505(b) (2) NDA: THE UNEXPLORED OPPORTUNITY

PHARMACEUTICALS EXPORT PROMOTION COUNCIL
(Set up by Ministry of Commerce & Industry, Govt. of India)

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Introduction

In the present situation where U.S. generic market is approaching a stage of 'Generic Cliff, and the prohibitive costs of NCEs research keeps them out of reach of medium/startup biotech and pharma companies, 505(b)(2) approval procedure offers a simplified route for obtaining an NDA from U.S. FDA based on bridging clinical/non-clinical studies between RLD and proposed product. Under section 505(b)(2), U.S. FDA permits the applicant to rely on safety and efficacy data of listed drug (RLD) or published literature without a "Right of Reference". It is also known as hybrid NDA that contains more data than ANDA but less than stand alone NDA.

- Firms can innovate by improving an existing drug, into:
  - More desirable dosage form
  - Novel formulation
  - New indication
  - New combination and
  - New derivatives.
- Other opportunities include:
  - Drug repositioning and
  - Bio-generics

Objective

To demonstrate the opportunity for start-up & medium scale enterprises to get into branded drug with U.S. FDA through modification of an existing drug.

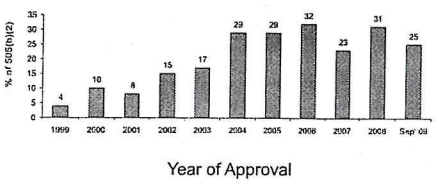
Research Methodology

All the core data was gathered from drug@fda and electronic Orange book of U.S. FDA. A total of 175 505(b)(2) NDA's were identified through study of approval histories, administrative documents/Letters, Reviews including Chemical, Pharmacological, and medical, and all other related documents. A comprehensive analysis of 505(b)(2) NDA was then carried out with respect t on approval trends & correlation between various dosage forms, Chemical types and Patent /exclusivity protections. Statistical analysis was carried out using SPSS software 13.1 version and the sales figures were collected from valuate harmadata base.

Results

Significant growth in approval trend: over the past decade, there has been a continuous growth in 505(b)(2) approvals

Chart:1: Year-wise % 505(b)(2) NDAs among total NDAs granted by U.S. FDA



Year of Approval

Table 1: Comparative Study of 505(b)(1) NDA, 505(b) (2)/Hybrid NDA & ANDA

Sl. No.	Parameters	505(b)(1)/Stand-alone NDA	505(b) (2)/Hybrid NDA	505 (J)/ANDA
1.	Marketing Option	Brand	Brand	Generic
2.	Scientific Studies	Full Pre-clinical and Clinical study	No Pre-clinical study, Limited Clinical studies	Bioequivalence study
3.	Patentability	Yes	Yes	No
4.	Market exclusivity	Yes	Yes (Based on Clinical study)	Yes (First Successful Paragraph-IV patent challenger)
5.	Patent Challenge/ 30 month stay provision	No	Yes (In the case of Para IV Patent certification)	Yes (In the case of Para IV Patent certification)

Source: www.camargopharma.com, www.klgates.com'...;PublicationAttachment/5230fc20-36b0-4c6a-b5f4-7cdb5b1a5645/FDA_Final.pdf

Topicals & Parenterals rank High

Among 505(b)(2) approvals, oral dosage forms account for maximum approvals followed by parenterals and topicals (refer chart 2). However, the proportion of topicals and parenterals is higher as compared to their proportion in total products approved with U.S. FDA.

Chart 2:505(b)(2) Product Approvals based on Route of Administration (%)

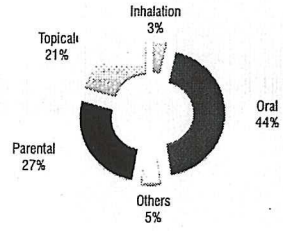


Table 2: Average Sales (2008) of Sample 505-(b)(2) Products

Types of Modifications	Number of Approvals	Sample size considered for Sales Data 2008	Average Sales 2008 (USD mn)
New Formulations	78	36	156.19
New Manufacturers	45	17	161.29
New Combinations	18	11	161.84
NMEs	13	4	186.84
New Derivatives	5	3	104.97

The average sales of products approved through 505(b)(2) in 2008 is estimated to be ≈ USD150mn. Further, these products are growing 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%). [IMS 2008]***

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

Priority Rank	Code	Expansion	Protection period	No. of Applns.
1.	NCE	New Chemical Entity	5 years	6
2.	NC	New Combination	3 years	6
3.	NDF	New Dosage Form	3 years	4
4.	NP	New Product	3 years	20
5.	NPP	New Patient Population	3 years	1
6.	ODE	Orphan Drug Exclusivity	7 years	3
7.	PED	Pediatric Drug Exclusivity	+6 months	1
8.	Others			14

Source: Electronic Orange Book

Table 4: Modifications Approved Through 505(b)(2) Route

Chemical Types	Description	Examples &Respective NDA No.
New Formulation	Includes products characterized by advanced formulations, NDDS and different route of administration.	[10187] Methylphenidate (Tablet; Oral) → [21514] Film, Extended Release; Transdermal
New Combination	Combination of existing drugs individually approved by FDA	[21410] Metformin Hydrochloride; Rosiglitazone Maleate
New Derivatives	Includes various salts and new ester forms of existing molecules	[21299] Paroxetine HCl → Paroxetine mesylate
New Manufacturer	Includes products that differ from RLD with respect to excepients or manufacturing process.	[22276] Nicardipine HCl (i.v.) : "Sorbitol replaced with NaCl" & "Citric acid monohydrate replaced with Benzoic acid"
New Indication	Includes the molecules repositioned for new therapeutic use never before approved by FDA	[20785] Thalidomide for Erythema Nodosum Leprosum (ENL); Orphan Disease
New Molecular Entities (NME)	In certain cases where approval is based on some studies not conducted or sponsored by applicant.	[21859] Hyaluronidase Recombinant Human (Bio-Generic)

Based on Research of CDER, U.S. FDA Review Documents

Discussion

Analysis of 75 approvals received during last 3 years reveals that more than 50% of 505(b)(2) get market exclusivity for a period of 3-7 years based on their chemical type (refer table 3).

Comparative analysis of chemical type shows that majority of the new formulations have earned exclusivity/patent protection indicating the need of clinical study. Our study reveals that Usually, a limited phase-III and Pharmacokinetic study was carried for these requirements.). The case is reverse in case of new manufacturer. Statistical analysis of chemical type and formulations establishes very significant relationship between new manufacturer and parenteral dosage form. Most of these product approvals did not require any clinical study and thus not protected by patent/exclusivity. This finding is supported by the fact that modification in the formulation of paranteral is not permitted in ANDA and therefore 505(b)(2) is the preferred route to by-pass the formulation patent of the innovator company.

Opportunity with 505(b)(2) Process

Approval time: Similar to ANDA.

Our analysis identifies that most of the applications received approval in 1 year time (mode) with mean approval time of 1.56 years which is nearly same as the average approval time of ANDAs (1.5 years).

Economy of studies required

Experts have made it a priority to extract all available public documents when assembling a 505(b)(2) applications, eliminating or decreasing the need for studies required for approval. At an average there are 40,000 published literature for molecules approved by US.FDA.

Drug Repositioning for new clinical indication: Could be applied to the drugs present in the market, drugs discontinued from the market and also several Investigational New Drugs (INDs) failing in various stages of clinical trial. This is supported by enormous clinical & nonclinical data available for such molecules.

Cost of filling may be waived (PDUFA)

Study reveals that application is charged only in case when the product label indicates unique data generated for the approval. However, firms (including affiliates) with less than 500 employees have the options to request for waiver of the fees for first submission.

Potential pathway for Bio-Generics

To date no formal regulatory process exists in US to bring these drugs to the market as they are considered on case to case basis. However, all four Bio-Generics (Somatropin, Glucagon, Calcitonin & Hyaluronidase) approved to date by U.S. FDA have come through 505(b)(2) process.

Summary

- Marketed as branded products rather than Generic
- Earns Patent and Exclusivity.
- Unlike ANDA not effected by discontinuation of RLD
- Insulated from high market competition
- Suitable approval pathway for non-infringing products
- Potential route for Bio-Generics.
- Average sales of 505(b)(2) approved products is US$150mn in 2008.

India's Scenario

Indian Pharma Companies has insignificant presence in advanced formulations and parentrals in U.S. Market. More than 75% of the products marketed by Indian companies are conventional TABs & CAPs, [Jena et al, 2009]. In 2009 Aurobindo, Hetero & Emcure entered in 505(b)(2) NDA business.

It provides an opportunity for generic firms to innovate and enter in to branded products with less development cost involved.

Bibliography:

CDER US FDA Data bases

IMS Japan(2008), Press release 17 June

Jena D, Mohan V, Appaji P.V. et al., Presence of Indian pharmaceutical industry in US market: An empirical analysis. Journal of Generic Medicine (2009),Vol. 6,4, 333-334.

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