Landscape Analysis: WHO’s Role in Supporting Emerging Vaccine Manufacturers

Promoting the availability and affordability of high quality vaccines of public health priority

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Introduction

Since the early days of WHO, there has been a tradition of supporting vaccine manufacturers in developing countries. These vaccine manufacturers were in the public sector, the vaccines, such as BCG and DTP, being made used decades-old technologies, and the support was generally provided through other public sector manufacturers who provided technical advice and testing services. However, the vaccines that resulted from this support were for use only in the country of manufacture.

After the beginning of the Expanded Programme on Immunization (EPI), large United Nations (UN) procurement agencies, including UNICEF Supply Division and the PAHO Revolving Fund (RF), began buying vaccines for countries that could not cater to their own vaccine needs, and, since 1987, have been using WHO’s prequalification system to advise them on the suitability of vaccines for purchase. The WHO prequalification system not only provides a basis for assuring the acceptability of products for UN agency procurement, but has evolved into something of a gold standard for countries doing their own procurement. The activities involved in the prequalification process also include strengthening National Regulatory Authorities (NRAs), and apply to all manufacturers aiming to sell vaccines on this public sector international market.

1 For the purpose of this paper, emerging manufacturers are those located in developing countries, either in the public or private sector, that have recently entered the international market.
2 Consultant to WHO, University of Maryland School of Medicine.
3 Developing country means any country classified or listed as such by the United Nations, i.e. any country other than Andorra, Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Japan, Luxembourg, Monaco, the Netherlands, New Zealand, Norway, Portugal, San Marino, Spain, Sweden, Switzerland, the United Kingdom, and the United States of America, it being understood that the status of any republic, previously included in the former Union of the Soviet Socialist Republics and the former Federal Socialist Republic of Yugoslavia, as well as Albania, Bulgaria, the Czech Republic, Hungary, Poland, Romania, and the Slovak Republic, shall be determined by the first document emanating from the United Nations system classifying or listing it as either a developed, a developing, or least developed country. Republics classified or listed in such document as a developing or least developed country shall be deemed as a developing country. Polio Eradication Initiative. Call for Expressions of Interest (EoI), Developing Sabin-Inactivated Polio Vaccine (sIPV), July 2010
Historically, prequalified vaccines have been bought from manufacturers in industrialized countries. Table 1 shows the evolution of UN agency purchase from emerging manufacturers (EMs), indicating that these vaccines are now a significant proportion of the market, especially for the older vaccines.

Table 1. Proportion of prequalified products made by Emerging Manufacturers (EMs)

<table>
<thead>
<tr>
<th>Year</th>
<th># EMs with functional NRAs (includes Rep Korea)</th>
<th># preQ products (not including influenzas)</th>
<th># preQ products made by EMs</th>
<th>% preQ products made by EMs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td>--</td>
<td>35</td>
<td>2</td>
<td>5.7</td>
</tr>
<tr>
<td>1996</td>
<td>--</td>
<td>50</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>2006</td>
<td>8</td>
<td>75</td>
<td>34</td>
<td>45</td>
</tr>
<tr>
<td>2010</td>
<td>9</td>
<td>90</td>
<td>51</td>
<td>57</td>
</tr>
</tbody>
</table>

However the market is unbalanced. Figure 1 shows the evolution of GAVI funds spent on these vaccines, indicating the lag in purchase of EM-produced vaccines, even those that were already prequalified, by UNICEF Supply Division. Part of the reason for this was to ensure vaccine security.6

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6 Vaccine security is defined by UNICEF Supply Division which uses a number of strategic procurement initiatives to ensure adequate supplies of the vaccines it needs.
Figure 1. % value of vaccines for the GAVI Alliance procured from emerging manufacturers

Source: UNICEF Supply Division

The fact that more pentavalent vaccines from EMs are now prequalified suggests that there will be a larger proportion of these vaccines bought and a concomitant decrease in the weighted average price, according to UNICEF Supply Division.\(^7\) Figure 2 shows the GAVI projection of the decline in the weighted average price of pentavalent vaccines as more EM products are prequalified, and this price is expected to decline still further as two pentavalent vaccines of a potentially large volume supplier, the Serum Institute of India, recently became prequalified.\(^8\)

\(^7\) Ann Ottosen and Robert Mathews, UNICEF Supply Division, personal communication, July 2010

Nevertheless, there are other factors that will impact vaccine prices and availability. The purpose of this paper is to examine the activities of WHO in providing support to EMs, the outcomes of these efforts, and their impacts on the availability of affordable high quality vaccines of public health importance, and to fit this information into an overall vaccine supply framework.

The Vaccine Supply Framework

The supply and demand continuum for vaccines starts with R&D for product development and proceeds to the end product, the vaccine that is administered to children to prevent disease. Chronologically, this continuum can be described in four steps, as seen in Figure 3.
The first step is R&D, which include basic research, access to technologies and intellectual property rights (IPR), and product development. WHO inputs in this area have included support for catalytic research (IVR, Sabin inactivated polio vaccine (Sabin IPV) development) and acquisition of product rights (pandemic influenza initiative, Meningitis Vaccine Project – MVP). The second area is production, where WHO has contributed by the development of guidelines (activities of the Expert Committee on Biological Standardization – ECBS), seed grants (pandemic influenza initiative), development of technology hubs (pandemic influenza initiative, Sabin IPV, Global Adjuvant Development Initiative), and support through Product Development Partnerships (PDPs) such as MVP. The regulatory area includes prequalification activities, the development of standards and guidelines by the ECBS, and the NRA strengthening initiative, including capacity building activities of the Global Learning Opportunities in Vaccine Quality (GLO-VQ). Finally, the area of marketing and distribution has been supplemented by WHO in the development of Target Product Profiles (TPPs), support to National Immunization Advisory Groups (NITAGs), support to procurement activities, and price negotiation (MVP).
This schematic flow chart with existing WHO interventions (not an exhaustive list) shows the process. However, in practice any vaccine product can be classified in terms of the vaccine market and the impacts of four characteristics which are in tension. In this session we will be looking not only at the desirable WHO inputs along the vaccine supply continuum, but also at a general framework that features these four characteristics of the market. Figure 4 shows these: product availability, product affordability, market sustainability, and product quality. The aim will be to balance the tensions to provide a healthy, balanced market, and to then define optimal WHO inputs to achieve this.

**Figure 4. Vaccine Market Characteristics**

<table>
<thead>
<tr>
<th>Product Availability</th>
<th>Product Affordability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innovation</td>
<td>Product output costs</td>
</tr>
<tr>
<td>Vaccine security</td>
<td>Price structure</td>
</tr>
<tr>
<td>Product characteristics</td>
<td>Competitor</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Market Sustainability</th>
<th>Product Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Competitor to demand</td>
<td>Regulation</td>
</tr>
<tr>
<td>Adequate supply</td>
<td>Quality systems</td>
</tr>
<tr>
<td>Product acceptability</td>
<td>Prequalification</td>
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<tr>
<td></td>
<td>Safety &amp; efficacy</td>
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</table>

**Case Studies**

The most recent activities of IVB/IVR in assisting EMs provide four case studies: the Meningitis Vaccine Project, the influenza vaccine initiative for pandemic preparedness, Sabin IPV, and an intellectual property-free adjuvant platform. These case studies illustrate four different models of support:

1. A Product Development Partnership
2. Direct support
3. Support through a technology hub
   a. Transfer of a technology for vaccine production to the clinical lot stage
   b. Transfer of a precompetitive R&D platform technology.
Meningitis Vaccine Project (MVP)

This project was officially started in 2001 with an award by the Gates Foundation of $70M to PATH and WHO (IVB/IVR) to develop a conjugate meningitis A vaccine that would be effective in eliminating the outbreaks of this disease in the African meningitis belt, although work on it started at WHO several years before that. When it became apparent that no multinational manufacturer was interested in developing this vaccine for a price judged affordable for the target countries (less than $0.50 per dose), a supply agreement was entered into with the Serum Institute of India (SII). MVP was to provide technology transfer and other inputs to make sure the vaccine was developed, prequalified, and introduced, and SII agreed to develop the vaccine and to make it available to the target groups at the agreed price.

In 2010 the vaccine was licensed and prequalified, and it was planned to start the introduction process with a phase 4 study in several districts in 3 meningitis belt countries. MVP had provided strong inputs as well as technology, funding, and the implementation of the clinical trial plan. WHO's role was primarily related to development of surveillance sites and coordination with countries in the African region, but WHO also housed some of the MVP staff and played an important role in the strategy and oversight of the process.

Generally, the MVP is felt by many of the stakeholders interviewed for this paper (see Appendix A) to provide a good model of the process of innovative vaccine development, including technology transfer. The process has taken roughly nine years, and has resulted in the licensing and prequalification of a product for which there was no manufacturer interest, and which will undoubtedly be of use in the meningitis belt to prevent meningitis outbreaks at an affordable price. Stakeholder comments have helped to focus on some of the lessons learned below.

1. Despite the lack of industrialized country manufacturer interest in the project, the SII was selected through a due diligence process by an Expert Advisory Group that reviewed portfolios from four developing country manufacturers and three multinational company (MNC) proposals. The technology is non-exclusive and other manufacturers could enter the market if they wish, although, given the current price and the size of the market, this is unlikely.

2. At the outset of this process, which was WHO-initiated, there were some who felt that all the funding should have gone to WHO, which made the initial stages of collaboration difficult.
(3) A major WHO role was provision of programmatic inputs, such as disease burden estimates, surveillance, and developing introduction strategies, inputs which could have been provided even if WHO had not been part of the MVP. However, the fact of WHO partnership in the MVP allowed market creation and introduction to proceed seamlessly.

(4) Although technology transfer was part of the process, SII has stated that the technology as delivered needed extensive development, as it had never been carried to the stage of clinical lot production.

(5) Because WHO also did the prequalification as well as participated in the process of getting the vaccine licensed in India, there have been claims of conflict of interest.

(6) The project resulted in a new needed product at much lower cost than if an MNC had been involved. However, this model, due to its specific context, in contrast to other Product Development Partnerships, focused on only one manufacturer and only one product, which is now available only from a single supplier.

Development of Pandemic Influenza Vaccines

In 2007 and again in 2009, WHO (IVB/IVR) implemented a process with funding from the United States Department of Health and Human Services (Biomedical Advanced Research and Development Authority - BARDA), the governments of Japan and Canada, and the Asian Development Bank, to support developing country efforts to develop pandemic influenza vaccines. At the time effort was directed against “avian flu” H5N1 virus; it was later directed against H1N1 “swine flu.” A total of 11 manufacturers have been funded under this program. Awards were on the order of $1-2M.

The awards process was based on a written application from prospective developing country manufacturers outlining their plans for production and their own project milestones. Selection criteria included government support, a functional NRA or one that was following an institutional development plan, and the manufacturer had to have produced at least one vaccine (later changed to one biological product). Funding went towards facilities and equipment, as well as for consultants and know how development. Many new producers received training through a technology hub, partly supported by IVB/IVR, the Netherlands Vaccine Institute (NVI). In addition, two producers have established long term agreements with NVI for ongoing production support.

Of the 11 countries funded, two were already producing influenza vaccines, and both of them developed and licensed pandemic influenza vaccine. Two others were able to develop pandemic influenza vaccine within the time frame, and one of those was
licensed and obtained WHO prequalification. Several manufacturers have products in clinical trials.

Most of the manufacturers used classical technology, but several produced live attenuated influenza vaccine from a process made available by WHO from Nobilon (WHO has acquired these IP rights for distribution to manufacturers). So, with a relatively small input of funding and in a relatively short time, new products have been made available for pandemic use. More important, the process has been sufficiently developed in the hands of the manufacturers so that in the event of a future pandemic more vaccine could be made available relatively quickly.

Lessons learned, from stakeholder interviews, include the following.

(1) Since a functional NRA was not an obligatory part of the process, the vaccine development process might not always be able to be completed to prequalification.
(2) A possibility of perception of conflict of interest was mentioned by some interviewees as WHO was prequalifying a vaccine they had helped to develop.
(3) According to their presentations at a meeting of manufacturers who had received support convened by WHO and BARDA in Viet Nam in May 2010, some of the manufacturers receiving awards have as yet made little progress.
(4) The level of sustained technical support really needed for a true technology transfer has not been available for this process.
(5) Given the usual cost of vaccine development, in the hundreds of millions of dollars, the relatively small amounts of the awards may have served in some cases to accelerate an already planned process. This may not qualify as a classical example of technology transfer, as some projects do not involve bilateral provider-recipient relationships.

One very positive outcome of the process was the acquisition and distribution of IP rights for the Nobilon product by WHO. Nonetheless, the vaccine production technologies were egg-based. It is conceivable that an effort to promote the development of cell culture technology for influenza vaccine production may be an approach that will allow greater scale up capacity for the future.

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9 A second one has reportedly met prerequisites for prequalification; but is not yet on the WHO website specified in reference 7.
10 Presentations at 3rd Meeting on Prospects for Influenza Vaccine Technology Transfer to Developing Country Manufacturers. Nha Trang, Viet Nam, 5-6 May 2010
11 Personal communication, PAHO Biologics Staff, September 2010.
Sabin IPV

It is foreseen that the eradication of polio will proceed to the point that the cessation of oral polio vaccination will occur in 2017.\textsuperscript{12} At that point it will not be possible to continue to produce OPV or IPV made with wild or attenuated polio strains except under high containment. Some countries will want to continue with polio vaccination, and an inactivated poliovaccine made with the Sabin strains is being developed in several countries. To increase the global supply and have this product available at the time of OPV cessation for an affordable price in developing countries, there is interest in some of these countries in producing a Sabin IPV.

WHO, through the Global Polio Eradication Initiative, has supported with funding the development to a clinical lot production (700 liter scale) of such a product at the NVI, and will also support the phase 1 clinical trials in Europe. The technology and knowhow will be available for transfer to EMs which will be selected from among applicants who have responded to a Call for Expressions of Interest recently published by WHO.\textsuperscript{13} According to the Call for Expressions of Interest, two applicants will be selected by WHO to enter into contractual Technology Transfer agreement with NVI at their own expense in 2011. More manufacturers may be selected in subsequent years, based on a new call for Expressions of Interest to be issued by WHO. The characteristics of these manufacturers, which will be selected by WHO through a review process overseen by an advisory committee, include the necessity to be from a developing country, preferably produce a prequalified vaccine, that they agree to follow the necessary containment specifications, that they will be able to produce the product seed lots in the targeted time, and that they agree to make a portion of the yield available on the global market. The products will preferably include both monovalent IPV and combined products. Further work will be done to ensure that the supply can be further augmented by the use of reduced doses through intradermal injection and/or by appropriate choice of an adjuvant.

This project is expected to produce products in 2015-2016, so it is premature to judge its impact. It is intended to supplement the supply of Sabin IPV, which is already being developed by several Asian manufacturers in Japan, China, and one in Indonesia with Japanese assistance. The use of a technology hub such as NVI, which will be paid by the recipients for the transfer, serves also to do some research outside of the technology transfer process and to keep WHO at arm’s length from the process.

The following comments on the Sabin IPV project were made during a workshop in June 2010 at NVI.

\textsuperscript{12} Oliver Wyman. The supply landscape and economics of IPV-containing combination vaccines: Key findings. Commissioned by the Bill & Melinda Gates Foundation. May 2010
\textsuperscript{13} At http://www.polioeradication.org/content/fixed/opvcessation/opvc_eoi.asp
(1) Some EMs feel that limitation of the technology transfer to only two manufacturers in 2011 followed by additional manufacturers in subsequent years will unnecessarily delay the timely availability of sufficient Sabin IPV at the time of OPV cessation.

(2) There is a need for further regulatory guidelines. If, for example, the WHO ECBS determines the need for demonstration of lack of neurovirulence more frequently than just at the seed lot stage, this could make the project economically unfeasible.

(3) There is some doubt about the Sabin IPV containment regulations in the GAP-3 (containment for the Global Action Plan after OPV cessation, which specify the containment required IPV production) rules as it may obviate any financial advantage of producing Sabin IPV rather than Salk IPV.

(4) There is uncertainty about the future of the Sabin IPV market, which makes the investment in the development of this new product more risky than the production of Salk IPV, which has a known track record. ¹⁴

(5) The competition by MNCs seems to be far ahead as they seem able to supply the global market with Salk IPV within several year’s notice. ¹⁴

(6) Time to license Sabin IPV, after completion of the technology transfer will take longer than alternative approaches like intradermal application of Salk IPV.

**Adjuvant platform**

Through the recently initiated Global Adjuvant Development Initiative (GADI), WHO (IVB/IVR) is supporting the development of a vaccine formulation platform based at the University of Lausanne (UNIL), Switzerland. The laboratory at UNIL functions as a training and service center on adjuvants and to facilitate the access to vaccine adjuvants by public sector and private partners. The services and training courses are open to all, although there is prioritization for developing country institutions. In parallel to the formulation services, the GADI laboratory at UNIL is also being established as a technology hub for technology transfer of adjuvants, including oil-in-water emulsions, for developing countries. The development of such a technology hub is felt by many stakeholders to be a useful role for WHO, as it is expected to impact significantly vaccine production capacity worldwide (pandemic influenza, polio…) and reinforce vaccine development autonomy by developing countries. This initiative, which is still in early development, is directed towards a clear need; however it is only one of many needs for development of innovative vaccines.

¹⁴ PATH. An economic analysis of strategies to reduce the cost of routine IPV immunization. April 20, 2010
WHO Policy Statements

WHO recognized the difficulties in providing manufacturing support, and in particular the fact that much of the effort in the 1970s and 1980s to support developing country vaccine manufacture had not resulted in sustainable vaccine production. After a series of visits by teams from the Children’s Vaccine Initiative, the conclusions were summarized in a publication,¹⁵ and developed into a WHO policy statement,¹⁶ which stated that WHO would provide neither technical nor financial support unless the manufacturer worked under the oversight of a functional National Regulatory Authority (NRA) and had developed a strategic plan for viability. The dependence on the functionality of the NRA, especially for prequalification purposes, has sometimes delayed or prevented the prequalification of vaccines that would have been useful on the global market, and so in 2003 SAGE advised that in emergency situations WHO should devise a process enabling appropriate regulatory support to maintain prequalification status.¹⁷ In addition, in complex global emergencies, the SAGE and other WHO bodies have adapted the 1990 policy statement. For example, in the case of an expected influenza pandemic, SAGE advised that WHO facilitate local production of influenza vaccine in developing countries.¹⁸

Recently, because of the increase in instances of technology transfer for medicines production, WHO’s Medicines group is developing guidelines for such technology transfer, a main principle of which is that the receiving and sending units be of similar levels of technical achievement.¹⁹ This might be useful to keep in mind when considering the case studies presented above.

Lessons Learned

Table 2 summarizes some of the major lessons learned from the case studies presented above. The general consensus is that WHO is more effective when its efforts are focused on what it does best: regulatory capacity building, mandated activities such as prequalification, disease surveillance and vaccine introduction activities, and the ability to convene appropriate groups to make strategic policy recommendations. WHO is less successful as an awarder of grants or primarily focused on providing technical support to vaccine production, while other organizations are better resourced to do this.

¹⁶ WHO/VSQ/90.82. Ensuring the quality of locally produced vaccines and the viability of local production
¹⁷ Recommendations of the SAGE. Weekly Epidemiologic Record, No. 5, p 44, 30 January 2004
¹⁸ Recommendations of the SAGE. Weekly Epidemiologic Record, No. 1, p 7, 6 January 2006
¹⁹ QA8/08.259/Rev2, WHO Guiding Principles on Transfer of Technology
Table 2. Lessons learned from case studies

<table>
<thead>
<tr>
<th>Project</th>
<th>WHO Input</th>
<th>Perception</th>
<th>Outputs</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVP</td>
<td>Program support, standards</td>
<td>PDP, potential WHO conflicts, monopoly supplier</td>
<td>Affordable preQ product in absence of MNC interest</td>
<td>Widely considered successful model, immediate impact</td>
</tr>
<tr>
<td>Pandemic Influenza</td>
<td>Funding, training, technical advice</td>
<td>Mandate from EB and SAGE to increase supply, relatively small awards</td>
<td>Several preQ products</td>
<td>May not be best way to increase current and future supply</td>
</tr>
<tr>
<td>Sabin IPV</td>
<td>Funding for clinical lots, Expressions of Interest</td>
<td>Rigorous criteria &amp; project management</td>
<td>NA : Project completion due 2016</td>
<td>To complement supply of needed product</td>
</tr>
<tr>
<td>Adjuvant platform</td>
<td>Selection, definition, support</td>
<td>Useful, within WHO mandate</td>
<td>NA : Project to start in 2011</td>
<td>Addresses only one aspect of issue</td>
</tr>
</tbody>
</table>

From the point of view of MNCs, there is a concern that the new vaccine introduction initiatives are primarily focused on price, while these MNCs are the primary providers of innovative vaccines, taking risks. The IFPMA members have provided numerous examples of their efforts in technology transfer through partnerships which have greatly increased the supply of innovative vaccines. The IFPMA desire is that the international community should depend more on what it calls market forces in the expectation that WHO will enforce one standard of quality.

The DCVMN members who have been successful at developing new technologies in general have welcomed the inputs of WHO in this area. However, there is also a recognition that to successfully transfer technologies and to develop R&D into viable products, a long term intensive partnership effort in final scale production facilities is most effective. Brazil has been effective in such technology development partnerships.

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20 Norbert W Hehme. H1N1 Vaccine Production: The Industry Perspective, presentation at 3rd Meeting on Prospects for Influenza Vaccine Technology Transfer to Developing Country Manufacturers, Nha Trang, Viet Nam, 5-6 May 2010
21 Dr Carlos Morel, FIOCRUZ, Brazil, personal communication, 2010
It is also important to recognize the contribution to vaccine security of the continuing large volume production of traditional vaccines; the bulk of which comes from EMs. However, recent years have shown that there can be gaps in the quality systems of vaccine manufacturers, especially EMs in countries where NRA oversight is not mature.

From the point of view of regional and country staff, WHO needs to emphasize the programmatic aspects that have been its traditional mandate, strengthening immunization delivery infrastructure, supporting country decision making bodies (NITAGs – National Immunization Technical Advisory Groups), providing capacity building activities and support for government procurement and pooled procurement mechanisms, developing surveillance systems to quantify disease burden and to show vaccine impact, and handling vaccine presentation issues. The update of the WHO prequalification guidelines are addressing this latter problem.22

On the other hand, countries and regions would like WHO to expand the vaccine production landscape, and support vaccine producing countries in each region. They have also suggested a study of the specific activities of public sector vaccine producers and whether they have a place in today’s vaccine market.

Finally, from PAHO comes the report of a collaboration between the PAHO RF and SII to achieve the elimination of measles and rubella in the region. The basis of the exclusive vaccine purchase award by the PAHO RF was prequalification, price, and performance. This partnership assured an adequate supply of vaccines of appropriate quality and price, a win-win situation. PAHO suggests this is one way in which they could support an EM, with an exclusive contract, while facilitating their disease control goals.

**Major Gaps and Issues**

In terms of WHO’s role in achieving availability and affordability of innovative high quality vaccines of public health importance, the following points stand out.

**Availability**

- Factors that will influence this include disease burden, government commitment and decision making process, and procurement expertise, to name a few.
- There is a need for activities focused on the development of innovative technologies (R&D) and their transformation into viable products.

22 Some of these issue have been addressed by the recently proposed revision of the prequalification process: [http://www.who.int/immunization_standards/vaccine_quality/pq_revision2010/en/index.html](http://www.who.int/immunization_standards/vaccine_quality/pq_revision2010/en/index.html).
- To have adequate production capacity for innovative vaccines, for the long term EMs must enter the market.
- The PAHO RF example given above illustrates how appropriate use of procurement power can assure availability of a particular product.

Quality

- Prequalification has become a benchmark, and the trend is putting more pressure on the prequalification team. The prequalification process needs to be open and transparent, perceived to be balanced, auditable, and not subject to time delay which can be expensive for manufacturers and thus impact the price of the product.\textsuperscript{21}
- Dependence on NRA oversight is important. However, for vaccine security and for manufacturers’ financial situations, there is a need for a failsafe process in the case of NRA failure which could delay or negate prequalification status. This has also been addressed in the proposed revision of the prequalification process.\textsuperscript{21}
- A challenge for the increasing dependence on EMs in the overall vaccine supply picture will be the assurance that performance gaps, such as the recent revocation of the prequalification of products supplied by Shantha Biotech, are closed. This will mean even more attention to quality systems and to stringent NRA oversight.
- Acceptance of products will depend on demonstration of safety and efficacy.
Affordability

- EMs may have lower cost structures but the key elements in vaccine prices are demand forecasts, analysis of future needs, scale decisions, cost of goods, and market guarantees.
- It is important to ensure an economic analysis prior to technology transfer including scale, demand, market structure, impact of number of suppliers.
- Access is not guaranteed by low prices alone. While price is one of the factors a government may consider in choosing to add a new vaccine to the immunization program, cost-effectiveness, that is the balance of disease burden and cost of care on the one hand, vs cost of prevention of the disease on the other, will be more important.

Sustainability

- Attention still needs to be directed to the challenge of maintaining an adequate supply of traditional vaccines, and maintaining vaccine security.
- Long term sustainability will depend on the definition and promotion of one standard of quality.
- A competitive market will be important in the long term for market sustainability, and this will depend on accurate demand forecasting and adequate sources of supply.
- An analysis of the role of public sector manufacturers could be a useful contribution.

Views of stakeholders

In the course of developing this paper, many people were interviewed, in person, by telephone, or by email. A complete list is given in Appendix A. From this list some concrete suggestions were received regarding the relative strengths and weaknesses, areas where WHO has a competitive advantage, and areas where other groups might be stronger. A compilation is given below.

- Vaccine production is a complex and high risk business, and WHO may not have a competitive advantage here. WHO cannot do everything and so it needs to choose the most effective approach given its mandate and resource constraints. It will be important to identify its current and potential roles and priorities in view of the roles of industry itself and those of other partners in the context of transparency, equity and competition to highlight the way forward. However, roles where WHO could be an important player include
• Precompetitive R&D platforms, or technology hubs
• Acquiring and administering IP rights
• Capacity building in regulatory affairs, testing and good practice standards in manufacturing, laboratory and clinical areas.

There are three clear roles for WHO in relation to quality of vaccines:
• Developing guidelines and standards
• Capacity building for NRAs and NCLs
• Prequalification

In the area of vaccine affordability, WHO has a strong power to convene groups to achieve a particular strategy. This power could be well used to achieve affordable prices for vaccines for neglected or priority diseases within the financial resources of low and middle income countries. Other activities in the area of affordability include the following:
• Removing barriers that add extra expense to vaccines, such as delays in prequalification and the need for additional licensing of prequalified vaccines in many countries, which could be expensive and time-consuming
• Support for procurement and to procurement mechanisms
• Support for country decision making. WHO involvement is very important in policy issues such as implications of choosing particular vaccine presentations.

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23 Term used in WHO/IVB/10.02. The Initiative for Vaccine Research Strategic Plan 2010-2020.
Summary and Recap

Table 3 provides, for each of the four categories for a healthy and balanced markets, several options for major gaps identified in this landscape analysis for actions by WHO and partners.

Table 3. Potential WHO Responses to Gaps

<table>
<thead>
<tr>
<th>Gaps</th>
<th>Potential WHO roles</th>
</tr>
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<tbody>
<tr>
<td>Sustainability</td>
<td>Tech transfer in exchange for price considerations</td>
</tr>
<tr>
<td></td>
<td>Policy recommendations</td>
</tr>
<tr>
<td></td>
<td>Support vaccine security</td>
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<tr>
<td></td>
<td>Let market play out without interventions</td>
</tr>
<tr>
<td>Availability</td>
<td>Technology hubs, License-in technologies</td>
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<tr>
<td></td>
<td>Define TPPs</td>
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<td></td>
<td>Support surveillance</td>
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<td></td>
<td>Strong recommendations on vaccine use</td>
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<tr>
<td>Quality</td>
<td>Provide technical, financial resources to NRAs &amp; mfrs</td>
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<tr>
<td></td>
<td>Define one standard of quality</td>
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<tr>
<td></td>
<td>Continue standard setting, CB, &amp; preQ</td>
</tr>
<tr>
<td>Affordability</td>
<td>Promotion of specific price negotiation model</td>
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<td>Support but not implement financing mechanisms</td>
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<td>Work for lowest possible price for vaccines for all DCs</td>
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These are selected to demonstrate a continuum of activities in terms of WHO’s active involvement in support to emerging manufacturers. Do these approaches need to be determined on a case by case basis depending on the vaccine under consideration? Or does the SAGE feel there are general principles that can be recommended that apply to all situations?
Appendix A. List of people contacted


PDPs: Alan Brooks & Carla Botting (MVI), Mike Brennan (AERAS), Marc LaForce (MVP)

PATH: Kathy Neuzil, Deb Atherly, John Boslego

Private consultants: Chris Nelson (ex-Merck, ex-WHO), Roy Widdus (ex-CVI)

NVI/RIVM: Jan Hendriks, Hans Kreeftenberg

UNICEF: Rob Matthews, Ann Ottosen

MSF: Daniel Berman

IFPMA: Ryoko Krause, Kathleen Vandendael, Jaco Smit, Olga Popova

DCVMN: Suresh Jadhav, Akira Homma, Lucia Leite, Mahima Datla

Biotechs: Melinda Moree, Piers Whitehead

Country: Rehan Hafiz, Pakistan; Carlos Morel, Brazil; Reinaldo Guimarães, Brazil

WHO Regional Offices: Jose Luis DiFabio, Maria de los Angeles Cortes, Cuauhtémoc Ruiz, Daniel Rodriguez (PAHO); Nadia Teleb (EMRO); Nihal Abeysinge (SEARO)

BARDA: Mike Perdue, Influenza program

Gates: Violaine Mitchell

NIH Fogarty Center: Mark Miller

IVI: John Clemens, Rodney Carbis

UNIL: Nicolas Collin

USAID: Ruth Levine