Article

Considerations for Potential Global Expansion of Serum Institute of India

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ABSTRACT

In a time of global vaccine shortages, especially for COVID-19 products, Serum Institute of India (SII) is straining to meet demand for vaccines in India. While this organization is not known worldwide, they entered into a recent alliance with AstraZeneca, who is partnered with Oxford University for COVID-19 vaccine, to manufacture their supply of vaccines for distribution in India. Several other such partnerships are also underway. And, SII is considering plans to become a much larger player, not only in India, but globally. This commentary is focused on if, when, where, why, and how global expansion could proceed. Our work was carried out as a class project to identify options and strategies appropriate for expansion and has been expanded subsequently as events continued to develop.

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INTRODUCTION

The October 2020 issue of *Fortune* magazine cited the vaccine manufacturer, Serum Institute of India (SII) as one of its top ten "Change the World" companies[1]. Although hardly a household name, and currently without market presence in the US, this company has been also been cited in published articles and reports from Reuters and The Economist as the world's largest vaccine manufacturer as measured by the **number of doses.** *Then, on April 20, 2021 Fortune reported that* "countries around the world counted on the Serum Institute of India, which produces 60% of the world's vaccines[2] each year, as a lifeline to supply them with COVID-19 vaccinations. Now, Serum Institute of India is struggling to meet even the vaccine demands of its home country as India battles its worst-ever wave of COVID-19 infections"[3].

SERUM INSTITUTE OF INDIA

Serum Institute of India (SII) is an Indian biotechnology and biopharmaceuticals company, located in the city of Pune, Maharashtra, India, and was founded by Cyrus Poonawalla in 1966.[4] Their product lines have since been expanded to cover different vaccines against bacterial or viral infections. Since 2014, the vaccines manufactured by Serum Institute of India have been used in international vaccination programs run by the World Health Organization (WHO), UNICEF, and the Pan American Health Organization (PAHO). Today, Serum Institute

1 https://fortune.com/company/serum-institute-of-india/change-the-world/. Accessed July 11, 2021.

2 https://edition.cnn.com/2021/04/17/india/covid-vaccine-shortage-covishield-covaxin-intl-hnk-dst/index.html. Accessed July 11, 2021.

3 https://fortune.com/2021/04/20/india-covid-cases-vaccine-vaccinations-serum-institute/. Accessed July 11, 2021.

4 https://en.wikipedia.org/wiki/Serum_Institute_of_India. Access July 11, 2021.

of India is run by Adar Poonawalla (son of Cyrus) of the Poonawalla Group and engages in research, development, and manufacturing. In effect, SII is a subsidiary of a family-controlled business.

The benefits of vaccines and vaccination are well-established in the US and other countries and extend beyond prevention of specific diseases in individuals to include societal and economic benefits. The vaccine business, a former laggard in the overall pharmaceutical market, is showing remarkable growth powered by new innovative vaccines coupled with new pricing strategies. Specifically contributing to this growth have been the varicella, hepatitis A, pneumococcal conjugate, shingles, rotavirus, meningococcal conjugates, and human papillomavirus (HPV) vaccines – many based upon discoveries licensed from the US National Institutes of Health (NIH). An overall prediction for the global vaccine market is that it will steadily grow at a rate of 8.1% in revenue between 2021 and 2026, propelled by the COVID-19 pandemic and need for vaccinations.[5] This increase is also driven by the worldwide increase in the incidences of several infectious diseases, and as well as new government interests in encouraging immunizations. The US vaccine industry is the most stringently regulated, but also the largest single market in terms of revenue in the world, holding approximately 40% of the global vaccine market share in 2020[6]. Hence, vaccine sales in the US are seen as desirable by all vaccine manufacturers including foreign vaccine manufacturers. However, entering this market is challenging, as it is currently dominated by a few large, global incumbents to be discussed later in this case study. So, new entrants must appreciate that entry, growth, and long-term persistence in the US, and worldwide vaccine marketplace can be a greater challenge than just an initial launch of a single product for a single disease. Given the costs involved in vaccine development, manufacturing and supply, as well as the traditionally smaller market size compared to that for pharmaceutical products, companies find that that this competitive market is largely dominated by only a few players who can truly handle the vagaries and challenges of vaccine supply and demand. Given these challenges, and with a growing traction in smaller foreign markets, this case study outlines some strategic considerations that underly consideration by SII as they explore collaborations with US and UK/EU-based institutions to demonstrate their ability to perform with trust in US and other global markets. Is the timing too early, just right, or too late?

Traditionally in the development of strategies for new market entries, one would start with a SWOT (strengths, weaknesses, opportunities, and threats) analysis to evaluate and assess the overall situation. Accordingly, a SWOT analysis is included later in this case study. To expand, a company such as SII would require development of a validated, differentiated, and compelling value proposition; identification of a suitable MEP (market entry point); and, then development of a credible pathway from market entry, to growth, and then expansion through its various phases of evolution. Strong global partners would undoubtedly be required along the way, and to achieve that objective requires development of a common vision and trust. For example, this may mean an entry by SII into other Asian markets first, prior to US and EU entry, or it may focus on some limited partner-based entries into the US in a supporting role. This approach would give insights into the value chain and what parts of the value chain are likely for the "extraction of rents" to SII that would provide for a return on their investment. And, most importantly validation as a trustworthy partner in the value chain, to the end consumers, and to their respective governments.

In this case study, we identify a few key strengths of SII. These include ownership of significant and relevant intellectual property, and manufacturing facilities approved by the US Food and Drug Administration (FDA). SII also has a history of ownership and control of the business by the Poonawalla family (see The Economist article dated March 3, 2021)[7]. And, they are committed to exploring and funding global expansion, e. g. EU/UK and US, beyond their present markets. We also note a more recent agreement for manufacturing vaccines with AstraZeneca/Oxford, and also with several other US and UK early stage companies. It has been noted in the recent Economist article[7], SII has entered into several US partnerships (with Novavax for Covid and Codagenix for a nasal vaccine); and with SpyBiotech, a British emerging company. Weaknesses include that they have not yet demonstrated the development or articulation of a credible expansion strategy. However, the company has engaged in some key partnerships associated with COVID-19 that may form a base for expansion. They are facing formidable competition from larger, well-funded and regarded global players. However, the opportunity is so large and pressing, that it is attracting many of the larger companies. Therefore, as noted earlier, it would be worthwhile for SII to gain traction in their current endeavors, and earn trust in the

5 https://www.imarcgroup.com/vaccine-market. Accessed April 25, 2021.

6 R. Gordon Douglas and Vijay B. Samant. *The Vaccine Industry.* Plotkin's Vaccines. 2018 : 41–50.e1.

7 https://www.economist.com/business/2021/03/03/a-billion-plus-covid-19-shots-in-2021-can-serum-institute-do-it. Accessed July 11, 2021.

international market, before identifying a partner who would be willing to work with a new entrant for expansion and acceleration of growth. Perhaps a focus on demonstrating success in smaller global markets that would be easier to penetrate, might be a good strategic step beyond their current endeavors. The threat, of course, as we have noted previously is that the vaccine market is difficult, and expensive. Additionally, trust must be established in global markets outside India.

OVERVIEW OF GLOBAL MARKET SETTING FOR VACCINES

According to a recent report from MarketWatch, the global vaccine market is projected to reach $48 billion dollars by 2025.[8] The vaccine industry in the US conforms to the pharmaceutical industry in that both are heavily regulated by the FDA, are R&D intensive, and involve high costs for entry and operation within the US. However, the vaccine industry also has numerous features, trends and deciding forces that make it unique. Unlike the pharma industry, federal and state governments are major purchasers in the vaccine industry and recommendation by the Center for Disease Control and Prevention (CDC) improves the chances of a vaccine being covered by private and public insurance agencies. However, market exclusivity is rarely seen, as vaccines that have high demand also require the involvement of multiple vendors across the value chain to meet these demands. The advent of new technologies, vaccine combinations, delivery methods as well as vaccine manufacturing methods can lead to new company entries into the vaccine marketplace. However, the vaccine market itself remains concentrated with four large manufacturers (GSK, Pfizer, Merck, and Sanofi) controlling 90% of global vaccine sales according to World Health Organization figures for 2020. In this category, SII is listed as a distant fifth at 3% (Figure 1A). However, this picture changes significantly when looking at volume of vaccine doses. While the market based on volume is also concentrated with the top five companies holding a collective 60% share, it is SII that is the market leader here with its 28% market share based upon the number of doses sold (Figure 1B). While current market shares by sales and volume are important considerations, there are other vaccine market challenges and factors that could

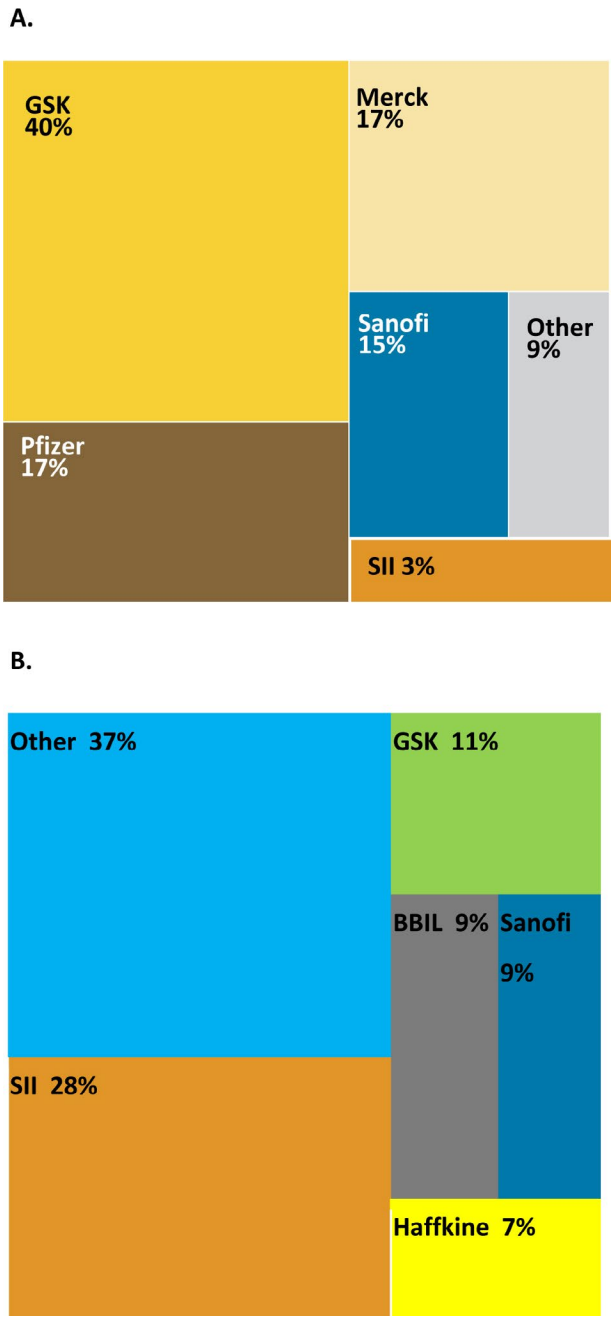

Figure 1: World Health Organization Charts showing vaccine manufacturers share by global value (A) and volume (B) as of December 2020[9].

8 https://www.americanewshour.com/2021/07/02/vaccines-market-overview-by-technology-live-toxoid-recombinant-disease-pneumococcal-influenza-dtp-rotavirus-tt-polio-mmr-varicella-dengue-tb-shingles-rabies-route-im-sc-id-oral/701149/. Accessed July 11, 2021.

9 https://www.who.int/immunization/programmes_systems/procurement/mi4a/platform/module2/2020_Global_Vaccine_Market_Report.pdf?ua=1. Accessed April 25, 2021

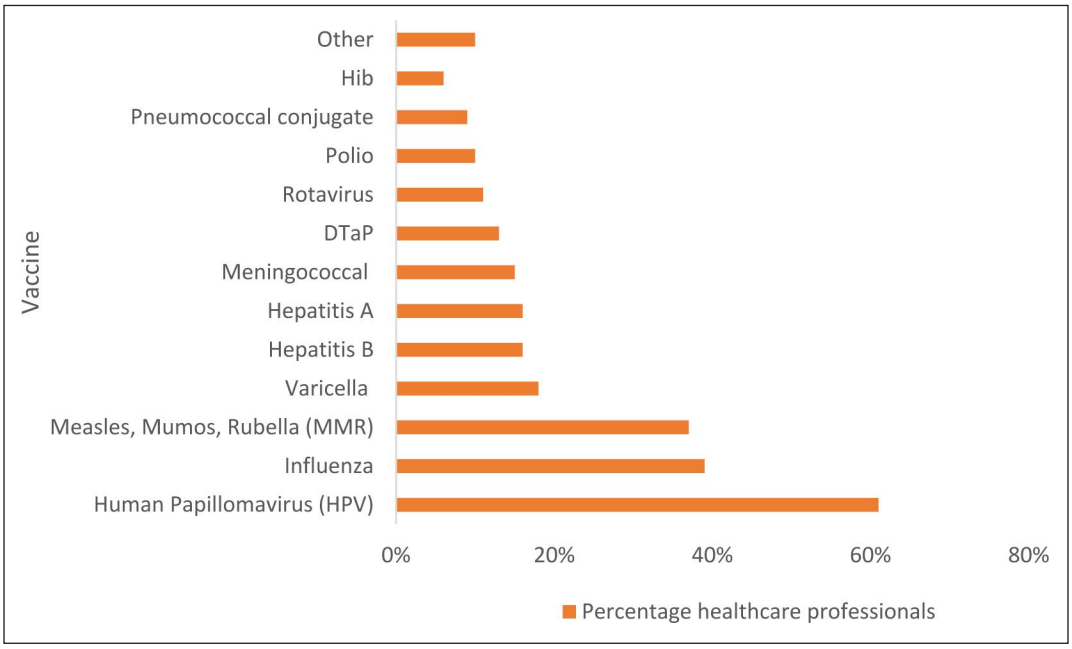

Figure 2: Graph showing vaccines health care professionals said families were most likely to refuse or request on an alternative schedule in the U.S. as of 2016. Modified from www.statista.com[11]

help predict the successful operation of foreign vaccine manufacturers within the US market.

CHALLENGES OF THE VACCINE MARKET

The main forces that regulate the vaccine market include costs, regulatory requirements, ability to adopt and adapt to new technology, etc. However, another important factor that can sway the market is 'vaccine hesitancy'. In 2014, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) defined vaccine hesitancy: "Vaccine hesitancy refers to delay in acceptance or refusal of vaccines despite availability of vaccine services. Vaccine hesitancy is complex and context specific, varying across time, place, and vaccines. It is influenced by factors such as complacency, convenience and confidence".[10] A survey and analysis performed recently among health care professionals in the US revealed that there were many vaccines that families refused to take or requested on an alternative schedule (Figure. 2). For example, 61% professionals said that families refused to take the Human Papillomavirus (HPV) vaccine. Aversion to vaccination due to several false reports associating autism as a consequence of vaccination, lack of awareness about the advantages of being vaccinated, and a fear of needle-and-syringe vaccination are the main reasons for this hesitancy towards vaccination, that may significantly affect vaccine sales in the next few years. This may however be offset by a possible reduction in 'vaccine hesitancy' due the multiple, and different vaccine delivery technologies that are entering the market such as better enteric coatings for oral delivery, needleless injection, patch delivery, intranasal delivery, etc.

Another challenge of this market is merging the commercial *vicious cycle* of demand, supply and financing with affordability and global immunization. Market dynamics that lead to uncertainty about demand, limits manufacturer investment to ensure supply capacity. Low capacity limits supply and keeps prices high. This in turn raises questions about value for previous investments made in this market and further limits future investments, thus leading to a vicious cycle that can easily lead to the exit of manufacturers from the market. Although logical, based on vaccine market dynamics, this hypothesis is of course difficult to prove. Foresight at the outset can help manufacturers overcome this hypothetical challenge. Vaccine production units should be built, at least to be able to cater to a few markets that have historically been shown to be steady purchasers of the manufactured product. This creates reliable and steady demand

10 https://www.who.int/immunization/sage/meetings/2014/october/1_Report_WORKING_GROUP_vaccine_hesitancy_final.pdf. Accessed April 25, 2021.

11 https://www.statista.com/statistics/668320/vaccines-families-most-likely-to-refuse-reported-by-health-care-professionals-us/. Accessed April 25, 2021.

that can be successfully met by the manufacturer and in turn leads to further investment to ensure adequate capacity and efficient production as the market changes. Subsequently, this can further drive down costs and draw in new manufacturers. Nonetheless, the market is typically only profitable at certain levels of demand vs supply. Contingency planning can also help with managing finances and having a comprehensive understanding of another challenge unique to the vaccine market, which is the potential loss of market upon eradication of disease, as has been seen in the case of smallpox.

POTENTIAL BUSINESS STRATEGIES TO ENTER AND PERSIST IN THE US VACCINE MARKET

It is important for foreign vaccine manufacturers to identify strategic measures that can be considered for entrance into the US market as well as for foreign companies and small companies already within the US market to keep their US market presence. Any business strategy that is devised should of course keep in mind a clear picture of the current and future dominant players in the global vaccine market. The US market is one of the most stringently regulated vaccine markets in the world, makes up 40% of the global vaccine market and is driven by public payors and private insurance companies with pricing that is not regulated by the government.[12] Despite the regulatory hurdles and the corporate competition that make entry and continued operations in the US difficult, it is a lucrative, highly reputed, and credible market — entry into which immensely increases the global visibility of a company.

Given their respective competitive positions, resources, processes and values, foreign companies considering US access could adapt and employ one or more of the general strategies cited as used for pharmaceuticals. We list 7 potential approaches, each of which will be each discussed in more detail below.

1. Collaborate and partner with established vaccine producers in the US.
2. Build spinout companies dedicated to developing novel, specific technologies, or processes.
3. Switch to multivalent vaccines.
4. Develop, license, or collaborate to develop the R&D needed for production of more complex vaccines such as cancer/HIV vaccines or mRNA vaccines.
5. Invest in R&D or license for novel vaccine delivery technology.
6. Develop or license technologies for vaccines that are more stable/efficacious.
7. Develop a strategy that recognizes trust as an important component in any partnership and in dealing with consumers. An airtight paper trail and documentation are steps that can help build trust, with time, for these manufacturers and with US market regulators and payors.

1. Collaborate with established vaccine producers in the US

An example of a collaboration between a US vaccine giant and an Indian company is the deal signed in 2012 between GSK and India's Biological E Limited to create a vaccine that combines GSK's polio vaccine with a Biological E vaccine that protects against diphtheria, tetanus, whooping cough/pertussis (DTP), hepatitis B (HepB) and *Hemophilus influenzae* type b (Hib) in a 50:50 joint venture. This '6-in-one' shot system is projected to be a huge success. This liquid hexavalent vaccine is not yet on the market but is high on the list of 'vaccines in the pipeline' according to Biological E's website. With its enormous and existing manufacturing capacity, we noted above that SII has also recently entered into agreement to manufacture 1 billion doses of both AstraZeneca's and Novavax's COVID-19 vaccines for low- and middle-income countries.

2. Spinout companies dedicated to development of a specific process for vaccine development

In 2012, Sanofi established a collaboration with Sutro Biopharma to use Sutro Biopharma's cell-free protein synthesis technology to develop two new undisclosed vaccines. Sutro Biopharma spun out a startup called SutroVax dedicated to developing this cell-free method to produce complex protein antigens that could serve as vaccine backbones. SutroVax rapidly developed the malaria antigen component and raised $100 million in a short period of time. Successful spin out companies allow the dedicated development of promising technology and the influx of extra research funding. Spinout companies may also get acquired by the corporate giants thus leading to tremendous profits for the parent company.

3. Switch to multivalent vaccines

In 2012, a US FDA panel endorsed a move to quadrivalent flu vaccines in the United States to help improve the efficacy of products for the influenza

12 https://www.who.int/immunization/programmes_systems/procurement/market/world_vaccine_market_trends.pdf. Accessed April 25, 2021.

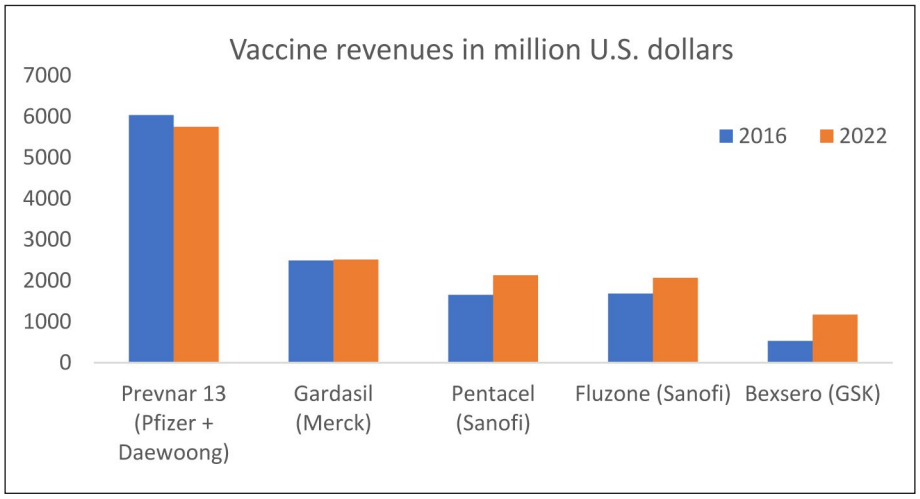

Figure 3: Top 5 global vaccine products based on revenue (in million US Dollars) in 2016 and projected for 2022. Source: adapted from www.statista.com

vaccine market. Hence, there is an increased probability that the US regulatory process in general will be conducive to multivalent vaccines now and in the future. This potentially includes vaccines targeting multiple strains of the same organism or two or more different microorganisms. Several collaborations between vaccine companies and R&D laboratories have been indicative of this trend. These include Pfizer's Prevnar13, the 13-valent Pneumococcal vaccine stands testament to the popularity of multivalent vaccines. Prevnar13 had been losing sales in the past few years after the initial boom and massive early uptake. However, the 4th quarter of 2017 saw Pfizer earn $1.53 billion in Prevnar13 sales (7% greater than 4Q16), due to government purchases in the US and international markets. [13] It has also been projected to be one of the top selling vaccines in 2022 (Fig. 3).

4. ***Perform R&D for more complex vaccines such as cancer/ HIV vaccines or mRNA vaccines***

The Indian market is predominantly centered around vaccines against infectious diseases and the target demographic is mostly children and young adults. Vaccination against cervical cancer is still rare within the Indian subcontinent. However, development of these vaccines using approved, yet more cost-effective methodology could help India and other foreign country vendors penetrate the vaccine market in the US. mRNA vaccines are attractive novel alternatives to conventional vaccines and are being currently brought to market. mRNA vaccines are cheaper to develop and safe to administer. Exogenous mRNA is also inherently immunogenic.[14] Instability issues have recently been overcome using novel technologies and mRNA vaccines also hold great promise for development of personalized neoepitope cancer vaccines. [15] As noted, mRNA vaccines (Moderna and Pfizer BioNTech) have gained a particular market share.

5. ***Invest in R&D for novel vaccine delivery technology***

An Australian startup, Vaxxas, has been conducting extensive research on 'Nanopatch' a novel vaccine delivery system that targets the vaccines to immune cells below the skin surface. Merck has invested an undisclosed amount in this research. Studies have found the Nanopatch to be 100 times more efficient than needle and syringe vaccination. In 2020, Vaxxas received a $22 million award from US Government to advance the Vaxxas Needle-Free

13 https://www.fiercepharma.com/vaccines/pfizer-s-prevnar-posts-1-53b-q4-sales-beating-consensus-by-10. Accessed April 25, 2021.

14 Pardi N, Hogan MJ, Porter FW, Weissman D. *mRNA vaccines – a new era in vaccinology*. Nat Rev Drug Discov. 2018 Apr;17(4):261-279.

15 *Ibid*.

16 https://www.businesswire.com/news/home/20201005005168/en/Vaxxas-Announces-22-Million-Award-from-U.S.-Government-to-Advance-Vaxxas-Needle-Free-HD-MAP%E2%84%A2-Vaccine-Patch-Technology-for-Pandemic-Response . Accessed April 25, 2021.

HD-MAP™ vaccine patch technology for pandemic response.[16]

Another novel vaccine delivery system that has been studied and holds potential (particularly as intratumoral vaccines) for further development and commercialization are thermosensitive hydrogels loaded with nanoparticles.[17] Therefore, it appears that several biopharmaceutical companies are at the forefront of developing alternate routes of vaccination.

6. ***Develop vaccines that are more stable/ efficacious***

In October 2017, SII brought out a thermostable version of the rotavirus vaccine RotaSIIL® as well as Rabishield®, a monoclonal antibody to be used as a supplement in treating rabies. Rabishield® was developed in collaboration with the University of Massachusetts Medical School while RotaSIIL® was developed in collaboration with the NIH.

7. ***Establish Trust***

It will also be important for SII to invest time and efforts into identifying tangible solutions to address the problem of the general lack of international trust, especially with regard to biological products from developing nations such as India. Perhaps a more sensitive and informative PR strategy could be developed and implemented to help establish this trust. Also, more stringent quality control involving the DCGI (Drug Controller General of India); and, interest and traction in the current scenario with the technology being used in the development and deployment of COVID-19 vaccines could be used to advantage.

CONSIDERATIONS REGARDING POTENTIAL ENTRY OF SERUM INSTITUTE OF INDIA INTO THE GLOBAL VACCINE MARKET INCLUDING THE US

Additional Background and Current Status of SII

Dr. Cyrus Poonawala started the Serum Institute of India Pvt. Ltd. (SII) in 1966 with the philanthropic aim of producing life-saving immune-biologicals at an affordable price for the Indian market. The company later went on to produce other vaccines and life-saving biologicals and successfully made India self-sufficient for tetanus anti-toxin and anti-snake venom serum, DTP (Diphtheria, Tetanus and Pertussis) group of vaccines and later the MMR (Measles, Mumps and Rubella) group of vaccines. SII entered the international market in 2010 with MenAfriVac®, the meningitis vaccine that was produced for sale in the West Africa (at $0.50/dose) under the Meningitis Vaccine Project funded by the Bill and Melinda Gates Foundation using in part technology sublicensed from PATH that was originally licensed from the NIH. Currently, 65% of all the children in the world are immunized with at least one vaccine developed by SII. A recent publication reports that affordable vaccines, the majority of which are manufactured and sold

Table 1: Classes of products that SII sells in the international market. The listed products are available in additional formulations and formats. Source: SII[19]

SII Products for Overseas Sale
Bacterial Vaccines
Diphtheria & Tetanus Vaccine Adsorbed (Pediatric) (Thiomersal Free)
Diphtheria & Tetanus Vaccine Adsorbed for Adults & Adolescents
Viral Vaccines
Measles Mumps Rubella Vaccines in various formats
RABIVAX-S® Rabies Vaccine Inactivated
RotaSIIL® – Rotavirus Vaccine
Combination Vaccines
DTP HepB
DTP HepBHiB – Liquid and Freeze-Dried
Polysaccharide Conjugate Vaccines
HiB
MenAfriVac®
Influenza Vaccine
NASOVAC-S® – H1N1 Vaccine (intranasal)
Antisera
Tetanus Antitoxin
Anti-rabies Serum
Recombinant products
Hepatitis B Vaccine (rDNA) (Pediatric & Adult) (Thiomersal Free)
REPOITIN®-Recombinant Human Erythropoietin (rHuEPO) Injection
RABISHIELD®-Rabies Human Monoclonal Antibody

17 Gong C, Qi T, Wei X, Qu Y, Wu Q, Luo F, Qian Z. *Thermosensitive polymeric hydrogels as drug delivery systems.* Curr Med Chem. 2013;20(1):79-94.

18 Kaufmann S.H.E. *Highly affordable vaccines are critical for our continued efforts to reduce global childhood mortality.* Human Vaccines and Immunotherapeutics. 2019 May 17; 15(11):2660-2665.

19 http://www.seruminstitute.com/product_overseas.php. Accessed April 25,2021.

by SII, make a significant contribution to reducing global childhood mortality.[18]

SII made two important recent acquisitions and investments in production capability in recent years that have equipped it to enter regulated markets and be able to ensure supply to large markets. Acquisition of Bilthoven Biologicals, Netherlands in 2012 gave SII rights to produce and sell the injectable polio vaccine internationally. Acquisition of Praha Vaccines in the Czech Republic in 2017 gave SII additional manufacturing capability with BSL3 and cGMP compliant facilities. SII also has a new manufacturing facility with a production capacity of 13 million doses of biosimilar monoclonal antibodies and the HPV vaccine. This facility has been certified by the National Regulatory Authority, maintains the same standards as its WHO accredited manufacturing facility and is dedicated to vaccine/ biosimilar monoclonal antibody production for the US and European markets.

Table 1 lists the products that SII has available on the international market. However, not many of these products will be applicable or able to penetrate the competitive US vaccine market. NASOVAC-S® and RotaSIIL® are attractive candidates to enter the US markets. NASOVAC-S® holds some promise as it is an intranasal vaccine and hence capitalizes on its ability to target the segment that refuses vaccination due to fear of needles. FluMist® from AstraZeneca is the only other non-injectable influenza vaccine in the market. Although NASOVAC-S only targets H1N1, SII has proven its ability to bring a flu vaccine into the market in less than 12 months.[20] If SII capitalizes on that ability and makes an FDA-approved multivalent intra-nasal influenza vaccine, it will be able to capture a large share of the market and possibly have monopoly over the needle-free influenza vaccine market. US is one of the largest markets in the world for the influenza vaccine. Using manufacturing facilities in the EU also brings SII one step closer to overcoming 'trust issues' surrounding vaccine manufacturers from developing countries.

RotaSIIL® is the first ever thermostable 5-valent rotavirus vaccine containing the G9 strain and is the most cost-effective product in the market. Thermostability of RotaSIIL® further reduces cold-supply chain requirements and associated costs. This is another vaccine already with close ties to the US with the underlying technology originated and licensed from the NIH.

SII has received approval from Maharashtra State agencies in India to carry out HPV vaccine and biosimilar monoclonal antibody (mAb) production at the new production facility dedicated to manufacturing for regulated markets. These would both be promising entrants for the US market albeit for different reasons. Gardasil® (4-valent), Gardasil 9® (9-valent) from Merck and Cervarix® (type 16, 18) from GSK are the only FDA approved products currently available. GSK recently stopped Cervarix® sales in the US due to diminishing market as its vaccine that targets only two HPV strains and is not competitive with Gardasil®. SII product is quadrivalent and will likely be less expensive than Gardasil® and has a market that is now more open because of Cervarix® leaving the market and Gardasil® going off-patent. Effectiveness of Gardasil® is limited by the 2-/3-dose regimen required to ensure immunity. If the HPV vaccine that SII has in the pipeline can ensure immunity with a single dose, it will potentially be able to capture substantial market share.

Entry and Viability Barriers

It is also important to consider the potential barriers to the entry and sustainability of vaccine manufacturers in the US, and EU/UK, and the prospective competitive position of SII in this regard. There are a few long-term viability factors that every foreign company should consider when entering these markets especially the US vaccine market:[21,22]

1. **Ability to make upfront investments in R&D, infrastructure, and FDA regulatory requirements**

   SII continues as a privately held entity that has proven its capacity to entirely fund its R&D, operations, and acquisitions. It will likely remain privately held for the foreseeable future. Additional funds could potentially be raised as SII maintains the option of going public, or also consider potential mergers with larger partners.

2. **Manufacturer independence, cGMP compliance and consistency of production**

   SII has acquired two manufacturing units in Europe in 2012 and 2017. It has also recently invested > $30 million on a dedicated manufacturing facility for the US and EU markets. SII has historically been

20 Dhere R, Yeolekar L, Kulkarni P, Menon R, Vaidya V, Ganguly M, Tyagi P, Barde P, Jadhav S. *A pandemic influenza vaccine in India: from strain to sale within 12 months*. Vaccine. 2011 Jul 1;29 Suppl 1:A16-21.

21 Milstien J, Batson A, Meaney W. *A systematic method for evaluating the potential viability of local vaccine producers.* Vaccine. 1997 Aug-Sep;15(12-13):1358-63.

22 Luter N, Kumar R, Hozumi D, Lorenson T, Larsen S, Gowda B, Batson A. *An updated methodology to review developing-country vaccine manufacturer viability.* Vaccine. 2017 Jul 5;35(31):3897-3903.

Table 2: List of US process patents that SII holds supporting their potential ability to enter the US vaccine marketplace

	US Patent No.	Title	Filing date
1	9878029	Process for preparation of polysaccharides	May 9, 2011
2	9700615	Adjuvant formulations and methods	May 13, 2013
3	9580734	Production of high yields of bacterial polysaccharides	November 13, 2013
4	9283270	Method for stabilization of biological molecules	January 18, 2013
5	9249439	Process of cultivating bacteria for yield improvement of capsular polyoses	December 15, 2011
6	9198977	Immunogenic composition	January 29, 2013
7	8795686	Stable, dried rotavirus vaccine, compositions, and process for preparation thereof	November 6, 2009
8	8501186	Adjuvant composition for vaccine	May 5, 2010
9	8398985	Antigenic polysaccharides and process for their preparation	September 6, 2007
10	8383783	Simple method for simultaneous removal of multiple impurities from culture supernatants to ultralow levels	December 20, 2010
11	8097437	Highly pure polysialic acid and process for preparation thereof	July 13, 2007

successful in keeping its failed lots to <5% and meet the demands in the target markets.

3. **Ability to adapt and adopt new technology and market trends**

SII has been at the forefront in this regard. The company understands the need for more stable vaccines as evidenced by the thermostable rotavirus vaccine, RotaSIIL® and a dengue virus vaccine (stable at room temperature) that is in the pipeline. SII has also made newer versions of all its vaccines and is moving from live attenuated to subunit vaccines and using rDNA technology to develop its newer products such as RABISHIELD®.

4. **Ability to meet vaccine demands (by volume)**

SII has sold more than 1.5 billion doses of vaccines annually and holds a 3% portion of the global vaccine market share in terms of sales.

5. **International trust issues**

Problems of 'international trust issues' for products from India in general due to a history of compromised quality and widespread patent infringement. These are not an issue for SII, based upon its record to date. But these need to be dealt with in partnering discussions and negotiations. Patent infringement is not a primary concern for SII because they have been developing their own IP with granted US patents as shown in Table 2 or licensed IP from institutions such as NIH. Further, in the case of biosimilars, IP issues are typically not a cause for concern.

STRENGTHS, WEAKNESSES, OPPORTUNITIES AND THREATS (SWOT) ANALYSIS

Strengths:

1. **Patents**

SII owns 11 process patents in the US (Table 2) and hence holds the rights to bring biologicals made using these processes into the US vaccine market. In addition, SII has licensed similar technologies from both NIH and other US research programs.

2. **WHO (World Health Organization) accredited manufacturing facilities in India, Netherlands, and Czech Republic**

SII owns and operates current Good Manufacturing Processes (cGMP) compliant manufacturing units in Europe and India with regular, periodic inspections of the facilities also being performed. This ensures strict maintenance of the quality of the products being manufactured.

3. **Ability to handle very high production scale**

SII has established a reputation and track record by delivering vaccines at low costs within the stipulated time limit. SII has proven its ability to supply vaccines to markets demanding very large volumes as well as cater to fluctuating market demands. SII has sold >1.5 billion doses in about 140 countries – but not in the US to date.

4. **Competitive pricing**

SII has supplied meningitis vaccines to African countries at $0.50/ dose. RotaSIIL® is priced much below its counterparts from other companies and RABISHIELD® is available at half the price of the

current standard of care — showing the ability of SII to provide competitive pricing.

Weaknesses:

1. **Reputation not established in some parts of the world:** SII is well known in the global vaccine industry but would be a novice in the US markets. This might be at odds with the successful entry of SII especially in markets with US government purchasing.

2. **Stringent regulatory process:** SII may be able to obtain FDA license for its vaccines that have been extensively used in other countries. For the established vaccines, SII could use clinical trial data from trials in other countries and perform an additional bridging trial to get FDA approval. However, there are risks and restrictions to using data from foreign clinical trials and hence, SII may end up investing much more than expected to redo clinical trials for at least some of its products. Intranasal vaccines are a category that can require a lot of investment in clinical trials and still fail.

Opportunities:

1. **CDC recommendation:** Given the experience SII has in supplying vaccines to low-income countries and the competitive prices of their products it might be possible that the Center for Disease Control and Prevention (CDC) could recommend SII products for use in the US and other markets. This would improve chances of insurance coverage by Medicare/ Medicaid as well as private agencies.
2. **Non-cooperative pricing strategy:** The US vaccine market is driven by a non-cooperative pricing mechanism. This means that if many companies have similar/potentially substitutable products, non-cooperative pricing can cause prices to fall to marginal cost. This causes all except the product with the lowest marginal cost due to better technology or efficient production, to exit the market. Foreign manufacturers capable of supplying a closely substitutable product at a lower cost would have an advantageous market position in this scenario.

Threats:

1. **Market Acceptance:** SII has active patents in US, but FDA approval is determined by the proven safety, purity and efficacy of the product, and FDA approval is yet to be achieved for any of their products. However, market acceptance determines the ultimate success of the product. CDC allots federal funds to state and local procurement agencies, but the decision about which vendor to use is dependent on the local procurement agencies which may not choose a vendor from India probably due to a lack of awareness about the stringent manufacturing processes that these vaccine manufacturers employ. Physician purchase groups can also sway the market against a foreign vendor. Starting a wholly owned US subsidiary may help SII mitigate these threats.
2. **Highly competitive and dynamic market**: The US vaccine market is driven by 4 main players (GSK, Merck, Pfizer, and Sanofi) who are generally efficient meeting the vaccine demands. Penetrating a market as stable in general as this could be a difficult challenge for SII.
3. **Rapidly changing technology**: The Advisory Committee on Immunization Practices (ACIP) that recommends vaccines to CDC always favors technologically advanced, more stable, efficacious products. It is a vacillating market and a company can lose a steady market share overnight as was seen with the recommendation of GSK's Shingrix (Subunit vaccine) over Merck's Zostavax (Live attenuated virus vaccine) for protection against shingles in 50+ adults for the 2018-2019 immunization cycle.

CONCLUSIONS

Recent acquisitions, technological enhancements, and investments in scale up have elevated Serum Institute of India to a position that enables their potential entry and long-term participation in the US, European and other international vaccine markets. The company now has a long history of providing critical, low-cost vaccines to under-served populations. This demonstrated expertise, that makes 1.5 billion vaccine doses annually now has great potential through US/EU partners or separately for selective market entry into the US. Investing in a business plan that includes work with marketing and consulting firms

within the US would also improve the competitive position of SII. Setting up off an offsite branch for US manufacturing and operations may be a wise consideration for the future and vaccine bundling at competitive prices to private practice and hospital healthcare providers could help ensure continued operations by the company within the US marketplace. The world's top 4 vaccine market leaders already have a presence in the US, so how could we make a strong case for adding the 5th largest vaccine market company (but 1st largest in total production), Serum Institute of India, to that list as well. This would clearly require some creative partnering where trust already exists and working relationships already established. Alternatively, and as suggested in our Introduction, should SII consider an entry first into EU or Asian markets first, prior to US entry? Perhaps it is premature to make that decision now while EU and other Asian markets are still being developed in the SII portfolio. That decision should be revisited as events continue to evolve and is beyond the scope of our current case study.

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