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FAST TRACK APPROACHES FOR DRUG APPROVAL ACROSS THE GLOBE

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ABSTRACT

Drug development is a challenging way to make profits. Thousands of once-promising compounds wash out in the preclinical phase and hundreds more fail in clinical trials and only one is likely to be approved for marketing. Hundreds of millions of dollars are spent on pharmaceuticals or biologics that fail to make it to market. The successful to reach here the market, developed in this way takes approximately 12-15 years. However, there are alternatives to spending enormous sums in developing drugs. One of the approach is to concentrate on developing products for niche markets that may have smaller market potential, but that can be approached with dramatically lower development costs and time using section 505(b)(2) pathway to FDA approval. The second approach is the request for biowaivers i.e. *in vivo* bioequivalence and bioavailability study waivers in accordance to the principles of the Biopharmaceutical Classification System (BCS) that can significantly save time and cost. Third one is the generic drug approval pathway in which only BA/BE studies are done comparing the proposed product to the innovator product. The present review apart from giving a brief overview of the above approaches highlights the present status and future prospective of these approaches. It also gives a brief overview of impact of these fast track approval procedures on the global market of medicines.

Keywords: 505(b)(2) NDA, hybrid applications, reference listed drug, clinical studies, generic drugs, biowaivers, market exclusivity.

Introduction

Drug development is a process of bringing a new drug to the market once a lead compound has been identified through the process of drug discovery. It includes pre-clinical studies, clinical studies and finally the step of obtaining regulatory approval to market the drug [1]. The full cost of bringing a new drug to market – from discovery through clinical trials to approval – is complex and controversial and is highlighted in the study published in 2006, which estimates that costs vary from around $500 million to $2 billion depending on the therapy or the developing firm (Table 1 & 2) [2]. The success rate for a new drug to treat a disease might theoretically include from 5,000 to 10,000 chemical compounds. Thus, new drug development is both an extensive as well as expensive process [3]. However, there are novel approaches to boost the drug development. There are three different approaches which can be helpful for developing drugs with reduced period of time and cost. These are as follows:

1. Request for Biowaivers
2. Generic Drug Approval Pathway
3. 505(b)(2) NDA

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Table 1: 505(b)(1) vs. 505(b)(2) Drug Development Timeline

NDA	Discovery	Preclinical Research	Clinical Studies
505(b)(1)	2-5 years	1-3 years	8-15 years
505(b)(2)	<1-3 years	<1-2 years	2-5 years

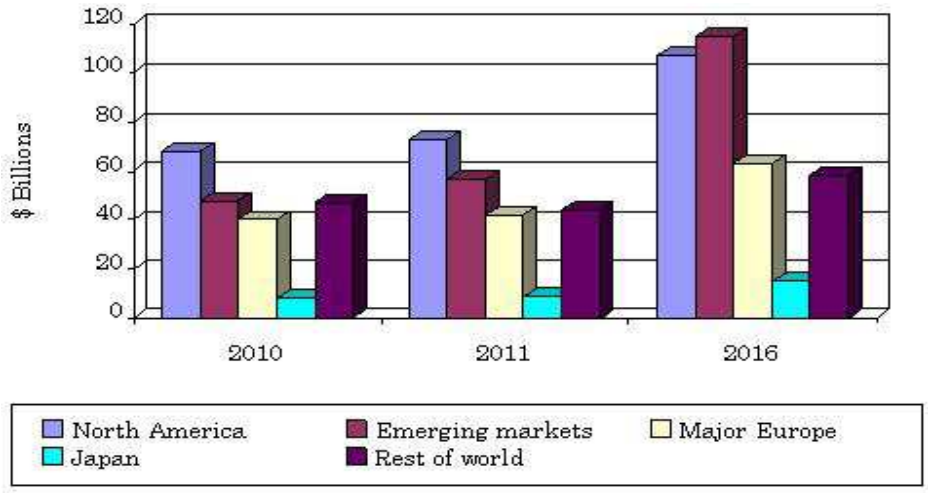
Table 2. Comparative Analysis of Timing & Costs for 505(b)(2) NDA & ANDA

	Estimated Duration	Estimated Cost
ANDA		
• BE study(ies)	4-6 months	$50k-$750k
• Submission	1-2 months	
• Time to approval	18+ months	
505(b)(2) NDA		
• Clinical trial(s) (if needed)	12-24 months	$2m-$10+m
• BE studies	4-6 months	$50k-$750k
• Submission	1-2 months	
• Time to approval	10 months	

BE (Bioequivalence Studies), NDA (New Drug Application), ANDA (Abbreviated New Drug Application)

Both FDA and EMA accept BCS based biowaivers for Class I drug substances, but the threshold for complete absorption is lower for the EMA (85% fraction absorbed) than the FDA (90%). The biowaiver market shows greater number of biowaiver submissions over the past three years and the wider use of *in vitro* test systems for permeability[3]. While 505(b)(2) NDA approvals are increasing at higher rates than 505(b)(1) approvals. In 2012, a record number of 47 505(b)(2) applications were approved by FDA as compared to 31 505(b)(1) applications [4]. The global generics market is estimated at about $225 billion in 2011. By 2016, it is expected that the value of the total global generics sector will have risen to $358 billion, representing more than 18% of all pharmaceuticals, a projected compound annual growth rate (CAGR) of 9.7% between 2011 and 2016. Emerging market represents the second largest market category for generic drugs with the expected sale of $57 billion in 2011. This should reach nearly $115 billion in 2016, for a CAGR of 15.1% (Figure 2) [5].

Figure 2: Major Generics Markets, Through 2016



Definitions

Biowaiver: A biowaiver is considered as the waiver of clinical bioequivalence studies when the active pharmaceutical ingredients meet certain solubility and permeability criteria *in vitro* and when the dissolution profile of the dosage forms meets the requirements for the immediate release dosage forms [6, 7].

505(b)(2) NDA: An application that contains full reports of investigations of safety and effectiveness but 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 [8].

Patent: A patent is an intellectual property right, which gives the holder the right to exclude others from making, using, selling, offering for sale, or importing the patented product [9].

Data Exclusivity: It is a period of non-reliance and non-disclosure that a government must provide to pharmaceutical registration data [10, 11].

Market Exclusivity: It is a period between the approval of a drug by the regulatory authorities and the expiry of the patent term during which no only innovative company can market that drug [12].

Listed Drug: A new drug product that has an effective approval by the FDA and which has not been withdrawn or suspended or which has not been withdrawn from sale as reasons of safety or effectiveness determined by FDA is termed as a listed drug. Listed drug status is evidenced by the drug product's identification as a drug with an effective approval in the current edition of FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" or any current supplement thereto, as a drug with an effective approval [13].

Reference Listed Drug: The listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application [14].

Literature: Literature in this context refers to published reports of well-controlled studies that support safety or effectiveness; prosed and final monographs published in the *Federal Register* the data supporting a *Federal Register* notice announcing a product's safety and/or effectiveness [15].

Generic Drug: A drug product which is comparable to a reference listed drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use [16].

Request for Biowaivers

The term biowaiver describes the use of an *in vitro* assessment to waive the need for in vivo (bio) studies [6]. It is considered as waiver of clinical bioequivalence studies [4,5]. It was originally proposed by Amidon and co-workers in 1995 [17] and subsequently adopted by the US FDA, WHO, and European medicines Agency (EMA) for implementation in the approval of some generic drug products [18-20]. Thus, pharmaceutical companies can request for biowaivers according to the Biopharmaceutical classification System (BCS) for NDA and ANDA filing as well as to scale-up and post approval changes in drug manufacturing. It is estimated that the in vivo bioavailability and bioequivalence studies cost upto $ 250,000 each and require upto 2 months to complete, whereas, the in vitro laboratory tests are rather inexpensive and fast [21]. However, the regulations on BCS based biowaivers differ between the FDA, EU and WHO. The FDA allows the biowaiver only for BCS class I drug substances whereas current WHO and EMA guidances allow products containing class III drug substances to be considered for the biowaiver.

Other countries following the BCS based biowaiver concept as one of the three main guidance documents (US FDA, EMA, WHO) or a combination of specific requirements are Brazil [22], Australia, Association of Southeast Asian Nations (ASEAN) countries, South Africa [23], India [24], Argentina [25], Southi Arabia [26]. While Switzerland, Canada, Japan [27] have not yet implemented the BCS based biowaiver as a means to ensure bioequivalence of different drug products in any shape or form.

Risk Associated With Using Request For BCS Based Biowaiver

- Risk of bioinequivalence between a test and a reference drug product due to excipients and/or manufacturing effects.
- Risk of approving a test product according to the biowaiver procedure, when infact if it was compared with the reference product in an *vivo* stydy it would fail to meet bioequivalence standards.

- Risk to patients associated with a false, biowaiver-based acceptance of a drug product, which would actually fail to be bioeqiuivalent to the comparator product in an vivo study.

Therefore, merely classifying a drug substance according to the BCS is not a sufficient basis for determining whether products containing the substance can be biowaivered or not and there is a need to develop more stringent criteria for biowaiver [6].

About 30 biowaiver monographs have been documented up to date by the joint effort of FIP and WHO which are working on a running biowaiver monograph project. These monographs have a great impact on the approval of multi-source drug products as many applicants have submitted dossiers which refer to the results summarized in the monographs, without being asked by the regulatory agencies to repeat the studies, thus saving the applicants time and money [6].

Future Prospectives

The BCS based biowaiving is an innovative technique which significantly saving the time and cost in the approval of drug products. Research is ongoing in this field by exploring more ways to increase the utilization of this technique. Some of the future prospective are as follows:

- In the future, the biowaiver monograph project will extend to fixed dose combinations.
- Developing science-based risk calculations to make the biowaiver decision more objective [28].
- A key future activity in the BCS based biowaiver area should be global hormonization of biowaiver regulations. Therefore, various regulatory authorities should change and improve their regulations, so that they will apply "best science" practice to BCS biowaiving [7].

Generic drug Approval Pathway

Generic drug approval pathway is another fast track approach to expedite the approval of proposed drug product(s) by just showing bioequivalence to the reference listed drug. Bioequivalence is demonstrated through studies, which prove that the active ingredients work in the same way and in the same amount of time in the human body [29]. Generic drugs approved in this way are much cheaper than brand drugs and provide significant saving to consumers. 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 drugs [30]. In US, the legislation for generic drugs came into effect on 1984 after the enactment of the Hatch-Waxman Act which allows generic drugs to enter the market without repeating extensive clinical trials required for their brand-name counter parts after expiry of the patent and certain exclusivities. The pharmaceutical companies seeking approval of their generic drug must file Abbreviated New Drug Application (ANDA) to FDA. The FDA after thorough review of the application and assuring safety and efficacy either approve or discard the application [31].

A pre-requisite for filing ANDA is that applicant is required to make patent certifications for the reference listed drug. There are four types of patent certifications for which the ANDA can submit.

1. Paragraph I certification: That the patent information was not submitted to FDA by the reference listed drug company.
2. Paragraph II certification: That the patent has expired.
3. Paragraph III certification: That the patent will expire on a specific date.
4. Paragraph IV certification: That the patent is invalid or will not be infringed.

Apart from getting approval in a short period of time with reduced cost, the first to file ANDA applicant for the reference listed drug would get 180 days market exclusivity [32]. Often the legal proceedings occurs between the branded and generic company but they may agree on a settlement and the 180 days market exclusivity granted to the first filed ANDA would get delayed and further halt the entry of other generic drugs for that reference listed drug.

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 amended three major rules pertaining to listed drugs, thirty-month stays and approvals of ANDAs [33]. The innovator drug company could not further delay the entry of generic drugs by filing multiple patent infringement lawsuits in order to obtain multiple 30-monthstays. Further the final rule on generic drugs which became effective on Aug 19, 2003 would allow faster access to generic drugs while maintaining fair incentives for innovative new drug development [34].

In Europe, regulations for generic drugs are on similar principles and are set out in Article 6 of regulation (EC) No. 726/2004 and Article 10(1) of Directive 2001/83/EC, as amended [35]. Generally, the decentralized procedure or national mutual recognition procedure is followed for the approval of generic drug products. However, at the request of an applicant, be accepted for consideration under the centralised procedure, when the applicant shows that the medicinal products constitute:

- A significant therapeutic, scientific, or technical innovation,
- The granting of a Community authorization for the medicinal product is in the interest of patients at the Community level.

In Canada, the regulatory agency Health Canada regulates the pharmaceutical products. Other countries like in Brazil, The Generics Law, 1999 and the ANVISA regulate the implementation of generic pharmaceuticals policy. In Japan, the Ministry of Health, Labour, and Welfare (MHLW) is in charge of the pharmaceutical regulatory affairs and the Pharmaceutical Medical Devices Agency (PMDA) and the generic drugs are submitted under Japanese ANDA to PMDA which reviews the application. While countries from Asia Pacific and Gulf have almost harmonized their regulatory environment through the ASEAN and Gulf Co-operation Council (GCC) organizations [36].

However, generic drug product manufacturers must formulate a drug product that will have the same therapeutic efficacy, safety, and performance characteristics as of its branded counterpart.

505(b)(2) NDA

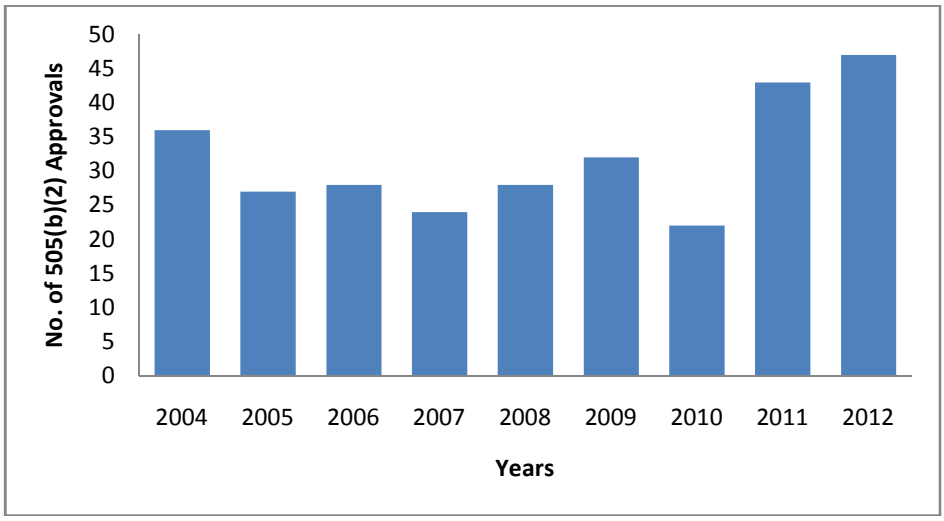
Another attractive alternative for companies seeking to enter a drug market is 505(b)(2) pathway, often referred to as a "paper NDA" [37]. It was added in 1984 as a part of the Hatch-Waxman Amendments to the Federal Food, Drug and Cosmetic Act, 1938, by FDA to encourage innovation and eliminate costly and time-consuming duplicative clinical studies. This pathway is a hybrid between the 505(j) accelerated pathway for generic drug applications, and 505(b)(1) as the standard de novo NDA pathway for proprietary drugs [38-40]. It allows a drug-maker to incorporate preexisting data, into its NDA by reference. This results in substantial savings in approval costs; the average 505(b)(2) approval costs $3-7 million, which is far less than the estimated $1.3 billion to bring a new drug to market under 505(b)(1) and achieve FDA approval in as little as 30 months [37]. Additionally, 505(b)(2) applicant may qualify for three, five, or seven years of market exclusivity, depending on the extent of the change to the previously approved drug and the type of the clinical data included in the NDA than 180 days exclusivity for generic drugs approved under section 505(j). The analogous regulatory pathway in Europe also appears to be very similar to that of U.S. and was introduced within the Article 10(3) of Directive 2001/83/EC in November 2001 and in the Regulation (EC) No. 726/2004. The analogous 505(b)(2) applications in EU are known as Hybrid Applications [41].

Regardless of the regulatory pathway one chooses for approval of an NDA the FDA standards for the demonstration of safety and efficacy are same; it is only the source of information that differs between the two paths. It is important to understand what constitutes sufficient evidence and therefore which specific studies can be replaced by existing data for individual compounds.

Market growth of 505(b)(2)

In the relatively few years since clearing legal hurdles, the 505(b)(2) process has rendered significant changes on the drug development landscape. Today, as the patents for many blockbuster drugs expire, smart marketers are seeking ways to create new differentiated products, new market niches and marketing exclusivity through 505(b)(2) development programs. In the fiscal year 2006, approximately 20 % of new small-molecule drugs were approved through the 505(b)(2) process; two years later, more than half of the small-molecule new drugs approved in the U.S. were based on this strategy. The FDA approval statistics for NDA approvals and 505(b)(2) approvals alone from 1996-2011 has been shown in Fig. 1 [38]. The average sales of products approved through 505(b)(2) in 2008 were estimated to be ~ USD 150mn. Further, these products were grown at a high compounded annual growth rate (CAGR) of 17.8% between the period 2006-08 which is three times higher than average growth of US pharmaceutical markets (6.4%) [42]. Judging from the rate at which investigational new drug (IND) applications are being filed today, it is expected that the percentage of 505(b)(2) approvals will be greater than 80% within the next few years [43].

Figure 1: FDA 505(b)(2) Approval Statistics 2004-2012 (blog.camargopharma.com)



General Advantages of 505(b)(2) type NDA

- Marketed as branded products rather than generic
- Relatively low risk because of existing safety and efficacy information
- Lower cost due to smaller scope and number of potential studies
- Increased speed due to fewer studies
- Potential for "AB" substitutability rating in the Orange Book
- Wide range of drug candidates with good market possibilities are available for rapid approval under 505(b)(2) pathway
- Potential route for biogenerics
- Unlike ANDA not affected by discontinuation of RLD
- Earns patent and exclusivity
- Insulated from high market competition
- Suitable approval pathway for non-infringing products
- An opportunity in Drug efficacy Study Implementation (DESI) drugs

Type of Changes Applicable Under 505(b)(2) NDA

The 505(b)(2) approval route can be utilized for a wide range of products, especially for those that represent a limited change from a previously approved drug. The following are examples of changes to approved drugs which would be appropriate to submit as 505(b)(2) applications:

- Changes in dosage form (e.g., oral to transdermal, lotion to foam).
- Changes in strength (higher or lower).
- Changes in route of administration (e.g., i/v to other parenteral routes).
- Changes in formulation (e.g., excipients changes).
- Changes in dosing regimen (e.g.., twice daily to once daily).
- Changes in indication (e.g., a new indication).
- A new combination product where the active ingredients have been previously approved.
- Change to an active ingredient (e.g., different salt, ester complex, chelate, etc.).
- New molecular entity when studies have been conducted by other sponsors and published information is pertinent to the application (e.g., a pro-drug or active metabolite of an approved drug).
- Change from an Rx indication to an OTC indication.
- Change to an OTC monograph drug (e.g., non-monograph indication, new dosage form).
- Drugs with naturally derived or recombinant (i.e, biological) active ingredients where additional limited clinical data is necessary to show the ingredient is the same as the ingredient in the reference drug.
- Bioinequivalence for drug products where the rate and or extent of absorption exceed or are otherwise different from the standards for bioequivalence compared to a listed drug. Additional studies might be required to

document the safety and efficacy at the different rate and extend of delivery [44].

Type of Changes Not Applicable Under 505(b)(2) NDA

- An application that is a duplicate of a listed drug and eligible for approval under section 505(j)
- For which the only difference is lower extent of absorption than the reference drug
- For which the only difference is an unintended lower rate of absorption than the reference drug

Type of application submitted as a 505(b)(2) NDA

- New chemical entity (NCE)/new molecular entity (NME): In case, 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.
- Changes to previously approved drugs: For changes to a previously approved drug product, an application may rely on the FDA's finding of safety and effectiveness of the previously approved product, coupled with the information needed to support the change from the approved product.

Information on which applicant can rely

- Published Literature: If the applicant has not obtained a right of reference to the raw data underlying the published study or studies, the application is a 505(b)(2) application.
- The Agency's finding of safety and effectiveness for an approved drug

Patent and Exclusivity criteria

The 505(b)(2) applicant may qualify for 3 years of Waxman-Hatch exclusivity if one or more of the clinical investigations, other than BA/BE studies, was essential to approval of the application and was conducted or sponsored by the applicant. A 505(b)(2) application may also be granted 5 years of exclusivity if it is for a new chemical entity and may also be eligible for orphan drug exclusivity or paediatric exclusivity (Table 3). However, the filing or approval of a 505(b)(2) application may be delayed due to patent or exclusivity protections covering an approved product. Section 505(b)(2) applications must include patent certifications for each patent which claims the drug or drugs on which investigations that are relied upon by the applicant for approval of its application were conducted or which claims a use for such drug or drugs, that, a patent is invalid, unenforceable, or will not be infringed [45]. The applicant must provide notice of certain patent certifications to the NDA holder and patent owner [46].

Table 3: Market Exclusivities granted by U.S. FDA through 505(b)(2) process

Priority Rank	Code	Extension	Protection Period
1.	NCE	New Chemical Entity	5 years
2.	NC	New Combination	3 years
3.	NDF	New Dosage Form	3 years
4.	NP	New Product	3 years
5.	NPP	New Patient Population	3 years
6.	ODE	Orphan Drug Exclusivity	7 years
7.	PDE	Paediatric Drug Exclusivity	+ 6 months

Regulations for EU Hybrid Drug Applications Analogous to the FDA's 505(b)(2) Pathway

The regulatory pathway for hybrid drug applications in Europe also appears to be very similar to that of US and was introduced within the Directive 2001/83/ EC in November 2001 and in the Regulation (EC) No 726/2004 [35]. In Europe, reference medicinal product has been granted a marketing authorisation by a Member State or by the Commission on the basis of a complete dossier, i.e. with the submission of quality, pre-clinical and clinical data in accordance with Articles 8(3), 10a, 10b or 10c of Directive 2001/83/EC

which is similar to FDA's 505(b)(1) NDA pathway. Similarly, Article 10(2) and Article 10(3) of the Directive 2001/83/EC are analogous to FDA's ANDA pathway and 505(b)(2) pathway respectively.

Article 10(2)

This article describes a ''generic medicinal product'' as a medicinal product that has the same qualitative and quantitative composition, the same pharmaceutical form and is proven to be bioequivalent to the reference medicinal product. The Article 10(2) allows the use of different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of the active principle as long as their safety and efficacy profile is equivalent to the original compound. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters, or derivatives of an authorised active substance must be supplied by the applicant. The various immediate-release oral pharmaceutical forms (e.g. capsules, tablets) shall be considered to be one and the same pharmaceutical form.

Article 10(3)

Product that do not fall under the Article 10(2), because bioequivalence can not be established through a bioavailability assessment or that are different to the reference medicinal product with regard to the active ingredient, the dose strength, dosage form/route of administration are considered as ''hybrid'' medicinal products. In this case the applicant has to provide in addition to the referenced data, results on appropriate non-clinical tests and clinical studies with the ''hybrid'' medicinal product.

Thus, hybrid applications, similar to 505(b)(2) NDAs, differ from generic applications in that the results of appropriate pre-clinical tests and clinical trials will be necessary for the following three circumstances:

1. The strict definition of a "generic medicinal product" is not met;
2. Bioavailability studies cannot be used to demonstrate bioequivalence; and
3. There are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic product compared to the reference medicinal product.

These applications will thus rely in part on the results of pre-clinical tests and clinical trials for a reference product and in part on new data. In contrast to the US regulations the major difference being that there is no provision for 3 years of exclusivity for the hybrid medicinal product, once the product is approved [47]. A comparative analysis of U.S. FDA 505(b)(2) NDA vs. EU Hybrid Medicinal Products has been shown in Table 4.

Table 4: Comparative Analysis of U.S. FDA 505(b)(2) NDA vs. EU Hybrid Medicinal Products

S.No.	Parameters	505(b)(2) NDA	EU Hybrid Medicinal Products
1.	Marketing Option	Branded	Not Branded
2.	Scientific Studies	(i) No Preclinical Study (ii) Limited Clinical Study	(i) No Preclinical Study (ii) Limited Clinical Study
3.	Patentability	Yes	No
4.	Market Exclusivity	Yes	No
5.	Patent Challenge	Yes (in case of Para IV certification)	No
6.	Potential Route for Biogenerics	Yes	No
7.	Fees	(i) Less fees than 505(b)(1) NDA (ii) Companies with <500 employees have the options to request for waiver of the fees for first submission	Reduced fees than full Marketing Authorisation Application

Data Exclusivity

At the time of submission of the generic/hybrid application, the protection period of the reference medicinal product should have expired in order to allow the applicant to rely on the dossier of the reference medicinal product which is described below:

- 8 years - Applications for generic/hybrid drugs cannot be submitted until expiry of 8 years of first marketing authorization. However, applicants have been allowed to use a reference product's data in compiling their own dossiers to obtain their own regulatory approvals after 8 years.
- 10 years (8 + 2) - Generic/hybrid drugs may not be sold in EU until 10 years have elapsed from the granting of the initial marketing authorization.

- (8+2+1) - Further one year extension if original authorization holder obtains additional authorization for a new therapeutic use of the product resulting in clinical benefits [48].

Conclusions

As the healthcare expenditure is increasing day by day, the pharmaceutical companies are shifting towards the shorter and less costly ways i.e. fast track approaches for developing drugs. The fast track approaches described above i.e. generic drugs approval pathway, request for biowaivers and 505(b)(2) NDA are economical approaches particularly for niche markets. Although there is a continuous process of harmonization of regulations taking place all around the world, still we see a huge challenge, which is yet to be overcome by the pharmaceutical industry in these cases. This is due to the heterogeneity in the regulatory landscape of the various countries.

The BCS based biowaiver have had a great impact on approval of multisource drug products. Drug products approved through the BCS biowaiver procedure and manufactured under Good Manufacturing Practice can be assumed to have the same quality as the reference product. In case of biowaivers, although there are a number of scientific opportunities to expand the use of biowaivers in the future, one of the greatest advances would probably be an international harmonization of possibilities to apply biowaivers. Further, a great opportunity to expand the usage of biowaivers would be to distinguish between testing for regulatory approval of generic products and approval of changes within a given product.

In case of generic drugs, the savings associated with the policies that encourage the utilization of low-cost generic drugs make them an obvious choice in struggle to contain health care costs. However, policymakers and researchers should address the questions surrounding the therapeutic equivalence of generic drugs.

While the third fast track approach i.e 505(b)(2) NDA process particularly attractive to investors because the product differentiation can provide significantly better market potential. However, the criteria to determine, what type of additional or "bridging" data needed to support the proposed change of the previously approved drug is still under question because this is determined on a case by case basis. To overcome this problem, proper meeting between the sponsors and regulatory professionals of FDA before filing 505(b)(2) application might be helpful for sponsors seeking 505(b)(2) approval. Further, there is a need of harmonization of 505(b)(2) regulations across the world to overcome the duplication of work for approving drugs in different regions.

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