Vaccine Presentation and Packaging Advisory Group: a forum for reaching consensus on vaccine product attributes

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In resource-constrained settings, getting vaccines safely and reliably to children in remote areas is a daily challenge. Exposure of vaccines to excessive heat or freezing temperatures, which often occurs in such settings, can compromise their potency.[1–4] Although developing countries have maintained cold chain infrastructure since the 1980s, they often find it difficult to power, repair and replace equipment and to transport and store vaccines at the appropriate temperature.[5] Suboptimal vaccine management practices lead to frequent stockouts of critical vaccines and supplies.[6,7]

Many developing countries also face critical health workforce shortages, especially in remote areas.[8,9] When training and supervision opportunities are limited, errors in vaccine stock management, in the preparation and administration of vaccines, and in the disposal of injection equipment are more likely to occur.[10,11]

The addition of new vaccine formulations or presentations to these already stretched systems can generate further problems.[12–14] Because newer vaccine products, such as pneumococcal conjugate vaccines and rotavirus vaccines, are much more difficult to research, develop and manufacture than traditional vaccines, they are more expensive.[15] As costs rise, it becomes increasingly important to manage inventories and minimize open and closed vial wastage.[12–14] In addition, many new vaccines are presented in a format and packaged in a way that can create handling difficulties for countries with poor infrastructure. Furthermore, the cold chain system, which was designed in the late 1970s to early 1980s for the transport of the six traditional vaccines that existed at the time, lacks the capacity to deal with the much larger number of vaccines that exist today.

In environments with few resources, protecting every child with lifesaving vaccines will not be possible without thoughtful improvement in at least two areas: (i) strengthening national immunization systems and providing support to health workers tasked with delivering vaccines, and (ii) improving vaccine design and presentation. Although efforts to strengthen country systems are well documented,[16,17] little has been published on efforts to influence vaccine design and presentation. This paper describes a novel approach to collaboration between the private and the public sectors, with a focus on ensuring that new vaccines are designed with attention to the needs and problems of national immunization programmes in low- and middle-income countries.

Forum for early discussion

The Vaccine Presentation and Packaging Advisory Group (VPPAG) was established by the GAVI Alliance in 2007 in response to a query from industry about the optimal number of doses per vial for vaccines used in GAVI-eligible countries (low- and lower-middle-income countries). At the time, there were concerns about the available presentations of the rotavirus and pneumococcal conjugate vaccines that GAVI was planning to support and the VPPAG was asked to provide input and guidance on the presentation and packaging of both vaccines.

In 2008, the World Health Organization (WHO) assumed responsibility for convening the group and expanded its mandate to focus on all new vaccines intended for use in developing countries. The group's three core functions are to: (i) provide a forum for dialogue between industry and the public sector on vaccine presentation and packaging and respond to industry requests for guidance; (ii) facilitate improvements in the presentation and packaging of vaccine products destined for developing country markets through specific preferred product profiles, and (iii) develop generic guidance on optimal packaging and presentation for vaccines used in resource-constrained environments.[18]

Accomplishments to date

The VPPAG's first major output was its guidance and technical input into a target product profile for pneumococcal conjugate vaccines.[19] The VPPAG also contributed to improvements in the presentation of a rotavirus vaccine. In one case a multicomponent vaccine requiring over 100 cm^3 of storage space per dose was changed to a ready-to-use liquid in a plastic tube requiring only 17 cm^3 of space to store and transport. Over the last few years, manufacturers have made large investments, under guidance from the VPPAG, to reduce cold chain capacity requirements and improve the presentation of rotavirus vaccines for resource-constrained settings.

In 2009, the VPPAG published its first generic preferred product profile (gPPP) for vaccines intended for use in public sector immunization programmes in low-resource settings. The

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gPPP provides guidance on key presentation and packaging decisions in four domains: formulation, presentation, labelling and packaging, and it identifies areas in which further evidence or data are needed. Each recommendation has been crafted to mitigate programmatic challenges by making vaccine administration safe and efficient, ensuring that the products are simple to use, limiting cold chain burden and reducing unnecessary vaccine wastage. Under *formulation*, for example, there is a recommendation to provide vaccines, wherever possible, in "ready-to-use" presentations that do not require the mixing of components. Such presentations are preferred because they enhance the safety, convenience and efficiency of immunization programmes. In some cases, lyophilized vaccines requiring reconstitution are unavoidable for thermostability reasons. However, "ready-to-use" liquid presentations – when producing them is feasible – reduce health workers' workload, eliminate the need to order, store and transport diluents and reconstitution syringes, and minimize the possibility of error when reconstituting vaccines.

Another gPPP recommendation – this one under *packaging* – is to reduce the volume and weight of secondary and tertiary packaging and to minimize the need to repackage vaccines for in-country supply chain distribution. This recommendation complements WHO guidelines on maximum per-dose packed volumes for existing vaccines.

Further research is under way to harmonize the sizes of secondary packaging for new vaccine products to enable better use of storage space in cold boxes and storage sites. This would greatly facilitate storage and distribution at the national and sub-national levels. The VPPAG is currently addressing this and other areas in need of research, and the results will be reflected in an updated gPPP in 2013.

Contributions to policy

WHO's vaccine prequalification service ensures the acceptability, in principle, of vaccine products purchased by United Nations agencies such as the United Nations Children's Fund (UNICEF), which procured vaccines for about 58% of the world's children in 2010.[20]

During the prequalification process, WHO validates available scientific evidence that the vaccines will work in low- and middle-income country settings and considers the programmatic suitability of each vaccine for such contexts. However, until the Programmatic Suitability of Vaccine Candidates for WHO Prequalification (PSPQ) process was developed, WHO had no formal definition of "programmatically suitable" products. In 2010, WHO established the Immunization Practices Advisory Committee to provide guidance to the Director of the Immunization, Vaccines and Biologicals department on programmatic issues related to immunization programmes. One of the first items brought before this committee was a request for input into and eventual endorsement of a set of PSPQ guidelines.[21,22]

Drawing on the gPPP as its starting point, WHO developed the PSPQ guidelines to help the international community assess whether new vaccine products satisfy the mandatory and critical requirements for programmatic suitability and to define the preferred characteristics of future vaccines. The Advisory Committee endorsed the PSPQ guidelines and WHO began using them in its prequalification process on 1 January 2012.

The impact of the gPPP and PSPQ can already be seen. Three manufacturers have voluntarily decreased the volume of their vaccine packaging to reduce impact on the cold chain. In addition, several manufacturers have improved their primary containers by using plastic instead of glass for diluent vials; by replacing bulky prefilled delivery devices made of glass with small, easy-to-use plastic squeeze tubes for oral vaccines; and by even building a new factory and filling line to package vaccines in compact, prefilled auto-disable devices.

In 2011, the VPPAG made recommendations to WHO on how to make optimal use of the limited space on vaccine labels and make these easier for vaccinators to read.[23] These recommendations were endorsed by the Advisory Committee and passed along for review by the Expert Committee on Biological Standardization, which has among its responsibilities to oversee policies related to vaccine package labelling. The Expert Committee on Biological Standardization supported VPPAG's initial recommendations and asked that a more detailed proposal and timeline be developed and submitted to it, at which point it will revise the global regulatory guidance on the basis of the recommendations.

The VPPAG is also conducting research and engaging in discussion on the utility of placing barcodes on vaccine vials for better management of vaccine stock, minimizing packaging volumes, and selecting optimal package sizes to make best use of storage facilities.

Value to public and private sectors

The VPPAG recognizes the need to have discussions about vaccine formulation and packaging much earlier in the process than was previously the norm, since reformulations and changes in the packaging presentations can be extremely costly and problematic. For example, including a new additive to improve the thermostability of a currently commercialized vaccine, when feasible, entails repeating clinical trials, the national regulatory approval and licensure process, and, potentially, the WHO prequalification process because, from a regulatory perspective, new formulations are considered new vaccines. Even a simple change in primary packaging (material in direct contact with the product) might involve interaction analysis, real-time stability tests, changes in a freeze-drying cycle and regulatory approvals.

Until the VPPAG was formed in 2007, there had been no forum where discussions between the public and private sectors could be held openly, where all voices could be considered on an equal footing, and where consensus among all parties could be pursued.

We believe that the VPPAG has made discussion between private and public sectors more productive, expedient and fruitful than they were in the past. Public sector partners now have a better understanding of the cost and market implications of product design and packaging choices. This understanding makes it easier to appreciate trade-offs and request characteristics that will minimize market disruptions while still improving product suitability for developing country contexts. Private sector partners, on the other hand, have come to learn the needs and constraints faced by low-income countries and are increasingly able to design products better suited for these environments. In making critical choices about new

products, industry greatly appreciates being able to speak openly and discuss product attributes before investing the time and money required to take a product to market.

The VPPAG's members view the entity as having also generated a sense of trust and partnership between public and private sector representatives and as having provided a venue for general, all-inclusive discussions about product design, formulation, presentation and packaging. All this is of value to donors eager to see vaccine development efforts more clearly meet the needs of immunization programmes in low- and middle-income countries. It is also of value to vaccination programmes in developing countries insofar as it ensures that products developed for their systems will be easier to deploy safely and efficiently.

How it works

The VPPAG holds monthly teleconference meetings chaired by UNICEF and supported by a secretariat at WHO. Meeting participants include representatives from the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA); the Developing Country Vaccine Manufacturers' Network; WHO's Expanded Programme on Immunization; the vaccine Quality, Safety and Standards team at WHO; PATH; John Snow, Inc.; the US Centers for Disease Control and Prevention; UNICEF's Supply Division and Programme Division, and GAVI.

As the group's work has gained credibility and produced visible impact, other partners, such as the Bill & Melinda Gates Foundation, have made requests to join the VPPAG. The VPPAG itself is extending invitations to key partners and agencies that were not originally involved in the VPPAG but whose input would be of great value, including the Pan American Health Organization, with its revolving fund.

Others may join the calls, but only designated spokespeople can represent their respective groups. Additionally, the VPPAG creates small working groups to advance specific topics and areas of research.

Why it works

VPPAG members and other stakeholders have attributed VPPAG's success to several complementary factors. One of the most important, and perhaps unique, is the way in which competing manufacturers can represent themselves through existing industry associations.

The International Federation of Pharmaceutical Manufacturers and Associations, which has existed since 1968, represents the research-based pharmaceutical industry, including the biotechnology and vaccine sectors, which are composed of most of the large multinational pharmaceutical companies producing next-generation vaccines. Before each VPPAG meeting or call, the Federation's members discuss each item on the agenda until consensus agreement on their position is reached.

Members of the Developing Country Vaccine Manufacturers' Network are also consolidating their voices. Created in 2000, the Network is composed of private and public manufacturers with different industry perspectives and is active in more than 14 countries in Africa, Asia, the Caribbean, Europe and Latin America. Its contributions to the VPPAG are important because it brings to the table the perspective of developing country manufacturers on issues related to supply and distribution needs and limitations. Overcoming time zone and language barriers, members of the Network consult with each other before stating a position during VPPAG calls.

Another factor contributing to the success of the VPPAG has been the consolidation of multiple voices from the public sector. Specifically, the engagement of WHO programmatic and regulatory experts and representatives of UNICEF's Programmatic Division and Supply Division makes it possible to openly discuss and resolve issues that may have different implications for regulatory, procurement and programmatic agencies.

VPPAG avoids conflicts of interest by making the interests of all parties explicit. This has made it possible to reach consensus in a way that addresses the interests of both industry and the public sector.

Conclusion

The VPPAG is an important forum where stakeholders from the vaccine industry and immunization programmes interact to discuss in depth vaccine product characteristics and their impact on immunization programmes. Already, the VPPAG has brought about meaningful changes in the way vaccines are packaged and presented for developing country programmes. (The group's 2008 terms of reference,[18] current gPPP[24] and a profile previously completed for the pneumococcal vaccine[19] are available for download on WHO's web site.)

The VPPAG could provide a model for organizations struggling to meet the needs of markets in both high- and low-income countries. Such organizations would benefit from feedback on product characteristics that could improve product applicability in markets with different infrastructures, and consumers in developing countries could benefit from access to a wider array of suitable products without unnecessary delay. Having a forum that allows constructive dialogue between the public and private sector furthers our shared goal of preventing disease, disability and death from vaccine-preventable diseases by designing products that can more easily reach those who will most benefit from immunization. ■

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