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

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Indian Pharmaceutical Congress (IPC)
13 December, 2009, Ahmedabad

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 procedures 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
  - New derivatives.
- Other opportunities include:
  - Drug repositioning
  - Bio-genics

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@nda 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 valuable harmeda database.

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

Table 1: Modificaitons Approved through 505(b)(2) Route

<table>
<thead>
<tr>
<th>Chemical Type</th>
<th>Description</th>
<th>Examples of Significant 505(b)(2) NDA’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Formulation</td>
<td>Includes products characterized by advancement in different routes of administration</td>
<td>(2010) Methonidazole (Tebon, Plavix) — (2013) Fab, Extended Release; Transdermal</td>
</tr>
<tr>
<td>New Pharmaceutical Formulation</td>
<td>Includes various oral and non-oral dosage forms of existing molecules</td>
<td>(2012) Paroxetine HCI — Promises Rayrolol</td>
</tr>
<tr>
<td>New Indication</td>
<td>Includes products that differ from RLD with respect to mechanism or manufacturing process</td>
<td>(2011) Nicardipine HCI (ix) — “Sustained Release” and “Sustained Release; Oral”</td>
</tr>
<tr>
<td>New Manufacturing</td>
<td>Includes manufacturing processes for new therapeutic use now approved by FDA</td>
<td>(2009) Trudiprofen for Ocular Fructose; Lamicons (FNL), Oral Formulas</td>
</tr>
<tr>
<td>New Molecular Entities</td>
<td>New chemical entities for which approval is based on some studies not controlled</td>
<td>(2015) Methimazole, Recombinant Human (Bio-Gene)</td>
</tr>
</tbody>
</table>


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

<table>
<thead>
<tr>
<th>Type of Modifications</th>
<th>Number of Approvals</th>
<th>Sales in $ (2008)</th>
<th>% of Sales in $ (2008)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Formulations</td>
<td>79</td>
<td>30.38</td>
<td>5.10</td>
</tr>
<tr>
<td>New Manufacturing</td>
<td>15</td>
<td>17.01</td>
<td>1.90</td>
</tr>
<tr>
<td>New Indications</td>
<td>16</td>
<td>15.98</td>
<td>0.18</td>
</tr>
<tr>
<td>NDA</td>
<td>11</td>
<td>18.46</td>
<td>2.77</td>
</tr>
<tr>
<td>New Derivatives</td>
<td>5</td>
<td>3.06</td>
<td>0.79</td>
</tr>
</tbody>
</table>

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 of growth of U.S pharmaceutical markets (6.4%). (IMS 2008)

Discussion
Analysis of 75 approvals 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 been earned exclusively/patient 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 formulizations establishes very significant relationship between new manufacturer and parenteral dosage form. Most of these products approved do 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 paracelatol 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 trend: 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-year).

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 formulas 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) falling in various stages of clinical trial. This is supported by enormous clinical & non-clinical data available for such molecules.

Cost advantage may be a factor, too.

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 pathways for Bio-Genetics
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, in India Bio-Genetics (Formigen, Osiagoch, Caldicokin & Hyperdrokin) 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 affected by discontinuation of FILD
- Insulted from high market competition
- Suitable approval pathway for non-infringing products
- Potential route for Bio-Genetics.

Average sales of 505(b)(2) approved products is USD$50mn in 2008.

Indian Scenario
Indian Pharma Companies has insignificant presence in advanced formulations and parenterals in U.S. Market. More than 75% of the products marketed by Indian companies are conventional TBAs & CAPs. (Jena et al. 2008). In 2009 Aurynabs, Helios & Emcor entered in 505(b)(2) NDA business.

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

Bibliography:
ECDR USFDA Data bases
NAS-Japan (2018), Press release 17-June

Acknowledgements
Our thanks to Mr. Poddar Babar, Asst. Director Pharmexcil for his immense support and contribution to this work.