

An illustration of a young child with dark skin and curly hair, sleeping peacefully. The child is wearing a teal-colored garment. On their upper right arm, there is a small, rectangular, light-colored bandage. The background is a soft, abstract composition of warm colors: a large white shape on the left, a large orange shape at the top, and a dark green shape behind the child's head. The overall style is clean and modern.

Measles-rubella microarray patch (MR–MAP) target product profile

JUNE 2019



World Health
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Preface

This target product profile (TPP) describes the minimal and optimal product characteristics for a measles and rubella (MR) microarray patch (MAP) vaccine, with a particular focus on delivery considerations for low- and middle-income countries (LMICs). It is intended to inform MAP developers, vaccine developers, procurement agencies and funders on MR-MAP research and public health priorities, and to facilitate the most expeditious development of MR-MAP candidates that would address the greatest and most urgent public health need in LMICs.

The document is based on an initial MR-MAP TPP developed by PATH and the World Health Organization (WHO) in 2016. It has been updated following input from a WHO working group of independent subject matter experts from diverse areas of expertise, including epidemiology, immunology, manufacturing and clinical development, regulatory affairs, health economics and policy. Specific aspects of the TPP were refined through consultations with various immunization stakeholders including the Immunization Practices Advisory Committee (IPAC) and the TechNet-21 community.

A draft was disseminated widely for public consultation in December 2018 among relevant stakeholders including MAP developers and vaccine manufacturers. The comments received were reviewed by the WHO MR-MAP working group and, where appropriate, incorporated into the TPP. This updated version is endorsed by the United Nations Children's Fund (UNICEF) and co-published with WHO.

While this document contains assumptions concerning regulatory considerations to help frame the rationale for the proposed characteristics, this TPP should not be considered as a regulatory document. The TPP will be updated as product development of MAP technology evolves, or as other changes in the identified need or research and development landscape emerge.

The document is divided into three major sections:

1. General considerations comparing the attributes of an MR vaccine delivered by MAP with those of the current, lyophilized MR vaccine;
2. Generic product characteristics for an MR vaccine on solid coated or dissolvable MAPs; and
3. Generic product characteristics for MAPs for delivery of MR vaccines.

Sections 2 and 3 describe the minimally acceptable and optimal targets for MR-MAP product attributes. However, these attributes are not currently listed in order of priority or importance; should an MR-MAP profile be sufficiently superior to the minimal characteristics under one or more categories, this may outweigh deficiencies in meeting a specific minimal characteristic in the suitability of product procurement.

The primary target audience for this TPP is any entity intending to develop a vaccine for national immunization programme use, including in low resource settings, and eventually to seek WHO prequalification and UNICEF procurement following licensure of its product. However, it is important to note that while this TPP defines aspirational goals for MR-MAP vaccine attributes, it does not supersede the evidence-based assessment by WHO's Strategic Advisory Group of Experts on Immunization (SAGE) for policy recommendation on use; other existing WHO guidance on vaccine development or prequalification; or assessments conducted by national regulatory authorities (NRAs), the European Medicines Agency (EMA), or the United States Food & Drug Administration (FDA).

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Abbreviations

CCID₅₀	50% cell culture infectious dose	ORI	outbreak response immunization
COGS	cost of goods sold	PDVAC	Product Development for Vaccines Advisory Committee
CTC	controlled temperature chain	PQ	prequalified
EMA	European Medicines Agency	PSPQ	Programmatic Suitability for Prequalification
gPPP	generic Preferred Product Profile	PTTI	peak temperature threshold indicator
HCW	health care worker	RI	routine immunization
HF	human factors	SAGE	Strategic Advisory Group of Experts on Immunization
ID	intradermal	SC	subcutaneous
IPAC	Immunization Practices Advisory Committee	SIAs	supplementary immunization activities
IQR	inter-quartile range	TCID₅₀	50% tissue culture infective dose
LMIC	low- and middle-income countries	TPP	target product profile
MAP	microarray patch	UNICEF	United Nations Children's Fund
MCV1	measles-containing vaccine first dose	VPPAG	Vaccine Presentation and Packaging Advisory Group
MCV2	measles-containing vaccine second dose	VVM	vaccine vial monitor
MMR	measles–mumps–rubella	VVM–TI	vaccine vial monitor with an integrated threshold indicator
MMRV	measles–mumps–rubella–varicella	WHO	World Health Organization
MR	measles–rubella		
NRA	national regulatory authority		
NS	needle and syringe		

1. Introduction

The potentially favourable product attributes of microarray patches (MAPs, also known as microneedle patches) render them of considerable interest for delivery of measles–rubella (MR) vaccines, particularly within low- and middle-income countries (LMICs). MAPs possess perceived operational advantages that could ultimately increase equitable coverage and facilitate vaccine administration in inaccessible areas, especially if they contain thermostable vaccine. The MR–MAP would constitute a new vaccine product, based on a potentially disruptive technology (i.e. an innovation that creates demand, eventually disrupting an existing market). For this reason, the product attributes of MR–MAPs need to be competitive with those of existing licensed MR vaccines that require a stringent end-to-end cold chain, reconstitution followed by storage in the dark at 2–8°C and administration with an auto-disable (AD) needle and syringe (NS)¹ by a trained health care worker (HCW).

In order to rationalize the product development, procurement and introduction costs that will be required for implementation, MR–MAPs should have all or some of the following properties,

in addition to comparable safety and equivalent immunogenicity with a currently prequalified (PQ) MR vaccine: less costly to deliver (thermostable, small footprint, administered with minimal instruction); easier and safer to administer (remove the need for and risks associated with reconstitution); easier to dispose of (free of sharps); and be considered acceptable by recipients and vaccinators (pain- and/or needle-free).

The following is a target product profile for a MAP presentation based on dry vaccine formulations of a live-attenuated MR vaccine. It articulates preferences for both solid coated and dissolvable microneedle formats but is not relevant for hollow microneedle arrays intended to deliver liquid or reconstituted vaccines. Delivery of combination MR vaccines has been identified as a priority public health use case for MAPs, to help achieve the measles and rubella elimination targets set by the Global Vaccine Action Plan.² The MR combination was selected for the likelihood that it will be used widely by the time that MR–MAP products are expected to be available for programmatic use in LMICs in the late 2020s.

¹ World Health Organization, United Nations Children's Fund, United Nations Population Fund. Safety of injections: WHO-UNICEF-UNFPA joint statement on the use of auto-disable syringes in immunization services. Geneva: World Health Organization; 2003.

² Global vaccine action plan 2011–2020. Geneva: World Health Organization; 2013.

2. General considerations for an MR vaccine delivered by MAPs

Indication



Current, lyophilized MR vaccine

Prophylactic vaccination against both measles and rubella virus infection of susceptible infants, children, adolescents and adults.



Guidance for MR-MAP

Same as for the currently lyophilized MR vaccine.

Notes: Measles–mumps–rubella (MMR) or measles–mumps–rubella–varicella (MMRV) vaccines are typically delivered as measles-containing vaccines for high-income countries, but these vaccine combinations are unlikely to be widely used in low-income countries.

Use-case scenarios



Current, lyophilized MR vaccine

For use in routine immunization (RI) service delivery, supplementary immunization activities (SIAs), outbreak response immunization (ORI) and vaccine stockpiling of MR vaccine.



Guidance for MR-MAP

Same as for the currently lyophilized MR vaccine. In addition, with its potential ease of use and improved thermostability profile, MR-MAP could be used in “house-to-house” campaigns and temporary or fixed post sites, potentially enlisting an expanded cadre of vaccinators.

Notes: The WHO position paper states that *all children with 2 appropriately timed doses of measles vaccine should be the standard for all national immunization programmes. Countries aiming at measles elimination should achieve ≥95% coverage with both doses equitably to all children in every district (regardless of measles-containing vaccine first dose (MCV1) coverage rates).*³

To reach this goal, countries should take all measures to increase delivery of two doses of MCV through routine services. In addition, SIAs in a variety of targeted age groups are utilized in most LMICs, in addition to vaccination offered through RI.

MR-MAPs are ideally suited for delivery through RI, SIAs and ORI due to ease of use. MR-MAPs have a strong comparative advantage in the context of weak health systems such as fragile and rural/remote settings, and nomadic and urban poor populations. In situations without health support, such as refugee camps and post-disaster communities, in which trained HCW may not be available, the potential for vaccine administration by community health volunteers becomes essential.

In certain settings, nationwide immunization campaigns may not be programmatically efficient, cost-effective or feasible (e.g. due to variations in subnational RI coverage, civil unrest, political instability, or financial constraints) and targeted subnational SIAs may be implemented to reduce the accumulation of susceptible individuals. The number of doses administered in national or subnational SIA settings is dependent on the coverage of MCV1 and measles-containing vaccines second dose (MCV2) achieved through routine immunization; thus, projections are possible for different RI performance scenarios.

³ Measles vaccines: WHO position paper. Wkly Epidemiol Rec. 2017;92(17):205–27.

Dose regimen and schedule



Current, lyophilized MR vaccine

First dose (MCV1): aged 9 months and above.

Second dose (MCV2): ideally delivered at 15–18 months, or in accordance with WHO recommended schedules.

The minimal interval between MCV1 and MCV2 is 4 weeks.³

Children as young as 6 months may receive a dose of MCV in special circumstances³ (called MCV0 and not counted toward the two recommended doses).

All commercially available live attenuated measles vaccines, either as monovalent vaccine or in combination with rubella, mumps, or varicella vaccines, or some combination of these, can be used interchangeably to protect against measles.³



Guidance for MR–MAP

Same as for the currently lyophilized MR vaccine.

MR–MAP may be used interchangeably with currently available measles and rubella vaccine.

Notes: MR–MAP requires safety data from 9 months of age, and data to demonstrate a short-interval repeat dosing (i.e. 4 weeks between doses) is acceptable providing the immunogenicity is comparable with conventional vaccines.

For more information on inclusion of additional age groups, please refer to the “Target Population” in section 3.

As for the current vaccine, MR–MAP vaccines should be able to be co-administered at different anatomical sites and with other vaccines including Japanese encephalitis, yellow fever, DTP-containing vaccines, meningococcal vaccine, hepatitis B, inactivated poliovirus, Haemophilus influenzae type b conjugate vaccine, and pneumococcal vaccines.³

Formulation



Current, lyophilized MR vaccine

Formulation contains MR vaccine as the active ingredient. Current formulation requires an end-to-end cold chain and reconstitution at the point of use.



Guidance for MR–MAP

Additional or alternative excipients/additives might be needed depending on MAP format (solid coated or dissolvable), particularly to improve thermostability and light sensitivity.

Notes: It will be imperative that MR–MAPs are compliant with relevant quality and manufacturing attributes to ensure safety, quality and efficacy as well as programmatic suitability. These will be defined during development of the product and assessed by regulatory experts to ensure license of the products.⁴ All the necessary excipients/additives/stabilizers would be evaluated as part of the final formulation, to be approved for parenteral administration and within the acceptable limits.

Presentation



Current, lyophilized MR vaccine

Current presentation consists of multi-dose vial of lyophilized MR vaccine that must be stored at 2–8°C. It is reconstituted with diluent prior to injection and stored in the dark at 2–8°C for up to 6 hours before discarding.



Guidance for MR–MAP

A single dose presentation, composed of an integrated MR–vaccine delivery device in which MR vaccine is presented as a solid coated or dissolvable microarray format.

Notes: Because of the possible dose-sparing advantages of MAPs for intradermal (ID) delivery, there is the potential for a reduced dose of virus compared to current MR doses.⁵ This will be based on confirmed non-inferiority studies of immune response with supporting evidence of virus replication after MR–MAP delivery. It should be noted, however, that to date, there are no data from studies in humans or non-human primates to suggest that ID or MAP delivery of measles or rubella vaccine results in dose-sparing.^{6–8}

⁴ Requirements for measles, mumps and rubella vaccines and combined vaccines (live). In: WHO Expert Committee on Biological Standardization: forty-third report. Geneva: World Health Organization; 1994: Annex 3 (WHO Technical Report Series, No. 840).

⁵ Moon S et al. Dose sparing and enhanced immunogenicity of inactivated rotavirus vaccine administered by skin vaccination using a microneedle patch. Vaccine.2013;doi:10.1016/j.vaccine.2012.11.027.

⁶ Cutts FT, Clements CJ, Bennett JV. Alternative routes of measles immunization: a review. Biologicals. 1997;doi:10.1006/biol.1997.0103.

⁷ Edens C, Collins ML, Goodson J L, Rota PA, Prausnitz MR. A microneedle patch containing measles vaccine is immunogenic in non-human primates. Vaccine 2015;doi:10.1016/j.vaccine.2015.02.074.

⁸ Joyce JC et al. A microneedle patch for measles and rubella vaccination is immunogenic and protective in infant rhesus macaques. J Infect Dis.

3. Generic product characteristics for an MR vaccine on solid coated or in dissolvable MAPs

Two targets (minimally acceptable and optimal) have been assigned for each of the following MR-MAP attributes, according to the current understanding and development status of this technology.

- **Minimally acceptable target:** This case represents the “should meet” requirements necessary for suitability of the MAP technology within current MR delivery settings in LMICs. If these criteria are not met, the MR-MAP technology is likely to be considered unsuitable for programmatic delivery of MR vaccine.
- **Optimal target:** This case represents the “should aim for” recommendations. The criteria represent a potential scenario that would be a significant improvement over the current presentation of lyophilized multi-dose vials that require administration by a trained HCW, resulting in a quantifiable reduction in total systems cost and increased reach of the MR-MAP vaccine.

Target population



Minimally acceptable target

Routine Immunization: infants aged from 9 months for the first dose, and at least 1 month later for the second dose.

Campaigns (i.e. SIAs and ORIs): children aged 9 months and above, adolescents and adults at risk.



Optimal target

Same as minimal, with the addition of infants aged 6–9 months, if supported by effectiveness data post-licensure.

Notes: WHO recommends that in countries with ongoing transmission in which the risk of measles mortality among infants remains high, MCV1 is administered at 9 months of age, with the routine dose of MCV2 at age 15–18 months.

WHO recommendations, unless otherwise stated, are global, and based on epidemiological analysis that may target wide age groups, such as adolescents and susceptible adults, that are beyond the current age range targeted by funding agencies. Thus, the target population is not restricted to infant/child age groups but includes all susceptible individuals above 9 months of age.

For MCV0 recommendation, see “dose regimen and schedule” in section two. Immunogenicity and safety data in 6 month-old infants immunized with MR-MAPs should be collected as part of post-licensure studies to support a licence indication in this population; however, preclinical data suggest that maternal antibodies in infant rhesus macaques cannot be overcome by MR-MAP administration.⁹

Target countries



Minimally acceptable target

All countries currently providing MR vaccines.



Optimal target

Availability and use of MR-MAP in all countries, including those where MMR and MMRV are recommended.

Notes: According to the Global Measles and Rubella Strategic Plan: 2012–2020,¹⁰ all six WHO regions have committed to measles elimination, four of which have also set rubella control or elimination targets.

Countries using MR or MMR in their national schedule should use the combined vaccine rather than measles-only formulations in all children, including those aged 6 months to <1 year.¹¹

Ideally, the MAP manufacturing platform would support production of MCV for the global market (i.e. including MMR and MMRV vaccines).

⁹ Joyce JC et al. A microneedle patch for measles and rubella vaccination is immunogenic and protective in infant rhesus macaques. J Infect Dis. 2018;doi:10.1093/infdis/jiy139.

¹⁰ Global measles and rubella strategic plan 2012–2020. Geneva: World Health Organization; 2012.

¹¹ Measles vaccines: WHO position paper. Wkly Epidemiol Rec. 2017;92(17):205–27.

Safety



Minimally acceptable target

Adverse events should be no more serious than those of the current NS delivery using the subcutaneous (SC) route.



Optimal target

Adverse events should be less frequent and less serious than those for current NS MR vaccination using the SC route.

Notes: The safety of MR–MAPs would need to be established in prelicensure safety studies in the target population for whom this product is indicated. With the current MR vaccine, adverse reactions following measles vaccination are generally mild and transient. Within 24 hours of vaccination, vaccine recipients may experience sensation and tenderness at the site of injection, which usually resolve in 2–3 days. Approximately 7–12 days after vaccination, systemic reactions occur in about 5–15% of recipients including fever of $>39^{\circ}\text{C}$ for 1–2 days. A transient rash may occur in about 2% of recipients. Adverse events, with the exception of anaphylactic reactions, are less likely to occur after MCV2 vaccination.

The application of a dissolvable MAP coated with an inactivated influenza vaccine resulted in a mild and transient reactogenicity, mostly reported as tenderness (66% recipients), erythema (40% recipients), and pruritus (82% recipients), lasting on average between 2–3 days. Of participants scored, 80% indicated they experienced no pain.¹² No serious adverse events have been recorded with MAP vaccine delivery to date, but few vaccine delivery studies have been undertaken (refer also to the reactogenicity paragraph in section 4).

Risks related to reconstitution with wrong, or incorrect use of diluents will be eliminated, and risks related to other types of operational errors should be reduced.

Immunogenicity



Minimally acceptable target

Seroconversion rates should be non-inferior to a currently prequalified SC MR vaccination when given at 9 or 10 months of age (reported seroconversion 92.2%, inter-quartile range (IQR) 84–96).¹³



Optimal target

Same as minimal target.

Notes: Antibodies to H and F measles proteins contribute to virus neutralization and are the best correlates of protection against measles virus infection. The presence of neutralizing antibodies demonstrated by appropriate standardized serologic assays and validated by WHO is considered the most reliable correlate of protection (protective level, >120 IU/mL).¹⁴ Other assays such as commercial enzyme immunoassay (EIA) kits have been used previously to measure immunogenicity.¹⁵ The choice of assay will need to be agreed with the relevant NRA.

Non-inferiority should be demonstrated in comparison to the immune response with NS administered vaccine. The 5% margin has been used previously in a non-inferiority trial of an aerosolized measles vaccine.¹⁶ However, the appropriate non-inferiority margin needs to be selected in consultation with regulatory agencies, and the established seroconversion rate of the licensed SC vaccine considered,¹³ as well as statistical analysis and clinical judgement in accordance with established protocols.^{17,18}

Frequently cited figures show that 89.6% (IQR 82–95) of children seroconvert when vaccinated at 8–9 months of age; 92.2% (IQR 59–100) seroconvert when vaccinated at 9–10 months of age; and 99% (IQR 95.7–100) of children seroconvert when vaccinated at 11–12 months of age.¹³

In a review of field studies, rubella vaccination induced a seroconversion rate of $>95\%$ after a single dose in susceptible individuals aged 12 months and older.¹⁹

¹² Rouphael NG, Paine M, Mosley R, Henry S, McAllister D V., Kalluri H, et al. The safety, immunogenicity, and acceptability of inactivated influenza vaccine delivered by microneedle patch (TIV-MNP 2015): a randomised, partly blinded, placebo-controlled, phase 1 trial. *Lancet* 2017. doi:10.1016/S0140-6736(17)30575-5.

¹³ The immunological basis for immunization: measles. Geneva: World Health Organization; 2009.

¹⁴ Chen RT et al. Measles antibody: reevaluation of protective titers. *J. Infect. Dis.* 1990;doi:10.1093/infdis/162.5.1036.

¹⁵ Wiedmann RT et al. M-M-R@II manufactured using recombinant human albumin (rHA) and M-M-R@II manufactured using human serum albumin (HSA) exhibit similar safety and immunogenicity profiles when administered as a 2-dose regimen to h. *Vaccine*. 2015;doi:10.1016/j.vaccine.2015.03.017.

¹⁶ Low N et al. A randomized, controlled trial of an aerosolized vaccine against measles. *N Engl J Med*. 2015;372:1519–29.

¹⁷ Guideline on the choice of the non-inferiority margin. Brussels: European Medicines Agency; 2005.

¹⁸ Center for Drug Evaluation and Research. Non-inferiority clinical trials to establish effectiveness: FDA guidance. Washington (DC): United States Food and Drug Administration; 2016.

¹⁹ Rubella vaccines: WHO position paper. Geneva: World Health Organization; 2011

Stability



Minimally acceptable target

Vaccine potency stability profiles should be superior to current MR vaccine stability, i.e. vaccine vial monitor 14 (VVM14) when stored at 2–8°C (24 months), and must be amenable to controlled temperature chain (CTC), i.e. a single excursion for at least 3 days at 40°C.²⁰



Optimal target

Stability profiles should have enhanced thermostability, i.e. use under CTC conditions for at least 2 months.^{21,22}

Shelf life to be longer than 24 months at 2–8°C, particularly if to be considered for stockpiling.

MR-MAP should offer improved storage conditions over current MR vaccine requirements.

Doses should be formulated to prevent risk of damage from freezing.

Notes: Stability condition definitions:

Condition	Temperature	Stability timeline minimum
Full cold chain ("shelf life")	2–8°C	24 months
CTC	At least 40°C	≥ 3 days, 2 months preferred

CTC applies to vaccines capable of tolerating at least 40°C for a minimum of 3 days prior to use, designated for use in campaign or special strategy settings, labelled with specific use conditions, and licensed for this use by the relevant regulatory authorities. Testing and validation of MR-MAP stability characteristics should be implemented according to WHO guidance on extended controlled temperature conditions (ECTC).²² Based on assessment of common supply chain structures, up to 2 months thermostability would remove reliance on cold chain equipment and logistics at health posts and stocking of vaccines at unequipped facilities. This would also offer the potential for house-to-house delivery.^{21,23} This target was proposed by immunization programme experts including IPAC members. However, the cold chain would still be required for the majority of other EPI vaccines at the current time.

Vaccine vial monitors (VVM)



Minimally acceptable target

Individual MR-MAPs should be labelled with an appropriate VVM.



Optimal target

Individual MR-MAPs should be labelled with an appropriate VVM and accompanied by a peak temperature threshold indicator (PTTI), or a VVM with an integrated threshold indicator (VVM-TI).

Notes: The creation of a new VVM type may be needed to fit the thermostability characteristics of the product if thermostability exceeds 30 days at 40°C.²⁴ VVM or VVM-TI should be placed on the primary packaging of the individual MR-MAP.

PTTI could accompany the vaccine or be placed on either primary or secondary packaging depending on the delivery strategy and microplanning.

²⁰ Controlled temperature chain: frequently asked questions. Geneva: World Health Organization; 2016 (www.who.int/immunization/programmes_systems/supply_chain/resources/CTC_FAQ_English_November_2016.pdf?ua=1, accessed 5 March 2019).

²¹ Karp CL et al. Evaluating the value proposition for improving vaccine thermostability to increase vaccine impact in low and middle-income countries. *Vaccine*. 2015;doi:10.1016/j.vaccine.2015.05.071.

²² Guidelines on the stability evaluation of vaccines for use under extended controlled temperature conditions. Geneva: World Health Organization; 2016.

²³ Kahn A-L, Kristensen D, Rao R. Extending supply chains and improving immunization coverage and equity through controlled temperature chain use of vaccines. *Vaccine*. 2017;doi:10.1016/j.vaccine.2016.10.091.

²⁴ What is VVM and how does it work? Geneva: World Health Organization; 2011.

Dosage



Minimally acceptable target

Target dosage should be defined by the quantity (i.e. virus potency on product release) of vaccine required to give a non-inferior immune response to the currently available injectable vaccine delivered in 0.5 mL by the SC route (≥ 1000 of 50% cell culture infectious dose (CCID₅₀) of each virus per dose) throughout projected shelf life of product.²⁵



Optimal target

MR-MAP should require a reduced quantity (potency on product release) of active biologic ingredient compared with amount of active biologic ingredient contained in 0.5 mL of injectable MR vaccine without reduction in induced immunogenicity throughout projected shelf life of MR-MAP product.

Notes: Endpoint dilution assays such as the 50% tissue culture infective dose (TCID₅₀) or CCID₅₀ are used to measure the infectious virus titre. These assays measure the amount of virus required to kill 50% of inoculated tissue culture cells, and are recommended in the manufacturing process and production control for measles and rubella by WHO.²⁶

WHO recommends a minimal potency for measles vaccine of 1000 viral infective units (3.0 log₁₀ TCID₅₀). Vaccines with potencies between 3.0 and 4.6 log₁₀ are considered to be standard titre vaccines, and vaccines with potencies above 4.7 log₁₀ are defined as high-titre vaccines.²⁶

Measures of potency using methods other than TCID₅₀ are in development and may be considered as a future basis for licensure, subject to approval by relevant NRAs.

²⁵ Measles vaccines: WHO position paper. Wkly Epidemiol Rec. 2017;92(17):205–27.

²⁶ Requirements for measles, mumps and rubella vaccines and combined vaccines (live). In: WHO Expert Committee on Biological Standardization: forty-third report. Geneva: World Health Organization; 1994: Annex 3 (WHO Technical Report Series, No. 840).

4. Generic product characteristics for MAPs for delivery of MR vaccines

Product registration path



Minimally acceptable target

Following licensure by a WHO listed authority, MR-MAPs should be eligible for prequalification by WHO; and should comply with its programmatic suitability for prequalification (PSPQ) guidelines.



Optimal target

Same as minimal target.

Notes: MR-MAPs would be considered a novel vaccine product and need to be evaluated for regulatory approval.

WHO PQ would be needed for UNICEF procurement of MR-MAPs. The PQ process would include discussion with a relevant WHO listed authority and the Standing Committee on PSPQ, as the MAP vaccine product would fall into the category of 'unique' characteristics.²⁷

Article 58 of Medicines for use outside the European Union,²⁸ including vaccines, aims to facilitate patient access to essential medicines in LMICs, including new or improved therapies for unmet medical needs, which are intended to prevent or treat diseases of major public health interest. The procedure combines EMA's scientific review capabilities with the local epidemiology and disease expertise of WHO and national regulators in the target countries, to provide a unique development and assessment pathway.

Experience with some analogous technologies (such as transdermal patches with small or large molecule non-vaccine medicines) may be useful for drafting initial regulatory guidelines.

Dose presentation



Minimally acceptable target

Product should be provided in an integrated (vaccine and patch combination) single dose, single-use (disposable) MAP format.



Optimal target

Same as minimal target. The size of MR-MAP should be driven by the minimal surface required to achieve the optimal antigen dose.

Notes: MR-MAPs do not require diluent nor the step of vaccine reconstitution. Relevant MAP formats are either dissolvable or vaccine coated onto a solid or porous substrate.

²⁷ Joyce JC et al. A microneedle patch for measles and rubella vaccination is immunogenic and protective in infant rhesus macaques. J Infect Dis. 2018;doi:10.1093/infdis/jiy139.

²⁸ Medicines for use outside the European Union. Brussels: European Medicines Agency; 2015 (www.ema.europa.eu/en/human-regulatory/marketing-authorisation/medicines-use-outside-european-union).

Primary and secondary packaging



Minimally acceptable target

Primary packaging (in direct contact with vaccine) should seclude patch projections to prevent intervention resulting in damage and/or contamination of projections during shipping and storage.

For patches that require storage at 2–8°C: product should be contained within suitable secondary packaging compatible with the immunization supply chain, with a cold-chain storage volume per dose no greater than a single dose vial of injectable MR vaccine (21.09 cm³).



Optimal target

Primary package requirements same as the minimal target.

For patches that require storage at 2–8°C: product should be contained within suitable secondary packaging that is compatible with the immunization supply chain and require less cold-chain storage volume per dose than a 10-dose vial of injectable MR vaccine (2.11 cm³).

Notes: Suitable secondary packaging for MR-MAPs will protect them against damage, moisture transfer, and sunlight exposure if deemed necessary. If the patches require an applicator (single use or re-usable), it should be integrated or shipped together with the patches, and ideally not in the cold chain.

Secondary packaging configuration should minimize volume, weight and the need to repackage for in-country distribution, as defined by the Vaccine Presentation and Packaging Advisory Group's (VPPAG) generic Preferred Product Profile (gPPP) for vaccines.²⁹

Current packing vial volumes per dose:³⁰

Storage volume of single dose vaccine (diluent)	Comparison MR product
2.11 cm ³ (3.14 cm ³)	10-dose glass vial
4.22 cm ³ (5.48 cm ³)	5-dose glass vial
21.09 cm ³ (12.53 cm ³)	1-dose glass vial

Note: Diluent is not stored in the cold chain but is to be kept cool. Currently, UNICEF only supplies 5- and 10-dose vials, as countries have not expressed a preference for smaller presentation volumes. For patches that do not require cold storage, comparator volume for total packaging (CTC and out of cold chain) is vaccine vial with diluent (33.62 cm³) + syringe (~60 cm³).

Secondary packaging that allows the vaccinator to visualize the number of remaining doses should be considered.

Tertiary packaging



Minimally acceptable target

Product should be contained within suitable tertiary packaging that is compatible with the existing immunization supply chain.



Optimal target

Same as minimal target.

Notes: Tertiary packaging should comply with the VPPAG's gPPP recommendations. Compatible packaging is defined as that which minimizes weight and volume and limits the need for repackaging for in-country supply chain distribution.²⁹

Labelling



Minimally acceptable target

Primary container labelling should meet recommendations outlined by the VPPAG's gPPP for vaccines, and WHO's PSPQ guidelines as outlined by the Committee on Biological Standardization (ECBS).



Optimal target

Same as minimal target.

Notes: The VPPAG's gPPP for vaccines outlines recommendations for minimal labelling content, conventions and font. If CTC is indicated, additional labelling is required (see section 3, Vaccine Vial Monitors). MAPs can be labelled on their primary package (e.g. foil pouch) as well as on the secondary packaging (e.g. carton).

²⁹ Generic preferred product profile for vaccines. Geneva: World Health Organization; 2015.

³⁰ WHO prequalified vaccines [Extranet]. Geneva: World Health Organization.

Route of administration



Minimally acceptable target

Product should be suitable for delivery to dermis or epidermis in an anatomic site that is acceptable to immunization programmes.



Optimal target

Same as minimal target.

Administration should not result in visible external serum leakage onto a disposable component.

Notes: The term ID has been used for the delivery route and target tissue for MR-MAPs. Some patches might deliver primarily ID, but others might deliver to both the epidermis and dermis. There are insufficient data to specify the optimal depth or target tissue within the skin.

Human factors (HF)



Minimally acceptable target

A summative usability evaluation must demonstrate that safety-related use errors related to the device, applicator (if needed), labelling, and training have been identified and mitigated.



Optimal target

Same as minimal target.

Notes: For intended users and the scenarios of use for MR-MAP (section 2, Use-Case Scenarios), HF of the device must be assessed in the relevant target population (children and adults) and geography. The usability engineering process in IEC 62366-1:2015 Medical devices – Part 1: Application of usability engineering to medical devices should be followed in order to verify and validate the final MR-MAP design and applicator (if required for use). This includes establishing a usability engineering file. HF principles outlined in ANSI/AAMI HE75 Human factors engineering – Design of medical devices should be adhered to. Key components of HF for an MR-MAP are described in other sections of this TPP, including labelling, packaging, user training requirements, application site, delivery time, wear time, applicator, indication of successful vaccination, and disposal.

Application



Minimally acceptable target

MAP delivery requires a single-use applicator (while maintaining compliance with packaging requirements).

Applicator (if required) should fixate to the skin and provide an impact for penetration. Minimal force to be required for the application reproducibly ensuring complete delivery.

Any patient-contact surfaces of an applicator should be disposable to prevent cross-contamination among vaccinees.



Optimal target

MAP should be able to be delivered onto the skin consistently and successfully without the need for a separate applicator.

Notes: If an applicator is required, packaging the applicator(s) and MAPs together, or integrating them, would be preferable from a usability and logistics perspective, provided this has no unacceptable negative impact on cost or cold chain storage volume.

User training requirements



Minimally acceptable target

Minimal device training is required; HCW or trained lay health worker with printed instructions should be able to administer MAP correctly after minimal training.



Optimal target

No device training required; HCW, trained lay health worker or caregiver should be able to administer MR-MAP correctly using printed pictorial instructions.

Notes: Some studies have shown that people with minimal training can apply MAPs.^{31,32} Ideally, MR-MAPs are to be used by minimally trained HCWs in routine vaccination settings or by lay health workers with printed instructions in campaign settings after training. The MR-MAP should be simple, intuitive, and easy enough to use in clinic-based or outreach vaccination settings since it is expected that MAPs will be used in both rural and urban settings (particularly in fragile contexts in low-resource settings).

Printed instructions must be made available in at least one of the recognized languages of the destination country, pre-tested for comprehension, and revised as needed.

Delivery time: time required to apply the MAP



Minimally acceptable target

For SIAs, total time for delivery of one MR-MAP should be comparable to that of one SC MR injection with NS, including time for reconstitution from a vial.

For routine settings, delivery time should be acceptable to the immunization system in question (informed by usability evidence).



Optimal target

For SIAs, total time for delivery of 10 MR-MAPs should be comparable to that of 10 SC MR injections, including time for reconstitution from a 10-dose vial.

Notes: “Total delivery time” consists of preparation and administration. Because MR-MAPs are to be used in both routine activities and SIAs, decreasing the time required to deliver each dose would have a significant impact on overall programme logistics and capacity.

Preparation and application of MAP should be comparable to the estimated time required for reconstitution and delivery of a lyophilized vaccine from a 10-dose vial in routine settings (approximately 70 seconds for reconstitution and delivery of the first dose and 20 seconds for each subsequent dose; after the assessment of the vaccinee and vaccine-related paperwork).³³

Wear time: minimal time that the MAP must be worn for the entire dose of the vaccine to be successfully delivered



Minimally acceptable target

Up to 5 minutes, under observation, before removal of MAP by HCW, trained lay health worker or caregiver.



Optimal target

Less than 1 minute, under observation, before removal of MAP by HCW, trained lay health worker or caregiver.

Notes: Specifying and monitoring acceptable “wear time” of the patch is likely to be critical to ensure effective immunization as some MAP technologies might require extended (and monitored) wear time after patch application for reliable antigen delivery: from seconds to several minutes. Wear time is determined by clinical studies to evaluate the immune response induced by the MR-MAP in the appropriate target groups; desirable and acceptable wear times have been solicited from experts in the immunization field, including members of IPAC. Operational research will be needed to determine the acceptable time in the context of MR-MAP RI and SIAs.

RI is often performed alongside other vaccinations and health interventions and so an extended wear time for the MR-MAP might not extend the total time per vaccinee. A wear time of up to 5 minutes is deemed acceptable, given the recommendation to observe vaccinees post vaccination (including those administered by NS).

Appropriate systems for verification of the 5-minute period will need to be established. As a general principle, reduction of MAP wear time should be prioritized by developers to further reduce the risk of removal by infants and toddlers. There should be minimal safety concerns associated with leaving the patch on for longer periods.

³¹ Donnelly RF et al. Hydrogel-forming microneedle arrays can be effectively inserted in skin by self-application: a pilot study centred on pharmacist intervention and a patient information leaflet. *Pharm Res.* 2014;doi:10.1007/s11095-014-1301-y.

³² Norman JJ et al. Microneedle patches: usability and acceptability for self-vaccination against influenza. *Vaccine.* 2014;doi:10.1016/j.vaccine.2014.01.076.

³³ Pentavalent Vaccine in the Uniject™ Injection System: A Time and Motion Study. Seattle WA: PATH; 2014.

Delivery: indication of a successful vaccination



Minimally acceptable target

The design should include at least one functional, auditory or visual cue during or after application of a single dose as an indicator of successful MAP application.



Optimal target

The design should include more than one functional, auditory or visual cue during or after application of a single dose as an indicator of successful MAP application.

Notes: The specific indicator for a successful vaccine delivery depends on the tolerance of the system for over- or under-application pressure and the subsequent effect on immunogenicity and adverse events. Some delivery systems might include a visual (such as patch colour change, dye transfer or intrinsic change in skin colour) or auditory or pressure cue (such as a click) for correct application. Note that the cue indicates the correct skin application (penetration) of the MAP but not necessarily confirmation of vaccine delivery, which depends on skin penetration and correct wear time.

Effectiveness of visual cues may be dependent on skin tone/ texture and end-user acceptability concerns with this method may need to be assessed.

Cue must only be able to be activated once per MAP; failure to activate the cue will indicate the MAP has already been used or the application process was faulty.

MR-MAPs that are integrated with an applicator for successful delivery are prevented from being repeatedly applied by an MR-MAP spring mechanism, i.e. once activated, they are disabled.

Delivery: application site



Minimally acceptable target

Site of application should not impede efficacy of vaccination.



Optimal target

Same as minimal target.

Notes: Whether the MR-MAP would be dislodged during application by the vaccinee (or person administering) is unknown and resistance to this should be designed into the device. Ideally, the patch and applicator should be of minimal visual interest, particularly for paediatric vaccines. Locations on infants and toddlers that are less likely to be disturbed and/or removed (such as the scapular region), and the upper arm in older children are likely to be more favourable, assuming they are not detrimental to immunogenicity. Some MAPs in development are being tested on other anatomical sites such as the wrist, forearm, shoulder and thigh.

Minimal patch size is a consideration for application to infants.

Reactogenicity



Minimally acceptable target

Local reactogenicity is expected to be more serious or frequent than that associated with SC MR vaccination, albeit with less perception of pain.



Optimal target

Same as minimal target

Notes: Visible erythema is expected to occur post vaccination with MR-MAP and may take weeks to fully resolve. The frequency and severity of such reactions should be assessed in prelicensure clinical safety trials and prior to introduction to assess vaccine acceptability, taking into consideration other benefits of the MR-MAP vaccine and the NS comparator.

Cost per immunized child



Minimally acceptable target

Incremental increase (to be decided) to cost of goods sold (COGS) should be acceptable if MAPs offer sufficient additional programmatic benefits, including reducing vaccine hesitancy, which could enable greater vaccine reach.



Optimal target

Total cost to immunize a child (COGS plus delivery) should be lower than standard SC injection delivery methods.

Notes: Any incremental increase in COGS should reasonably be able to be offset by costs associated with delivery, such as cold chain, administration and disposal, assuming acceptability to end user, resulting in the ability to reach a greater proportion of the target population, i.e. as measured by the total systems effectiveness approach.

Disposal



Minimally acceptable target

Product should allow for safe disposal as biohazard or sharps waste, at a health care facility, with similar sharps waste volume compared with NS delivery and reconstitution.



Optimal target

Product should not be considered sharps waste and thus be acceptable as biohazardous waste. It should also have lower clinical waste volumes compared with NS delivery and reconstitution.

Notes: After application, the MR-MAP will need to be disposed of, either at the immunization setting itself or, in the event of extended wear, in a community setting.

Both dissolvable and solid coated patches can carry residues of live attenuated virus and should be considered as biohazardous waste and need to be disposed of within the clinical waste system. If the MR-MAP is not capable of penetrating or lacerating the skin without an applicator, it could be considered as non-sharps waste, but consultation with appropriate regulatory and programmatic agencies will be needed to confirm this based on field data.

The degree of risk to the vaccinator and community is likely to be much less than for traditional NS application (and previous reconstitution), if the MAP and its packaging have been suitably designed or if studies demonstrate that accidental exposure is not possible. In a survey of IPAC and TechNet-21 members, both dissolvable and solid patches were considered biohazardous waste.

In line with the VPPAG's gPPP, materials used in delivery devices, primary containers, and secondary and tertiary packaging should be chosen to minimize the environmental impact of waste disposal for resource-limited systems. MAPs and disposable applicators need to be made of a material that can be safely treated and be compatible with available waste treatment methodologies in health centres (incineration and/or disinfection) without causing harm directly or indirectly to the environment and health.

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