The role of emerging manufacturers in access to innovative vaccines of public health importance

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Abstract

The role of developing country manufacturers in assuring global access to innovative vaccines was compared to the situation in 2005. These producers now supply over 60% of traditional vaccines doses globally and an increasing value (up to 15% in 2007) of innovative products. More suppliers are now strong players in global market, and an even larger group has potential to do so. These manufacturers are not a homogeneous group and most of them are now at a crossroads. Decisions made by their management and governments as well as by the international community will have a large impact on their existence and future and their ability to manufacture innovative vaccines at affordable prices.

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1. Introduction

Emerging vaccine manufacturers are those located in developing countries and essentially owned by domestic agents, whether public and/or private. Some of these manufacturers are now active players on the global market, especially for traditional vaccines, because of technology transfer which occurred over the years for such products, which use decades-old technology. Several new vaccines have recently been added to national immunization programs, and more are projected in the near future. Because of this, emerging manufacturers have begun to access these new vaccine technologies, and are already providing a significant percentage of newer vaccines such as hepatitis B, Haemophilus influenzae type b (Hib), and combinations of these, on the global market.

Although most of these manufacturers were initially constituted as public sector organizations, many are now in the private sector. Even those in the public sector are being managed so as to maximize their ability to innovate and to assure the quality of vaccines so as to be well-positioned in the new global marketplace. However, these manufacturers do not constitute a homogeneous group as will be showed later in this paper.

Recently, in a study (hereafter referred to as the Boston Consulting Group (BCG) study) for the Global Alliance for Vaccines and Immunization (the GAVI Alliance, or GAVI) [1], a subset of 17 manufacturers in seven countries1 was selected, the members of which were felt to have potential as active manufacturers on the global market. The purpose of this paper is to examine the role of emerging manufacturers as players in assuring global access to innovative vaccines of public health importance. We will draw on and update the findings of the 2005 BCG study. We will also describe the evolution and attractiveness of emerging markets and the role of emerging producers at global level with some of the more innovative products as examples. Before outlining potential projections for the future, we will compare the “focus” and “capability” of emerging manufacturers today relative to the situation found in the 2005 study, illustrated by specific case reports and by some of their main strengths and weaknesses.

In terms of methods, the analyses, projections and case studies included below were based, in addition to the BCG study documents, on our field observations as well as on published and unpublished data and reports.

1 These countries were Brazil, China, Cuba, India, Indonesia, the Republic of Korea and Mexico. Although Korea is no longer considered a developing country, two Korean manufacturers were included in the study because they were supplying vaccines on the global market but were not considered multinational companies. One of these has since, through mergers, become part of an international company; however, because of its history and product lines we have continued to include it here.
2. The increasing attractiveness of emerging markets

The developing country market has historically been high volume, low profit traditional vaccines, and as such was not especially attractive to most vaccine-producing multinational companies (MNCs). However, with more purchases of innovative vaccines of public health priority in developing countries, both because of increasing wealth and the availability of donor funds, emerging markets have become more attractive. In fact, the emerging pharmaceutical markets, including China, India, Brazil, the Russian Federation, the Republic of Korea and Turkey, are expected to grow at 12–13% per year and to become larger than developed markets by 2020 [2]. The vaccine markets in India and China alone are expected to grow 16 and 17.8% respectively from 2006 to 2013 [3]. Sanofi-Pasteur has reported in 2008 that emerging market sales account for almost one-quarter of total vaccine sales ($814M of $2.86B) [4].

3. The role of emerging manufacturers in vaccine supply

3.1. The supply of traditional vaccines

Vaccines for provision to national immunization programs in developing countries are often supplied through procurement by large United Nations (UN) agencies. Vaccines must be prequalified to be considered in these tenders. Prequalification is a procurement term which refers to a process used to narrow the number of eligible manufacturers in an open tender process. For vaccines for UN agency purchase, it is WHO that devises the process and makes the determination [5], and posts a list of those products which are prequalified and their manufacturers on the WHO website, updated monthly.

In 1994, the first emerging manufacturers had products prequalified for supply to UN agencies. That process has continued, with more products from emerging manufacturers being prequalified every year. Currently of 24 manufacturers that have products on the prequalified list, 12 are from the countries covered by the 2005 BCG study. For traditional vaccines, excluding oral polio vaccine, 64% of doses come from developing country manufacturers [6]. Considering products for GAVI purchase (Hep B, Hib, and their combinations, yellow fever vaccines), 42% of supply in volume came from these developing country manufacturers in 2007, compared to 15% in value. However, these percentages are increasing (Fig. 1), and as more emerging manufacturers’ products are prequalified, will continue to increase.

3.2. The supply of innovative vaccines

One of the facets of the BCG study was an analysis of the pipelines of all the selected manufacturers. A few products of specific interest to GAVI, including DTP-based combination vaccines, rotavirus vaccines, and pneumococcal conjugate vaccines, were chosen for particular focus. For the purpose of this paper, we will consider in depth the DTP-based combination vaccines, for which the most data are available.

In 2005, there were at least six prequalified hepatitis B (Hep B) vaccines, for which at least four of the producers were emerging manufacturers. There were two prequalified *Haemophilus influenzae* type b (Hib) vaccines, both produced by MNCs. For DTP-Hep B and DTP-Hep B-Hib (pentavalent vaccine), there was only one prequalified product each, both produced by the same MNC. There was a second manufacturer of these two latter vaccines, an emerging manufacturer, but those products had not been proposed for prequalification. At that time there was a large overproduction of Hep B, while the supplies of combination vaccines (about 28 M doses total for all combinations) were not sufficient to meet demand.

Based on the data found, the study team proposed that there would soon be an oversupply of these combination vaccines, because of the number of pipeline projects for their development. In 2005, the study team predicted that as of the end of 2007, there would be five prequalified pentavalent vaccines, of which three would be from emerging manufacturers, and the available supply would exceed 250 M doses per year. In 2005, the price of the pentavalent vaccine was $3.60 per dose, and the study team also predicted a drop in the price, considering the production costs to be less than $2 per dose, and given the expected oversupply.

In September 2009, there were five pentavalent combination products (two from a single MNC) available and prequalified, three of which are from emerging manufacturers, plus at least three additional products that are not yet prequalified (see Table 1).

There are five prequalified DTP-Hep B combination vaccines, one of which is from an MNC. In addition, the supply of both Hib and Hep B vaccines has increased, with five and nine prequalified products, respectively, manufactured mostly by emerging manufacturers. The supply [7,8] thus should far exceed the demand, which was about 60 M doses for pentavalent and 22 M doses for DTP-Hep B in 2008 [9]. These manufacturers are also supplying other countries; for example, Panacea is supplying combination vaccines to the Philippines [10]. Moreover, the price of the pentavalent vaccine had decreased to as low as $1.90 per dose [11] in 2009 (down from a high of $3.75 per dose in 2007). The price of DTP-Hep B was as little as $0.71 for a 10 dose vial presentation [12].

### Table 1

Emerging manufacturers producing licensed pentavalent vaccine in 2009.

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Country</th>
<th>Prequalified product</th>
<th>Volume/value on international market</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bharat Biotech International Ltd</td>
<td>India</td>
<td>N</td>
<td>US$ 34.2M to UNICEF [7]; &gt;15 M doses</td>
</tr>
<tr>
<td>Shantha Biotechnics Private Ltd</td>
<td>India</td>
<td>Y</td>
<td>In 2008, supplied &gt;29 M doses through UNICEF/GAVI [9]</td>
</tr>
<tr>
<td>Berna Biotech/Crucell</td>
<td>Republic of Korea</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>Serum Institute</td>
<td>India</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Biological E</td>
<td>India</td>
<td>N</td>
<td></td>
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</tbody>
</table>
3.3. Vaccines for the future

In the countries being considered, there are a large number of innovative vaccines in the pipeline, some of which are already licensed and prequalified. Table 2 presents a selection. Where available, prequalification status, price and quantity have been included; the availability of some of these products at very low prices compared to some current products is striking.

4. Focus and capabilities of emerging manufacturers

4.1. Comparison with 2005 situation

To be able to assess more quantitatively the potential of emerging manufacturers, the same assessment of focus versus capacity was done as in the 2005 BCG study [1]. The manufacturers considered in 2009 were those included in the 2005 BCG study, as well as those manufacturers of prequalified products not included in the 2005 BCG study, and a few manufacturers, in Vietnam, Thailand, and Egypt, who were not in either category. The two subsidiaries of MNCs, Chiron India and Shenzhen Sanofi Pasteur, were omitted.

The characteristics used to assess focus were:

- percentage and number of pipeline products of interest to the developing world;
- percentage of vaccine sales to global public agencies;
- percentage of total sales from vaccines portfolio;
- extent to which manufacturer has invested in and prepared for prequalification;
- manufacturer’s flexibility to invest in vaccines for export.

Those characteristics assessed for capacity were:

- previous experience with WHO prequalification;
- appropriate production facilities;
- access to investment;
record of production scale-up;
ability to bring a product quickly to market;
access to components, technologies, know-how and intellectual property rights (IPR);
ability to acquire missing elements through partnering with a manufacturer of prequalified products;
functional national regulatory authority in the country of production;
robust quality assurance system.

The results are shown in Fig. 2, along with the results from the previous study.

It can be seen in both analyses that there is a group of manufacturers with high capacity and high focus, another group with a lower level of capacity and/or focus, and finally, a group which is neither interested in nor capable to supply the UN agencies procurement market. The results in 2009 show a maturing of the emerging manufacturers as a group. Compared to 2005, there is a group tightly focused on this market and highly capable to serve it. These are all manufacturers of prequalified products, and they are homogeneous in character. These manufacturers are all private sector, all capable of large volume production, have access to ready financing, and have managed to access necessary technologies, through a combination of in-house research and development (R&D) and strategic alliances. It should be noted that even though Berna Biotech/Crucell has been a member of this group, being located in an emerging market, it is also part of the MNC, Crucell.

The second group as well includes a majority (9/13) of manufacturers who produce at least one prequalified product; however, this group tends to be comprised of national or public sector manufacturers, many of which have less well developed R&D capacity, GMP compliance, or ability to consistently supply large volumes through UN agencies. The third group is larger, and of higher capability than the equivalent group in 2005, but is slightly less focused on this market.

4.2. Case studies

To illustrate the evolution of these manufacturers since 2005, a few case studies are useful.

4.2.1. An innovative large volume public sector manufacturer partnering with an international public health group

For this first case study, we have selected Chengdu Biological Products, one of the large public sector vaccine manufacturers in China which is part of the Chinese National Biotec Group. All of these manufacturers (there are seven, plus two additional companies in the group) have as a primary focus, to fill the public health needs of the Chinese population for basic vaccines, and they are required to produce certain amounts of the traditional vaccines and sell them at a fixed price, which is widely regarded as lower than the cost of production. Thus, most of these manufacturers have taken steps to discover and produce vaccines against a wider range of diseases that they can sell at higher prices to the wealthier provinces in China, as a way of staying financially afloat.

One of these products is the live 5A-14-14-2 vaccine against Japanese encephalitis developed by Chengdu, and grown on primary hamster kidney cells. Through a long history of international assistance, most recently through PATH’s Japanese Encephalitis Vaccine Project, Chengdu has built new facilities and has received much training in GMP and quality assurance. To date, however, none of this support has been validated by the prequalification of this product, although that is the ultimate goal. Prequalification will likely depend on (1) continued upgrading of the Chinese regulatory authority, and (2) a continued culture of GMP at the Chengdu facility, which would include control of raw materials, processes, testing, facilities, and packaging. Nevertheless, Chengdu has succeeded in exporting this product to a number of countries in South Asia, including Thailand, Nepal, India, and Sri Lanka, due to its low price and demonstrated efficacy. Chengdu has now entered additional agreements for development of vaccines such as the pneumococcal conjugate vaccine (also with PATH) and rotavirus vaccine (using the NIH Kapikian technology). One of the aspects of the Japanese encephalitis vaccine virus agreement with PATH is the requirement to sell a certain number of doses at a price that is below the Chinese market price in exchange for PATH assistance – a requirement that is not particularly attractive to Chengdu. However, this agreement has provided Chengdu with much vaccine production hardware and software that they would not ordinarily have, and thus gives them an advantage on the international market, even if they cannot control the sales price. Such agreements are allowing Chengdu to improve its production facilities and processes, and may be important in raising the quality of products on the Chinese national market as well.

4.2.2. An innovative large volume private sector manufacturer partnering with or acquired by an MNC

Of all the private sector manufacturers in India, Shantha has been one of the ones that has attracted the attention of investment analysts. Originally set up by Dr Varaprasad Reddy to make recombinant hepatitis B vaccine as a humanitarian effort, Shantha has been heavily research-based, with ample funding, state of the art production facilities, knowledgeable staff, many recruited from other successful Indian vaccine manufacturers, and a variety of priority products. Shantha’s recombinant hepatitis B vaccine was the first Indian hepatitis B vaccine to be prequalified; likewise for its pentavalent vaccine, which has a large share of the global market. Most analyses of successful vaccine manufacturers in India put Shantha near the top of the list.

However, a few years ago, the majority stake in Shantha was acquired by Bio-Mérieux. In July 2009, this stake was acquired by Sanofi Pasteur so that the French vaccine manufacturer would have
a “manufacturing and research base” in India, to “allow Sanofi to provide important vaccines at affordable prices around the world” [13]. It is not clear how this acquisition will impact the future viability of Shantha, nor its place as a key supplier of innovative vaccines on the global emerging market.

4.2.3. An innovative moderate volume public sector manufacturer partnering with an MNC

The Brazilian manufacturers, BioManguinhos and Butantan, have invested in R&D, have knowledge of intellectual property concerns, are supported by a well-functioning national regulatory authority, and are together providing the majority of Brazil’s public sector vaccines. This success has been based on a long history of manufacturing, plus a strong government interest in strategic planning. Although only BioManguinhos currently produces prequalified products (yellow fever vaccine and meningitis AC polysaccharide vaccine – in collaboration with Cuba’s Finlay Institute, another example of South–South cooperation), both have attracted the attention of large vaccine MNCs, who have transferred vaccine production technology starting from filling of imported bulk vaccines. BioManguinhos has had such an agreement in force with GlaxoSmithKline for many years for filling of oral poliovirus vaccine, and recently concluded one for measles-mumps-rubella vaccine. Also through a GSK agreement, they have progressed to full-scale production of Hib vaccine, and will shortly commence filling of imported pneumococcal conjugate bulks as a step towards a full technology transfer of that vaccine. Sanofi Pasteur has had a similar arrangement with Butantan, which is now starting full-scale influenza vaccine production. The advantages of such agreements are that they allow the country to benefit from a new vaccine technology sooner, and will eventually result in national ownership of the technology. However, the disadvantages are that the prices may be higher than could eventually be attained by these national manufacturers, and they are not able to be offset by export sales, which are controlled by the MNC.

4.2.4. An innovative low volume quasi-private sector manufacturer partnering with an international public health group

Vabiotech is a company formed in 2000 as part of the National Institute of Hygiene and Epidemiology in Vietnam. Its mission is to make vaccines for the national domestic program, but its strategic directions may include exporting some of their larger volume and more desirable vaccines on a global level. One of these is likely their oral cholera vaccine, the technology of which has been improved and standardized through collaboration with the International Vaccine Institute, and was recently transferred to Shantha, whose product has now been licensed in India. Through international assistance, the company has been improving its GMP compliance, and plans to increase its production volumes, which are now fairly low (4 million doses for the largest volume product) [14]. However, without strong regulatory oversight and a significant infusion of cash, the future of this company on the global market is unclear.

5. Strengths and weaknesses of emerging manufacturers

The previous section provides some idea of what will be the prerequisites for emerging manufacturers to be successful on the global market. Aside from being large volume, GMP-compliant and research-based manufacturers, they will need regulatory oversight at least to a level sufficient to allow their products to be pre-qualified, and ideally, to a level that allows them to compete on internationally regulated markets. They will need access to sufficient funding to maintain the facilities, product technologies and processes current, and sufficient autonomy from the technology holder and the government to allow them to export their products on the global market at prices which will allow them to stay in business. Currently, the successful emerging manufacturers have the following characteristics which may aid them to supply the global public market:

- Large volume production capability.
- A public health focus.
- Relatively lower infrastructure costs than MNCs, despite an increasing requirement for investment in GMP [15].
- Generally a lighter regulatory burden than the MNCs, although this is increasingly stringent for all products on the international market.

On the other hand, they have disadvantages which could inhibit such success, particularly for innovative vaccines, such as less ability to spread investments and risks over a wide range of products. An important disadvantage is the lack of R&D. Even for those manufacturers who have invested in R&D, the breadth and depth of the research efforts for the emerging manufacturers is limited. The 2005 BCG study found that the most innovative emerging manufacturers spent up to $6M per year on R&D, or 4–14% of sales, while MNCs in contrast spent from $22M (for the smaller manufacturers) to >$200M per year for the same time period. For example, emerging manufacturer R&D may be focused on one or two products, but generally not on a cross-cutting advance such as a new adjuvant. Other disadvantages include the following:

- Lack of access to technologies and processes, as well as to vaccine seeds and strains, cell substrates, other raw materials that may be protected by patents.
- Lack of experience with bringing a totally new product to market.
- Lack of experience in dealing with products and processes that may be under patent.
- Limited experience in dealing with increasing regulatory barriers.
- Lack of experience in conducting clinical trials and managing IPRs.

It is evident that these manufacturers are at a crossroads, and the decisions they make now will impact their ability to move forward in this new market. Decisions made at the global level by the international community will also have an impact on their ability to strengthen their current efforts and overcome some of the main identified obstacles and weaknesses.

Moreover, outcomes have not always been positive for manufacturers, generally in the public sector, in developing countries. Despite concerted effort, domestic manufacture in Egypt, Iran, Thailand, Vietnam and South Africa has not developed to the same level as the more successful public sector manufacturers mentioned here. Several other facilities in Bangladesh, India, and some countries in South America, have closed their doors.

Table 3 summarizes the innovation status of manufacturers in three key countries, Brazil, China, and India. All are moving towards the ability to fully access innovative technologies; the future will allow an assessment of these efforts.

6. Possible directions and outcomes

What are the options available to emerging manufacturers on the global market? Some of them will choose to remain as producers of the traditional vaccines. To the extent that they can become high-volume manufacturers on the global market, this route could be sustainable. However, for those manufacturers that are supplying only a limited domestic market, no matter how large it is, with
vaccines that are becoming less and less expensive, it is doubtful that this will be a viable option.

Other manufacturers, notably those in Mexico and Brazil, as well as in other countries not traditionally associated with vaccine production, will opt for partnerships with MNCs to access newer technologies. This route will normally not result in their development as innovative producers of vaccines; however, it can be seen as the best route to assure newer vaccines to their countries. An anomaly here is Shantha, which finds itself as part of a MNC while developing innovative products for the Indian market. It will be important to follow how this arrangement plays out, and its impact on the affordable supply of innovative vaccines, not just for India, but on the global market.

Finally, there are some vaccine manufacturers who are prepared to develop innovative products through various technology access agreements, who are prepared to license these products on the global market, and who thus may find themselves facing a cost structure that is increasingly like that faced by the MNCs, although their overall costs may still be lower. Should this result in higher prices, as seems likely, the advantages on the global market of sourcing vaccines from emerging manufacturers may be relatively mooted, and it will be of considerable interest to follow the ability of these manufacturers to act in the interest of global public health by manufacturing innovative vaccines at affordable prices. This may become increasingly difficult as time goes by.

Decisions made by their management and governments as well as by the international community will have an impact on their future ability to manufacture innovative vaccines at affordable prices. Should innovative vaccines become unaffordable, this would mean that the current paradigm has failed. New strategic thinking and effort and enhanced international surveillance will be necessary to ensure that this failure does not take place.

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