance are all included in the specification. (1)

15. Section 3.2.S.4.2-

Contain the analytical procedure, including if appropriate, the analytical procedure used to perform a microbiological test of the drug substance.

16. Section 3.2.S.4.3-

• Full validation reports for in-house methods and their equivalency to USP procedures are included in the validation of analytical procedures.

• A check of the USP general chapter or the DMF method.

• Valid chromatograms and spectra for standard and test samples

• The availability of samples and the identification of the drug substance.

17. Section 3.2.S.4.4-

The batch analysis should be included, as well as COAs from both the drug substance and drug product manufacturers. The drug substance lot utilized in BE research should be properly identified by the applicant.

18. Section 3.2.S.4.5-

The FDA advises applicants to fill out the summary tables for the listing and characterization of impurities, as well as the justification of limitations in the drug substance and drug product.

19. Section 3.2.S.5-

Information on the reference standard or material is contained in this file. For the reference standard of drug substance and contaminants, appropriate certification, characterization qualification information should be provided.

20. Section 3.2.S.6-

Contains information about how to close the container. If the application includes a sterile substance that will be used in a sterile medicinal product. (1)

21. Section 3.2.S.7-

Contain stability information

22. Section 3.2.S.7.1-

At the drug product and drug substance manufacturing sites, a summary of contain stability and the conclusion of API expiration date should be presented.

23. Section 3.2.S.7.2-

Contain post-approval stability protocol.

24. Section 3.2.S.7.3-

Contain stability data. The applicant may refer to DMF.

ii. Drug product:

1. Section 3.2.P:

Contains the most up-to-date information on the medication product.

A drug product containing diluent should have its section, as should a drug product containing numerous active tablets and inert tablets.

2. Section 3.2.P.1:

The description and content of the drug product are included.

- The quantitative content and function of each component in a generic drug product, including any solvents or processing aids employed in the medicine's production.
- Information on the product's physical characteristics and comparison to RLD.
- Component quality standards, color composition, and flavor profiles.
- The number of their inactive substances that are appropriate per the inactive ingredient database, as well as the reasoning for those amounts, preferably in tabular format.
- For injectable products, the conversion from % to mg/ml; for oral solutions, the conversion from percentage to mg per dosage for the dry powder to the oral solution.
- An absolute alcohol in terms of percent volume v/v is a product that contains alcohol.

3. Section 3.2.P.2-
    - Contain pharmaceutical development report (for product and manufacturing process) and microbial attributes and antimicrobial effectiveness testing for multidose, sterile products and if the sterile drug product is packaged, single-use or multidose or pharmacy bulk. (1)
        - The applicant should include:
    - A table comparing all exhibit and commercial batches' equipment, process parameters, and in-process control. The application must specify which procedure was utilized to prepare to BE batches and which is being considered for commercial production.

4. Section 3.2.P.3-

    Manufacture of the generic drug product: information

5. Section 3.2.P.3.1-
    - Include information regarding the manufacturer of the drug product, such as the name and full address of each manufacturer and contractor.
    - Manufacturer's role or duty.
    - The creation of a central file number, the installation of a facility, and data universal numbering.
        - This also includes all of the form 356h's features.

6. Section 3.2.P.3.2-

    Contain the batch formula for the generic drug product including:
    - The total number of ingredients, including processing aids. (A quantitative comparison of the pilot-scale and commercial scale in tabular form is recommended, including the total number of dose units.)

7. Section 3.2.P.3.3-

    Manufacturing process and controls description:
    - A description of the manufacturing process and the manufacturing facilities.
    - Flowchart depicting the process flow, process parameters that apply, and in-process controls.
    - The master packaging record for marketing purposes.

8. Section 3.2.P.3.4-
    - Exhibit batch acceptance criteria and test results.
    - A comparison of the display and commercial batch manufacturing controls and equipment, as well as information on holding durations.

9. Section 3.2.P.3.5-

   Include data to show that the manufacturing process creates a dosage form that matches the product specification, such as an analysis of the data obtained for critical material qualities and critical process parameters that satisfied scale-up guidelines or acceptance requirements.

10. Section 3.2.P.4-

    Contain information on the control of the excipient including identifying the source of inactive ingredients. (1)

11. Section 3.2.P.4.1-

    Testing specifications which include retest schedule and the excipient manufacturer or supplier COA.

12. Section 3.2.P.4.2-

    Non-compendial methods used to test excipients must include the analytical procedure; compendial excipients must reference the USP or national formulary but do not need to include the analytical procedure.

13. Section 3.2.P.4.3-

    Contain the validation data of the non-compendial or in house analytical procedure

14. Section 3.2.P.4.4-

    Contain a justification of the specification and includes:

    - Residual solvents claim from the producer
    - Bovine spongiform encephalopathy transmissible spongiform encephalopathy, melamine certification as relevant

15. Section 3.2.P.5-

    Contain information on the control of drug products.

16. Section 3.2.P.5.1-

    Contain the specification for the drug product which include microbiological specification. This specification should include test, acceptance criteria, references to methods in a table form.

17. Section 3.2.P.5.2-

    Contain a description of the analytical procedures used for testing drug products including any microbiological test.

18. Section 3.2.P.5.3-

- If relevant for the drug product, validation reports for in-house methods and their equivalence to USP procedures.

- If applicable, verification of USP general procedures. (1)

- For both the reference standard and the test sample, readable spectra and chromatograms are required.

- An example declaration of availability and identification of the medication product's completed dosage form

19. Section 3.2.P.5.4-

Include a completed CoA for all presentations or strengths of the finished dosage form in the batch analysis. The applicant's medicinal product batches should be specified in any BE studies. (1)

20. Section 3.2.P.5.5-

This section describes how to characterize impurities. FDA recommends that, track should be kept if degradation products or process solvents are used during the manufacture of a completed dosage form.

21. Section 3.2.P.5.6-

Contains justification of the specification but not limited to references to compendia.

22. Section 3.2.P.6-

Reference standard or Reference material information is provided which is used for testing drug products.

23. Section 3.2.P.7-

Gives the information on container closure system.

24. Section 3.2.P.8-

Contain the stability data.

25. Section 3.2.P.8.1-

- The pre-approval stability methodology
- The completed dosage form stability summary and conclusion for marketing packaging, a proposed expiration date has been proposed.
- If relevant, propose an expiration date for bulk packing.

26. Section 3.2.P.8.2-

If the applicant and the drug product producer are separate businesses, the applicant shall demonstrate a post-approval stability protocol. An analytical process and testing plan for maintaining microbiological product quality should also be included in this area.

27. Section 3.2.P.8.3-

Contain data on stability:

- Accelerated and long-term data
- Intermediate data on the stability
- The same batch number on the stability record as the test batch.
- The start date of the stability investigations.
- For each testing time point, the date on which each stability sample was removed from the stability chamber.
- Information on the container closure system in all of its forms.

- This section can also include the following statistics and information:

- A one-time specific stability study was undertaken to ensure that the produced medication product was of good quality.
- Studies on one-time thermal cycling
- Stability studies for oral liquid and other dosage forms that are only used once.

4 Module 4- nonclinical study reports

ANDA generally does not contain data that are typically included in module 4.

5 Module 5: - comprises of clinical study reports.

• Clinical study reports.

• All clinical study report data required to support the application and establish that the generic drug product is bioequivalent to RLD is contained in the clinical study reports. (1)

1. Section 5.2-

   Contain listing of all clinical studies in tabular form e.g., Pivotal, pilot, and failed studies.

2. Section 5.3-

   Contain reports of clinical study and its related information.

3. Section 5.3.1-

   Contain the overall study data for the biopharmaceutic studies and lot numbers and strength of products used in BE studies. (1)

4. Section 5.3.1.2-

   reports of comparative bioavailability and bioequivalence studies are given. And contain information on in vivo BE studies. (1)

5. Section 5.3.1.3-

   Contain in vitro and in vivo correlation study reports.

6. Section 5.3.1.4-

   Reports on bio-analytical and analytical methodologies are included. If a method is used in several studies, it should only be included once in section 5.3.1.4, along with its validation.

   In section 2.7, all comparative dissolution data from in vitro to in vivo correlation study reports should be placed. and the data provided in this part should support the summary tables submitted in section 2.7.

7. Section 5.4-

   Keep copies of any papers mentioned in the application. A published article, official meeting time, or other regulatory guidance or advice which is offered to the applicant may be included in the document. [4]

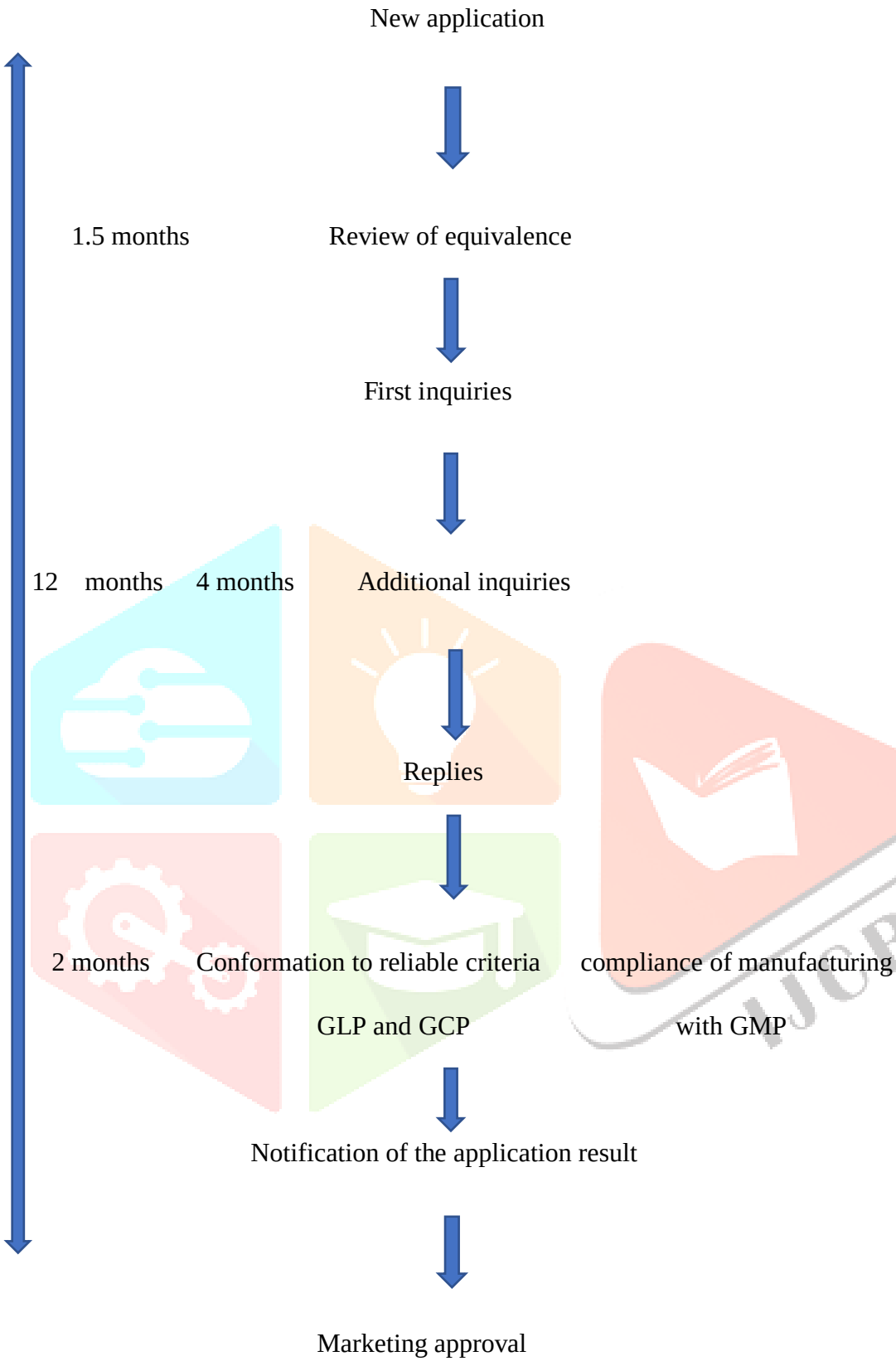
GENERIC DRUG REGULATION IN JAPAN

- By 2020, the Japanese government wants to boost the usage of generic medications by 80%.
- Generic drugs have the same API, strength, method of administration, dosage form, dose and administration, and indications as brand-name drugs.

a) Requirements for application for approval of generic drugs

1. The original product's re-examination period has expired.
2. At the time of approval, there was no valid patent (substance or utility patent for the active ingredient.)
3. A warranty of comparable quality and bioequivalence to the original product is provided. [6]

Newly applied generic products timeline. **(7)**



b) Documents listed at the time of generic drug application:

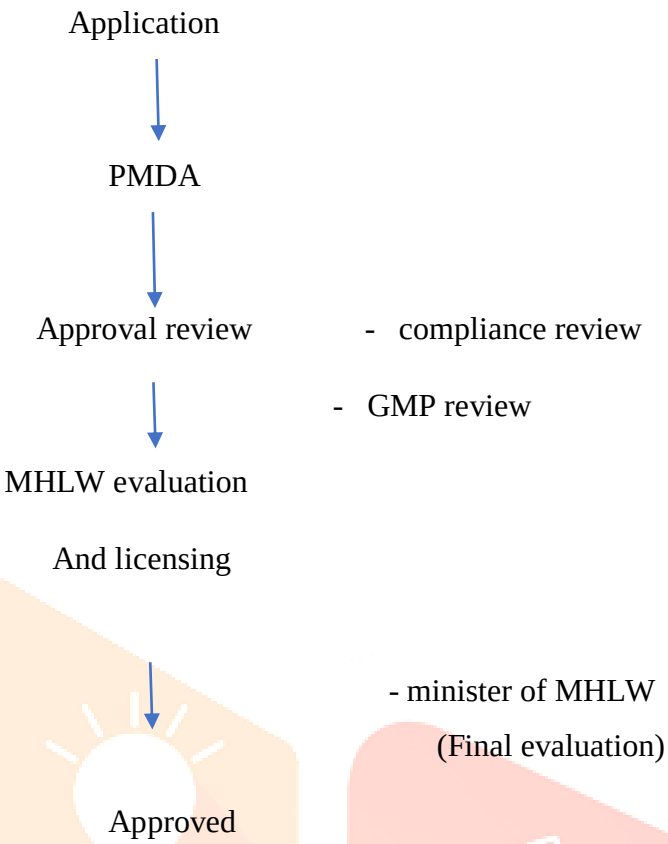
1. Specification
2. Test methods
3. Accelerated testing
4. Bioequivalence.

Additionally, if drug stability cannot be assumed, then submission of long-term storage test data may be required based on the original drug.

c) Approval content in Japan include:

1. Indication
2. Effects
3. Direction
4. Dose
5. Specification
6. Test method
7. Method of storage
8. Period of validity
9. Method of Manufacturing
10. Manufacturing site or formulation
11. Brand name

Fig 3: Complete overview of the approval process in Japan.



d) Approval application for marketing a drug

When a drug is being marketed, it is required to get approval for each product by having it tested for efficacy and safety.

- A product approval application can only be submitted by a MAH (marketing authorization holder).
- To gain product approval in Japan, the manufacturer must be licensed as a foreign manufacturer (FMA) and hold a foreign manufacturer accredited certificate.
- The application is sent to the PMDA, which is in charge of the rest of the process.

e) Approval review of generic drugs:

For active substances, there is a master file scheme.

- Contains information about the quality and manufacturing procedure of the active ingredient that will be utilized in the drug product.

- The manufacturing process is thoroughly examined. The benefit of MF registration is that it prevents data on the active component from being disclosed to pharmaceutical product applications.
- Registered data can only be used for numerous users who have signed a contract.

f) Japan Review timeline for generic drug approval.

1. First inquiry- 5 months
2. Answer preparing- 1.5 months
3. Enquiry answer- 2.5 months
4. GMP inspection- 3 months

} 12 months

g) Requirements of data in the application in Japan

1. Analytical process and specification

- The drug substance and drug product ensures product quality and consistency which also include specification.
- Ingredient or unit of potency content limits, description, identification test, particularly physical or chemical values, purity test, water or loss on drying, residue on igniting, assay, and so on. [(2)]
- Assay
- Establish acceptability criteria based on batch and stability data to ensure similar efficacy and safety.
- Impurities
- Check for contaminants that were not discovered in the original medicine using ICH recommendations.

2. Manufacturing process

- The marketing approval document outlines the entire process, from raw ingredients to packaging.
- An applicant must show that the method of manufacturing has ability of consistently producing high-quality drug material and drug products.

3. Stability:

- 6 months of accelerated stability data is submitted by an applicant. [(2)]

4. **Bioequivalence**
   - Give the assurity of therapeutic equivalence between generic drug and original drug.
   - Comparison of bioavailability is done between a generic drug and the original drug [2]

5. **Filing:**
   - Before becoming available to patients, generic medications are subjected to a thorough evaluation process by the PMDA to ensure their quality.
   - The PMDA evaluates multiple aspects of a generic drug's bioequivalence, chemistry, and manufacture before approval.
   - All PMDA high criteria must be met for critical areas such as drug components, drug stability, packaging, manufacturing process, and facility descriptions. The regulatory authority receives all of the required data in paper format. (1)

6. **Approval application for marketing a drug:**
   - Only MAH license holders are eligible to submit a product approval application.
   - To gain product approval in Japan, the manufacturer must be licensed as a foreign manufacturer (FMA) and provide a certificate.
   - The application is sent to the PMDA, which is in charge of the rest of the process. (4)

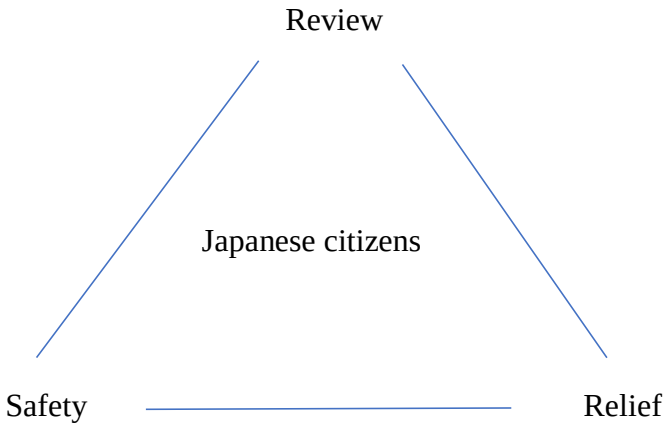
h) Steps involved in registration of generic drugs in Japan

❖ If a foreign manufacturer wish to manufacture drugs or medical devices in other countries and export them to Japan then it 2must be accredited as an accredited foreign manufacturer by the MHLW, as defined in PAL article 13-3. (Pharmaceutical affairs law)

❖ The MHLW has the jurisdiction to provide accreditation to a foreign manufacturer, while the PMDA inspects manufacturing company buildings and facilities for accreditation.

❖ A Japanese marketing approval holder applicant needs to submit a business number registration form before applying for accreditation. (1)

Fig 4: Japanese three pillar system:



PMDA reviews the submission of application for drug approval, foreign manufacturing accreditation (FMA), (DMF)

Review gives the information on reduction in risk
Safety guides you about continuous risk mitigation efforts
Relief, measures for health damage caused by risk factors. [2]

i) Application form and CTD documents of Japan

- Application form (in Japanese)
- Analytical procedure and acceptance criteria manufacturing process.
- Module 2 (QOS) (in Japanese)

  Specification

  Analytical procedure

  Development of pharmaceutical

  Process of manufacturing

  Batch analysis

  Justification

- Module 3 (in Japanese or English)

3.2.S4.1- include specification
3.2.S4.2- shows an analytical procedure
3.2.S4.3- gives information on analytical procedure for validation
3.2.S4.4- batch analysis
3.2.S4.5- specification is justified

I. Chart 1: Comparison of bioequivalence study for generic drug in US and Japan

	Comparison	US	Japan
1.	Subjects employed in Bioequivalence study	Age, sex, and race of healthy participants were taken into account. If the medication product is intended to be utilized mostly by the elderly, sponsors should include as many subjects as feasible who are 60 years or older.	20 healthy volunteers.
2.	Bioequivalence and bioavailability requirements presented in a legal document	21 CFR part 320	The division of medicines has developed bioequivalence testing guidelines for generic approval.
3.	Bioequivalence study requirement	RLD/US innovator FDA authorized center under fast/fed circumstances	PMDA/ OGD recommends fasting/feeding conditions.
4.	Bioequivalence study design	Two periods, two sequences, two treatment, single-dose cross over study	Single-dose cross-over study.
5.	Accepted Bioequivalence Limit	80-125%	80-125%

II. Chart 2: Comparative study of US and JAPAN regulation:

Sr.no	Requirement	U. S	Japan
A.	**ADMINISTRATION**		
1.	Agency	Food and Drug Administration	Ministry of health labor and welfare
2.	Authorities involved in review	1. Centre for drug evaluation and research 2. Office of generic drugs.	1. Pharmaceutical medical device Agency 2. Office of generics 3. Ministry of Health Labour and Welfare.
3.	Application	ANDA	New generic drug application
4.	Debarment certification	Required	Not required
5.	No. of copies	3(archival, review, field)	Not specified
6.	Approval time	18 months	12 months
7.	Presentation	eCTD and paper	eCTD
8.	Pharmacovigilance	Not required	Required
9.	Agent authorization	Required	Not required
10.	Review report	Pilot stage	Pilot stage
11.	Module Required	Module 1, 2, 3 and 5	Module 1, 2, 3 and 5
B.	**FINISHED PRODUCT CONTROL**		

1.	Assay	90-100%	90-111%
2.	Disintegration	Not require	Required
3.	Color identification	Not required	Required
4.	Water content	Required	Required
C.	**MANUFACTURING CONTROL**		
1.	No. of batches	1	1
2.	packaging	A minimum of 100000 unit	not required
3.	Process validation	Not required at the time of submission	Required
D.	**LABELING REQUIREMENT**		
1.	Prescription status	Rx	RX
2.	Labels	Vials/ carton/ PIL	Vials, Ampoules, Injections
E.	**STABILITY**		
1.	Data at the time of submission	3 months accelerate and 3 months long term	6 months accelerated
2.	Container orientation	Inverted upright	Do not address
3.	QP certification	Not required	Required

4.	Retention of sample	5 years from the date of filing the application	Not required

SUMMARY:

An abbreviated new drug application (ANDA) is a documented form that comprises information which is submitted to the FDA's Center for Drug Evaluation and Research (CDER), Office of Generic Drugs (OGD), for assessment and approval of a generic drug product. [(2)] It is a request to the US Food and Medicine Administration (USFDA) seeking generic drug approval of a currently licensed prescription or approved drug.

The Drug Price Competition and Patent Term Restoration Act of 1984 amended the federal food, drug, and cosmetics act, establishing the contemporary system of generic approval via abbreviated new drug applications.

The office of generic drug part of the pharmaceuticals and medical devices Agency (PMDA), is responsible for the approval review of generic drugs in Japan.

The comparison of generic drugs regulation is done between these two countries with their application forms, their labeling requirement, and method of manufacturing with its bioequivalence comparison.

US and JAPAN have different regulatory authorities with the same modules for generic drug regulation i.e., module 1 to module 5. As for generic drugs we do not need clinical practice, so module 4 is not done for the same.

CONCLUSION:

As we all know that, India produces the most generic pharmaceuticals in the world. This pharmaceutical industry produces more than half of the world's vaccine demand, United Kingdom with 25% of all medicine, and 40% of generic drug demand in the United States. (2)

In 2020, U.S generic drug market reached till $127.8 billion. This generic drug market is expected to exhibit strong growth during 2021-2026. (3)

As of September 2020, generics had a volume share of roughly 78.3 percent in the Japanese prescription medicine market, till 32.5 percent in 2005. The Japanese health ministry failed to attain the target of 80% generic medicine utilization by September 2020, which was set. (4)

In most countries, the generic market share is rapidly expanding, and generic pharmaceuticals are quickly becoming significant competitors to branded drugs. Because of their low price and effectiveness comparable to branded pharmaceuticals, the number of generic drug approvals is increasing year after year.

According to the comparison above, the United States and Japan does not have the same approval procedures and each is unique in its way. To protect public health and offer quality medications, the United States maintains strict procedures to approve generic drugs, scrutinizing the generic application and the dossier supplied in support of the application inflexibly manner.

The ministry of labor, health, and welfare, and the office of generic pharmaceuticals in Japan are in charge of the generic drug approval procedure. In Japan and the United States, the approval requirements are nearly identical.

References

1. *comparative study of regulatory requirements and registration process of generic drugs in japan and china.* **Chandra, Konuri Dinesh.** Guntur : international journal of drug regulatory affairs, Dinesh et al., 2015. ISSN: 2321-6794.

2. **Varadarajan, Siddharth.** [Online] nonprofit organization, 2015. https://science.thewire.in/health/what-you-need-to-know-about-generic-drugs-and-why-they-matter/.

3. **[Online] business wire. https://www.businesswire.com/news/home/20210812005500/en/US-generic-drug-market-report-2021-market-surpassed-a-value-of-125-billion-in-2020---forecast-to-2026---ResearchAndMarkets.com.**

4. [Online] Statista. https://www.statista.com/statistics/799622/japan-generics-market-volume-share/.

5. [Online]

6. pharmaceutical and medical devices agency. [Online] www.pmda.gov.

7. abbreviated new drug application. [Online] https://www.fda.gov/drugs/types-appplications/abbreviated-new-drug-application-anda.

8. CFR- Code of federal regulations title 21. [Online] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=314.

9. ANDA submission- content and format guidance for industry. *FDA.* [Online] June 2019. https://www.fda.gov/media/128127/download.

10. Guidelines on submission of documentation for a multisource (generic) finished product. general fomat: preparation of product dossiers in common technical document format. *WHO.* [Online] https://www.who.int/medicines/areas/quality-safety/quality-assurance/guidelinesSubmissionDocumentationMultisourceGenericGeneralFormatTRS961Annex15.pdf. 961,2011.

11. regulatory system on generic drugs in japan. [Online] ministry of helath labour and welfare, feb 5, 2020. https://www.pmda.go,jp/files/000234055.pdf.

12. japan drug regulatory overview 2014. [Online] 2014. www.pacificbridgemedical.com.