From the Board Room

EmergingCo: A Virtual "South-South" Biotech Model

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ABSTRACT

The article proposes a "virtual" biotech model for the emerging markets - termed *EmergingCo* - and develops a comparative financial model to argue that such a virtual biotech can deliver drug candidates from discovery through proof-of-concept (Phase II) more cost effectively than the traditional drug development paradigm. Data from published studies on drug development costs have been compared with a cost structure model for *EmergingCo* using a framework where all R&D can be accomplished through a virtual network of partnerships within emerging markets. A couple of case studies from China and India are used to lend support to the cost structure model. Such a model, either as a venture backed company or a virtual unit of big pharma, could provide an alternate vehicle for delivering mid-to late stage clinical candidates, similar to Lilly's Chorus model.

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INTRODUCTION

The increasing pharmaceutical R&D cost pressures have led companies to seek innovative models for delivering drugs, including investments and partnerships in emerging markets. Previous studies have evaluated the strengthening biomedical innovation landscape, increasing number of biotech companies and the innovative biotech partnerships within the emerging markets.[1,2,3] This article proposes a virtual "south-south" model – a biotech that would perform the entire value chain of R&D through a network of collaborations and funding from the emerging markets – that can potentially deliver proof-of-concept (Phase II) drug candidates more cost effectively.

Key emerging markets have built strong expertise in specific areas of pharmaceutical R&D.[1] Israel has strengths in novel biology and targets and Israeli institutions have discovered several innovative drugs such as copaxone, azilect and doxil, apart from producing five Nobel laureates since 2000. China has built multiple bioclusters and fully integrated CRO platforms across chemistry, genomics, toxicology, biologics and manufacturing.[4,5] In contrast, Korea has built deep expertise in translational sciences, especially in oncology, producing early clinical data for industry drug development programs such as crizotinib. Russia has exceptional expertise in the area of computational biology and predictive sciences, and India leads in data management and analysis. Specific countries also have build therapy and disease area expertise; for example, China and Korea in oncology, S. Africa and Brazil in infectious disease and India in metabolic diseases.[6] China, Russia and Singapore based venture and sovereign funds are providing risk capital to early stage biotech companies, locally as well as globally. There is also an increasing intensity of deal making between emerging markets pharmaceutical firms to tap into such inter-country expertise (Table 1).

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Table 1: The data for biotech investments and collaborative deals between emerging markets companies was gathered from various country-specific public sources such as ChinaBio (China), Globes (Israel), International Finance Corporation (IFC), PharmAsia and financial intermediaries such as Barclays Asian Healthcare Reports. The dataset was further supplemented by internet keyword search for emerging markets pharmaceutical and biotech deals. Proprietary databases such as BiotechGate, Citeline®, IMS Health and Decision Resources were also screened to search for various emerging markets deals. A few representative transactions are shown

Year	Acquirer	Innovator	Deal structure
2014	Guangxi Wuzhou (China)	Hebrew Univ. – Integra Holdings (Israel)	$3 Mn investment into Integra to develop and commercialize Hebrew technology in China
2014	WuXi AppTec (China)	Pontifax (Israel)	Pontifax and WuXi to co-invest in Israeli technology and products
2014	Guangxi Wuzhou (China)	Oramed (Israel)	$5 Mn investment into Oramed for developing diabetes drugs
2014	3SBio (China)	PharmAbcine (Korea)	In-licensing of Tanibirumab, a cancer antibody
2014	Harbin Gloria (China)	Boryung Pharma (Korea)	~$5 Mn for China rights to hypertension drug
2013	Chia-tai Tianqing Pharma (China)	BioLineRx (Israel)	In-licensing of HCV drug candidate for China; potential deal value ~$30 Mn
2013	Tecpar (Brazil)	Biocad (Russia)	Development and manufacturing of biosimilars for Brazil market
2013	Fosun (China)	Alma Lasers (Israel)	$240 Mn acquisition of medical aesthetics device company
2011	Hikma (Middle-East)	Celltrion (Korea)	Commercialization rights for biosimilars in Middle East and Northern Africa

EMERGINGCO MODEL

A virtual "south-south" biotech—let's name it '*EmergingCo*'—can tap into these specific expertises from key emerging markets and effectively build an end-to-end R&D capability (Figure 1). The *EmergingCo* could seek novel assets from Israel, leverage the service platforms of China, access translational sciences in Korea, and utilize the bioinformatics capabilities of Russia and India. Funding can be structured from Russian, Chinese, Middle Eastern or Singaporean investors.

The costs of progressing a molecule from discovery through Phase II for *EmergingCo* could be significantly lower as compared to an industry program. A recent Tufts study[7] calculated that the industry costs to deliver a drug from discovery stage through Phase II studies are ~$490 million over 8 years with a probability of success of ~7.5%. Using an average cost of capital of 11%, the risk-adjusted present value of these costs are ~$300 million. Assuming a comparable probability of success, timeline and cost of capital, *EmergingCo* costs for a similar program would be ~$120-150 million, almost 65-75% less expensive than the Tufts study, while the risk-adjusted present value of such costs would be ~$60-80 million (Box 1).

Two comparable data points, although less rigorously estimated than the Tufts study, are the research costs of novel molecules at Beta Pharma in China and Glenmark in India (Box 2).[8,9] These companies have advanced molecules through proof-of-concept studies in two contrasting emerging markets and provide a template for such an *EmergingCo*. Both Beta and Glenmark, on average, spent <$25 million for delivering a proof-of-concept molecule, and in the case of Beta successfully launched an oncology drug in China.

Post Phase II, the *EmergingCo* would ideally out-license the molecule to big pharma to finance its early pipeline. The average upfront payment for a Phase III ready compound sold by a small-to-mid-sized biotech to big pharma is ~$40 million.[10] The upfront payment would help cover the costs of the early pipeline candidates while still allowing the *EmergingCo* to retain substantial downstream milestones and royalties. The returns can be further levered by accessing non-dilutive funding from public sources, such as the Office of Chief Scientist (OCS) in Israel, FAPESP in Brazil or Skolkovo in Russia, that match research funding for portions of work conducted in their respective countries.[1]

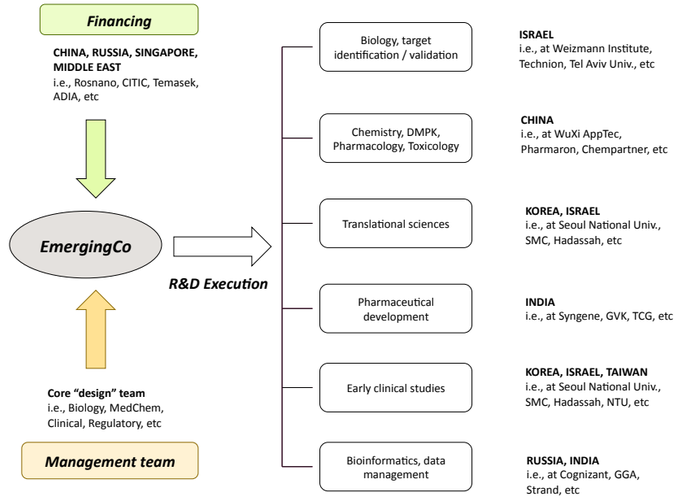

Figure 1: Global end-to-end R&D

Box 1: Cost of progressing a molecule through Phase II: Traditional vs. *EmergingCo* model

(i) Costs model for traditional development (a): The table below adapted from Tufts center for the study of drug development study for 2014.[7]

	Discovery	Preclinical	Phase I	Phase II
Probability of success	50%	69%	60%	36%
Average costs ($Mn)	8	10	20	80
# of projects	13.4	6.7	4.6	2.8
Total costs	107.4	67.1	92.6	222.2
Duration/phase (yrs)	2	1.5	1.5	2.5
Cost of capital	11%			
Present value, costs ($Mn)	96.7	46.6	54.9	101.6

(ii) Cost model for traditional development (b): The table below is adapted from Paul *et al* article.[14]

	Target-to-hit	Hit-to-lead	Lead Op	Preclinical	Phase I	Phase II
Probability of success	80%	75%	85%	69%	54%	34%
Average costs ($Mn)	1	2.5	10	5	15	40
# of projects	15.5	12.4	9.3	7.9	5.4	2.9
Total costs	15.5	31.0	92.9	39.5	81.7	117.6

Duration/phase (yrs)	1	1.5	2	1	1.5	2.5
Cost of capital	11%					
Present value, costs ($Mn)	13.9	23.8	58.1	22.2	39.4	43.7

(iii) Cost model for *EmergingCo*

The probabilities of success, duration per phase and cost of capital for the *EmergingCo* cost model are assumed to be comparable to estimates in the studies (i) and (ii) above. The *EmergingCo* could potentially progress molecules through discovery and preclinical faster than the industry norm, although a challenging regulatory framework in key emerging markets may result in slower clinical progress, hence a similar overall timeline was assumed for the calculations.

The average costs per project for the cost model are based on project quotes from a sample of CROs based in China,[5] Singapore, Taiwan and Korea.

The costs range from:

- $3-8 Mn for discovery and preclinical;
- $1.5-5 Mn for a 50-patient, typical Phase I; and
- $5-10 Mn for a 100-150 patients, typical Phase II program per indication.

Mid value of the ranges were used for the calculations in the model below.

	Target-to-hit	Hit-to-lead	Lead Op	Preclinical	Phase I	Phase II
Probability of success	80%	75%	85%	69%	54%	34%
Average costs ($Mn)	0.5	0.8	4.0	1.5	3.5	7.5
# of projects	15.5	12.4	9.3	7.9	5.4	2.9
Total costs	7.7	9.9	37.1	11.8	19.1	22.1
Duration/phase (yrs)	1	1.5	2	1	1.5	2.5
Cost of capital	11%					
Present value, costs ($Mn)	7.0	7.6	23.2	6.7	9.2	8.2

IMPLEMENTATION CHALLENGES AND RISK MITIGATION

There would, no doubt, be significant operational and execution challenges of implementing such an *EmergingCo*. The sustainability of novel targets and molecules from the emerging markets is a key hurdle, given paucity of substrate originating from these markets to date. A key challenge would also be regulatory, especially for countries such as China and India where it can take several months to years to obtain clinical trial approvals for drugs not locally discovered or manufactured. The *EmergingCo* could run the early clinical studies in Taiwan, Korea or Israel, where the regulatory framework is more progressive, to overcome such hurdles. An additional challenge is the complexity of managing dispersed aspects of research work in a China and Israel lab simultaneously, for example, that often progress smoothly in an integrated in-house R&D organization. Finally, quality assurance at the clinical centers, CROs and manufacturing is another concern, and will need strong controls to maintain high standards.

Nevertheless, such issues will largely be similar to any virtual biotech that outsources key aspects of drug discovery[11] or of structuring and running a large multi-party consortia.[12] Further, to manage such risks, an ideal model would be to structure the *EmergingCo* as a virtual unit within a big pharma that can pursue cost-effective innovation by leveraging the broader network of the parent company. If successful, it can provide an alternate vehicle for delivering mid-to late stage clinical candidates, similar to Lilly's Chorus model.[13]

Box 2: Case study for comparable R&D costs at Beta Pharma (China) and Glenmark Pharma (India)

Beta Pharma:
Estimated total R&D investments during 2001-2011 period was estimated at ~$50-60 Mn (non-capitalized).[8] Additionally, Beta Pharma costs are estimates based on presentations from Beta Pharma management at conferences.

Drug candidate delivered during 2001-2011 period was 1 new chemical entity (Icotinib) that entered the clinic and was subsequently launched in China in 2011. The 2013 sales of Icotinib in China were $100 Mn+.

Glenmark Pharma: Note that the numbers are estimates from publicly disclosed information[9] and public filings, but may differ from yearly accounting recognition of Glenmark. Further, R&D investment data was only available from 2004 onwards, and data for 2001-2003 is assumed to be same as 2004.

The total R&D investments during 2001-2011 period were estimated to be ~$120 Mn.

Drug candidates delivered during the 2001-2011 period were 6 new chemical entities (NCEs) that entered clinic and 2 progressed to Phase II. All 6 candidates were out-licensed to global pharmaceutical companies such as Sanofi, Eli Lilly, Merck and Forest Labs. None were successful in Phase II.

The milestone payments from pharma partners during 2001-2011 period were estimated to be ~$180 Mn.

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
R&D Investments ($Mn)	5.8	5.8	5.8	5.8	5.8	9.5	14.2	16.9	19.6	17.2	12.6
Upfront + Milestones from deals ($Mn)	0	0	0	0	20	30	45	15	0	20	50

The milestones payments are from Sanofi (2010 and 2011), Forest (2005 and 2008), Eli Lilly (2007) and Merck (2006). Note that the payment timing is assumed as per the press releases, and actual cash payment timing may differ from the timeline assumptions in the table above.

The figure above does not include any potential future milestone payments and royalties from partners to Glenmark.

INVESTOR STRATEGY

From a financing perspective, a potential challenge is the appetite of emerging markets domiciled investors to fund cross-border emerging markets firms rather than support "local heroes" within their own countries. There are, however, some recent examples that suggest investors are receptive to such transactions. Aslan Pharma, a virtual company based in Singapore, is backed by BioVeda Capital from Singapore, Morningside Group from Hong Kong and Cenova Ventures from China. The company is running clinical studies primarily in Taiwan and Korea, and most of the CRO work is conducted in China. One key difference between Aslan and the *EmergingCo* model, however, is that Aslan assets are still primarily sourced from US and Europe whereas

EmergingCo model proposes that these assets can be sourced from key emerging markets. Another example of investment firms partnering on such deals is the association of Integra Holdings in Israel and Guangxi Wuzhou Group in China to leverage the innovation (asset sourcing) from Israel and the CRO (execution) services from China. WuXi AppTec, the largest CRO in China, has also partnered with Pontifax, an Israeli investment fund, on similar lines. Russia and Middle East investors do favor the "local hero" transactions and groups such as Rosnano prefer to invest in companies that can build subsidiaries in Russia (i.e., their investment in BIND). It has been driven by their desire to also build local expertise and capabilities that have been lagging as compared to Israel, China, India or Korea. Such investors will, hopefully, find *EmergingCo* a much more encompassing model to explore, other than their favored "local hero" model.

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