Pharmaceuticals Export Promotion Council of India

(Set up by Ministry of Commerce & Industry, Government of India)

REGULATORY & MARKET PROFILE OF UNITED STATE OF AMERICA

Demography

SL. No	Parameter	Description
1	Region	North America
2	Country	United States of America
3	Capital	Washington, D.C.
4	Population	326,625,791 (July 2017 est.)
5	Population growth rate (%)	0.81% (2017 est.)
6	GDP (purchasing power parity)	$19.36 trillion (2017 est.)
7	GDP - real growth rate (%)	2.2% (2017 est.)
8	GDP - per capita (PPP)	$59,500 (2017 est.)
9	Epidemiology	Ischemic heart disease, Alzheimer disease, Lung cancer, Cerebrovascular disease, COPD Lower Respiratory tract Infections etc
10	Population below poverty line	15.1% (2010 est.), No update available
11	Age structure (%)	0-14 years: 18.73%
		15-24 Years: 13.27%
		25-54 years : 39.45%
		55-64 years: 12.91%
		65 years & over: 15.63%
Source: CIA World Fact Book updated to july 2017		

MARKET REPORT

Introduction

The US will continue to reinforce its position as the leading pharmaceutical manufacturer. The majority of the largest drugmakers are based in the country, and these firms are outperforming rivals in Western Europe and Japan. Considerable investments in R&D by US companies is resulting in the introduction of increasing numbers of new products, which are produced locally for domestic demand and exported for foreign markets. Over time, however, US manufacturing of mature products is often offshored to lower cost bases and integrated in global pharmaceutical supply chain.

Pharma market has touched $ 373 Billion in 2017 and is expected to grow to $ 385 billion in 2018 with a growth of 3.2%.

Key trends

- In May 2018,President Trump issued his blueprint on lowering drug prices; the proposals are contained in a document, entitled: American Patients First - The Trump Administration Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs. Department of Health and Human Services (HHS) Secretary Alex Azar, commented in a press briefing that there are four major problems the US faces: high list prices for drugs; government rules that hinder negotiations for the Medicare programme; foreign countries 'freeriding off of America innovation;' and high out-of-pocket costs. The blueprint also focuses on generic and biosimilar drugs.
- The value of pharmaceutical exports from the US will remain essentially level over the next five years, increasing marginally from USD43.38bn in 2017 to USD43.83bn in 2022. This low rate of growth aligns with the recent historic average. The leading destination for US-produced pharmaceuticals is Belgium (USD3.13bn), followed by Canada (USD2.36bn) and Japan (USD2.26bn). As of 2017, the US exported the third highest value of pharmaceuticals, behind Germany (USD74.56bn) and Switzerland (USD68.31bn). If Puerto Rico is considered part of the US (it is an unincorporated territory of the US), annual pharmaceutical exports from the US would exceed USD80bn.
- In May 2018, the FDA approved Retacrit (epoetin alfa-epbx) as a biosimilar to Epogen/Procrit (epoetin alfa) for the treatment of anemia caused by chronic kidney disease, chemotherapy, or use of zidovudine in patients with HIV infection. It is the first epoetin alfa biosimilar approved in the US for the treatment of anemia.
- An analysis released by the US Department of Health and Human Services' (HHS) Office of the Assistant Secretary for Planning and Evaluation (ASPE) has found that the Medicare programme, through its Part D plans, spent nearly USD9bn on brand name drugs when generic equivalents were available [1]. Had these prescriptions been dispensed as generics, the Part D programme and its beneficiaries would have saved nearly USD3bn.
- Citing data from an IQVIA(Earlier IMS) report, the ASPE analysis noted that by 2017, 90% of retail prescriptions filled in the US were for generics. With regard to the Medicare Part D programme, in 2014, 85% of prescriptions paid for in Medicare Part D plans were for generics,

up from 61% in 2007 and rising to 86% in 2016. Despite accounting for 86% of prescriptions, generics accounted for just 16% of total Part D spending in 2016. The report added that recent press coverage of price increases for brand drugs when generics are available highlight a potential need for regulatory or policy action, although in some cases, continued use of a brand drug may be medically warranted.

Strengths

- The world's largest pharmaceutical market by a significant margin.
- High per capita spending means access to high-value products.
- Limited pricing restrictions allow for high pricing.(present Crisis is the negotiations between distributors & companies)
- Strong intellectual property environment.
- World-leading R&D base.
- Direct-to-consumer advertising.

Weaknesses

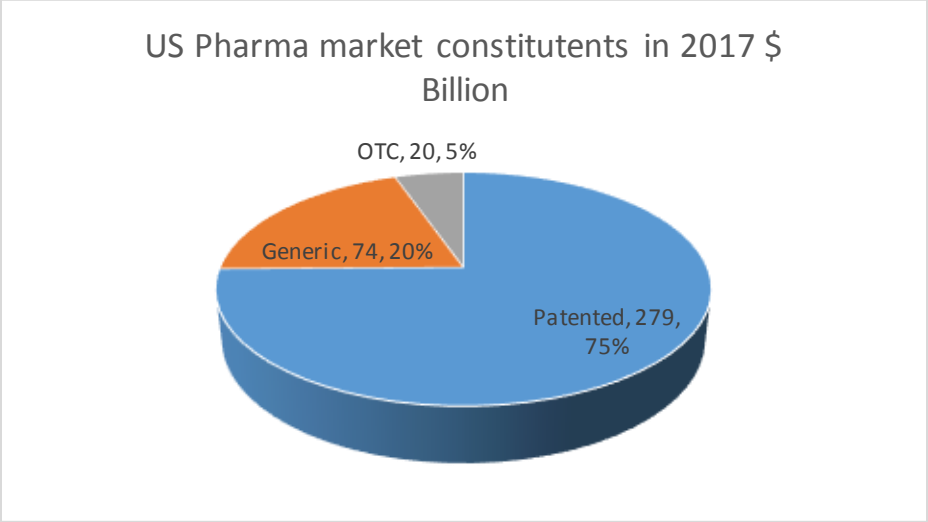
- A high proportion of the population is still uninsured, meaning many patients struggle to afford treatments.
- Growth rates are moderate, which is typical of a mature market.
- High operating costs limit export potential.
- Gaps in Medicare scheme limit access for certain patient populations.

Opportunities

- Rising generic penetration is a cause for optimism among generic drugmakers.
- Biosimilar legislation could open new market, but will extend exclusivity for originator biologics.
- Reform should give medicine access to many millions of uninsured patients.
- Growing and ageing population.
- Obesity boom to substantially increase non-communicable disease burden

Market

The US pharmaceutical market is a refuge for the leading drugmakers. Despite the recent drug price discourse, it is highly unlikely that punitive price controls, as witnessed across Europe, will be introduced. The market is also underpinned by political stability, unlike many emerging markets, and a recovering economy. Healthcare reform places downward pressure on margins and patent expiries will compress headline growth. Unique attributes include a highly liberalised advertising environment and a culture of over-medication.



Updates

Cancer has reinforced its status as the leading therapeutic area in terms of sales, and monoclonal antibodies are also proving their value to R&D-based firms

The 'Tax Cuts and Jobs Act' was pushed through by congressional Republicans and the Trump administration late in 2017. It reduces the Federal corporate income tax rate from 35% to 21%, and transitions the US international taxation system from a worldwide tax structure to a territorial tax arrangement. It also imposes a repatriation tax that is repayable over eight years on foreign earnings. Many leading US pharmaceutical companies explicitly welcomed the long-awaited legislation, and said that the changes will 'level the playing field' with foreign competitors. Tax reform would also provide more flexibility to their deployment of capital, such as R&D spending, share repurchases, reducing leverage and dividend payments.

US citizen consume large amounts of medicine and generally prefer branded drugs. Annual per capita spending will rise to USD1,179. Patented drugs account for the majority of the market (75%), and this will increase marginally over the 10-year forecast period, despite the uptake of generic drugs increasing as a cost-containment mechanism. Pharmaceutical spending as a percentage of GDP is 1.9%, which is above the global average of 1.5%. Through to 2027, this percentage in the US is expected to fall to 1.8%, in line with downward price pressures and patent expirations.

Despite increased accessibility to healthcare provision in the US, which will occur as a result of the nation's healthcare reform, the rising financial burden on healthcare insurance providers, the slow growth rates for consumer spending and the limited scope for market expansion (due to maturity) will conspire to keep pharmaceutical sales growth rates in low single-digit figures over the medium-term, at least. In the long-term, due to greater government involvement in state healthcare, pricing restrictions are likely to accelerate, possibly eroding profit margins and favouring the generic drug industry.

Implementation of an effective universal health insurance system will enable drugmakers to gain better access to a patient population of as many as 42mn people without health insurance.

Generic Drug Market

Size of US generic market in 2017 was $74 billion constituting 20% by value. However it is estimated that 87% of the prescriptions generated are of generic.

Generic drugs are generally favoured by patients, payers and prescribers, and this supports the outlook for the generic drug market. Companies that manage drug benefit plans, such as Express Scripts, are promoting the use of generic drugs by offering lower co-payments. In turn, this is reducing out-of-pocket expenditure for consumers. Through to 2022, generic drugs will continue to capture market share, with an acceleration rate.

In January 2018, the US Government Accountability Office (GAO) issued a report to Congress in which it recommends that the FDA make public its plans to issue and revise guidance on non-biological complex drugs (NBCDs). The report came about after the GAO was asked to assess the FDA's process for reviewing generic versions of NBCDs. The report identifies the scientific challenges the review of generic versions of NBCDs may present and identifies and evaluates the steps the FDA has taken that may help address the challenges related to the review of generic NBCDs. The GAO examined the FDA's product-specific guidance, and reviewed information related to the five NBCDs for which a generic version was approved prior to FY17. The GAOalso interviewed FDA officials and a selection of 19 stakeholders, including brand name drug sponsors, generic NBCD sponsors of both approved and not-yetapproved generics and external expert groups.

The US FDA approved 844 abbreviated new drug applications (ANDAs) in 2017, the highest number approved for the third consecutive year. This was 32.9% higher than the 635 new ANDAs approved in 2016 and represents the most ANDAs ever approved in a single year. Between 2002 and 2017.

By 2022, the generic drug market is forecast to reach a value of USD80.3bn, up from USD73.8bn in 2017,(BMI source) growing at a compound annual growth rate (CAGR) of 1.9%. Through to 2027, the market is likely to see moderate growth, with a CAGR of 1.4% projected over the full 10-year period.

Pharmaceutical Trade Forecast

The US will continue to reinforce its position as the leading pharmaceutical manufacturer. The majority of the largest drugmakers are based in the country, and these firms are outperforming rivals in Western Europe and Japan. Considerable investments in R&D by US companies is resulting in the introduction of increasing numbers of new products, which are produced locally for domestic demand and exported for foreign markets. Over time, however, US manufacturing of mature products is often offshored to lower cost bases and integrated in global pharmaceutical supply chain.

USA has exported $ 43.4 bn worth of Pharmaceuticals in 2017 and is likely to export $ 43.8 billion in 2018.

The leading destination for US-produced pharmaceuticals is Belgium (USD3.13bn), followed by Canada (USD2.36bn) and Japan (USD2.26bn). As of 2017, the US exported the third highest value of pharmaceuticals, behind Germany (USD74.56bn) and Switzerland (USD68.31bn).

The value of pharmaceuticals imported into the US will increase steadily over the next five years, increasing from USD91.21bn in 2017 to USD106.95bn in 2022.

The leading country of origin for US-imported pharmaceuticals is Germany (USD9.87bn), followed by Ireland (USD9.25bn) and Switzerland (USD8.63bn). As of 2017, the US imports the highest value of pharmaceuticals, and this is significantly more than Germany (USD48.65bn), Belgium (USD35.65bn) and the UK (USD33.14bn).

Risk/Reward Index for investing

With a score of 87.2out of 100, the US pharmaceutical market ranks first both regionally and globally within BMI's Innovative Pharmaceutical Risk/Reward Index, a reflection of its unquestionable attractiveness and limited risks relative to other markets.

Statistics:

India's Pharmaceutical exports to U S A $ Million					
Category	**2015-16**	**2016-17**	**2017-18**	**GR%**	**Contbn to Region**
BULK DRUGS AND DRUG INTERMEDIATES	402.97	361.07	352.83	-2.28	89.05
DRUG FORMULATIONS AND BIOLOGICALS	4984.35	5040.70	4599.74	-8.75	96.21
AYUSH	7.41	10.98	14.27	29.86	93.52
Herbal Products	81.02	94.90	105.08	10.72	97.39
Surgicals	29.08	38.75	42.64	10.03	96.85
Vaccines	8.95	17.13	1.78	-89.61	99.76
Total	5513.78	5563.54	5116.32	-8.04	95.70

IMPORTS

Top Ten Importing Partners of USA $ Million						
Rank	Country	2014	2015	2016	Gr%	Share%
1	Ireland	10356.31	15180.82	15855.94	4.45	17.16
2	Germany	14087.48	14598.36	13420.27	-8.07	14.52
3	Switzerland	9609.64	9454.09	10272.70	8.66	11.11
4	India	4949.05	6085.60	7567.14	24.35	8.19
5	United Kingdom	3847.15	5190.92	5383.00	3.70	5.82
6	Israel	4460.44	5979.50	5089.94	-14.88	5.51
7	Canada	4404.23	5260.43	4951.59	-5.87	5.36
8	Italy	2263.92	3159.41	4390.31	38.96	4.75
9	Denmark	3082.23	3364.27	3727.64	10.80	4.03
10	France	2491.81	2827.01	2890.90	2.26	3.13
	World	72959.23	85927.04	92422.63	7.56	100.00
Source: UN comtrade						

REGISTRATION AND LICENSING REQUIREMENTS

➢ Regulatory Authority	:	**U.S. Food & Drug Administration**
➢ Website of regulatory Authority	:	http://pharmacyboardkenya.org/
➢ Fees for Drug Registration	:	USD 1,71,823
➢ Normal time taken for registration	:	12-18 Months
➢ Registration Requirement [Dossier Format]	:	CTD
➢ Whether plant inspection is mandatory	:	Yes
➢ Requirement of Local agent/ Subsidiary	:	Subsidiary is required for supplying to public procurement agencies.

FDA is an agency within the Department of Health and Human Services.

The FDA's organization consists of the Office of the Commissioner and four directorates overseeing the core functions of the agency: Medical Products and Tobacco, Foods, Global Regulatory Operations and Policy, and Operations.

❖ Office of Commissioner:- National Center for Toxicological Research

1. Office of Medical Products and Tobacco:
   - Center for Devices and Radiological Health
   - Center for Drug Evaluation and Research
   - Center for Tobacco Products
   - Center for Biologics Evaluation and Research
   - Office of Special Medical Programs
   - Oncology Center of Excellence
2. Office of Foods & Veterinary Medicine:
   - Centre for Food Safety and Applied Nutrition
   - Centre for Veterinary Medicine
3. Office of Global Regulatory Operations and Policy,:
   - Office of International Programs
   - Office of Regulatory Affairs

4. Office of Operations:
    - Office of Equal Employment Opportunity
    - Office of Finance, Budget and Acquisitions
    - Office of Information Management and Technology

The Centre for Drug Evaluation and Research (CDER) regulates over-the-counter and prescription drugs, including biological therapeutics and generic drugs.

Laws, Regulations, Policies and Procedures

The mission of FDA is to enforce laws enacted by the U.S. Congress and regulations established by the Agency to protect the consumer's health, safety, and pocketbook. *The Federal Food, Drug, and Cosmetic Act* is the basic food and drug law of the U.S. The law is intended to assure consumers that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging is truthful, informative, and not deceptive.

Code of Federal Regulations (CFR)

The final regulations published in the *Federal Register* (daily published record of proposed rules, final rules, meeting notices, etc.) are collected in the *Code Of Federal Regulations (CFR)*. The *CFR* is divided into 50 titles that represent broad areas subject to Federal regulations. The FDA's portion of the *CFR* interprets the *The Federal Food, Drug, and Cosmetic Act* and related statutes. *Section 21 of the CFR* contains most regulations pertaining to food and drugs. The regulations document all actions of all drug sponsors that are required under Federal law.

How Drugs are Developed and Approved:

Types of Applications:

(1) INDs: Investigational New Drugs
(2) NDAs: New Drug Applications
(3) ANDAs: Abbreviated New Drug Applications for Generic Drug products

(1) INDs (Investigational New Drugs):

It's an application filed to the FDA in order to start clinical trials in humans if the drug was found to be safe from the reports of Preclinical trials. The IND application should provide high quality preclinical data to justify the testing of the drug in humans. A firm or institution, called a Sponsor, is responsible for submitting the IND application.

There are three IND types:

- An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.
- Emergency Use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR , Sec. 312.23 or Sec. 312.20. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.
- Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

There are two IND categories:

- Commercial
- Research (non-commercial)

The IND application must contain information in three broad areas:

- Animal Pharmacology and Toxicology Studies - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experience with the drug in humans (often foreign use).
- Manufacturing Information - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.
- Clinical Protocols and Investigator Information - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators--professionals (generally physicians) who oversee the administration of the experimental compound--to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.

Once the IND is submitted, the sponsor must **wait 30 calendar days** before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk.

The following regulations apply to the IND application process:

21CFR Part 312 Investigational New Drug Application

21CFR Part 314	INDA and NDA Applications for FDA Approval to Market a New Drug (New Drug Approval)
21CFR Part 316	Orphan Drugs
21CFR Part 58	Good Lab Practice for Nonclinical Laboratory [Animal] Studies
21CFR Part 50	Protection of Human Subjects
21CFR Part 56	Institutional Review Boards
21CFR Part 201	Drug Labeling
21CFR Part 54	Financial Disclosure by Clinical Investigators

For guidelines on IND applications please refer
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm#FDA%20Guidances%20for%20Investigational%20New%20Drugs

(2) NEW DRUG APPLICATION (NDA):

A new drug application (NDA) can be filed only when the drug successfully passes all three phases of clinical trials and includes all animal and human data, data analyses, pharmacokinetics of drug and its manufacturing and proposed labelling. The preclinical, clinical reports and risk-benefit analysis (product's beneficial effects outweigh its possible harmful effects) are reviewed at the Centre for Drug Evaluation and Research by a team of scientists. If clinical studies confirm that a new drug is relatively safe and effective, and will not pose unreasonable risks to patients, the manufacturer files a New Drug Application (NDA), the actual request to manufacture and sell the drug in the United States.

Generally approval of an NDA is granted within two years (on an average), however, this process can be completed from two months to several years. The innovating company is allowed to market the drug after the approval of an NDA and is considered to be in Phase IV trials. In this phase, new areas, uses or new populations, long-term effects, and how participants respond to different dosages are explored.

The goals of the NDA are to provide enough information to permit FDA reviewer to reach the following key decisions:

- Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.

- Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain.
- Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

Regulatory provision in Federal Law for NDA:

21CFR Part 314 - Applications for FDA Approval to Market a New Drug or an Antibiotic Drug.

Prescription Drug User Fee Act (PDUFA):

The Prescription Drug User Fee Act (PDUFA) was created by Congress in 1992 and authorizes FDA to collect fees from companies that produce **new human drugs and biological products**. PDUFA must be reauthorized every five years, and was renewed in 1997 (PDUFA II), 2002 (PDUFA III), 2007 (PDUFA IV), and 2012 (PDUFA V) and 2017 (PDUFA VI).

FDA is authorized to collect three types of user fees from applicants who submit certain new drug and biological product applications. They are

(1) ***Application Fee: Clinical Data required:*** A human drug application for which clinical data (other than bioavailability or bioequivalence studies) with respect to safety or effectiveness are required for approval is assessed a full application fee

(2) ***Application Fee: Clinical Data Not required:*** A human drug application for which clinical data with respect to safety or effectiveness are not required for approval is assessed one- half of a full fee.

(3) ***Program fee:*** Prescription drug product program fees are assessed annually for eligible products/ approved products as of October 1st of such fiscal year.

PDUFA User Fee Rates FY 2018 (posted 9/15/2017):

Application Fee – Clinical Data Required	$2,421,495
Application Fee – No Clinical Data Required	$1,210,748
Program Fee	$304,162

NDA Forms and Electronic Submissions

- Form FDA-356h. Application to Market a New Drug, Biologic, or An Antibiotic Drug For Human Use
    - Form FDA-356h instructions
- Form FDA-3397. User Fee Cover Sheet

- Form FDA-3331. New Drug Application Field Report
- Guidance Documents for Electronic Submissions

For guidelines on NDA applications please refer
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm

3) ABBREVIATED NEW DRUG APPLICATION (ANDA):

An abbreviated new drug application (ANDA) contains data which is submitted to FDA for the review and potential approval of a **generic drug product**.

A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use. All approved products, both innovator and generic, are listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book).

Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is performs in the same manner as the innovator drug. One way applicants demonstrate that a generic product performs in the same way as the innovator drug is to measure the time it takes the generic drug to reach the bloodstream in healthy volunteers i.e Generic drug should be Bioequivalent with the Innovator drug.

Hatch-Waxman Act & Amendments (Drug Price Competition and patent Term Restoration Act of 1984):

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (Hatch-Waxman Amendments) added section 505(b)(2) and 505(j) to the FD&C Act, which describe abbreviated approval pathways under the FD&C Act for drug products regulated by the Agency. With the passage of the Hatch-Waxman Amendments, the FD&C Act describes different routes for obtaining approval of two broad categories of drug applications: new drug applications (NDAs) and abbreviated new drug applications (ANDAs).

NDAs and ANDAs can be divided into the following four categories

(1) A "**Stand-alone NDA**" is an application submitted under section 505(b)(1) and approved under section 505(c) of the FD&C Act that contains full reports of investigations of safety and effectiveness that were conducted by or for the applicant or for which the applicant has a right of reference or use.

(2) A **505(b) (2) application** is an NDA submitted under section 505(b)(1) and approved under section 505(c) of the FD&C Act that contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use. For 505(b)(2) applications, applicant can rely on the following information

(a) Published Literature
(b) The Agency's finding of safety and effectiveness for an approved drug

A proposed generic drug may differ in significant ways from the Reference Listed Drug (RLD).Under these circumstances, the proposed generic drug must be approved through the Section 505(b)(2) paper NDA application process, which is a hybrid of a full NDA and an ANDA. This application includes less data than an NDA but more data than an ANDA.

What kind of application can be submitted as a 505(b)(2) application?

1. **New chemical entity (NCE)/new molecular entity (NME)**

   A 505(b)(2) application may be submitted for an NCE when some part of the data necessary for approval is derived from studies not conducted by or for the applicant and to which the applicant has not obtained a right of reference. For an NCE, this data is likely to be derived from published studies, rather than FDA's previous finding of safety and effectiveness of a drug. If the applicant had a right of reference to all of the information necessary for approval, even if the applicant had not conducted the studies, the application would be a considered a 505(b)(1) application.

2. **Changes to previously approved drugs**

   For changes to a previously approved drug product, an application may rely on the Agency's finding of safety and effectiveness of the previously approved product, coupled with the information needed to support the change from the approved product. The additional information could be new studies conducted by the applicant or published data.

Examples of 505(b)(2) Applications:

Examples of changes to approved drugs for which 505(b)(2) applications should be submitted are as follows: Changes in

- Change in Dosage form.
- Change in Strength.
- *Change in Route of administration.*
- *Substitution of an active ingredient in a combination product*.
- *Change in Formulation* like different quality or quantity of an excipient(s) than the listed drug
- *Change in Dosage regimen*, such as a change from twice daily to once daily

- *Change in Active Ingredient* such as a different salt, ester, complex, chelate, clathrate, racemate, or enantiomer
- *New molecular entity*, this is likely if the NME is the prodrug of an approved drug or the active metabolite of an approved drug
- *Combination product*, in which the active ingredients have been previously approved individually
- *Indication*. An application for a not previously approved indication for a listed drug
- *Rx/OTC switch*
- *OTC monograph*, a drug product that differs from a product described in an OTC monograph
- *Naturally derived or recombinant active ingredient*, where clinical investigations are necessary to show that the active ingredient is the same as an active ingredient in a listed drug

(3) An **ANDA** is an application for a duplicate of a previously approved drug product that was submitted and approved under section **505(j)** of the FD&C Act. An ANDA relies on FDA's finding that the previously approved drug product, i.e., the reference listed drug (RLD) is safe and effective. An ANDA generally must contain information to show that the proposed generic product

a) is the same as the RLD with respect to the active ingredient(s), conditions of use, route of administration, dosage form, strength, and labelling (with certain permissible differences) and

b) is bioequivalent to the RLD.

An ANDA may not be submitted if studies are necessary to establish the safety and effectiveness of the proposed product.

An ANDA may contain certain types of differences from an RLD (e.g. a change approved in a suitability petition or other permissible differences, such as certain differences in inactive ingredients, labelling, or container closure systems), as long as investigations are not necessary to establish the safety or effectiveness of the drug product proposed in the ANDA.

(4) A **petitioned ANDA** is a type of ANDA for a drug product that differs from the RLD in its dosage form, route of administration, strength, or active ingredient (in a product with more than one active ingredient) and for which FDA has determined, in response to a petition submitted under section 505(j)(2)(C) of the FD&C Act (suitability petition), that studies are not necessary to establish the safety and effectiveness of the proposed drug product.

Bundling:

In some circumstances, an applicant may seek approval for multiple drug products containing the same active ingredient(s) when some of these products would qualify for approval under the section 505(j) pathway and some would qualify for approval under the 505(b)(2) pathway. In these

circumstances, FDA has permitted an applicant to submit a single 505(b)(2) application for all such multiple drug products that are permitted to be bundled in a single NDA.

For example, an applicant seeking approval for multiple strengths of a product, only some of which are listed in the Orange Book as RLDs, would not have to submit both an ANDA for the strengths listed in the Orange Book and a 505(b) (2) application for the new strengths; instead, the applicant may submit one 505(b) (2) application for all of the proposed strengths.

Guidance document on "Determining Whether to Submit an ANDA or a 505(b)(2) Application" @ https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM579751.pdf.

NEW DRUG EXCLUSIVITY

A) Non-patent Exclusivities

Types	Term
Orphan drug exclusivity	**7 years**
New chemical entity exclusivity	**5 years**
New clinical study exclusivity	**3 years**
Pediatric exclusivity	**6 months**

(1) Orphan drug exclusivity: 07 Yrs.

Which is granted to drugs:

a) That treat a disease or condition that affects less than 200,000 people in the US; or
b) For which it is unlikely that US sales of the drug will recoup its development costs.

(2) New chemical entity (NCE) exclusivity: 05Yrs

This is granted if the FDA has not previously approved the "active drug moiety."

- NCE exclusivity bars a generic drug company from filing an application for approval of a generic drug five years from the first approval of the relevant NDA.
- However, a generic drug company may file an ANDA with a Paragraph IV certification four years after the first NDA approval.

(3)New clinical study exclusivity: 03Yrs

This applies when new clinical studies lead to new or changed formulations, dosing regimens or patient population. The applicant is entitled to this exclusivity if an application or supplement contains reports of new clinical investigations conducted or sponsored by the applicant that were essential for approval.

This exclusivity, sometimes called data exclusivity, prohibits the FDA from approving a generic drug application for the new dosage form or use for three years after the first NDA approval. However, it does not otherwise bar approval of generic drug applications.

(4)Pediatric exclusivity: 06 months

This applies if the FDA requested that the NDA holder conduct studies with the drug in pediatric populations. Pediatric exclusivity adds six months of exclusivity to any marketing or patent exclusivity.

B) Patent exclusivity and the orange book

An NDA holder must provide the FDA with the patent number and expiration date of any patent that claims either:

a) The drug, including the active ingredient and the formulation for the active ingredient.

b) A method of using the drug, but not other inventions such as metabolites, synthetic intermediates; or methods of making the drug.

When the FDA approves the NDA, the FDA publishes the patent information in the FDA's Approved Drug Products with Therapeutic Equivalence Determinations publication (also called the Orange book)

CHALLENGING PATENT EXCLUSIVITY

A generic drug company submitting either an ANDA or a Section 505(b)(2) application must make one of the following four certifications as to each patent listed in the Orange Book for an RLD:

a) Paragraph I certification that no relevant patent is listed in the Orange Book-
(FDA can approve ANDA when ready)

b) Paragraph II certification that the listed patent has expired.
(FDA can approve ANDA when ready)

c) Paragraph III certification that the listed patent, plus any other exclusivity, will expire before the requested approval.
(FDA can approve ANDA when patent expires and ANDA is ready)

d) Paragraph IV certification (PIV) that the listed patent is invalid or will not be infringed by the drug product proposed in the ANDA- (Complex approval landscape)

What brand must do: "list" Patents

- NDA sponsor must submit patents for listing within 30 days of approval of NDA or supplement, and patent issuance by PTO.If submitted after 30-day period ("Late listed" patent") – pending ANDAs do not have to certify to patent; Patent will not block ANDA approval.
  Result: Patents will block approval only of PIV ANDAs submitted after late-listed patent

PARAGRAPH IV CERTIFICATION: Section 505(j)(2)(B)

- After FDA notifies applicant that ANDA is sufficiently complete to review, applicant must notify NDA/patent holder of Paragraph IV certification. (Notice Letter)
- A generic drug applicant making a Paragraph IV certification must provide a Notice Letter to the NDA holder and the patentee, if different from the NDA holder, setting out:

  a) The existence of the ANDA.
  b) A detailed statement of its basis for believing that the listed patents are invalid or not infringed.

- Timing of Notice: within 20 days from ANDA "receipt" acknowledgement letter
  • Unless in an amendment post-receipt: then must notify immediately
- NDA sponsor can sue when it receives notice.
- Infringement lawsuit can start prior to ANDA approval and marketing = big gain for generics.
- If NDA sponsor sues within 45 days of notice, ANDA approval is **stayed for 30 months**.
- No lawsuit within 45 days = FDA can approve ANDA when ready
- The court may shorten or lengthen the 30-month stay period in a pending patent case if either party fails to reasonably cooperate in expediting the case. The 30-month stay terminates if a court issues a final order determining that the patent is invalid, unenforceable or not infringed

Types of ANDA approvals: a) Tentative approval

b) Final approval

Tentative Approval:

- ANDA ready for approval but blocked by patent, exclusivity, or stay = only eligible for tentative approval (TA).
- Full approval not automatic after TA – must show ANDA still meets requirements for approval at time of full approval, e.g., cGMPs still good.
- Tentatively Approved ANDAs must request full approval.

ANDA Exclusivity (180-day Exclusivity - Section 505(j)(5)(B)(vi))

The first filer of an ANDA with a Paragraph IV certification concerning an RLD is potentially entitled to a 180-day period during which the FDA will not approve any other ANDA having a Paragraph IV certification for a generic version of the RLD. However, the first filer may forfeit this exclusivity.

180-day exclusivity is only available to "First to File" (FTF) ANDAs containing PIV certification

• Commonly there are multiple FTFs = shared exclusivity for FTF cohort, e.g., NCE-1 ANDAs.

"Section viii" Carve-Outs: Section 505(j)(2)(A)(viii)

- "Section viii statement" = not seeking approval of the **use covered by a use patent** or exclusivity.
- Permissible so long as generic product safe and effective for remaining conditions of use.
- As a result, there is no certification or notice requirement. Generic drug companies may use the same procedure to avoid the three-year new clinical study exclusivity by carving out the information that relates to the clinical trials and relevant approval.
- First-filer exclusivity does not apply against an applicant who has filed a Section viii Statement because it is not a Paragraph IV certification.

PATENT TERM EXTENSION

The Hatch-Waxman Act provides a patent term extension for patents covering certain products and methods, including human drug products that are subject to FDA approval.

Only one extension can be granted in connection with a particular product, and it must be for a patent that claims either a:

a) Drug product, which means the active ingredient and any approved drug using that active ingredient.

b) Method of using a drug product.

c) Method of manufacturing a drug product

Bolar Amendment

Manufacturers of generic drugs are allowed to prepare ANDA data and conduct trials prior to the expiry of the relevant drug patent. This provision was made in an amendment to the Hatch Waxman Act, named the Bolar Amendment. This amendment aimed specifically to overturn an earlier court ruling (Bolar v Roche) that had ruled against such early preparation of ANDA material. The Bolar amendment does not, however, allow generic manufacturers to stockpile drugs and prepare a commercial launch of the drug prior to patent expiry, as has been the case in Canada.

The Bolar Amendment states:

'It shall not be an act of infringement to make, use, or sell a patented invention - solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs' (35 USC 271(3)(1)).

Changes to an Approved NDA or ANDA

Post Approval Changes are classified into 3 categories:

(1) Major Change (Prior Approval Supplement)
(2) Moderate Change:
    a) Supplement - Changes Being Effected in 30 Days
    b) Supplement - Changes Being Effected
(3) Minor Change: To be Reported in net Annual Report

(1) Major change:

- A change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product.
- A major change requires the submission of a supplement and approval by FDA prior to distribution of the drug product made using the change. This type of supplement is called, and should be clearly labelled, a **Prior Approval Supplement**
- An applicant may ask FDA to expedite its review of a prior approval supplement for public health reasons (e.g., drug shortage) or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. This type of supplement is called, and should be clearly labelled, a **Prior Approval Supplement - Expedited Review** Requested

(2) Moderate Change:

- Change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product
- **Supplement - Changes Being Effected in 30 Days:** Change requires the submission of a supplement to FDA at least 30 days before the distribution of the drug product made using the change. If FDA informs the applicant within 30 days of receipt of the supplement that information is missing, distribution must be delayed until the supplement has been amended to provide the missing information
- **Supplement - Changes Being Effected:** Changes for which distribution can occur when FDA receives the supplement. If, after review, FDA disapproves a changes-being effected-in-30-days supplement or changes-being-effected supplement, FDA may order the manufacturer to cease distribution of the drug products made using the disapproved change.

(3) Minor Change:

- Change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. The applicant must describe minor changes in its next **Annual Report**

ANDA Submissions: Content and Format of ANDA

CTD format is to be used for filing ANDA.

Guidance document for "ANDA Submissions — Content and Format of Abbreviated New Drug Applications" can be identified at
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM400630.pdf

Guidance for "Good ANDA Submission Practices" which emphasises common, recurring deficiencies that may lead to a delay in the approval of an ANDA and also the recommendations to applicants on how to avoid these deficiencies with the goal of minimizing the number of review cycles necessary for approval, can be identified at
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM591134.pdf

GDUFA-II: (Generic Drug User Fee Amendments-II):

On July 9, 2012, GDUFA was signed into law by the President as part of the Food and Drug Administration Safety and Innovation Act (FDASIA). GDUFA is designed to speed the delivery of safe and effective generic drugs to the public and improve upon the predictability of the review process. GDUFA must be reauthorized every five years. On August 18, 2017, the President signed the bill reauthorizing GDUFA through September 30, 2022.

GDUFA-II authorizes the Food and Drug Administration (FDA) to assess and collect fees for abbreviated new drug applications (ANDAs), drug master files (DMFs), generic drug active pharmaceutical ingredient (API) facilities, finished dosage form (FDF) facilities, contract manufacturing organization (CMO) facilities, and generic drug applicant program user fees.

Detailed guidance on GDUFA can be identified at
https://www.fda.gov/forindustry/userfees/genericdruguserfees/default.htm

FEE SCHEDULE FOR FY 2018 & 2019

User Fee Type		FY 2019	FY 2018
Application Fee	ANDA	$ 178,799	$ 171,823
	DMF	$ 55,013	$ 47,829
Annual Program Fee	Large Size	$ 1,862,167	$ 1,590,792
	Medium Size	$ 744,867	$ 636,317
	Small Size	$ 186,217	$ 159,079
Facility Fee	Domestic API	$ 44,226	$ 45,367
	Foreign API	$ 59,226	$ 60,367
	Domestic FDF	$ 211,305	$ 211,087
	Foreign FDF	$ 226,305	$ 226,087
	Domestic CMO	$ 70,435	$ 70,362
	Foreign CMO	$ 85,435	$ 85,362
Backlog		$ 17,434	$ 17,434
PAS		-	-

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Details of importing country embassy in India: **https://in.usembassy.gov/**

Contact details of Indian Embassy abroad: **https://www.indianembassy.org/**

List of Local Pharma Associations:

- Association for Accessible Medicines, 601 New Jersey Ave NW, Suite 850 Washington DC 20001 001 202.249.7100 — info@accessiblemeds.org www.accessiblemeds.org
- The American Pharmaceutical Manufacturers' Association (AmPharMA) — http://www.ampharma.org/