What are supergenerics or value-added generics?

Supergenerics or Value-Added Generics (also referred as New Therapeutic Entities or Improved Therapeutic Entities or hybrids) are modified versions of approved off-patent small-molecule drugs that offer a therapeutic advantage and thereby differentiate them from me-too generic drugs. The therapeutic advantage may be achieved through improved pharmacokinetics, route of delivery, efficacy, safety, patient convenience, stability, and/or manufacturing process.

The concept of offering improved therapeutic products, in the past, was considered by the innovator companies primarily as part of the product life cycle management. However, recently many generic companies have built the capacity for new chemical entity (NCE) development. This along with the availability of a large pool of off-patent molecules has given rise to the concept of hybrid or fusion model of R&D combining generic and NCE R&D capabilities. The innovation opportunities in the form of value-added generics or supergenerics arise primarily because by the time the patent on an NCE expires, new unmet needs are recognized by the stakeholders and newer technologies are developed.

Why is supergeneric strategy needed for sustainable growth?

Growth Story of Generic Companies

Patent expiry and loss of exclusivity of blockbusters such as Lipitor (atorvastatin), Diovan (valsartan), and Plavix (clopidogrel) have led to tremendous growth of generic companies. This has been further fueled by an increased emphasis on the use of generic drugs and introduction of generic prescribing in some countries with an aim to reduce the cost of healthcare.

Challenge of Sustainable Growth

The sustainability of the generic pharmaceutical industry is threatened by several factors. These include low margins, growing competition, increasing regulatory requirements for product approval and maintenance of marketing authorization (including pharmacovigilance, etc.), mature markets in developed countries, and the post-patent cliff arena after 2015. Increased IPR protection in emerging markets in view of TRIPS regime is also likely to prevent the generic companies from launching copycat drugs until patent expiry.

The shrinking pipeline of blockbuster drugs is a concern for generic companies too, as eventually there would be fewer drugs to copy on patent expiry.

SUPERGENERICS IS ONE OF THE HOTTEST AREAS OF INNOVATION IN THE GENERIC PHARMACEUTICAL INDUSTRY – AIMED TO CREATE VALUE-ADDED THERAPEUTIC OPTIONS FOR PATIENTS, PHYSICIANS, AND THE HEALTHCARE SYSTEM

Strategies for Sustainable Growth of Generic Companies

The generic pharmaceutical industry is evolving into a more innovative format. Companies have stepped up their R&D efforts to climb the value chain. One of the earliest examples of success in R&D efforts of an originally generic company is that of Copaxone (Glatiramer acetate). This is a random polymer of four amino acids found in myelin basic protein and was discovered by academic researchers in Israel. Teva Pharmaceuticals developed this molecule, and based on successful clinical trials, it was approved by FDA in 1996 for the treatment of multiple sclerosis. However, not many generic companies have succeeded in their NCE R&D efforts. Considering the risks and investments associated with radical innovation, generic companies are now adopting the easier approach of re-innovation in the form of supergenerics.

Advantages of Supergeneric Strategy

Compared to NCEs, supergeneric strategy offers the following advantages:

- Less data requirement — NDA 505(b)(2) route in the US and Article 10(3) hybrid route in the EU
- Low development costs
- Shorter development timeframe — 3-5 years
- Possibility of 3 years of clinical investigational exclusivity
- Low risk of failure due to established efficacy and safety

Further, compared to conventional generics, end product may gain a significant price premium depending on the value addition offered, and hence there is possibility of high returns on investment.
Key Drivers for the Growth of Supergenerics

**WHO SHOULD PURSUE THIS STRATEGY?**

Supergeneric strategy for growth would be well suited to the companies that possess:

- Large product basket offering greater opportunities for re-innovation
- Quality and cost-effective manufacturing capabilities
- Vast distribution network
- Experience in NCE development and generic R&D (e.g., FDCs and NDDS formulations)
- Regulatory know-how/goodwill to negotiate the most appropriate approval pathway

Further, alliances and partnerships can bring together the companies with complementary capabilities.

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EXPLORING SUPERGENERIC OPPORTUNITIES

Improved therapeutic products have been developed by innovator companies for product lifecycle management and also by certain companies specializing in new drug delivery systems based on the unmet clinical needs. Some improved therapeutic products approved through NDA 505(b)(2) route in the US include Voltaren Gel (topically acting diclofenac for improved safety profile), Zyprexa Zydis (orally disintegrating olanzapine tablets for intake without water), Triesence injectable suspension (trimcinolone for ophthalmic use), Ultram ER (extended-release formulation of tramadol to reduce dosing frequency), Horizant (gabapentin enacarbil for a new indication – restless leg syndrome), Triglide tablets (no-food-effect formulation of fenofibrate), Verelan PM capsules (Chronotherapeutic formulation of verapamil to control morning surge of BP).

Omeprazole is another good example of a drug for which NDA 505(b)(2) route was used to offer innovation. In 2006, a new combination of omeprazole with sodium bicarbonate (Zegerid capsule 20 mg/1.1 g) was approved by the FDA. This is intended to prevent acid degradation of omeprazole, thereby eliminating the need of enteric coating. In 2009, the same combination was switched from Rx to OTC.

Another combination of omeprazole with naproxen (Vimovo capsules) was approved by the FDA in 2010. This was intended to improve compliance as NSAIDs are recommended to be taken with proton-pump inhibitors in the treatment of arthritis.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Innovation (Value addition)</th>
<th>Molecule</th>
<th>Original product (brand name, company name, YOA)</th>
<th>New product (brand name, company name, YOA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>New route (improved safety)</td>
<td>Diclofenac</td>
<td>Voltaren 25/50/75 mg delayed release tablets, Novartis, 1988</td>
<td>Voltaren Gel 1%, Novartis, 2007</td>
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<td>3</td>
<td>New formulation (extended release to reduce dosing frequency)</td>
<td>Tramadol</td>
<td>Ultram 50/100 mg, Janssen Pharmas, 1995</td>
<td>Ultram ER, Valeant Intl/Janssen Pharmas, 2005</td>
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<td>4</td>
<td>New indication (restless leg syndrome)</td>
<td>Gabapentin</td>
<td>Neurontin capsules 100/300/400 mg, Pfizer Pharmas, 1993</td>
<td>Horizant (Gabapentin Enacarbil) extended release tablet 300 mg/600 mg, Xenopon Inc, 2011</td>
</tr>
<tr>
<td>5</td>
<td>New formulation (no food effect)</td>
<td>Fenofibrate</td>
<td>Tricor micronized capsules 67 mg/200 mg, Abbvie, 1993</td>
<td>Triglide tablets 50 mg/160 mg, SkyPharma AG, 2005</td>
</tr>
<tr>
<td>6</td>
<td>New formulation (Chronotherapeutic)</td>
<td>Verapamil</td>
<td>Isoptin Tablets 40/80/160 mg, FSC Pharma, 1982</td>
<td>Verelan PM capsules 100/200/300 mg, Elan Drugs, 1998</td>
</tr>
<tr>
<td>7</td>
<td>New combination (with NaHCO₃, to avoid need of enteric coating)</td>
<td>Omeprazole</td>
<td>Prilosec, AstraZeneca, 1989</td>
<td>Zegerid capsule 20 mg/1.1 g, Santarus, 2006</td>
</tr>
<tr>
<td>8</td>
<td>Prescription to OTC switch</td>
<td>Omeprazole/ NaHCO₃</td>
<td>Zegerid capsules 20 mg/1.1 g, Santarus, 2006</td>
<td>Zegerid OTC capsule 20 mg/1.1 g, MSD Consumer, 2009</td>
</tr>
<tr>
<td>9</td>
<td>New combination (improved compliance)</td>
<td>Naproxen/esomeprazole</td>
<td>Naprosyn 250/375/500 mg, Roche Palo, 1976; Nexium capsules 20/40 mg, Astra Zeneca, 2001</td>
<td>Vimovo capsules, Astra Zeneca, 2010</td>
</tr>
</tbody>
</table>
Recently, generic companies have also used NDA 505(b)(2) route to bring branded/differentiated generics to the US market. These include the new salt forms of amlodipine (amlodipine maleate: Amvaz) & desvenlafaxine (desvenlafaxine base: Khedezla). Docefrez is a newer version of docetaxel injection, manufactured by using a new process. These products represent incremental innovation, primarily aimed to gain early entry to the US market, prior to the patent expiry of the innovator product.

However, generic companies have also developed certain differentiated products to offer benefits to certain patient segments. Riomet, an oral solution of metformin, approved by the FDA in 2003, offers convenience to the pediatric/adult population who have difficulty in swallowing tablets. Higher strengths of Levetiracetam extended-release tablets (1000 mg & 1500 mg) and intermediate strength of Daptomycin (350 mg/vial) have been developed in view of the needs of specific patient segments. A new formulation of levodopa-carbidopa extended release (Rytary) claims to be more effective in reducing off-time in Parkinson’s wearing-off phenomena.

**WHAT ARE THE KEY QUESTIONS FOR THE PLAYERS GOING FORWARD?**

1. What are the key unmet needs in each therapeutic area and for each of the currently available drugs, and how would they evolve in future?

2. Can the unmet needs be addressed by making changes in dosage form, strength, route of administration, formulation, dosing regimen, or can a new indication be explored for an existing drug?

3. What is the value addition offered by the above approach and what is the available scientific evidence?

4. What is the likely target segment and how would prescribers react to the product?

5. Is the proposed modification technically feasible? What are the available technology platforms?

6. How can IP infringement be avoided while developing supergenerics, and IP protection gained for the supergenerics?

7. What kind of studies would be required to demonstrate the claimed differentiation and safety of the new product? What would be the appropriate development plan? What is the probability of success?

8. What are the regulatory requirements for approval and do they differ across geographies?

9. What are the geographies of interest for a product? What is the role of emerging markets?

10. When and who to partner with?

11. What is the likely impact of market access parameters, pricing and reimbursement policies?

12. What would be the stand-alone revenue potential - revenue drivers, commercial uncertainties?

To capitalize on existing success and to chart a higher trajectory of sustainable profitable growth, generic companies must embrace innovation and adopt technology to create value-added therapeutics. This will address unmet medical needs, and will consequently improve clinical outcomes and build cost-efficient healthcare systems. Furthermore, it will also assist the generic companies move up the value chain and create value for their shareholders.