Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 12 [9] August 2023: 320-329

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

REVIEW ARTICLE **OPEN ACCESS**

Trends and challenges in Generic formulation development research

Jailani. S*[1], C.K.Dhanapal[2], Noohu Abdulla Khan[3]
[1]Research Scholar, Dept. of Pharmacy, Faculty of Engineering and Technology (FEAT), Annamalai University, Annamalai Nagar, Chidambaram, Tamil Nadu, India.
[2]Professor, Dept. of Pharmacy, Faculty of Engineering and Technology (FEAT), Annamalai University, Annamalai Nagar, Chidambaram, Tamil Nadu, India.
[3]Assistant professor, Dept. of Clinical Pharmacy, College of Pharmacy, King Khalid University, Abha, Kingdom of Saudi Arabia.
*Corresponding Author's e-mail ID: jailanipharmacy@gmail.com

ABSTRACT
In the pharmaceutical sector, developing a generic drug product requires a scientific and technical approach as opposed to creating an innovator product, which must go through numerous phases and years of development before it can be registered. In comparison to the innovator company, the development of a generic product doesn't take as long or as much money. Generic medication products are more affordable than their corresponding brand-name counterparts. The therapeutic effects and active components of a generic medicine are identical to those of the brand-name drug. This analysis looks at some R&D ideas, presents business practices, and research scenarios that are better suitable for their setup. Undoubtedly, this research also offers the pharmaceutical industry requirements and challenging issues in complex generic development. Companies that wish to lead the pharmaceutical industry in innovation can learn something from this article or use it to build knowledge integrator models.
Keywords: *Generic drug, Innovator product, Challenges, Drug development, Research.*

Received 04 .05.2023 Revised 15.07.2023 Accepted 27 .08.2023

INTRODUCTION

A generic drug product is developed using a scientific and technical method in the pharmaceutical sector, as opposed to an innovator product, which must go through numerous stages and years of development before it can be registered [1-3]. Comparatively speaking to the innovator company, the development of the generic product does not take as much time or money. Compared to their respective brand-name counterparts, generic drug goods are more affordable. A generic medicine has the same therapeutic effect as a brand-name drug and includes the same active components. Unbranded, Branded, Authorized, and Special Generics are the four basic categories of generic drugs. The impact that generics play in lowering healthcare costs cannot be overstated [4-6]. A complex generic, on the other hand, has a complex molecule and complex formulation and offers a lucrative market for manufacturing companies, but only if they can adapt a more challenging and difficult development process [7-9]. A simple generic is a copy of the small molecule reference drug and is identical to the brand product. Hybrid drugs are another name for complex generics [10].

Bio-equivalence describes a generic drug product as being almost identical to the unique product in terms of the active ingredient(s), strength, and dosage form, technique for administration, quality, safety, performance characteristics, and therapeutic indication [11-13]. Traditional generics and complicated generics are viewed from a regulatory point of view where the Mfg. Process can differ from RLD while Quality should be the same or can be better and Stability is not always the same as RLD. The *in-vivo* performance ought to be identical to the RLD for both. Traditional generics may not have the same composition as RLD; however complex generics must have the same composition as RLD [14, 15].

R&D trends for new drug discovery research

Each year, the pharmaceutical business works on developing a wide range of brand-new medicines that offer significant medical advantages. The pharmaceutical industry devoted approximately 6000 thousand drugs discovery in 2001 which has been increased 18,582 in the year 2021 among them approximately

9700 and 10, 300 were entered preclinic al phase in the year 2020 and 2021 respectively while 2500 to 2600 are in phase I and phase II trial. Only 1000-1029 trials have been reached to faze 3 in the year 2020 and 2021. With respect to above data, about 1300 products have been launched while 60 and 42 products have been suspended [16].

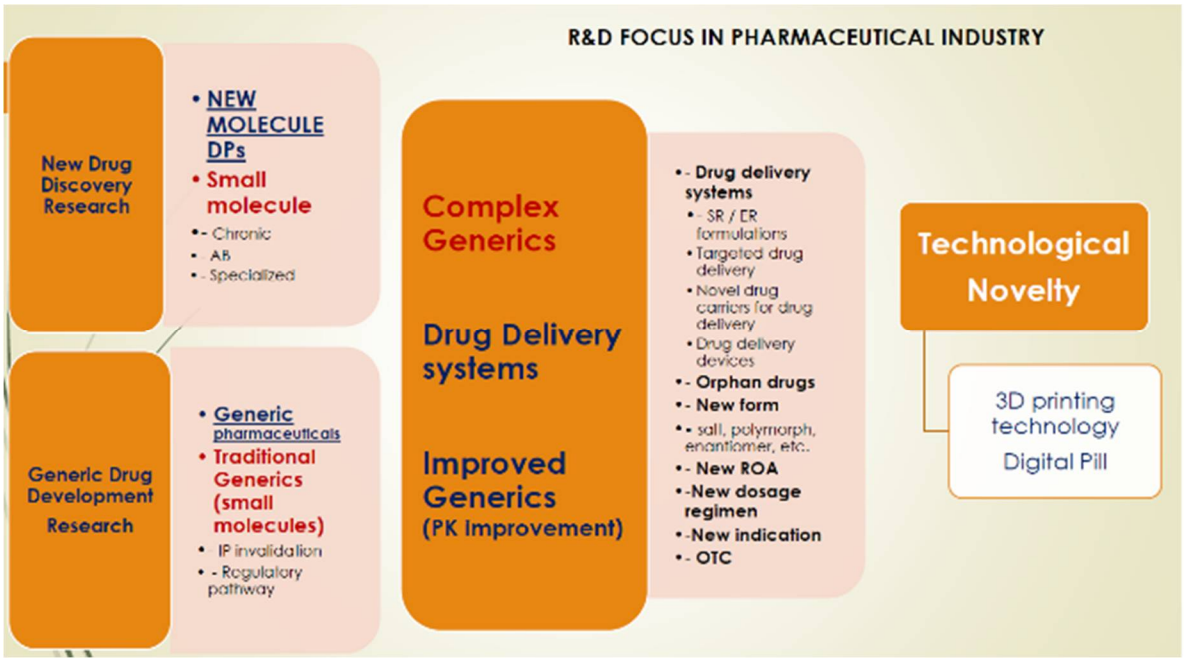

Figure 1: Research & development focus in pharmaceutical industry

New drug discovery research pattern

It can take up to 12–13 years to complete new drug discovery research because it requires so many various stages and steps, from conceptualization through development to authorization. Typically, it can be divided into four main stages: Research, development and Regulatory Approval.

Research Phase: For each possible drug candidate, up to 5,000–10,000 compounds are put through a thorough screening procedure that lasts 3-6 years and consumes 21.5% of the budget and the likelihood that it will succeed will be below 0.01%. The molecule discovered throughout Early Drug Discovery is then extensively investigated in a laboratory or using other models during the Pre-Clinical Phase.

Development phase: Clinical trials are conducted during this phase, which lasts 6-7 years. Up to 65% of the budget is allocated during this time, and the probabilities of a successful outcome are 65% in Phase I, 40% in Phase II, and 50% in Phase III.

Regulatory approval phase: When a clinical study for an active drug is finished, data are then collected and examined. With a budget contribution of up to 3.5%, the approval phase lasts for 0.5 to 2 years.

Post marketing surveillance: this is also known as Phase IV Trials which requires duration of 0.5 to 2 years with continuing share of budget equal to 10% having a chance for return on investment is in ratio of 1:3.

In addition, it involves extensive research from the scratch with potential risk of failure, huge investment, pre-clinical and clinical studies and prolonged time to market due to which innovator products are costlier [16].

Different kinds of marketing exclusivity in pharmaceutical development

Only when a drug has received FDA approval and following the fulfillment of all legal requirements is marketing exclusivity granted. According to 21 CFR 314.108, the most popular kinds of exclusivities are specified.

Following countries have different guidelines for data exclusivity.

Japan: Japan has 8 years- re-examination period among which 4 years re-examination period+ generic approval time and 1 + years for new indications.

Canada: 8 years exclusivity with no extension for new indications and restrictions on scope of products

European Union: It has 10 years exclusivity with 1 year extension for new indications

United States: for Chemical entitles, there it 5 years exclusivity + FDA approval time (+1 year) while 3 years extension for new indications. In case of Biologics USA permits 12 years exclusivity. New drug

discovery and innovations are encouraged and rewarded by regulations. New drug discovery and innovations are encouraged and rewarded by regulators.

Novel antibiotic research

The 'wonder drugs' for fighting microorganisms are antibiotics. We discovered a number of novel antibiotics and evaluated their stage of development, mechanism of action, range of activity, and approved uses. The process of developing novel drugs takes a lot of time, work, money, and scientific research. High investments in novel antibiotics or for research are necessary for a profitable antibiotic business model. According to prescription sales and R&D expenditure in 2021, major brand companies which include Pfizer, Novartis, and Novartis were amongst the top 50 pharmaceutical corporations. In that year, Pfizer sold around 72 billion USD worth of prescription drugs. According to prescription sales and R&D expenditure, big brand companies including Pfizer, Novartis, and Novartis were amongst the top 50 pharmaceutical businesses in 2021. Approximately 72 billion dollars' worth of prescription drugs were sold by Pfizer in that year. [17].

Generic drug products Global acceptance and regulatory perspectives

In the United States, the generic drug industry was estimated towards being worth USD 171.8 billion in 2020, which is anticipated to increase to USD 239.5 billion by 2026. While the global market for generic drugs was valued at 278.4 USD billion, it is expected towards reaching USD 786.0 billion by 2030, growing at a 10% CAGR between 2020 and 2030 due to the growing use of robotic process automation, the patent expirations of branded medications, and the rise in chronic disease prevalence. Considering the magnitude of the generic drug industry globally, growth is anticipated to keep going throughout the projection period. With a 7% growth rate, the number of USFDA ANDA approvals per fiscal year increased from 565 in 2010 to 1171 in 2019 [17].

Drug Development process

Each phase of the process of developing drugs must be completed such as product selection, product development, pilot bioequivalence, exhibit batches, 3 months stability data, pivotal bioequivalence, filling, review time, approval and product launch. Except filling (25-30 months) all stages take time duration of 4-6 months. First to market generics are rewarded by USFDA. USFDA offers 180 days exclusively for first to file generic (para IV) [17].

The generic pharmaceutical market in Europe is subject to a regulatory environment

The primary source of profit for the pharmaceutical industry is regulatory exclusivity rather than non-patent exclusivity. The introduction of regulatory exclusivity for pharmaceutical products was justified by the fact that the length of time required to obtain marketing authorization frequently left little time for the drug product to enjoy a functional patent protection period. Data exclusivity, which allows access to data of a generic application and provides a uniform degree of confidentiality for originator products for a period of ten years, but prevents the launch of the generic version until the ten years have passed [17].

Data Exclusivity-8+2+1 regime

The 8+2+1 system is used in the EU for data exclusivity. 8 years of data exclusivity are provided to originator businesses, in addition to an extra 2 years of market exclusivity, and no generic competitors are permitted to get market permission for the product. A further year will only be granted for new product suggestions in addition to those moving since presentation-only to OTC status. Only when 11 years of total market exclusivity have passed can generic drugs be sold.

European Bolar Cause

It enables the start of generic research and development before patients' brand expiration. The use of brands as reference products by generic companies can't be prevented by brand withdrawal prior to generic entry.

Sunset clause

For products that haven't been on the market for three years, the marketing authorization may be canceled. Generic firms may be unable to file for registration more than 3–4 years prior to expiration due to legal objections brought by patient owners. Regulators encourage research on genetically modified product development [17].

Generics trend in GCC- Progressive, slow and steady growth

In 2016, the generic medication industry in the GCC was worth close to US$ 1,550 million, showing a CAGR of 15% from 2009 to 2016. The region's expanding capacity for pharmaceutical production, which has been encouraged by ambitions for regional integration and a greater emphasis on GCC-produced medicines, is one of the key factors anticipated to drive the industry. The initiatives to lessen reliance on imported drugs will encourage domestic drug production, particularly of generics. Additionally, the governments of Saudi Arabia, Oman, and the UAE have launched initiatives to raise awareness of the benefits of substituting generic drugs for name-brand ones. In summary, the market is anticipated to keep expanding and surpass US$ 1500 million in value by 2023 [18].

Product registration sequence

With a CAGR of 15% from 2009 to 2016, the GCC generic drug industry had grown to a size of roughly USD 1550 million in 2016. Additionally, the governments of Saudi Arabia, Oman, and the UAE have launched initiatives to raise awareness of the benefits of switching from branded to generic medications. Overall, the industry is anticipated to keep expanding and surpass $1 billion by 2022. First is generic product registration sequence which will be dealt with as innovated product while 2nd innovated product registration sequence will be dealt with as 1st generic product which will be dealt with as 1st generic product. Pricing of generic products has three schemes which are products manufactured locally, or in countries like Japan, EU or USA and 3rd one is in other countries [18, 19].

Why generics are allowed and promoted by USFDA, EMA, SFDA and international regulators and agencies and governments worldwide.

A generic drug offers affordable treatment as quality treatment at cheaper cost, avoid repetition of research work already carried out by Innovator / RLD, Cost savings at governmental levels, Make ease availability of affordable drugs to public, Alternatives available if a RLD is withdrawn from market, Helps governments to frame policies in offering quality health care at free or economical medical care to the citizens, Contributing towards Improved patient compliance, Improves physicians' confidence while prescribing the patient can complete the entire course of treatments, switching over to lowest cost generic version in order to continue the treatment and thus minimizes abandonment of treatment due to relatively high cost of versions of other generics and RLD [19].

Saving due to generics

Cost comparison of top 10 brands vs generics in US market. Nine out of ten prescriptions in the US are filled with generic drugs. 2019 saw generic drug savings for American patients of $313 billion. Savings over the past ten years total over $2.2 trillion. The savings produced by generic versions free up funds to invest in novel therapies, fostering creativity, and leading to significant advancements against some of the most expensive and difficult diseases. Generics saved almost $ 2.2 trillion over 10 years, whereas biosimilars saved $ 4.5 billion [20].

Why generics drugs are cheaper?

A generics drug involves dedication application research with list risk, comparatively less investment, bioequivalence studies and shorter time to market.. Top 20 generics companies by 2020 revenues are Sandoz, Teva, Vitara's, Sun pharma, Fresenius Kabi, Aurobindo, Cipla , Hikma, Lupin, DR. Reddy's, Stada, Sawai, Glenmark, Amneal, Sanofi, Torrent Pharma, Endo, Mallinckrodt pharmaceuticals, Biocon and Piramal.

Path to approval

Regulatory pathways-product filling in the US MARKET

New drug products may be permitted by the FDA in the United States using one of three possible regulatory approval processes: 505(B)(1) or NDA, 505(B)(2), or 505(J) or ANDA.

505(b)(1)

NDA, This kind of application, often known as an NDA, is typically connected to a new brand of goods. The applicant or a third party (including variables for example a Contract Research Organization (CRO) conducts the clinical investigations that are used as a basis for the prospective endorsement of the new medicinal product. The applicant may also get a reference or usage right for the clinical investigations.

505(b)(2) New Drug Application

Often mentioned to as an NDA, this document is used by a firm to produce treatments that frequently have identical active ingredients as drugs that have already received approval but differ in ways like dosage form, active ingredient combination, or method of administration. A business can seek clearance through the 505(b)(2) pathway rather than submitting these unique drugs through the 505(b)(1) sanction procedure and repeating investigations of related drugs that have previously received approval.

ANDA/505(j) Application OR Generic ANDA

A 505(j) application, sometimes referred to as an expedited approval pathway, is an abbreviated New Drug Application (ANDA). A proposal for a product is included in an ANDA if it can be demonstrated that it is equivalent to an RLD in terms of active component, dosage form, strength, method of administration, labeling, quality, performance attributes, as well as projected usage. Clinical studies are not required to be included in ANDAs, but information demonstrating bioequivalence near the RLD is. Commonly speaking, the bioequivalence decision permits an ANDA towards relying on clinical studies filed together with the RLD as well as FDA conclusions regarding the security and effectiveness of the RLD [6].

Hatch-Waxman and ANDA routes [15, 20].

Generic (ANDA)

Information demonstrating that the proposed generic product is therapeutically equivalent (TE) to RLD must typically be included in an ANDA.

(1) Pharmaceutical Equivalence (PE)
(2) Bioequivalence (BE)

ANDA Para IV

FDA aims to enhance engagement with applicants prior to submission of an ANDA (abbreviated new drug application).

Paragraph I

There are no patents listed. It displays patent exhibits, but they haven't been filed or the information hasn't been filed. The ANDA might be accepted right away.

Paragraph II

It says that the stated patents are no longer valid. The applicant's patent certification for the ANDA application for paragraph II certification must specify that such patents have expired.

Paragraph III

The drug listed here still has a valid patent. Whenever an applicant does not intend to market the generic drug until the original drug's patent expires, a Para III petition is prepared.

Paragraph IV

When the applicant feels that the utilization of its product does not violate the innovator's patents, or when the applicant feels that such patents are invalid or unenforceable, a Para IV filing for the introduction of generic drugs is made. No competitors are allowed to join the market for a period of six months [21, 22], according to paragraph IV.

PARA – IV Filing & 180 day's exclusivity

The generic drug manufacturer claims the patent is at least one of the following in a Paragraph IV filing: (1) invalid; (2) not infringed; or (3) unenforceable. Paragraph IV Legal disputes between the manufacturers of generic medicines and the owners of those proprietary drugs have multiplied as a result of certifications under Hatch-Waxman. The first genetics business to successfully challenge a patent in court is given 180 days of market exclusivity.

Top ANDA filers in India in 2020

Alembic and Aurobindo pharma were the top Indian companies with maximum generic filers company in 2021. This was followed by the Hetero labs and Dr Reddy's lab. Last but not the least sun pharma and Mylan filed 4 ANDA applications. While Teva pharmaceuticals has garnered 133 PIV Filings during the year 2017-2019 and Mylan and apotex followed them with numbers 81 and 57 in the same time duration [21, 22].

R & D Trends in complex generics (incremental innovation research)

With 6,085 goods in active development from Phase I through regulatory submission in 2021, less than 1% more than in 2020, the research and development pipeline reached a plateau. According to the definition of USFDA, Complex formulations and active ingredients, it is difficult to "copy" them (such as their formulations or drug delivery systems) by using traditional methods.

- Active Ingredient: Mixture of APIs, Polymeric compounds, Peptides
- Formulation technique: According to the definition of USFDA, Complex formulations and active ingredients, it is difficult to copy them such as their formulations or drug delivery systems by using traditional methods.
- Locally acting drugs delivered via a convoluted route: Complex drug-device combinations, including transdermal systems, nasal sprays, metered dose inhalers, and dry powder inhalers
- Carrier based delivery systems: Liposomes, Nanoparticles, Microspheres, Monoclonal antibodies, Niosomes, Resealed erythrocytes as drug carriers

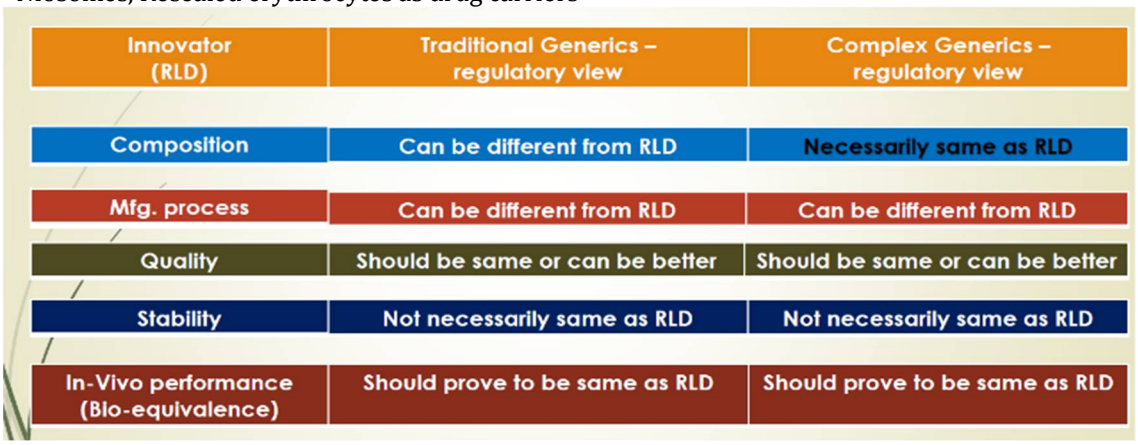

Figure 2: Possible differences between Generics and Complex Generics in comparsion to Innovator

Regulatory pathways (Improvised product filing s DNA)

NDA

A "stand-alone NDA" is an application that has been submitted and authorized under section 505(b)(1) and comprises complete reports of security and efficacy investigations that were carried out by the applicant, for the applicant, or for whatever the person applying has a right of reference or usage.

S-NDA (Super generic)

A 505(b)(2) application is an NDA that has been submitted and approved and that includes full reports of the efficacy and safety investigations. At least some of the information needed for approval originates from studies that were not carried out by or for the applicant and for which the applicant did not obtain a right of reference or usage.

Complex generic drug products

In general, complicated generics are either complex drug-device combinations or products with complex active components, formulations, dosage forms, or modes of administration. Complex brand-name drugs (i.e., drugs in reference lists) can be more challenging to create as generics. As a result, complex drugs may have a lower likelihood of having generic accessibility.

Regulatory procedures used today for complicated generics

A generic drug product with a potential therapeutic equivalence rating may be approved through one of two condensed regulatory pathways: the "traditional" generic application via 505(j), also known as the abbreviated new drug application (ANDA), and, in theory, the 505(b)(2) application.

The latter is less frequently employed for this persistence but has been utilized in the past to approve generic drug items for commercialization based in part on data from the RLD, as in the case of several recombinant pharmaceuticals. Since the clinical studies required to prove TE are outside the purview of the 505(j) method, the FDA has demonstrated that the 505(b)(2) option could offer an intriguing substitute for the sanction of a complicated generic. In contrast to 505(j) applications, which automatically result in a therapeutic equivalence rating, 505(b)(2) applications may not always result in such a rating. However, as shown by multiple topical treatments and extended-release products that were given a therapeutic equivalency rating by the FDA, it is conceivable to get a therapeutic equivalence rating with a 505(b)(2) application.

A generic drug product must be both pharmaceutically and bioequivalent to the reference listed drug (RLD) in order towards being licensed and recognized as therapeutically equivalent (TE). This method presents difficulties for PE and/or BE when dealing with complicated generics, but it is appropriate for "simple" small molecule generics. The FDA proposes supplementary proportional physicochemical assessment of the test and reference products to show PE in terms of formulation and microstructure arrangement sameness in order to solve the problems of complicated generics. This equivalence demonstration compares the RLD step-by-step in terms of analytical characterization and, occasionally, clinical trials [21, 22].

Orphan drugs

Pharmaceutical companies have historically not prioritized orphan drug development, but recent regulation has been sympathetic. In the US, pharmaceutical companies' new benefit from up to seven years of market exclusivity, tax credits of 50%for certain R& D efforts and fast track drug approvals. In Europe, pharmaceutical companies benefit from up to 10 years of market exclusivity, tax credits, exemptions from certain licensing fees and EU and national grants.

Rare disease 505 (B) (2) Approvals

Rare Disease Patient Populations Full Phase 1-3 Clinical Development Programme may Not Be Feasible for Rare Disease Patient Populations, Rare Strategies for Development that Leverage the 505(b)(2) Regulatory Pathway can be Particularly Relevant. The 505(b)(2) method was used in more than one-third (36%) of NDA approvals for orphan drugs.

Challenges for generic product development

The generic sector has aggressively expanded by leaps and bounds. Generic drugs prescribed in the US now account for about 90% of all prescriptions, up from just 19% in 1984 when the Hatch Waxman Act was passed. The generic may even fall short of being a First-To-File (FTF) for the coveted 180-day marketing exclusivity, which is the goal of any generic. The factors or challenges which affect product development are Competition of generic players, Cost effectiveness (Development and manufacturing cost), Time to market (first to file) (development time), Force need for alternative innovation (PARA IV), Patent restrictions (API, Compositions, MFG, Technology), Patent infringement claim by innovator and facing litigation, Patent by innovator and generics (Para IV).

In addition, followings are the most difficult challenges faced by generics

Increasing competition: Favorable regulatory policies and high demand has resulted in an overcrowded market place.

Price erosion: Selling prices of generics are known to decline by 9% every year due to multiple reasons.

Low profit margins: Deflation in drug price result in diminishing profit margins for generic developers.

Active ingredient sameness: characterizing mixture of APIs.

Pharmaceutical equivalence: By classifying complex formulations, comparing inactive constituents where necessary, and classifying contaminants when necessary.

Bioequivalence: The Generic Drugs User Fee Act's (GDUFA) increased filing fees for the Abbreviated New Drug Application (ANDA) and the difficulty in achieving safety and effectiveness requirements add to the burden placed on generic medication developers. In the event of complicated products, the procedures for proving bioequivalence might not be available, in which case FDA guidance would need to be obtained. Since 2013, the FDA has mandated the use of Quality by Design (QbD) in order to guarantee the quality of the generic drugs made available to consumers and to identify ways to improve the manufacturing process.

Bioequivalence

The biochemical similarity amongst two (or more) drugs with the similar active ingredient(s) and patient-wanted outcome(s) is known as bioequivalence. When administered at the same molar dose under similar conditions in a study that is properly designed, it is the absence of an apparent distinction in the rate and extent that determines whether the active ingredient or active moiety in pharmaceutical alternatives or pharmaceutical alternatives turns accessible at the site of drug action. To determine the amount and rate of absorption, the three main measures are AUC (area under the curve), Cmax, and T max [23] in bioequivalence studies and a generic product must prove that it is bioequivalent to its respective innovator product.

Q1/Q2 Requirement for Generic Parenteral Products

Typically, a drug product intended for topical use, solutions for aerosolization or nebulization, or nasal solutions must contain the same inactive ingredients (Q1) as the reference listed drug. Similarly, a drug product aimed for intravenous administration must contain the same inactive ingredients (Q1) and in the same concentration (Q2) as the reference listed drug.

Q1/ Q2 assessments

Q1: What is the name of the inactive ingredient? An applicant must offer comprehensive details on the chemistry, grade, and, if necessary, characterization data for each inactive substance.

Q2: Use the formula [(T-R)/R] x 100 to calculate the difference (%) between an inactive ingredient in the Test (T) and Reference (R) goods. The variation shouldn't be greater than 5%.

How to characterize similarity?

(Components & composition) Q1/Q2 Similarity reduces the risk of known failure modes relating to vehicle contribution to efficacy, formulation contact with diseased skin, irritation, and sensitization, stability, solubility, etc. of the drug. Q3: Structural similarity: known as arrangement of matter i.e., same amounts of the same components arranged in the same way [23].

Challenges bioequivalence complex generics

- Mechanistic modeling and simulation are frequently used by the FDA's Office of Generic Drugs to support regulatory decision-making, and it has directly aided in the development of modeling.
- Physiologically based pharmacokinetic (PBPK) modeling and computational fluid dynamics (CFD) modeling are two examples of these mechanistic modeling techniques.
- Mechanistic modeling offers an acceptable alternative way for establishing BE that does not require the necessity for extensive comparison clinical endpoint BE studies in patients, making it a tool that can be utilized to enhance access to complex generics.
- Mechanistic modeling can also be quite useful in non-complex oral drug items to assist alternative BE techniques.
- Mechanistic modeling of generic drug compounds for oral inhalation.
- Mechanistic modeling of generic pharmaceuticals for the skin.
- Mechanistic modeling of additional generic drugs with local action.
- Oral PBPK as a substitute BE strategy.
- Oral PBPK for assessing how diet affects BE.
- Oral PBPK difficulties and victories.

Reverse engineering and characterization of the drug product

Reverse engineering, which is the process of decoding the formulation characteristics of an innovative product, can make it easier to determine the excipient composition of the original medicine and carry out further formulation optimization stages. These variables include the active pharmaceutical ingredient's

(API) solid-state characterization, the production method, and the innovator product's quantitative makeup. Molecular, particle, or bulk solid-state properties of the API can be identified (for more information, see the sidebar titled "Importance of solid-state properties for pharmaceuticals"). Goods alike crystalline forms, hydrates, solvates, and amorphous forms are all included at the molecular level. These forms are distinct from one another in terms of solubility, manufacture ability, bioavailability, and stability due to variations in intermolecular configurations and free energy.

Using methods like differential solubility, filtration (with filters of a particular pore size or molecular weight cutoff), high-performance liquid chromatography (HPLC), high-performance thin-layer chromatography (HPTLC), and size-exclusion chromatography, the excipient must first be separated from the tablet matrix. The quantity of interfering components present and their physicochemical characteristics must be taken into account while choosing the separation approach. A gravimetric or detection tool, such as ultraviolet (UV)-visible light, the refractive index, an evaporative light-scattering detector for HPLC, or spectroscopic methods (such as infrared attenuated transmittance reflectance or near-infrared [NIR] spectrometry), must be used for quantification after separation [24, 25].

Wet granulation, dry granulation, or direct compression can be used to establish solid oral dosage forms, depending on the API's stability profile, the API-total tablet weight ratio, and the physical technical qualities (such as the flow characteristics and compressibility of the main ingredients). The drug's stability and performance in the in vitro and in vivo environment (i.e., solubility and bioavailability) can be impacted by the manufacturing technique in addition to process capabilities. A generic pharmaceutical company's success depends on cost and quickness of market entry. Development must focus on achieving bioequivalence to the RLD while reducing the possibility of bio failures. To more effectively verify bioequivalence, reverse engineering is a useful strategy when creating generic products. A sound reverse-engineering approach that includes the solid-state characterization of the API, the manufacturing procedure, and the decoding of the quantitative formula of the RLD may shorten development times and lower costs [24, 25].

Need for reverse engineering of innovator products

Lacunae of generic companies: empirical methodology for product development, traditional manufacturing process, Poor product and process understanding, stringent timelines and sometime unrealistic. Reverse engineering helps in Mechanistic methodology for product development, ease of developing strategies formulation development, reduce the number of batches for stability, reduce the cost and time of development, generating meaningful data (Product metrics) which will help for product life cycle management [24, 25].

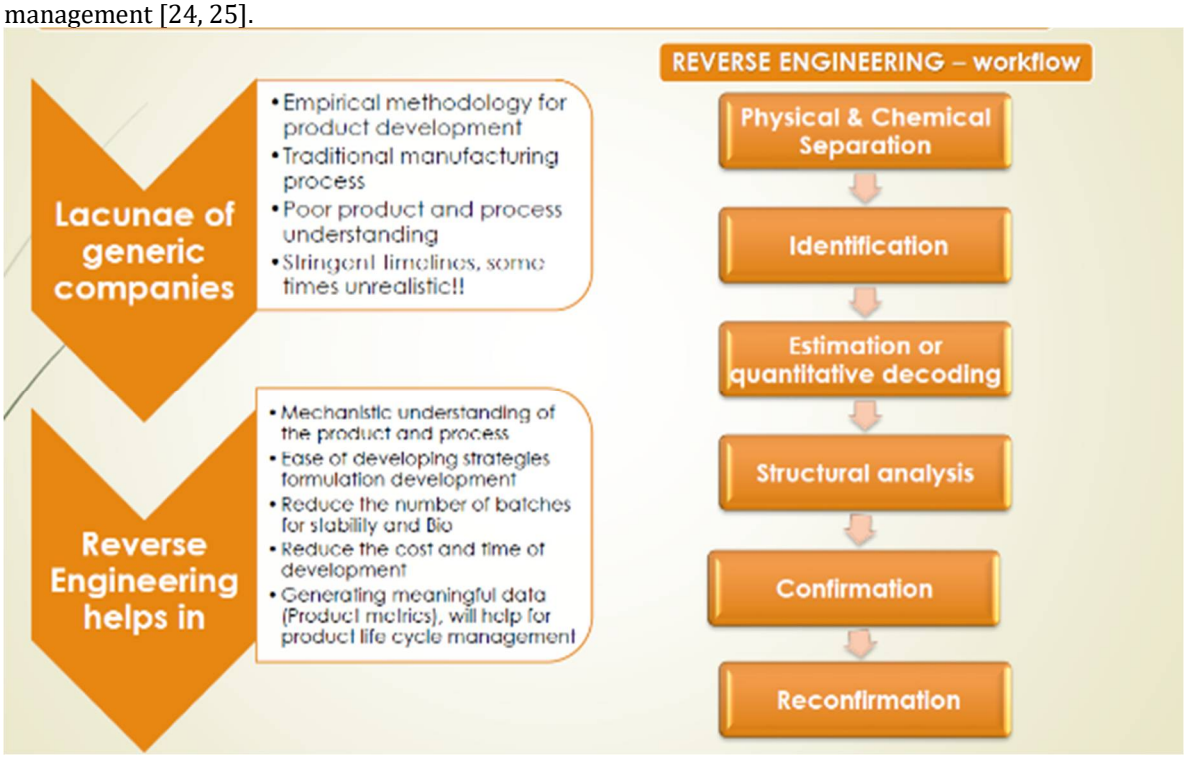

Figure 3: Reverse engineering needs and workflow

Challenges in Generic product development research

The three main areas are mainly concerned or challenges for successful stability (critical excipient evaluation), Stability prediction and Qbd establishment to avoid SUPAC. This review will help in research and educational scholars or companies to characterize or development of complex generics.

CONCLUSION

This review examines some R&D concepts, current trend and research scenario that are more appropriate for their set-up. Certainly, this report also provides a criteria and difficult challenges and complexities in generic development for the pharmaceutical industry. Companies which want to be top among the generic product development research in the pharmaceutical industry can gain some the knowledge or develop knowledge integrator models by this article.

ACKNOWLEDGMENT

The author(s) received no financial support for the research, authorship, and/or publication of this article.

CONFLICT OF INTEREST

Conflict of interest declared none

AUTHOR'S CONTRIBUTION

All three authors have contributed in the research design and data collection and review and to the writing of the manuscript.

REFERENCES

1. Alfonsa-Cristancho, R., Andia, T., Barbosa, T., & Watanabe, J.H. (2015). Definition and Classification of Generic Drugs across the World. Applied Health Economics and Health Policy, https://www.ncbi.nlm .nih.gov/pmc/articles/PMC451962
2. Overview of Generic Drug. (n.d). (2017). Retrieved January 20, http://msdmanuals.com/home/drugs/brand-name-and-genericdrugs/overview-of-generic-drugs-and-drugnaming
3. CDER/USFDA., (2014). June, Guidance for Industry ANDA Submission- Content and Format of Abbreviation New Drug Application, 1-29.
4. CDER/USFDA. (2014). ANDA Filing Checklist, us-fda, 1-12.
5. CTD chart. Retrieved January 20 http://uploadWikimedia.org/Wikipedia/commons/c/c2/CTD_img 004.gif.
6. Naiqi Ya, (2014). Inactive Ingredient Database -FDA Update - June 18, Acting Director for Chemistry Division IV Office of Generic Drugs Food and Drug Administration, The USP Excipient stakeholder Forum.
7. (2004). Retrieved June 10, http://www.fda.gov/ohrms/dockets/ac/03/slides/3968S1_02_FDA-Mele.ppt#8,
8. (2012). Retrieved January 12, http://www.wikipedia.org/wiki/European_Union
9. (2019). Retrieved January 29, http://www.canada.ca
10. Guidance for Industry Submission of Summary Bioequivalence Data for ANDAs.
11. Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products
12. Guideline on stability testing for application, ema/champ/cvmp/qwp/441071/2011_rev. 2. Retrieved January 19, www.ema.europa.eu/docs/en_gb/document_library/seientific_guideline/2014/04/wc500164972.pdf.
13. U.S. FDA. Generic Drug User Fee Amendments (GDUFA). (2017). Retrieved October 31, https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm
14. U.S. Food & Drug Administration. Abbreviated New Drug Application (ANDA). (2017). Retrieved November 28, https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm. Accessed 28 Nov 2017.
15. Meghraj, S., (2020). An overview on comparative study of registration requirements for generics in US, Canada and Europe. International Journal of Research in Pharmaceutical sciences and Technology. 1(4), 117-123. DOI: https://doi.org/10.33974/ijrpst.v1i3.196
16. Scrip (2019). Bristol/Celgene made perfect sense, but doesn't provide Big M& A year, EY says. Retrieved November 28, https://scrip.pharmaintelligence.informa.com
17. Drivers of Indian pharmaceutical exports, RBI Bulletin, July 2021, pg.no. 53.
18. GCC generic drug market, industry trends, share size, growth, opportunity and forecast, 2017-2022 by business wire.
19. Generic drug and biosimilar access and savings in the U.S report association for accessible medicines (AAM), 2020.
20. Draft Guidance, USFDA, CDER, Oct. 2017 generics, determining whether submit an ANDA or A 505(b) 2 application guidance for industry.
21. Retrieved November 28, https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/patent-certifications-and-suitability-petitions
22. Hauschke, et al. (2007). Bioequivalence studies in drug development–methods and applications, John Wiley and sons Ltd.
23. Niazi, S.K., (2007). Handbook of bioequivalence testing, Drugs and the pharmaceutical sciences, Informa healthcare, New York.
24. Retrieved November 28, www.fda.gov via https://accessiblemeds.org/sites/default/files/2019 11/ Xiaohui_%28Jeff%29_Jiang_GRxBiosims2019.pdf.

25. Haleblian, J.K., (1975). Characterization of Habits and Crystalline Modification of Solids and their Pharmaceutical Applications. Journal of pharmaceutical sciences, 64(8), 1269–1288. DOI: 10. 1002/jps.2600640805

CITATION OF THIS ARTICLE

Shalini M, Salman A , Mohammad K A K. Host Immune Response to B. pseudomallei Infection: Insights for Therapeutic Strategies and Vaccine Development . Bull. Env. Pharmacol. Life Sci., Vol 12 [9] August 2023: 320-329