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Generic Drug in India: A Cost-Effective Approach

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ABSTRACT

After the expiry of patent or marketing right of the patented drug, generic drug are marketed. Generic drug are available at affordable prices with maintaining quality. These 'GENERIC' formulation balance public interest as critical disease like cancer, AIDS etc. in situation where demand for medicines exceed supply, criminally minded people tend to profit out of crime by manufacturing and distributing counterfeit medicines as a substitute for genuine medicines (branded and generic). India's pharmaceutical market grew at 15.7% during December 2011. This study revises various aspects of generic, branded and counterfeit drug and their impact on the Indian pharmaceutical industry. The United States – food and drug administration (U.S. FDA) has its own regulatory strategy to approve and generic drug into market, which is named as generic drug submission review. FDA has introduced generic drug for the intended use and to make them available to consumers in short management to ensure that consumer contains to receive the significant benefits offered by generic drug.

INTRODUCTION

After the expiry of patent or marketing rights of the patented drug, generic drugs are marketed. Generic drugs are available at affordable prices with maintaining quality. These 'Generic' formulations balance public interest as a critical disease like cancer, AIDS, etc. It is widely accepted both developed and developing countries. An estimated half of all prescriptions in the USA are now filed with approved generic drugs. In order to market drugs, U.S. generic manufacturers must have a permit and approval from the Food and Drug Administration (FDA) indicating that the active ingredient is approximately the same as that of the brand name. India's Pharmaceutical market grew at 15.7% during December 2011. Globally India ranks third in terms of manufacturing pharmaceuticals product by volume.[1] The Indian pharmaceutical industry is expected to grow at a rate of 9.9% till 2010 and after that 9.5% till 2015. The Indian pharmaceutical market is expected to touch the US $72 billion sales by 2020 from the US $11 billion. The market has further potential to reach the US $70 billion by 2020. India ranks 17th in terms of export its product to more than 200 countries around the globe including highly regulated markets of USA, Europe, Japan, and Australia. The world health organization (WHO) is also worried about Indians high out-of-pocket (OOP) expenses to medicines. This paper presents various aspects of generic, branded and counterfeit drugs and their impact on the Indian Pharmaceutical Industry.

Branded drugs and generic drugs:

One of the most debated issues in health care today concerns the difference between brand name (also called branded, innovator, and pioneered) drugs and their generic versions. Evolution of every drug starts from a research laboratory and ends in a medical shop. Many new molecules are invented in research laboratories. Specific pharmacological formulations require tedious technology and procedures. Many of such molecules never achieve final approval. After the formulation of a drug, it is tested on animals and then on human volunteers. These quality controls are stringent and FDA certification is necessary for avoiding side effects and toxicity of drugs. Only after testing the drug in a large number of patients in drug trials, the drug comes in market. Drug companies spend a lot of money on formulating each drug. Thus every drug cost depends on the expenditure of the research and procedures of approval. Every newly launched drug is thus very expensive, to begin with.[2] In order to address this problem the following definition has been developed by the World Health Organization (WHO): "A counterfeit medicine [3] is one which is deliberately and

fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging." [4]

The growth of the Generic Drug Industry:

The generic market reached 100 billion dollars in 2010. Generic growth is three times higher than the overall growth of drugs. 20 drugs will lose patent protection between 2010 and 2014 with the total market value of 107 billion dollar[s] [5]. According to the expectation of the pharmaceutical industry, the percentage of generic drugs in the US market will rise from 14 to 21. This growth will enhance the export of pharmaceutical products from India will double every year. In future contribution from the Indian pharmaceutical companies will increase due to the low cost of a worker, innovation, recent success in track record in design operation of high tech manufacturing, testing, quality control, research, clinical testing, and biotechnology. Most of the Indian companies have United States Food and Drug Administration (USFDA) approved plants, about 20% of all Abbreviated New Drug Applications (ANDA) to the USFDA are field by Indian companies. Now India's share of the generic market is about to 35%. Hence the contribution of the Indian pharmaceutical industry for the growth of generic drugs in the world is very high.

Table 1: Top 12 Listed Indian Public Pharmaceutical companies (Rank wise 2010)

RANK	Indian public pharmaceutical companies	RANK	Indian public pharmaceutical companies
1.	Cipla	7.	Glaxo
2.	Ranbaxy	8.	IPCA labs
3.	Dr. Reddy's labs	9.	Wockhardt
4.	Lupin	10.	Torrent Pharma
5.	Aurobindo Pharma	11.	Sterling bio
6.	Dabur	12.	Biocon

Table 2: Top 10 International Generic Companies

S.NO	COMPANY	LOCATION	REVENUES IN 2010 (IN $ BILLION)	GROWTH OVER 2009 (%)
1	Teva	Israel	11.03	+17.90
2	Sandoz	Germany	8.52	+13.70
3	Mylan	Us	4.99	+7.00
4	Actavis	Switzerland	2.52(estimated)	NA
5	Hospira	Us	2.35	+13.30
6	Watson	Us	2.27	+38.20
7	Sanofi	France	2.04	+41.50
8	Greenstone	Us	1.72	(2009 revenue NA)
9	Stada	Germany	1.50	0.70
10	Dr. Reddy's	India	1.16	16.70

COMPARATIVE STUDIES GENERIC DRUG AND BRANDED DRUG:

Generic Drugs are available all over the world at affordable prices with maintaining quality. These ‘Generic' formulations balance public interest like a critical disease like cancer, AIDS, etc. FDA does not allow a 45 percent difference in the effectiveness of the generic drug product. The average difference in absorption into the body between the generic and the brand name was 3.5 percent.[6]

PHARMACEUTICALLY EQUIVALENT:

Two drugs are considered pharmaceutical equivalents when they contain the same chemically active ingredient(s) and are identical in dosage form and strength. Pharmaceutical equivalence may be affected by many things.

1. Variations in inert ingredients

2. Plants in different parts of the world

3. In oral drugs, capsule content may be 7% over or 7% under the stated content, e.g. a 100 mg. the capsule may be as low as 93 mg. or as high as 107 mg.

4. Manufacturers may shift their source of supply.

5. Once a drug has been approved by the FDA, manufacturers sometimes make changes to the formula which was originally submitted.

6. Many arthritic patients are elderly. The age of the patient may be a factor in pharmacokinetics. Digestive tract absorption of an oral drug may be altered by a variety of factors, including higher gastric pH, accelerated gastric emptying, and thinning and reduction of the absorptive surface.[7]

BIOAVAILABILITY:

Bioavailability is the measurement of the extent of therapeutically active medicine that reaches the systemic circulation at the site of action. In bioavailability, it can be assumed that the drug's effectiveness is related to the amount of product absorbed and the speed of absorption. However, in some cases, the pharmaceutically equivalent products can have different bioavailability. They may be absorbed either faster or slower than the brand name drug which may or may not be clinically significant. For most medicine that is taken orally, the active ingredient is released in the gastrointestinal tract (GI).[8-9]

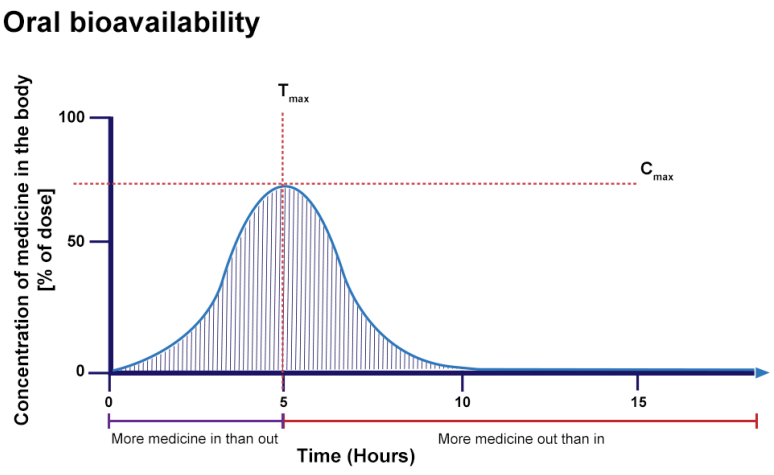

Figure: 1 Oral Bioavailability Concentration of a Medicine in the Body

∫=concentration active ingredient in the body

AUC =area under the curve

T_{max} =time at which concentration is at its maximum point in the body

C_{max} =maximum concentration of active ingredient in the body

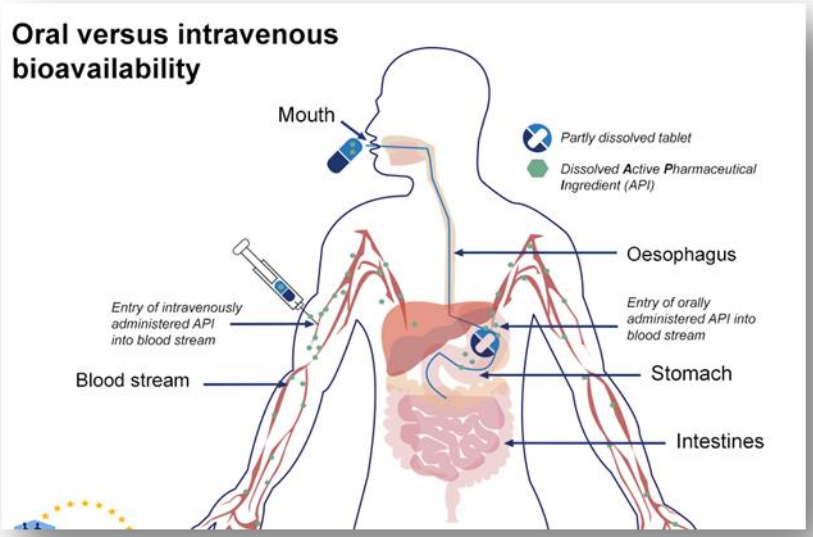

Figure: 2 Oral versus Intravenous Bioavailability

BIOEQUIVALENCE:

In order for a generic medicine to successfully enter the pharmaceutical market, it must be bioequivalent to the branded medicine. That is, the effect the generic medicine has on the body must be statistically the same as the effect the original medicine has on the body. To determine whether two medicines are bioequivalent, a pharmaceutical company needs to scientifically show that its generic medicine has the same bioavailability as the branded medicine. That is, the medicines need to have similar absorption, distribution, metabolism, and excretion. For these reasons, the generic medicine must undergo rigorous bioequivalence testing in order for the Therapeutic Goods Administration (TGA) to approve them for sale as generic medicines. Once a pharmaceutical company has successfully demonstrated to the TGA that the generic product is bioequivalent to the original, it can produce and market the generic. The generic medicine can also be considered for listing on the pharmaceutical benefits scheme (PBS).

BIOEQUIVALENCE TESTING

Bioequivalence trials are not as time-consuming, costly or large-scale as clinical trials, which companies that develop new medicines must conduct to prove the safety and effectiveness of their product. However, bioequivalence trials are still considered to be rigorous evaluations of generic medicine.

WHAT DO BIOEQUIVALENCE TESTS ASSESS?

The aim of the trials is to compare the bioavailability of the generic medicine in question to that of the branded medicine. The bioavailability of the medicines is determined by:

- Peak plasma concentration
- Time is taken to reach a peak plasma concentration.

PEAK PLASMA CONCENTRATION:

This is the maximum concentration the active ingredient reaches in the person's blood, measured by testing a blood sample. The concentration varies based on the time since the medicine was taken. Before taking the medicine, a person will not have any active ingredient in their blood. After taking the medicine, the concentration will increase as the active ingredient is absorbed until it reaches the peak concentration. It will then reduce until all the medicine has left the person's bloodstream (unless more medicine is taken).

TIME TAKEN TO REACH PEAK PLASMA CONCENTRATION:

Measured by taking a series of blood samples and recording the amount of time between the person taking the medicine and the blood sample with the peak plasma concentration being drawn. [10]

Table 3: Example of Generic Alternative for Commonly Prescribed Branded Name of the Medication [11]

Common medical condition	Generic medication used to treat a medical condition (branded equivalent, for reference	Brand name medication also used to treat a medical condition
Arthritis	Ibuprofen (For Motrin) Naproxen(For Naprosyn)	Bextra, Celebrex, Vioxx
Acid reflux	Ranitidine (For Zantac)	AcipHex, Nexium, Prevacid, Protonix.
Diabetes	Glipizide (For Glucotrol) Glyburide (For Diabetes Or Micronase) Metformin (For Glucophage)	Actos, Avandamet, Avandia, Glucovance, Glucophage XR
Depression	Fluoxetine (For Prozac)	Celexa, Lexapro

ADVANTAGES OF GENERIC DRUG:

- The major advantage of generic drug is cheaper in rate (or) cost. The generic medicine are cannot be marketed at higher price than the brand name of the medicine, so it is often cheaper, four both consumer and government who pay for the part of the cost of the medicine in pharmaceutical benefit.

- The use of the generic drug can add up to marked saving for everyone.

- A generic drug does not have a side effect on an individual.[12-13]

DISADVANTAGES:

There are two main points that you need to understand if you are considering the switch to generic medication:

1. Even though a generic medicine may taste, look and be packaged differently, it has the same active ingredient as the branded medicine you are used to taking. Therefore, the two medicines cannot be taken together.

This will lead to an overdose of that particular medicine. Always remember that one replaces or is substituted for another.

2. Generic medicine has been thoroughly tested by the pharmaceutical company. The generic medicine is interchangeable with the branded medicine. This means that it will have the same actions in the body as the original medicine.

The only differences exist in the inactive ingredients, which will not have any negative effect unless you have an allergy (or) intolerance. [13]

SCOPE OF GENERIC DRUGS IN INDIA:

In today's era, the scope of generic drugs is increasing day by day especially in several ill health conditions such as diabetes, cardiovascular and in microbial diseases etc. When any patent expires, new generics are introduced into the market. According to this, a generic manufacturer challenges the original patented drug and claims that the generic version proposed to be launched by the manufacturer does not infringe the patent holder's version. In case a patent challenge is won, it entitles the first to file Para IV generic manufacturer a 180 days exclusivity, if company come up with an equivalent of the innovator's branded formulation.[14]. 'Bolar provision' allows generic manufacturers to prepare and develop regulatory procedures before patent expires, so that, products are ready for market as soon as the patent ends. With these provisions, in India, the scope of generic drug manufacturing has also increased.[15]

PHARMACEUTICAL INDUSTRY IN INDIA:

The pharmaceutical industry is one of the highly regulated industries, with many rules and regulations enforced by the government to protect the health and well-being of the public. Therefore, the aim of the pharmaceutical industry is to identify and develop a generic drug product which can be tailor-made to meet the diverse market requirements. As per global market trend, it is estimated that approximately $150 billion worth of drugs will be off patented during the period 2010 to 2017, which will serve as a platform for pharmaceutical companies to develop generic drug.[16] the pharmaceutical industry in India has shown a remarkable growth which in turn has risen the economy of India.[17]

INDIA AS A GENERIC PHARMACEUTICAL MARKET:

The Indian pharmaceutical market is the third largest in terms of volume and the thirteenth largest in terms of value. India is the largest generic drug provider globally with about 20 %

of global exports in terms of value. Indian pharmaceutical companies received about 304 approvals and 61 tentative approvals for their ANDAs from the USFDA in 2017. India has the second largest number of USFDA approved manufacturing plants outside of USA.

• **Production Cost:** The cost of production in India is about 33 % lower than the US. Further, the cost of setting up a production plant in India would be 40 % lower than the Western countries;

• **Labour:** The labour cost in India is about 50 % lower than Western countries. Further, India has a high level of technical competence and skilled workforce as compared to other Asian countries.[18]

GENERIC DRUG APPROVAL PROCESS AND REVIEW PROCESS:

Generic drug approval process: In general to get marketing approval for a generic drug form U.S. food and drug administration include various junctures such as finding basis for submission, getting drug substance from approved DMF vendors, finished product development, clinical/bioequivalence-bioavailability studies, plant inspection, dossier writing and finally submission to authorities. The diagram (Figure -3) after the submission of a dossier to the regulatory authority. [19-20]

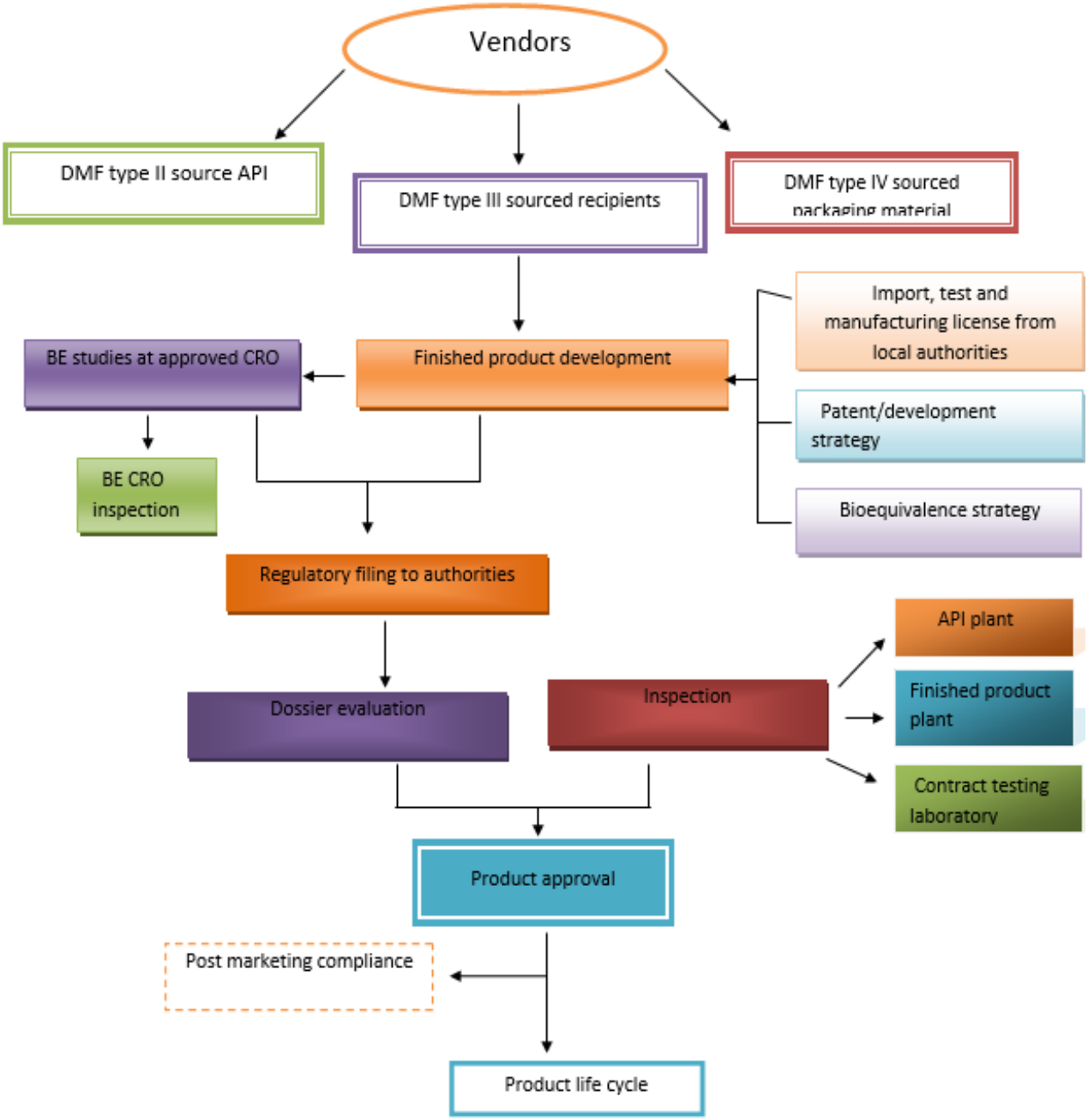

Figure: 3 Generic Drug Approval Process

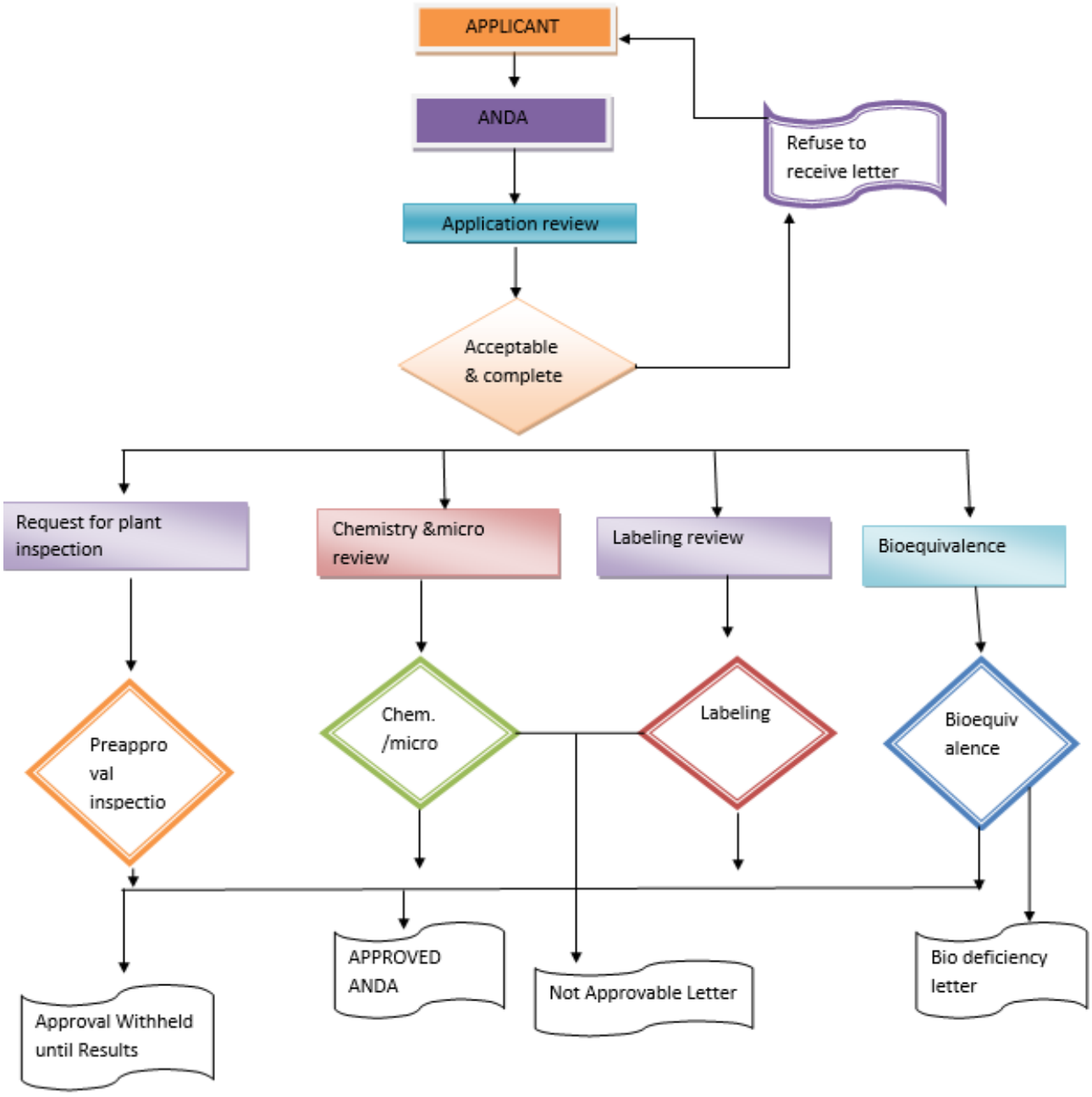

Figure: 4 Generic Drug Review Process

GENERIC DRUG USER FEE AMENDMENTS OF 2012 (GDUFA) ANDA:

GDUFA (Public Law 112-144, Title III) was signed into law by the President of the United States on July 09, 2012. GDUFA was designed to speed the delivery of safe and effective generic drugs to the public and reduce costs to industry. GDUFA enables FDA to assess user fees to support critical and measurable enhancements to FDA's generic drugs program. The diagram (Figure 5) illustrates the various elements involved in obtaining approval for a generic product post-GDUFA. [20-21

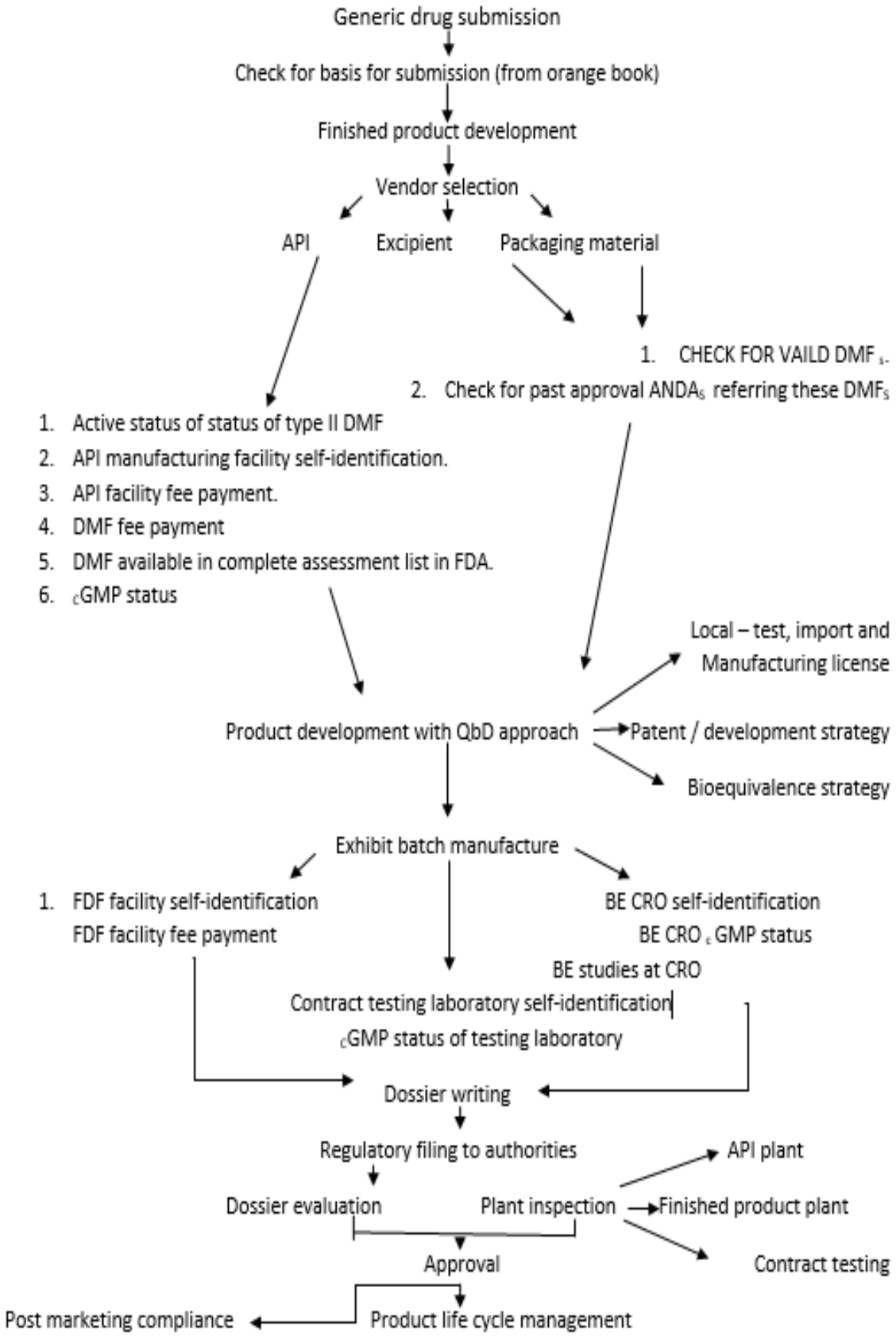

Figure 5: Components of Regulatory Filing Post GDUFA Implementation

NEW DRUG APPLICATION (NDA):

- NDA (new drug application) submitted based on FD and C act 505(b)
- NDA_s are submitted for:
  - New molecular entity
  - A new formulation of a previously approved drug
  - A new combination of tow our more drug
  - New indication for already market drug

Abbreviated new drug application (ANDA):

- ANDA submitted based on FD and C act 505(j)
- ANDA is submitted for :

- Generic drug: a NDA must be previously approved and listed, known as the reference listed drug (RLD)

Table 4: Requirement of NDA and ANDA

NDA	ANDA
1. Chemistry 2. Manufacturing 3. Testing 4. Labeling 5. Inspection 6. Animal studies 7. Clinical studies 8. Bioavailability	1. Chemistry 2. Manufacturing 3. Testing 4. Labeling 5. Inspection 6. Bioequivalence

Table 5: Submission for NDA vs. ANDA

Module Regional administrative information	Module Summaries	Module Qualities	Module Nonclinical study reports	Module Clinical study report
Labeling	Quality overall summary (QOS)	Chemistry, manufacturing, controlling, labeling.		Bioequivalence

Table 6: Review process of NDA VS ANDA

NDA	ANDA
➢ Lower volume (average 25ν approvals/year) higher complexity (pre-clinicalν and/or clinical trials, etc.) ➢ One drug one applicationν ➢ Pre-submission face-to-faceν meetings (IND phases) ➢ User fee (PDUFA) from 1992	➢ Higher volume (more than 500 approvals/year) ➢ Lower complexity (safety and efficacy already established) ➢ One drug multiple applications ➢ User fee (GDUFA) from 2013

GENERIC DRUG RESEARCH & DEVELOPMENT PROCESS:

The generic drug R&D timeline is significantly shorter than for branded , Safety and efficacy are not being proved, Steps are less “linear” and can often be undertaken simultaneously Pivotal Bioequivalence is where the drug is proven to be identical, Key reduction in timeline as bioequivalence studies require much smaller populations and can be done in a matter of weeks/monthsGeneric manufacturers themselves estimate that the cost of successfully developing a commercializable generic drug ranges from $10m to $100m. The latest estimate for theν cost of successfully commercializing a branded drug is approximately US$2.

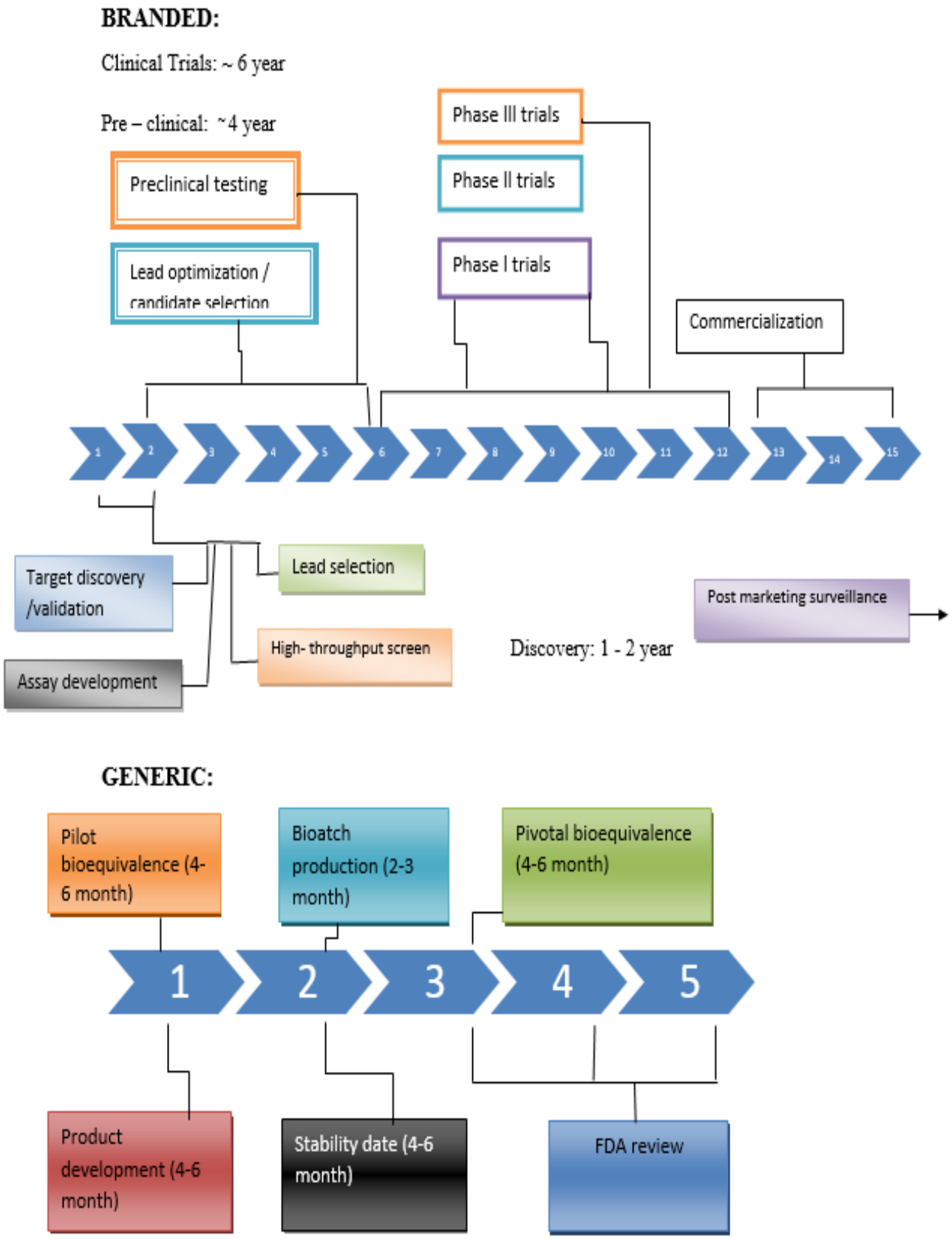

Figure: 6 Branded vs. Generic Research & Development Timeline

BRANDED PHARMA R&D – PROGRESSION PROBABILITY:

• The risk of total failure in the R&D process for generic drugs is extremely low because the safety and efficacy of the active ingredient has already been establishing.

• The "relative simplicity" vs. the branded pharma R&D process is integral to the low-cost nature of generic drugs. [22]

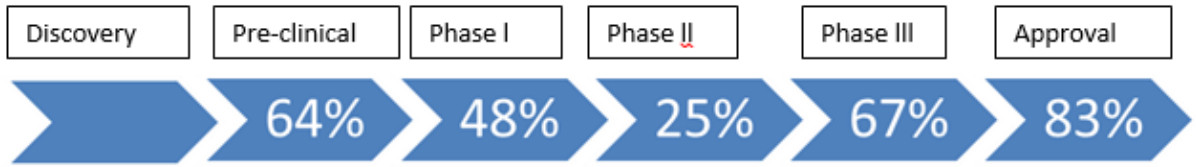

Figure: 7 Branded pharma R &D-progression probability

CONCLUSION:

While brand name drugs certainly play an important role in medicine, generic drugs are a cost effective alternative. Pharmaceutical costs are increasing faster than any other portion of the health care expense. Not only are generic drugs cost effective, but they are safe. Generic drugs are bioequivalent to their brand name twins. As generics tend to be older, they are generally less risky than new drug therapies. Generic drugs offer sound treatment options for patients.

The implementation of GDUFA program is yielding good improvements in FDA's division of Office of Generic Drugs (OGD) i.e., advancing/improving the review pattern of a generic application without compromising quality and efficacy for intended use of a generic product. Further, FDA is planning to increase the staff to assess the Risk-based quality approach and making every effort to allow the generic drugs into the market for the availability of patients/customers.

The future of generics is in development of complex generics, biologics or biosimilars for which there is an increased exclusivity period of 12 years in favor of the innovator in contrast to the 5 years new chemical entity (NCE) exclusivity It is highly critical for pharma companies to move on from vanilla generics towards complex generics, specialty products, biosimilars, and innovative products, which will drive future pharmaceutical growth. Thus,

the implementation of Generic Drug User Fee program benefits customers economically and benefits generic industries in facilitating the early launch of generic products into the market.

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