WHO Microarray Patch (MAP) Product Development Workshop

Geneva, Switzerland, 8 December 2015

Executive Summary

Background and objectives of the workshop

In line with the Global Vaccine Action Plan (GVAP), WHO's mission is to increase equitable vaccine coverage against vaccine preventable diseases, as well as to accelerate development, approval and implementation of new vaccines and delivery technologies. Microarray patches (MAPs) are a novel vaccine delivery methodology that has the potential to become a game-changer (otherwise known as a disruptive technology) for immunization programs in low- and middle- income countries (LMICs), which mostly rely on vaccine storage and transportation at 2-8°C and trained healthcare workers to administer injectable vaccines by needle and syringe.

MAPs are currently in preclinical development for a number of existing vaccines, including influenza, tetanus toxoid, measles-rubella, inactivated poliomyelitis vaccine (IPV), as well as for vaccines in development such as inactivated rotavirus and dengue. However, there are a number of unknowns with respect to the appropriate product development strategy and the most expeditious regulatory pathway to licensure, since this is considered a novel vaccine combination product. In addition, the desired product characteristics and perceived impact for a particular vaccine/MAP combination in LMIC and high income country (HIC) markets may differ, resulting in a complex and potentially weak value proposition for vaccine and MAP developers to invest in this innovative technology. This workshop sought to better define and tackle the technical, economic and programmatic challenges facing vaccine/MAP product development, to establish assumptions or scientifically-based evidence where they are known, and to propose areas of focus and research where it is needed.

The WHO Department for Immunization, Vaccines and Biologics convened patch developers, vaccine manufacturers, regulators, funders and other key stakeholders to discuss these issues. This high level summary captures the major conclusions and recommendations; a more detailed paper on the considerations for MAP product development will be forthcoming.

Vaccines that may be applicable to MAP delivery

PATH has developed a broad framework to evaluate the potential benefits of new vaccine improvement and/or delivery technologies that, if available and implemented, could significantly impact vaccine accessibility and improve coverage. MAPs have emerged from this analysis as offering clear advantages for vaccine delivery, including increased vaccine thermo-stability, reduced packaging volume, ease of delivery, safer administration and disposal—possibly enabling delivery in new scenarios such as by minimally trained health workers and volunteers. Such attributes would significantly ease the logistics and reduce cost of vaccine delivery, which would be particularly impactful for increasing the coverage and equitable use of vaccines that are highly effective, but challenging to deliver. MAPs may also offer an attractive platform for vaccines targeted to HIC markets or outbreak scenarios, where they could conceivably be delivered to intended recipients with minimal supervision.

The 'most appropriate' vaccine with which to establish immunological and regulatory precedent for the MAP technology, whilst also representing a reasonable investment case, was discussed throughout the meeting. Currently three patch developers have been engaged by the Global Polio Eradication Initiative at WHO and BMGF to develop MAPs for delivery of IPV and are currently in preclinical and manufacturing process development with Phase I/IIa studies anticipated to start in late 2016 or early 2017. From a public health perspective, IPV/MAP may facilitate maintenance of

the high coverage rates as the oral poliomyelitis vaccine (OPV) is being phased out, and be amenable to efficient stockpiling for outbreak responses. However, the development pathway beyond Phase I is yet to be defined, and the partnership or commercialisation plan needs still to be developed with stakeholders.

Patch developers are also assessing delivery of influenza vaccine, for which it is possible to demonstrate rapid clinical proof of concept (POC) using hemagglutination inhibition titre as a correlate of protection. Stability of influenza vaccine at elevated temperatures appears to be feasible and early clinical data is encouraging with the demonstration that seroconversion rates and absolute antibody titers at 1 mo post immunization (full dose) are similar or superior to i.m. administration, which suggests the possibility of dose sparing. Seasonal influenza appears to offer a more compelling MAP business case for vaccine manufacturers, however commitment to development beyond phase I, which will include process scale up and investment in manufacturing infrastructure, is not clear.

Delivery of measles/rubella (MR) vaccine by MAP would confront a clear and urgent public health need. There are approximately 140,000 deaths per year due to measles and a further 110,000 cases of congenital rubella syndrome despite the availability of a safe, effective and affordable vaccine. The reasons for the immunization gap are several, including stringent cold chain requirements, reluctance to 'waste' vaccine by opening a large multi-dose vial and the need for careful reconstitution, handling and sharps disposal. For these reasons, routine immunization coverage remains sub-optimal and house-to-house campaigns to deliver these vaccines by needle and syringe are not feasible, and an alternative methodology, such as MAP, is desperately needed to reach the last mile.

The value proposition of MAP delivery of Measles and Rubella (MR) Vaccine

Although MR/MAP is a clear public health priority, HIC markets would seek vaccines that also contain mumps and potentially varicella (MMR/V). Accessibility to the HIC market segment may incentivise investment, however the technical feasibility of mumps or varicella vaccine delivery by MAP is not known, the inclusion of these components will increase the cost, and the likely development pathway and timeline for a quadrivalent vaccine on a novel delivery platform is likely to be protracted and complex. From the WHO perspective, the need for an alternative vaccine delivery strategy for MR is the most urgent need if we are to close the immunization gaps in LMICs, so that elimination and ultimately eradication of measles and rubella may become achievable in the nearer term.

As with any innovation, there are a number of key assumptions which support the notion that the new product will ultimately be cheaper and/or better. In the case of MR/MAP, the hypotheses are that: efficacy, safety and the total systems effectiveness will be comparable to if not better than MR delivery by syringe and needle; that end-users and vaccine recipients will prefer MAPs to injections; that MAP performance will be consistent across geographical populations, ages and vaccinator skill level, and that there is a feasible regulatory pathway to approval and implementation. At this stage in development, a number of these aspects are unknown, or not yet described. In addition, the demand forecast for MR/MAPs is not clear; current estimates are that 150 million doses of MR are required annually for campaign use, and up to 2 x 134 million doses (based on the birth cohort) for routine use, but a model defining the transition and scale up to a MAP based vaccine, and the use of this product in routine immunization would inform the potential return on investment.

In order to define the acceptability and suitability of a MR/MAP product, the Vaccine Packaging and Product Advisory Group (VPPAG) and the Delivery Technologies Working Group are currently engaging in a consultative process to develop a draft Preferred Product Characteristics (PPC) document to guide both MAP developers and vaccine manufacturers, as well as global stakeholders.

The PPC can inform vaccine impact modelling studies, and sensitivity analyses will help to better understand the trade-offs and tolerances between the various product attributes.

Preferred product Characteristics (PPC) for an MR/MAP product

The MR/MAP PPC seeks to define the acceptable and optimal attributes, specifically for use in LMIC settings. In this context, the appropriate ranges may differ from industry derived target product profiles (TPPs) that are commercially focused. WHO PPCs are nonetheless critical as they describe the attributes that would meet the requirements for WHO prequalification, which is a pre-requisite to vaccine procurement by UN Organizations (e.g. UNICEF, PAHO Revolving Fund) and implementation in GAVI eligible countries.

Since MR/MAP is considered a novel[1] vaccine combination product, the features that define the desired attributes need to be established. The following are some characteristics that were identified as needing further consideration:

- Requirement for thermo-stability: Stabilization of a vaccine up to 40°C to enable transportation and storage out of the cold chain or in controlled temperature chain (CTC) is ideal, however the absolute requirement for this will depend on other factors that may impact programmatic cost and logistical complexity, such as packaging volume or waste disposal;
- The use of an applicator: whilst a MAP that does not require an applicator would be preferable, one may be needed, and there are relative merits of a single use compared to multi-use applicator (cost vs validation requirements regarding contamination and performance reproducibility);
- The wear time: shorter contact time is preferable, particularly if wear time must be supervised. Duration and ease of administration of the MAP is critical to programmatic feasibility and human factor studies will have to evaluate this.

Manufacturing considerations

There has been much debate regarding the need for aseptic manufacturing of MAPs considering that the patches are exposed to a non-sterile environment upon administration, applied to non-sterile skin, and do not deliver vaccine parenterally. To date, early stage clinical studies with both vaccine and small molecules have been performed with 'low-bioburden' clinical material in which general safety and endotoxin levels of the MAPs are acceptable. In cases where a licensed vaccine has been administered by MAP, a repeat dose (and reproductive) toxicology study may not be necessary. However this will be subject of further consultations with the relevant regulatory authorities from countries where clinical trials are planned to be conducted and countries that use the vaccine.

With this in mind, a development strategy in which clinical POC studies are performed with non-aseptic MAPs, and in which the aseptic manufacturing process is scaled up in parallel to phase II POC studies to produce the three consistency batches in readiness for phase III testing, would shorten the timeline to clinical POC data whilst reducing the capital investment at risk. However this proposed strategy will require in depth consultation with the competent regulatory authorities based on the supportive data from the manufacturing process. Whether non-aseptic manufacturing would be acceptable for commercial product remains a question and would be dependent on the generation of supporting data for regulatory review as well as the risk tolerance of the manufacturer.

[1] With "novel" a new innovative vaccine is meant, in contrast with a "new" vaccine, which can be an old technique produced by a new manufacturer. Regulatory requirements are more severe for a novel compared to a new vaccine.

Currently, MAPs can be produced on a small scale (up to hundreds) in a GMP-like environment. Investment into the construction of a pilot plant that is able to aseptically produce several hundred thousand MAPs annually will be needed to support phase III studies and initial commercialisation. Currently this is a significant gap in the development strategy for MAP delivery of any vaccine, and capital expenditure estimates vary significantly. Full costs for manufacturing scale-up, clinical, and regulatory development may require investment of tens to hundreds of millions of dollars. The willingness to invest in such infrastructure will likely only emerge following technical feasibility including clinical POC for a target vaccine, and an understanding of the demand and business case for a particular vaccine/MAP combination. The platform potential of MAPs could also support the value proposition, i.e. how much knowledge from the development of vaccine/MAPs for one indication can be transferred to another. Even once facility plans are in place, the timeframe from breaking ground to a fully validated operational pilot plant is 2-3 years. This will significantly delay the timeline to commercialisation if the investment in manufacturing infrastructure is deferred until clinical POC data are available, particularly if investment is dependent on a platform based approach requiring data from multiple vaccines.

Regulatory pathways

It is assumed that the Biological Licensing Application (BLA) or Marketing Authorization Application (MAA) for the vaccine/MAP product will be submitted by the vaccine manufacturer who already holds a license to manufacture and commercialise the vaccine. The optimal regulatory pathway will depend somewhat on whether the vaccine/MAP product is intended for use in LMICs only, or will also be marketed in HICs.

For a vaccine that is targeted solely for use in LMIC countries, such as MR, the most accelerated route for this target market is through the European Union's (EU), EMA Article 58 Regulation pathway, as this ensures early engagement of WHO prequalification (PQ) and facilitation of in-country vaccine registration and procurement mechanisms. Article 58 allows the Agency's Committee for Medicinal Products for Human Use (CHMP) to issue a scientific opinion, in co-operation with the WHO. WHO PQ would ensure the quality, safety and efficacy of the vaccine/MAP, and that prequalified products are clinically and programmatically suitable for the intended target population and use in national immunization programmes. WHO PQ is reliant on licensure/registration by the responsible NRA in which the vaccine/MAP is manufactured, and WHO can support user country NRAs in LMICs for oversight and registration of PQ'd vaccines.

The product could also be licensed directly in countries of use through their national licensure procedure.

If other markets are also targeted, EMA's Article 58 pathway might not be the ideal route. Depending on the chosen strategy[2], an Article 58 review could be initiated followed by a EU license provided that at that time point the applicant has submitted a Paediatric Investigation Plan (PIP) approved by the EMA's Paediatric Committee. In this case, the vaccine manufacturer must seek approval by the 'competent' supervising regulatory authority of the country of manufacture, such as the FDA or EMA (for products produced in these countries).

In the case of influenza, the MAP presentation would be considered a novel vaccine product that does not have appropriate comparators already authorised or used, and in this case demonstration of efficacy against relevant clinical outcomes in appropriate populations would likely be required to

[2] One could envisage going first for a positive opinion for use outside the EU with a fast PQ, followed by a license in the EU, based on public health arguments and greater needs of the product outside the EU.

support an authorisation in the EU. It may be possible to demonstrate efficacy in some age and population sub-groups and extrapolate to others based on immune response data.

The MAP presentation is considered as an interesting and innovative development and thus developers are strongly recommended to discuss their development plans with national regulatory authorities even during the very early stages of clinical development.

Summary and next steps

This meeting served to increase understanding of vaccine MAP delivery technology, particularly with regulators, donors, WHO and some vaccine manufacturers for whom this has not been a focus to date. Regular (annual) meetings that convene device developers, vaccine manufacturers and others to focus on regulatory requirements and development strategy would be extremely beneficial to review progress, and discuss needs and next steps. Working with its partners, and resources permitting, WHO would continue to support MR/MAP development by focusing on the following activities going forward:

- Through the VPPAG Delivery Technology WG consultation process, finalise the first version of the MR/MAP PPC to help guide developers and manufacturers
- Develop the strategic demand forecast and implementation strategy for MR vaccine on MAP to inform investment decision making
- An assessment on how house to house vaccination would impact easier administration and increase vaccination coverage of MR vaccine, over and above fixed post campaigning
- Convene a focus group of regulators and policy makers to define the regulatory pathway (roadmap) and data requirements for approval and implementation of MR vaccine on MAP.

Although specific to MR, these efforts would benefit MAP development for other vaccines, such as IPV, by setting precedence with regard to process, but also informing some of the translational product development elements, such as production and characterisation data requirements.