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Interview

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Recommendations and way forward for Indian biosimilars industry

THE VACCINE DILEMMA

Recent reports on adverse effects of MMR vaccine have reignited the age-old debate on whether to vaccinate or not. Industry experts and stakeholders share their views on this burning issue

Recommendations and way forward for Indian biosimilars industry: Road to a sustainable future

A research paper from Sathguru Consultants offers recommendations to nurture the vibrant biosimilars industry landscape and support in value realisation. Excerpts

The techtonic shift of global healthcare from small molecules to biologics is hard to ignore anymore and considering the imminent problems that biologic drugs bring forth in terms of drug pricing and affordability, the role of biosimilars has never been more important. While there has been no significant engagement in novel biologics from Indian pharma majors, biosimilars are a hard to ignore growth opportunity for Indian companies going beyond small molecule generics ridden with intense competition and price pressures. There is growing interest in the Indian landscape and is evidenced by increasing number of new companies jumping on the biosimilars bandwagon. The segment is critical if Indian industry is to obtain the targeted $100 billion bio-economy.

With record number of domestic approvals, active engagement in semi-regulated markets and growing footprint in regulated markets, the Indian biosimilar industry is poised at the cusp of growth. There is an active pipeline in the country today, with many companies marching towards regulated markets. *Check Table 1 that indicates pipeline of some of the leading players in the segment.*

It is imperative to nurture the vibrant industry landscape and support the industry in value realisation. It is important to equip participants with the right arsenal to combat commercial challenges around market entry and access in domestic as well as international markets.

Major areas of challenges to combat in order to secure a sustainable future for Indian-made biosimilars and key recommendations are summarised below.

Expanding markets in domestic landscape: Need for a multi-stakeholder approach: As highlighted in earlier sections of the publication, the volume penetration of biosimilars within the country is appallingly low, with less than 10 per cent for the largest biosimilar market of trastuzumab. Despite price control of key biosimilar drugs, overall penetration of drugs remains sub-optimal. Wielding price control as an arsenal has always been a double-edged sword and high caution needs to be exercised to ensure right balance between affordable access and reward for innovation. In the case of

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biosimilars, it has mostly resulted in shrinking of markets without a corresponding impact on expansion of access to care due to overall cost of care still being unaffordable for more than 80 per cent of the target population. The market has reached a point of limbo where value realisation has saturated at a very low level of market penetration and there is negligible commercial incentive for companies to expand markets further.

Thus, there is an urgent need for government intervention and a multi-stakeholder approach for expanding volume penetration and propelling the domestic biosimilars market towards success.

i. Better tranparency in pricing

Price competition in Indian biosimilars market mostly prevails at hospital level to win business vs competitors and the price benefit is not being transferred to the patients, despite the drugs being price controlled. This is a significant concern in a landscape where overall cost of care for indications such as cancer is already unaffordable for more than 80 per cent of the population. Transparency in pricing and margins at different stages of value chain is thus need of the hour, in order to trigger market expansion to patients who are currently out of the affordability net. This recommendation, if accepted will pave way for benefits of price competition to be transferred to patients.

ii. Inclusion of critical biologics in public programs

Considering the largely out-of-pocket nature of the Indian market, affordability qualms heavily limit market penetration, as the cost of care for biologic drugs remain a lofty luxury for majority of the population. In the case of oncology, in addition to cost of the drug itself, there has been high concern on patient drop-outs due to overall cost of care not being affordable. For instance, trastuzumab in the case of breast cancer is used as a primary systematic therapy and also as neo-adjuvant or adjuvant therapy. In the case of the latter, in addition to cost of the drug, overall cost of care includes cost of hospitalisation and cost of surgery and/or chemotherapy. To expand access, we need to address access issues for both, overall cost of care and the drug itself. In the current landscape, even in the few states where cancer care is paid for, Government schemes don't cover biosimilars or peptide drugs and only cover traditional small molecule drugs.

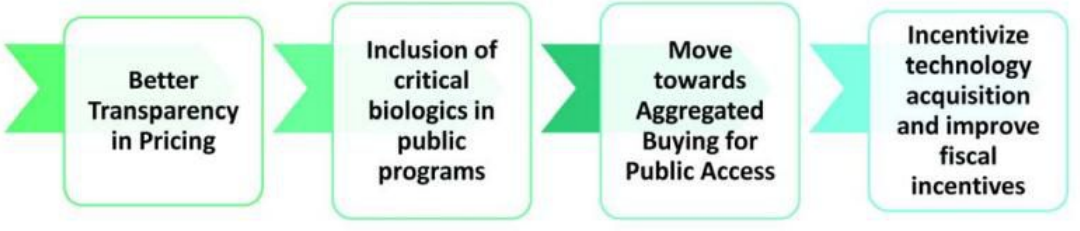
If we need to push the boundaries on adoption to achieve meaningful impact of affordable biologics on health outcomes, their inclusion in Government schemes is critical. At the current price levels, such inclusion is also likely to be supported by sound health-economic justification. More importantly, expanding coverage of healthcare schemes to biosimilars will be doubly rewarding for the nation - doing so will significantly enhance access to healthcare for the population while also building in financial viability for biosimilar makers in their home turf.

iii. Move towards aggregated buying for public access

Current price control mechanisms do not factor in the large economic diversity of the Indian population and are exercised as one-size-fits-all approach for capping prices to all sections of the population. The upper economic tiers have several times more propensity to pay than the fixed prices while the lower tiers come nowhere near affording the same price. In effect, this could have even resulted in shrinking the overall addressable market size for biosimilars, without substantially expanding the market size and overall level of penetration. Cross-subsidisation models in the vaccine industry in India, for instance, is a clear success story of achieving sustainable pricing economics ensuring both affordable access as well as value realisation for manufacturers. While substantial pooling of volume procurement in the public immunisation system has driven volume based price economics for affordable access, freedom of pricing in private markets has ensured reward for innovation and value realisation for manufacturers without compromising affordability. Inclusion of biosimilars in programs such as Ayushman Bharat will open windows for

TABLE 1

Company	Pipeline Info	Target Markets	Stage of Development7
Intas Biologicals	5 biosimilars in the pipeline for India, and 5 for regulated markets of EU and USA		
Biocon	Adalimumab		Global Phase 3 completed
	Trastuzumab	Approved in USA, Under review in EU, Canada & Australia, Filed/Marketed in Emerging markets	
	Pegfilgrastim	USA, EU, Canada, Australia, EM	Filing
	Bevacizumab	Marketed in India	Global Phase 3
	Filgrastim	-	Early Development
	Etanercept	-	
Dr. Reddys	Pegfilgrastim	EU, USA	Approval enabling studies initiated
	Rituximab	EU, USA	
	Bevacizumab	EU, USA	
	2 new molecules entering clinical development in coming months		
Zydus Cadila	8 biosimilars in the pipelines for regulated markets and India		
Reliance Life Sciences	14 biosimilars in global pipeline		
Lupin Pharma	5 biosimilars in global pipeline		
Wockhardt	4 biosimilars in global pipeline		



the government to explore similar models for biosimilars well. Considering the futuristic importance of large molecule drugs in allaying healthcare burden, it is critical to think of prudent ways to expand access in India and ensure our population does not lose out on such frontier medical advances, especially after being made more affordable through availability of biosimilars.

iv. Incentivise technology acquisition and improve fiscal incentives

Although many Indian companies have cracked the complex production know-how in biosimilars in microbial as well as mammalian platforms, there is a need to enhance focus on upstream technology development. Even companies that are ahead of the game in domestic markets are still grappling with issues related to manufacturing performance and production yield and are exploring organic as well as inorganic ways to improve manufacturing performance. Considering criticality of time to markets in the biosimilars market, it is important to support timely access of technologies that enable companies to forge a competitive market entry. High performing clones will be a critical competitive factor for companies as sustainable success hinges largely on production economics, especially as prices erode and unit cost and enhanced capex recovery become critical. Moreover, in an environment where prices crash with every additional competitor entering the market, companies without significant success in yield and manufacturing economics will lose competitiveness, and companies with better yields, even if late to

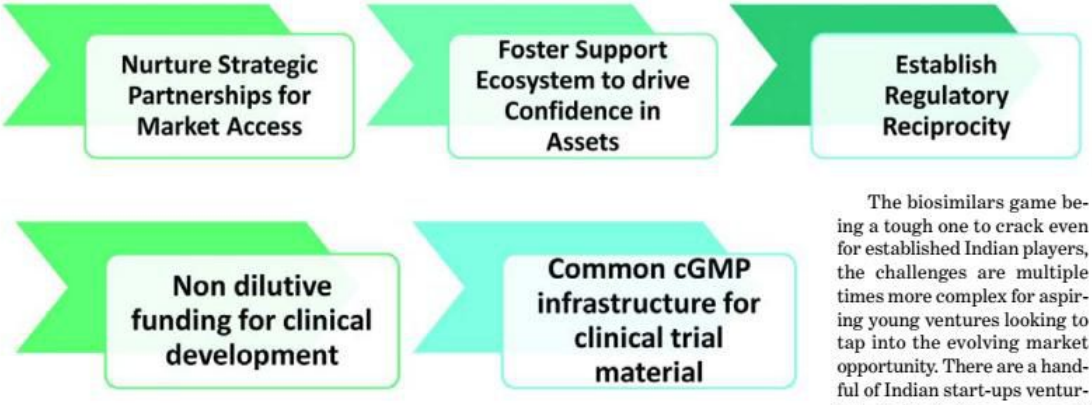
TABLE 2

Company	Product Pipeline Details
Apcegen Technologies Private Limited	Portfolio information undisclosed
Clonz Biotech Private Limited	Rituximab, Trastuzumab and Ranibizumab under preclinical development; Bevacizumab, Denosumab and Ustekinumab under clone development stage
Enzene Biosciences Private Limited (with strategic investment from Alkem Laboratories Limited)	Advanced stage of clinical development for 6 molecules for domestic market; One recombinant molecule and one monoclonal antibody in developmental pipeline for global markets
Epygen Biotech Private Limited	Advancing a biosimilar for Streptokinase licensed from Institute of Microbial Technology (IMTECH), Chandigarh, expected to launch in 2018. Pipeline includes Bevacizumab and Pegfilgrastim
Genesys Biologics Private Limited	Insulin Biosimilars Imgenex India Private Limited Trastuzumab in preclinical stage; adalimumab, bevacizumab, ustekinumab, and nivolumab in R&D
Levim Biotech	Streptokinase and GLP-1 biosimilar in pipeline

markets, can quickly aggregate and consolidate market share due to better price competitiveness.

- Much of global R&D begins in academia and thus capacity building for clone development can also be nurtured within the country via pooling scattered skilled resources through competent academia-industry collaboration through creating PPP consortiums for collaboration in core technology development.
- Bilateral government programs are another avenue to trigger capacity building within the country. It is time to take a leaf from legendary programs such as Indo-US Vaccine Action Programme (VAP), which has resulted in upstream development of safe and efficacious vaccines against some of the major communicable diseases through concerted efforts from eminent scientists, institutions and policymakers from both countries.
- Current non-dilutive funding mechanism from the government do not fund technology acquisition. Even current fiscal incentives are limited to in-house research and development and revenue from out-licensing of Indian patents. To equip the Indian biosimilar industry to be globally competitive in the near-term, it is critical that such fiscal incentives be extended to corporate investments in technology acquisition. Korea sets a good global benchmark for incentivising technology acquisition. Tax incentives are provided for M&A activities that furthers innovation potential of the country. When a domestic Korean firm merges with a technology-led SME, the merging/ acquiring company is eligible to avail a 10 per cent tax credit on the payment made, up to the value of the acquired technology. Technology acquisition is the starting point of risk investments made by companies and it is important that de-risking support be extended to the point of technology acquisition.

Establishing competence in global markets



The global biosimilars industry is at the cusp of transition, with regulatory framework evolving and streamlining in multiple countries. Much of Indian made biosimilars are yet to see light of the day in global markets, although initial momentum is seeded by a couple of frontrunners such as Biocon and Intas with their initial approvals in US and European markets. Considering much of future value lies in global markets, it is important to consider ways to accelerate engagement and trigger value realization in these markets. Such participation in high value markets and value realization will also be a critical precursor to expanding level of industry engagement, catalyzing further investments, and setting in motion the cycle of portfolio investments.

i. Nurture Strategic Partnerships for Market Access

High levels of binary risk and unsurmountable levels of investment are the main factors hindering active engagement of Indian companies in global markets. Considering existence of large stalwarts in the domestic market, pooling of resources will help in significantly defraying risks and yield more bandwidth for shouldering investments. Strategic collaborations with global counterparts could also achieve the same goal and additionally provide access to their regulatory and marketing strength in global markets. Such collaborations also elevate the quality confidence and reputation of Indian-made assets, which is much needed in the current landscape, where assets approved from India and the Indian biosimilar regulations are still perceived inferior to global ones. Leveraging co-investment collaborations will be critical to accelerate path to markets and translate current level of active engagement in Indian industry to significant value realisation.

ii. Foster support ecosystem to drive confidence in assets: While solutions for more optimal value realisation are very externally dependent on regulator and market forces, a more conducive export environment as well as more consolidated effort by industry can potentially make this engagement sustainable and scalable. Small molecule formulation exports from India are a formidable example of multiple ministries and industry working together to create a forthcoming export ecosystem and receptiveness for Indian products globally. Pharmexcil has played an instrumental role in driving export success of Indian-made generic drugs and in establishing their quality reputation in regulated markets. Given the expanse of investments with limited realised return, and the continuing misconception about inferiority of Indian biosimilar approval pathways, a similar thrust and a support framework is called for even in the biosimilars segment.

iii. **Establish regulatory reciprocity in ROW markets:** While the regulatory rigor between Indian National Regulatory Authority (NRA) approved products and US and EU regulations is hard to bridge, it is quite comparable with other emerging markets, yet different regulatory pathways in different countries call for significant bridging work to be done for approvals. Regulatory reciprocity for Indian National Regulatory Authority approved products will enable greater scalability in these markets. One such development that could help in better harmonization of country-level requirements is the WHO Prequalification Program. The WHO prequalification pilot is an encouraging global development in this direction and the industry will greatly benefit from concerted effort to ease market access and creation of any aggregated procurement mechanisms akin to antiretroviral drugs and vaccines. In the interim, facilitated regulatory guidance and advisory support for Indian companies pursuing this path for the first time would also greatly facilitate more efficient market access in this complex landscape.

Nurture the start-up ecosystem to encourage newer ventures

The biosimilars game being a tough one to crack even for established Indian players, the challenges are multiple times more complex for aspiring young ventures looking to tap into the evolving market opportunity. There are a handful of Indian start-ups venturing in biosimilars, some of which are highlighted in **Table 2**

The biosimilars game being a tough one to crack even for established Indian players, the challenges are multiple times more complex for aspiring young ventures looking to tap into the evolving market opportunity. There are a handful of Indian start-ups venturing in biosimilars, some of which are highlighted in the table.

Firstly the investment-heavy nature of the segment is a deterrent in multiple stages of the product lifecycle. Start-ups that are incubated well typically tend to be able to manage costs until early analytical work at lab scale, as bulk of the costs till then comprise of cost of consumables and small animal experiments which could be covered under grant funding. Early stage programmatic investments from DBT and other grant providers has been instrumental in catalyzing these ventures. Costs skyrocket in subsequent stages where products enter preclinical animal testing and clinical stage. There is a huge valley of death in terms of scale-up infrastructure at this stage characterized with negligible level of early stage venture capital.

Challenges also prevail in accessing quality genetically modified animal models for research. There is no domestic capacity in the country for GM animals and the research ecosystem today completely depends on imports for this critical need. Average waiting period for import ranges from 1.5 to 2 years thus unduly stretching time to markets. Additionally, there is a near void of affordable cGMP pilot facilities in India for manufacturing clinical grade material, which is a critical deterrent in advancing these programs towards market. Considering high binary risk in commercialization, upfront investments on manufacturing facilities is a risk factor even for

established companies with strong balance sheets. Globally, even innovators tend to outsource manufacturing of biomaterial for clinical trials to reputed contract organizations, which could cost as high as $ 2M for a single batch. Companies either work out larger CMO contracts or operationalize commercial facility investments only post product approval, in order to minimize sunk costs, should the product fail regulatory approvals. The same challenge prevails in biosimilar markets as well, especially affecting smaller ventures, with a clear market need for shared infrastructure in the country for manufacturing of clinical material. The current situation is such that younger ventures that embarked on biosimilar development have eroded in value and face highly uncertain future due to slow pace of portfolio development. The most significant impediment in the path of younger ventures has been dearth of investments especially in context of exalting level of capex for CGMP facilities for clinical trial lots in the absence of a strong CMO ecosystem or shared facilities in the country. While early stage programmatic investments from DBT and other grant providers has been instrumental in catalyzing these ventures, it is critical that scale-up infrastructure and followon investment ecosystem is nurtured with urgent attention.

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i. Non-Dilutive Funding For Clinical Development While India has a strong base of non-dilutive grant funding opportunities, thanks to DBT and BIRAC, for initial de-risking of technology, the quantum of such funding is insufficient in light of the long lifecycle of biosimilar product development and validation. While current nondilutive funding mechanisms from Indian Government can support young ventures in the first few steps of development, a well-structured funding to de-risk the most capital intensive step of clinical validation for global markets could truly be instrumental in Indian industry carving global presence in biosimilars. To be truly impactful, such funding mechanism needs to be of sizeable quantum and take cognizance of time sensitivity of the biosimilar commercialization process. DBT's $250 million i3 program or the National Biopharma Mission is a step in this direction, and such platforms need to be expanded to sustain the startup ecosystem engaged in biosimilars and novel biologics. ii. Common cGMP Infrastructure for Clinical Trial Material In the absence of a strong CMO ecosystem for bio manufacturing in the country, creation of common cGMP infrastructure for manufacturing of clinical trial material is the need of the hour. With several competitors struggling to make their mark in global markets, India's competence lies largely in low cost manufacturing and it is important to nurture a competent bio manufacturing ecosystem to achieve it. This could be facilitated through PPP models or strategic buying of private sector capacity. Both Indian as well as international companies can be employed to operate these facilities, to trigger local bio manufacturing competency. As a challenge that also impacts ventures developing vaccines and novel biologics, this challenge calls for immediate attention. Again, DBT's i3 program includes the mandate of creating such common manufacturing capacity and when operationalized could provide great respite to ventures pursuing biosimilars.