



Vaccine Presentation and Packaging Advisory Group

Generic Preferred Product Profile for Vaccines

Version 2.1

Recommendations

31 March 2015

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Summary

This paper provides recommendations for vaccine producers and developers on presentation and packaging of new vaccines for use by public-sector programmes in developing countries (Table 1). The recommendations are based on existing evidence and were generated by the Vaccine Presentation and Packaging Advisory Group (VPPAG) through review and consensus processes that included both public-sector and vaccine-industry stakeholders. This is the second published version of the *generic Preferred Product Profile for Vaccines*. This version contains previous recommendations as well as new recommendations (e.g., on product dimensions and bar codes). The VPPAG will continue to develop new recommendations or add specificity to existing recommendations as new data and issues arise.

Table 1: Vaccine Presentation and Packaging Recommendations

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Parameter	Recommendations for Producers and Developers
Formulation	
Single- vs. multi-component vaccines	Provide vaccines, whenever possible, in “ready-to-use” presentations that do not require the mixing of components.
Heat stability	Vaccines should be stable at standard cold chain temperatures (2° to 8°C). Maximise vaccine heat stability to the extent possible to improve effectiveness, enable higher-temperature storage, and enable taking the vaccines beyond the cold chain. License and label products for higher-temperature storage immediately prior to administration, using 40°C as the target threshold temperature whenever possible.
Freeze stability	Formulate vaccines so that they will not be damaged by freezing, where feasible.
Antimicrobial preservatives	Include preservative in multi-dose vials of injectable vaccines, where feasible, to allow safe use of opened containers in subsequent sessions.
Primary Container Presentation	
Product format	Provide vaccines in formats to minimise the (1) number of steps and (2) potential for error during preparation and administration.
Container type	Except for separately packed diluents, vial-filled presentations are strongly preferred over ampoule-filled presentations.

Parameter	Recommendations for Producers and Developers
Prefilled injection systems	<p>Vaccines packaged in prefilled injection systems should have both space-saving and auto-disabling features (i.e., be compact, prefilled auto-disable [CPAD] injection systems).</p> <p>CPAD injection systems offer advantages and savings over vials and syringes in terms of dose accuracy, ease and speed of preparation, and decreased volume and weight that should be considered against any additional product costs and used to determine appropriate vaccine applications.</p>
Optimal number of doses per primary container	<p>Minimise doses per container for routine vaccines that cannot be used on subsequent immunization days after the container is opened.</p>
Primary container dimensions	<p><i>For vials</i></p> <ul style="list-style-type: none"> – Vaccines in presentations from one to five 0.5-ml doses are recommended to be filled in a “2R” vial conforming to ISO (International Organization for Standardization) 8362 dimensions. Where technically possible, and if the dose size permits, manufacturers are encouraged to reduce the height of the vial from the current standard of 3.5 cm to 3.1 cm or less, both for reasons of volume reduction and dimensional harmonization. – It is recommended that vaccines in presentations of six to ten 0.5-ml doses be filled in a “4R” vial conforming to ISO 8362 dimensions. – It is recommended that vaccines in presentations of twenty 0.5-ml doses be filled in a “10R” vial conforming to ISO 8362 dimensions. – It is recommended that for vaccines with a dose size less than 0.5 ml, the most compact of these three vial sizes be used, depending on the number of doses in the presentation. – It is recommended that for vaccines with a dose size greater than 0.5 ml, the most compact of these three vial sizes be used, depending on the number of doses in the presentation. <p>Where possible, if changes are to be made to an existing prequalified vaccine product (e.g., changes in formulation or production that require regulatory resubmission), it is recommended that manufacturers select a primary container size that conforms to the relevant recommendation set out above.</p>

Parameter	Recommendations for Producers and Developers
Packaging	
Secondary carton dimensions	<p>Minimise volume and weight of secondary packaging and limit the need for repackaging for in-country supply chain distribution.</p> <p><i>Secondary cartons for vials</i></p> <p>It is recommended that secondary cartons should contain vials in one or more of the following formats:</p> <ul style="list-style-type: none"> - 10 vials in an array of 5 x 2 vials. - 25 vials in an array of 5 x 5 vials. - 50 vials in an array of 5 x 10 vials. - 100 vials in an array of 10 x 10 vials. <p>It is recommended that vials be packed in rectangular arrays, based on the above recommendations. The dimensions of the secondary carton should be the minimum necessary to accommodate the vials and the package insert, together with any internal dividers and subject to any necessary tolerances.</p> <p>Appropriate justification should be provided if the secondary carton arrangements differ from the above recommendations.</p>
Tertiary carton dimensions	<p>Minimise volume and weight of tertiary packaging and limit the need for repackaging for in-country supply chain distribution.</p> <p><i>Tertiary cartons for vials</i></p> <ul style="list-style-type: none"> - It is recommended that secondary cartons be packed into fibreboard tertiary cartons. The dimensions of the tertiary carton should be the minimum necessary to accommodate the chosen number of secondary cartons, subject to necessary tolerances. - It is recommended that the total number of vials packed in a tertiary carton be a multiple of 100 vials so that the contents are easy to count. - It is recommended that the gross weight of a tertiary carton not exceed 25 kg and should preferably be no greater than 10 kg. - It is recommended that the width dimension of the tertiary carton not exceed 45 cm. - It is recommended that tertiary carton dimensions be selected so that cartons can be efficiently stacked on standard ISO pallets with dimensions of 1.2 m x 0.8 m and/or 1.0 m x 1.2 m without overhanging the pallet footprint. - Tertiary packaging should be properly qualified to support the anticipated load. <p>Appropriate justification should be provided if the tertiary cartons differ from the above recommendations.</p>

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Parameter	Recommendations for Producers and Developers
Materials, including the primary container and delivery device	<p>Use materials for delivery devices, primary containers, and secondary and tertiary packaging that minimise the environmental impact of waste disposal for resource-limited systems.</p> <p>Optimize source reduction, reuse (where applicable), recovery, and appropriate and safe end-of-life handling using industry-wide standards (e.g., ISO 18601).</p> <p>Reduce volume of insulated packaging material required by maximising the heat stability of vaccines.</p> <p>It is recommended that secondary carton materials, including printing and attached labels, be resistant to long-term exposure to condensation.</p> <p>It is recommended that tertiary carton materials, including printing and attached labels, not be damaged by long-term exposure to relative humidity (RH) levels at the International Conference of Harmonization (ICH) standard of 75% RH.</p>
<i>Labelling</i>	
Primary container labels	<p>Minimum requirements could include: Product name, manufacturer, expiry date, batch/lot number, dose volume, and number of doses in the container. Storage conditions and method of administration might also be considered.</p> <p>Use of standard, generic names could create consistency and improve correct product use. Brand names could also be included.</p> <p>The format of the expiry date: An all numeric format: MM-YYYY should be the standard.^a</p> <p>A minimum font size and type should be required for label legibility.</p> <p>Specifying a minimum viewing area as part of vaccine labelling specifications could help to ensure the ability of health workers to view the vial or container contents (for example, to conduct the shake test or ensure that a vial has been fully reconstituted). The minimum viewing area may differ by type of vaccine and the number of doses per vial.</p>
Vaccine vial monitors (VVMs)	<p>Include VVMs on all vaccines, as recommended by the World Health Organization (WHO) and the United Nations Children’s Fund (UNICEF).</p>

^a Meaning that the product expires at the end of the month.

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Parameter	Recommendations for Producers and Developers
Secondary carton and tertiary packaging labels	<p>It is recommended that secondary and tertiary cartons be labelled on at least two opposing faces, with a preference for three opposing faces, following the design principles set out in <i>Guidelines for the Labelling of Vaccines: Proposed Amendments to the TRS 822 Document & Requirements for Pre-Qualified Products</i>. The printed content can consist of static information only. Dynamically applied information such as bar codes and serialization data may be on one face only.</p>
Bar codes	<p>Bar codes are recommended on all packaging levels used by manufacturers, with the exception of primary packaging, and should conform to GS1 standards and associated specifications.</p> <p>Bar code data should include the Global Trade Item Number (GTIN), lot number, and expiry date.</p>
Package inserts	<p>It is recommended that all package inserts should be supplied in the standard WHO format. Electronic versions, translated into the appropriate language for the procuring agency (e.g., English, French, Portuguese, and Russian for UNICEF and English and Spanish for the Pan American Health Organization), should be made available for download on the WHO vaccine database.</p> <p>In addition to the package insert, it is recommended that a simplified single-page fact sheet should be made available for download on the WHO vaccine database so that countries can translate, compile, and distribute the information to health workers.</p>

Glossary

Cold chain	Equipment, transportation, and logistical mechanisms used to keep and transport vaccines at refrigerated temperatures (2° to 8°C) from the point of manufacture to the point of use. A few vaccines are stored at frozen temperatures (e.g., -20°C) within portions of the cold chain.
Compact prefilled auto-disable injection system	A prefilled injection device with features to prevent reuse and minimise the space required for storage and shipping.
Controlled temperature chain	Storage and transport of certain heat-stable vaccines at temperatures above the traditional 2° to 8°C range for limited periods of time prior to administration, under monitored and controlled conditions, and, as appropriate, to the stability of the antigen.
Developing countries	Countries identified by the World Bank as having low-income, lower-middle-income, or upper-middle-income economies. ¹
Freeze protection formulation	A method to formulate vaccines (e.g., those containing aluminium adjuvant) that protects them from freeze damage. See the “Freeze stability” section for details.
Freezing	The conversion of a liquid to a solid due to exposure to cold. A vaccine’s freezing point is typically at a temperature below 0°C and varies by vaccine type and brand.
Generic preferred product profile	Recommendations for vaccine developers and producers regarding formulation, presentation, labelling, and packaging attributes for new vaccines intended for use in developing countries.
Global Trade Item Number	An identifier for trade items developed by GS1 to look up product information (e.g., by inputting the number by scanning a bar code).
Packed volume	The volume of the primary container and its secondary packaging. ²
Primary container	The immediate vial, ampoule, prefilled syringe, dropper, dispenser, or other receptacle in direct contact with the vaccine as distributed for sale (also known as the “first level” or “final” container). ²
Package insert	Folded instruction leaflet, generally packed inside the secondary carton.
Secondary packaging	The intermediate or second level of packaging that holds the primary container(s) (e.g., cartons containing one or more vials or prefilled syringes of vaccine). ² This is generally the relevant volume for calculation of storage requirements.

Session	A gathering of individuals for immunization at a specific site and at a specified time.
Shake test	A means for assessing whether an adsorbed vaccine has been damaged by freezing. ^{3,4}
Tertiary packaging	The third level of packaging; the outer box or the shipping box containing multiple secondary packages. ²
Vaccine vial monitor	A label containing a heat-sensitive material that is placed on a primary vaccine container to register cumulative heat exposure over time.
Vial clip	A device that holds a primary container of vaccine together with other required components of the vaccine product. For example, a plastic connector that holds a vial of lyophilised vaccine together with a corresponding vial of diluent.

Acronyms

CPAD	compact prefilled auto-disable (injection system)
CTC	controlled temperature chain
DCVMN	Developing Countries Vaccine Manufacturers Network
DTP vaccine	diphtheria-tetanus-pertussis vaccine
gPPP	generic preferred product profile
GTIN	Global Trade Item Number
Hep B vaccine	hepatitis B vaccine
Hib vaccine	<i>Haemophilus influenzae</i> type b vaccine
HPV vaccine	human papillomavirus vaccine
ICH	International Conference of Harmonization
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
ISO	International Organization for Standardization
MDVP	multi-dose vial policy (of the World Health Organization)
PQS	Performance, Quality and Safety (of the World Health Organization)
SKU	stock keeping unit
UNICEF	United Nations Children's Fund
VPAT	Vaccine Packaging Assessment Tool
VPPAG	Vaccine Presentation and Packaging Advisory Group
VVM	vaccine vial monitor
WHO	World Health Organization

Purpose

The purpose of this document is to provide guidance to the vaccine industry and other vaccine development groups on preferred presentations and packaging for vaccines intended for public-sector use in developing countries.

Background

The Vaccine Presentation and Packaging Advisory Group (VPPAG) was established in 2007 by Gavi, the Vaccine Alliance (formerly called the Global Alliance for Vaccines and Immunization), to provide advice on preferred presentations for new pneumococcal and rotavirus vaccines. In 2008, the World Health Organization (WHO) took over responsibility for the VPPAG and extended its mandate beyond Gavi-supported vaccines.^b See Annex 1 for background information on VPPAG.

Recognizing the need for early guidance to vaccine developers on vaccine presentation and packaging issues, the VPPAG has developed this generic preferred product profile (gPPP) as a reference document for vaccines in development. The gPPP parameters defined in this paper are based on current evidence. The VPPAG will continue to add new recommendations and update existing recommendations as new data and issues arise.

The gPPP does not replace the need to develop preferred product profiles for specific vaccines but highlights key issues and can serve as a starting point for dialogue between industry and public health agencies during the early phases of product development.

Context

Immunization programme context

Immunization programmes in developing countries deliver vaccines in resource-constrained environments that differ from the industrialized country settings for which most new vaccines are initially developed. The establishment of a cold chain in developing countries in the 1980s enabled the distribution of the traditional childhood vaccines to nearly 80% of children worldwide.⁵ However, the cold chain does not work perfectly, and exposure of vaccines to both hot and freezing temperatures frequently occurs.⁶⁻⁹ For example, intermittent availability of power to operate refrigerators and cold rooms is a common constraint as is the limited availability of parts for equipment repair and skilled/motivated staff members to maintain the equipment.¹⁰

In developing countries, childhood vaccines have traditionally been provided in multi-dose (most often 10- and 20-dose) presentations that generally require only 3 cm³ or less of storage space per dose.² The cold chain capacity to store the additional volume of new vaccines varies by country but is generally limited.

^b See terms of reference on VPPAG site: <http://www.who.int/immunization/policy/committees/vppag/en/>.



Since the launch of the Bill & Melinda Gates Foundation's support for immunization and Gavi's creation in 2000 at Davos, Switzerland, the focus has been on accelerating access to needed vaccines for all the world's children. But the cold chain and logistics infrastructure of the previous era is insufficient in terms of capacity and performance. Many of the new vaccines supported by Gavi come with much higher packed volumes than the previous generation of vaccines. These new vaccines typically come in single- or low-dose presentations.¹¹ Some prefilled syringe presentations have total volumes of up to 112 cm³ per dose and also lack an auto-disable feature so could not be accepted for prequalification by WHO or supported by Gavi. In comparison, all doses of the six original vaccines in common use since the 1980s have a combined volume of about 43 cm³.^{12,13}

Many developing countries are facing critical shortages in their workforces. The lack of available and adequately trained health workers is a common problem, especially in remote areas. The addition of new vaccines and vaccine presentations into these already stretched systems can be particularly challenging. Vaccine management practices are often not optimal—leading to stock shortages and over stocking. These conditions may lead to requests for earlier shipments or postponement of shipments to subsidiary levels. There are also issues of errors in preparing, administering, and disposing of vaccines, which are a greater challenge in developing than in industrialized countries. Products produced for developing-country markets are likely to be more appropriate when they are well-labelled, have inherent safety features, and are intuitive and easy to prepare and administer.

Vaccine-specific immunization strategies

The immunization strategies used for a particular vaccine may impact its preferred profile in a number of ways. Most important are the distribution of session sizes that influence the wastage and hence the optimal number of doses per primary container. For example, the birth dose of hepatitis B (Hep B) vaccine, which should be given within 24 hours of birth, requires having a single dose of vaccine for each newborn when the dose is delivered in home settings; in contrast, a measles vaccine given in a mass campaign requires many doses for a single session and so can be configured in multi-dose vials without risk of much wastage.

The type and training of the vaccinator, the age(s) of the target group(s), and the diversity of strategies (e.g., measles vaccine is given routinely as well as in campaigns) can also impact the ideal preferred product profile for each vaccine.

Vaccine characteristics and constraints

The VPPAG recognizes that vaccines may have inherent technical constraints that prevent the achievement of some of the recommended product characteristics (e.g., measles vaccines must be lyophilised for sufficient stability, and rotavirus vaccines require a large bulk of buffer liquid to be stable). Additionally, there may be a need to trade off one parameter versus another (e.g., keeping all constituents of a multi-component vaccine together to avoid errors versus the benefit of reducing cold chain storage volumes by removing diluent from the cold chain). These trade-offs are best assessed and dealt with during the development of preferred product profiles for specific vaccines, taking into account the specific contexts in which the vaccine will be used.

Product cost

Many improvements to vaccines and their associated development and regulatory activities are costly and take time, and some improvements are influenced by factors internal to vaccine producers. For example, a decision to add a new filling line must take into consideration the ability to fully utilize the filling line for current and future products. Ideally, a specific preferred product profile will be created during the development of a new vaccine in an attempt to sort through the trade-offs between features and cost and thus promulgate product specifications that are realistic and cost-effective. The VPPAG serves as one forum to develop such profiles and to advance dialogue between industry and public-sector agencies, taking into consideration both the technical constraints of vaccine science and manufacturing, and the context and strategies of immunization programmes. Such dialogue can help ensure that there is appropriate justification and a market for sought-after improvements.

Innovation

Finally, these recommendations are largely based on knowledge about existing vaccines and technologies. They are not meant to restrict efforts to innovate nor to discourage new methods of safely and effectively delivering immunizations in developing countries.

Vaccine presentation and packaging recommendations

Generic recommendations based on existing evidence are described below for the categories of vaccine formulation, primary container presentation, labelling, and packaging.

Vaccine formulation

Single- vs. multi-component vaccines

Vaccines that are “ready-to-use” and do not require mixing of components are preferred for reasons of safety, convenience, and efficiency. Reducing the workload for vaccinators and preventing errors are especially important in resource-poor settings. Errors can include omission of a component of a multi-component vaccine (e.g., not combining lyophilised *Haemophilus influenzae* type b [Hib] vaccine with the liquid diphtheria-tetanus-pertussis [DTP]-Hep B component of pentavalent vaccine), using the wrong diluent for mixing (e.g., deaths have occurred when insulin was used mistakenly), contamination due to unsterile technique in preparation, and keeping reconstituted vaccines without preservative for more than six hours (e.g., deaths due to toxic shock have occurred when such vaccines have been injected).^{14–19}

The VPPAG recognizes that some vaccines may require the mixing of components for technical reasons. For example, some vaccines must be lyophilised to be sufficiently thermostable for a reasonable shelf life. However, there have been some notable success stories with both rotavirus and

pentavalent vaccines in which manufacturers responded to user concerns or preferences and converted lyophilised products to all-liquid presentations.

Recommendation

Provide vaccines, whenever possible, in “ready-to-use” presentations that do not require the mixing of components.

Heat stability

Vaccines used in developing-country settings need to be as heat stable as possible, and heat tolerance is of particular importance where electricity commonly fails and where vaccines are taken to distant locations via outreach, mobile clinic, or campaign strategies. At minimum, a vaccine should be stable for its entire shelf life if stored at standard cold chain temperatures (2° to 8°C). Most peripheral health centers do not have freezers and are unable to handle vaccines that must be frozen.

Enhancing vaccine stability can help to expand immunization coverage, ensure that administered vaccines are fully potent, and reduce vaccine wastage (when temperature excursions occur or are suspected). VPPAG supports the optimization of heat stability during early vaccine development to minimise the impact on product development timelines and costs. However, as with other product profile parameters, there will likely be trade-offs that need to be evaluated and prioritised between heat stability and other aspects of vaccine formulation—such as the choice between ready-to-use, but less heat-stable, liquid formulations versus more heat-stable, lyophilised formulations.

Use of certain heat-stable vaccines in a controlled temperature chain (CTC) allows these vaccines to be stored and/or transported at temperatures above the traditional 2° to 8°C range for limited periods of time prior to administration, under monitored and controlled conditions, and as appropriate to the stability of the antigen. WHO CTC guidelines recommend that vaccines used in a CTC are labelled with a vaccine vial monitor (VVM) to measure cumulative exposure to heat and that a threshold heat indicator travels with the vaccines to determine whether the vaccines have been exposed above the peak temperature limit. The CTC approach builds on a long history of taking vaccines beyond the cold chain to achieve specific public health goals such as outreach efforts toward polio eradication and Hep B vaccine birth dose administration in homes in parts of Asia.^{20–23} More recently, the CTC approach has been used in meningitis vaccination campaigns in parts of sub-Saharan Africa.²²

WHO and partners have carried out extensive work in recent years to advance the evidence base on CTC use of vaccines, including exploring and defining regulatory pathways to license specific vaccines for higher-temperature storage. As part of this effort, WHO has leveraged its regulatory collaborating centers initiative in order to obtain clarity and consensus on the processes for qualifying vaccines for CTC use (e.g., stability study design, appropriate assays, and statistical methods).²⁴ A target temperature limit of 40°C was agreed to be reasonable during recent consultations, and this is reflected in the current VPPAG recommendations.

The first vaccine prequalified by WHO that was labelled for CTC use was MenAfriVac®, a meningitis A vaccine. As an example, its label states: “The MenAfriVac® vaccine can be stored under a controlled temperature chain (CTC) up to 40°C for not more than four days immediately prior to administration, provided that the vaccine has not reached its expiry date and the vaccine vial monitor is still valid. It can be kept at up to 40°C for up to six hours after reconstitution.”^{25,26}

Qualification and labelling of additional vaccines for higher-temperature storage is encouraged—both to provide additional information to those managing vaccines when cold chain breaks occur and to

increase immunization coverage and ease logistics for vaccines given in campaigns, such as MenAfriVac® or cholera vaccines, or those that are provided via outreach strategies, such as delivery of human papillomavirus vaccine in schools or delivery of tetanus toxoid to women or Hep B vaccine to newborns in their homes.

Recommendation

Vaccines should be stable at standard cold chain temperatures (2° to 8°C).

Maximise vaccine heat stability to the extent possible to improve effectiveness, enable higher-temperature storage, and enable taking the vaccines beyond the cold chain.

License and label products for higher-temperature storage immediately prior to administration, using 40°C as the target threshold temperature whenever possible.

Freeze stability

Exposure of freeze-sensitive vaccines to freezing temperatures is a frequent occurrence in nearly all studies assessing cold chain performance in both developing and industrialized countries. Freezing temperatures appear to be more common during transport than storage but have been documented in both modes.^{6,27} In addition, some countries experience severe ambient temperature conditions that can result in the freezing of vaccines. There is some evidence in Mongolia of this leading to use of sub-potent Hep B vaccine; however, data remain limited on the clinical impact of use of frozen vaccines.²⁸

A novel formulation method has been proposed to prevent damage to freeze-sensitive vaccines containing aluminium adjuvant.²⁹ PATH is currently working with vaccine producers to test the applicability of the method to Hep B and DTP-Hep B-Hib vaccines in preclinical and upcoming clinical studies. The method involves the inclusion of a low-cost and commonly used excipient to vaccine formulations and has been placed in the public domain for availability to all vaccine manufacturers.³⁰

Recommendation

Formulate vaccines so that they will not be damaged by freezing, where feasible.

Antimicrobial preservatives

For some vaccines (e.g., measles and bacillus Calmette-Guérin vaccine), an antimicrobial preservative is not an option. For other injectable vaccines (e.g., diphtheria, tetanus toxoid, and Hep B), the presence of adequate quantities of preservatives in multi-dose vials improves safety by inhibiting growth of potentially harmful contaminants introduced when extracting vaccine from the primary container. Appropriate preservative enables safe use of opened vials in later sessions to minimise vaccine wastage. Many developing-country vaccine manufacturers produce multi-dose vials of liquid vaccines (e.g., DTP and Hep B) with preservatives to meet the needs of their markets for affordable products.

There are definite trends for first-generation vaccines for industrialized markets to be in fully liquid single- or low-dose (e.g., two-dose pneumococcal or human papillomavirus [HPV] vaccine) presentations without preservatives. Production of product without preservatives requires good manufacturing practices in aseptic production. Many customers prefer single-dose presentations for expensive vaccines to minimise vaccine wastage. Regulatory authorities and customer perceptions

have also been strongly encouraging vaccine manufacturers serving industrialized markets to develop and implement thiomersal-free vaccine formulations. Reformulation of these vaccines to include preservative for developing-country markets would be costly and time-consuming and, for technical reasons, may not be possible. In addition, manufacturers are concerned about the logistics and associated costs of having different products—with and without preservative—for different markets and the potential for perceptions of a double standard. One vaccine manufacturer from an industrialized country has received WHO prequalification for both HPV and pneumococcal two-dose liquid vaccine products without preservative meant for developing-country markets.^{31,32} A fully liquid two-dose product without preservative has the desirable attribute of taking less cold chain space and being potentially less expensive per dose than product in a single-dose vial. However, it represents a new presentation for liquid vaccines for developing countries. As a result, such novel presentations require explicit immunization programme guidelines and training materials to ensure that health workers understand proper vaccine-handling procedures and comply strictly to the recommendations as outlined in the WHO multi-dose vial policy (MDVP).¹⁵ The current WHO MDVP promulgates guidelines for which vaccines in opened multi-dose vials may be kept for use in later sessions and which need to be discarded at the end of the session or within six hours, whichever comes first. WHO recently updated the MDVP to include information on the numerous new products that are being developed and introduced into immunization programmes.¹⁵

For the time being, preservatives in multi-dose vials continue to play an important role in developing countries by preventing microbial growth, which, in turn, provides the benefits of minimising vaccine wastage, lowering costs, improving safety, and reducing cold chain volumes. If multi-dose products are being specifically developed for these markets, then consideration should be given to the benefits of preservatives.

Recommendation

Include preservative in multi-dose vials of injectable vaccines, where feasible, to allow safe use of opened containers in subsequent sessions.

Primary container presentation

Product format

Given the expected influx of new vaccine products that will require new methods for storage, transport, preparation, handling, and administration, it will become increasingly important over the next 10 to 20 years to ensure that products are as intuitive to handle and use as possible. Safety features should be built in and opportunities for error must be minimised in new vaccine product formats.

Recommendation

Provide vaccines in formats to minimise the (1) number of steps and (2) potential for error during preparation and administration.

Container type

In general, vials are preferred over ampoules for vaccines and diluents. Ampoules are more prone to break and are more difficult to open.³³ In addition, the VPPAG recommendations to harmonize primary container dimensions (see the “Primary Container Dimensions” section) are more easily

implemented if vials are used instead of ampoules. ISO (International Organization for Standardization)-compliant ampoule dimensions share no common dimensions with the ISO vial standards proposed in this document. In addition, if bundling of multi-component primary containers is pursued, the primary containers are more easily bundled together if they are of the same dimensions.^{34,35}

Recommendation

Except for separately packed diluents, vial-filled presentations are strongly preferred over ampoule-filled presentations.

Prefilled injection systems

Vaccines in prefilled syringes are increasingly used in industrialized countries, but many are not suitable for developing countries because they do not have auto-disabling features to prevent inadvertent or intentional unsterile reuse and are generally too bulky to be integrated easily into existing cold chain systems. For example, a 0.5-ml single-dose, prefilled, glass, disposable syringe can require as much as 60 cm³ per dose of cold chain volume compared to 12 cm³ to 18 cm³ per dose for single-dose vials of liquid vaccine.² Also, the glass syringe can present additional challenges to safe disposal.

Prefilled injection systems that are specifically designed to meet the needs of developing-country markets are now referred to as compact prefilled auto-disable (CPAD) injection systems. Their programmatic advantages relate to ease of use and speed of preparation, improved safety due to avoidance of errors (ready-to-use) and prevention of cross contamination, decreased vaccine wastage due to their single-dose format, decreased transport and disposal volume and weight, and simplification of logistics (dose and delivery system bundled together).¹⁴ To date, there is only one such product on the market—the Uniject™ prefilled injection system. The Uniject has been positively evaluated for delivery of Hep B vaccine birth doses and tetanus toxoid in campaigns and outreach settings.^{36–39} Based on these positive experiences, VPPAG has previously recommended CPAD injection systems as an appropriate option for both pneumococcal conjugate and HPV vaccines.^{40,41}

A pentavalent vaccine in Uniject has now been prequalified by WHO.⁴² While previous vaccines in Uniject systems required 25 cm³ to 30 cm³ per dose of storage space when packaged in a sealed foil pouch, the pentavalent vaccine in Uniject incorporates a novel secondary packaging design to minimise the storage volume of the Uniject™ CPAD injection system to equal the volume per dose of a single-dose vial format (15.2 cm³ for CPAD vs. 9.7 cm³ to 26.1 cm³ for single-dose vial).⁴³

Recommendation

Vaccines packaged in prefilled injection systems should have both space-saving and auto-disabling features (i.e., be compact, prefilled auto-disable [CPAD] injection systems).

CPAD injection systems offer advantages and savings over vials and syringes in terms of dose accuracy, ease and speed of preparation, and decreased volume and weight that should be considered against any additional product costs and used to determine appropriate vaccine applications.

Integration of vaccine and delivery device

Prefilled syringes are one example of integration of vaccine and delivery device. Vaccines delivered by other methods or routes, such as microneedles for intradermal delivery or jet injectors, can also be presented in prefilled devices containing a single dose.⁴⁴ As with prefilled syringes, the benefits of convenience, efficiency, and safety of other prefilled vaccine presentations will need to be weighed against their overall costs to immunization programs.

Optimal number of doses per primary container

Supplying vaccines in single-dose containers is a safe option and one that does not require divergence of product lines—with and without preservative—for manufacturers. Single-dose containers offer higher levels of safety as well as minimise vaccine wastage. Some new vaccine products require extremely rapid use (e.g., within minutes) after mixing or thawing and may require special recommendations if they cannot be used within the current six-hour guidelines.

The cost of vaccine wastage is higher with new vaccines as they are relatively more expensive than traditional vaccines. In general, wastage increases with more doses per vial, although this is less true if the opened vial can be used in subsequent sessions and the recipient country has implemented a policy to allow such use. On the other hand, single-dose vials require more storage space per dose and are significantly more expensive to fill and finish, and hence increase costs compared to multi-dose vials. The unresolved question is: at what point do these countervailing economic forces balance to indicate the optimal, most cost-effective number of doses per vial?

A key determinant of opened-vial wastage is the distribution of immunization session sizes, which is related to the immunization strategy. The session size is a function of:

- Target population size (and number of health facilities/workers delivering vaccine).
- Frequency of delivery.
- Number of doses in the immunization schedule.
- Delivery strategy.

The cost of expansion of the cold chain to accommodate a new vaccine will vary by country and by level of the system. There are also differences between the impact on capital costs for purchase of equipment, running costs for that equipment, and transport. In some settings there is plenty of spare capacity and in others spare capacity is very limited. Cold chain costs are therefore hard to estimate in generic terms, and some assessment is needed. The Malaria Vaccine Initiative has created the Vaccine Presentation Assessment Tool (VPAT), which attempts to model the effects of different vaccine presentations on immunization programme costs, including cold chain costs. The VPPAG has reviewed and updated this tool and will continue to monitor studies to identify immunization programme costs and analyse optimal number of doses per container for new vaccines to see if they might be useful in development of generic guidelines.

Recommendation

Minimise doses per container for routine vaccines that cannot be used on subsequent immunization days after the container is opened.

Primary container dimensions

Cold chain capacity is a major constraint in most developing-country settings. The volume per dose for a particular product has a direct impact on transport, storage, and disposal costs. There is a

continuing drive to reduce the physical bulk of vaccines for developing-country immunization programmes. Reducing volume per dose enables countries to add new vaccines to their schedules while limiting the additional burden on cold chain and logistics systems.

To date, the only standards for vaccine product dimensions have been the WHO norms for maximum packed volume per dose.² However, reducing volume per dose is only a partial determinant of optimum use of cold chain volume because the widely varying dimensions of existing vaccine packs lead to inefficiencies in the use of available storage and transport space. A VPPAG subgroup undertook detailed analyses of vaccine packaging dimensions and options to establish new standards for primary containers and secondary and tertiary cartons, which address this issue and point the way to more rational and efficient packaging.^{45,46} The work took place over two years—September 2012 to September 2014—and involved engagement of country-level stakeholders as well as the entire memberships of the IFPMA (International Federation of Pharmaceutical Manufacturers & Associations) and DCVMN (Developing Countries Vaccine Manufacturers' Network), taking into consideration public-sector constraints and preferences, as well as industry manufacturing and operational constraints, which determine initial packaging choices and identify barriers to changes. Modelling work was also undertaken to exemplify the impacts of current and proposed packaging on cold chain equipment utilization. The results of this work are the primary container and secondary and tertiary carton recommendations that follow.

The recommendations for vaccine vials are meant to ensure a limited number of primary container diameters and heights. In turn, this makes it possible to standardize the dimensions of secondary and tertiary cartons. Standard carton dimensions will help countries to make efficient use of valuable cold chain capacity. When there is a major change in the formulation or production of an existing vaccine, the opportunity should be taken to conform to the recommendations for the reasons stated above.

Recommendation

For vials

- Vaccines in presentations from one to five 0.5-ml doses are recommended to be filled in a “2R” vial conforming to ISO 8362 dimensions. Where technically possible, and if the dose size permits, manufacturers are encouraged to reduce the height of the vial from the current standard of 3.5 cm to 3.1 cm or less, both for reasons of volume reduction and dimensional harmonization.
- It is recommended that vaccines in presentations of six to ten 0.5-ml doses be filled in a “4R” vial conforming to ISO 8362 dimensions.
- It is recommended that vaccines in presentations of twenty 0.5-ml doses be filled in a “10R” vial conforming to ISO 8362 dimensions.
- It is recommended that for vaccines with a dose size less than 0.5 ml, the most compact of these three vial sizes be used, depending on the number of doses in the presentation.
- It is recommended that for vaccines with a dose size greater than 0.5 ml, the most compact of these three vial sizes be used, depending on the number of doses in the presentation.

Where possible, if changes are to be made to an existing prequalified vaccine product (e.g., changes in formulation or production that require regulatory resubmission), it is recommended that manufacturers select a primary container size that conforms to the relevant recommendation set out above.

Packaging

Secondary carton dimensions

Vaccines should be packed to minimise volumes and weight for transport and storage. The number of primary containers per secondary pack should take into consideration the need for in-country redistribution. WHO guidelines provide maximum per-dose packed volumes for some existing vaccines in secondary packaging and grossing factors in tertiary packaging.² Although assumptions can be made based on similarities with existing vaccines, guidance has not been provided in the past for new and upcoming vaccines. Generic figures for all types of vaccines are needed to provide guidance to vaccine producers for future products and to immunization programme managers for cold chain and logistics planning.

The VPPAG therefore proposes that an optimal number of primary containers per secondary packaging should be established to minimise the per-dose packed volume and the complexity of repackaging for in-country vaccine distribution. For stock management purposes, secondary cartons should be in formats that are easy to count. Rectangular vial arrays based on a five-vial unit and standardized vial diameters and heights provide the opportunity for dimensional harmonization between products. This in turn can lead to better utilization of cold chain storage volume.

Recommendation

Minimise volume and weight of secondary packaging and limit the need for repackaging for in-country supply chain distribution.

Secondary cartons for vials

It is recommended that secondary cartons should contain vials in one or more of the following formats:

- 10 vials in an array of 5 x 2 vials.
- 25 vials in an array of 5 x 5 vials.
- 50 vials in an array of 5 x 10 vials.
- 100 vials in an array of 10 x 10 vials.

It is recommended that vials be packed in rectangular arrays, based on the above recommendations. The dimensions of the secondary carton should be the minimum necessary to accommodate the vials and the package insert, together with any internal dividers and subject to any necessary tolerances.

Appropriate justification should be provided if the secondary carton arrangements differ from the above recommendations.

Tertiary carton dimensions

The rationale for the tertiary carton recommendations is based on the following:

- For stock management purposes, in cold rooms and freezer rooms, a tertiary carton is a more robust and convenient stock keeping unit (SKU) than a secondary carton.
- For stock management purposes, tertiary cartons should be in formats that are easy to count.
- The maximum weight of a tertiary carton should allow for safe lifting by a single person in accordance with European Economic Community (EEC) Council Directive 90/269/EEC.^{47,48}

- Shelf widths in cold rooms and freezer rooms are typically between 45 cm and 60 cm.^c
- Larger vaccine stores increasingly use pallet standing or pallet racking.

Recommendation

Minimise volume and weight of tertiary packaging and limit the need for repackaging for in-country supply chain distribution.

Tertiary cartons for vials

- It is recommended that secondary cartons be packed into fibreboard tertiary cartons. The dimensions of the tertiary carton should be the minimum necessary to accommodate the chosen number of secondary cartons, subject to necessary tolerances.
- It is recommended that the total number of vials packed in a tertiary carton be a multiple of 100 vials so that the contents are easy to count.
- It is recommended that the gross weight of a tertiary carton not exceed 25 kg and should preferably be no greater than 10 kg.
- It is recommended that the width dimension of the tertiary carton not exceed 45 cm.
- It is recommended that tertiary carton dimensions be selected so that cartons can be efficiently stacked on standard ISO pallets with dimensions of 1.2 m x 0.8 m and/or 1.0 m x 1.2 m without overhanging the pallet footprint.
- Tertiary packaging should be properly qualified to support the anticipated load.

Appropriate justification should be provided if the tertiary cartons differ from the above recommendations.

Multi-component vaccines

The use of vaccines according to the manufacturers' recommendations is essential to ensure safety. The key to this is ensuring that all components are available together at the point of delivery; to this effect, it is possible to keep multiple components of a vaccine together throughout the product's entire distribution process or during segments of the distribution process.

It would be useful for the VPPAG to evaluate the impact of the physical bundling of multi-component vaccines currently in use as well as the theoretical impact of physical bundling on cold chain capacities. Based on the findings, the VPPAG could consider recommending specific approaches in the future for all multiple component vaccines, including those with diluents. In the absence of physical bundling, secondary packages of vaccine and diluent from the same manufacturer should contain equal numbers of doses to reduce the risk of distribution mismatches and resultant wastage.

Materials, including the primary container and delivery device

Today, it is more important than ever to be conscious of vaccine waste disposal both in terms of the type and volume of packaging materials used and the ability of health systems to safely dispose of the delivery device, primary container, and packaging materials. These needs must be balanced with requirements for materials to be sufficiently durable to adequately protect the vaccine products from environmental factors and to ensure that labelling remains intact for product identification and appropriate use. Collaborative efforts by industry, regulatory, and scientific communities are under way to improve the sustainability of packaging. New packaging materials are also being developed

^c Based on data for 27 cold rooms. WHO Performance, Quality and Safety (PQS) specification E001/CR-FR01.3 requires shelves between 45 cm and 60 cm wide.

that may offer benefits in terms of reduced volumes and weight, improved durability, biodegradable properties, and ability to reuse.⁴⁹

A VPPAG working group led by vaccine industry members developed the following statement of intent and recommendations with regard to the future of vaccine containers and packaging.

Industry is fully supportive of reviewing and implementing new materials and/or standards that will limit the impact of packaging on the environment. The paramount concern for all manufacturers is to provide adequate protection and utility of our products. Thus, considerations such as using board stock suitable for refrigerated environments or protecting glass vials through transit to assure the glass remains integral are of our paramount concern. The selection of primary materials also tends to be constrained by many factors from extractables/leachables to maximising shelf life. Quantities of our packaging are often a factor of demand whereby we attempt to best optimize all of our customers' needs. Finally, the selection of insulated packaging is articulated in the *Guidelines on the International Packaging and Shipping of Vaccines*. As referenced earlier, we believe the greatest impact on limiting use of insulated packaging is to provide more heat-stable products as discussed through this document. Short of that, we are open to explore new systems that will minimise packagings' impact by supporting development and implementation of industry-wide standards such as ISO 18601 and related ISO standards that pertain to packaging and the environment.

In addition to interest in reducing the environmental impacts and volumes of packaging materials, there is a need to ensure that they can sufficiently withstand the conditions of use in developing countries. Secondary cartons are stored in refrigerators, which frequently operate in areas with intermittent power and high ambient humidity. Condensation on the internal surfaces of this type of equipment is a frequently observed phenomenon. Tertiary cartons are used as SKUs in cold rooms and freezer rooms only. Humidity in these environments is likely to be better controlled because continuous power is available and refrigeration unit evaporators collect and freeze condensate. Therefore, while tertiary cartons need to withstand some humidity, secondary cartons need to withstand higher levels of humidity. The recommendations below reflect this reality.

Recommendation

Use materials for delivery devices, primary containers, and secondary and tertiary packaging that minimise the environmental impact of waste disposal for resource-limited systems.

Optimize source reduction, reuse (where applicable), recovery, and appropriate and safe end-of-life handling using industry-wide standards (e.g., ISO 18601).

Reduce volume of insulated packaging material required by maximising the heat stability of vaccines.

It is recommended that secondary carton materials, including printing and attached labels, be resistant to long-term exposure to condensation.

It is recommended that tertiary carton materials, including printing and attached labels, not be damaged by long-term exposure to relative humidity (RH) levels at the International Conference of Harmonization (ICH) standard of 75% RH.

Labelling

Primary container label

In 2010, VPPAG became aware of two labelling issues that were causing confusion or difficulty within immunization programmes: the minimum font size for legibility and the format for the expiry date. VPPAG conducted an analysis and put forward a consensus position paper to WHO in 2011 recommending improvements to future vaccine labels.

Because text legibility is directly related to the quantity of text, the VPPAG requested that consideration be given to standardizing and minimising the information on primary container labels. The placement of multiple languages on labels further decreases available space and leads to minimum font sizes. VPPAG therefore suggested that multilingual information be placed on the carton and in the package insert.

At the time of the analysis, WHO had no minimum font size requirement, though there were minimum sizes in the United States and European Union. However, due to the quantity of information required, industry was sometimes forced to use even smaller fonts (down to 3 point Didot compared to the 6 or 7 point requirement in the United States and European Union, respectively) leading to challenges for legibility without a magnifying glass. Legibility depends not only on font size but also on the specific font used, so VPPAG requested that consideration be given to either specifying the “x height” or specifying the size for the specific font(s) used.

Difficulties with the use of a variety of different expiration date formats on vaccine labels caused confusion in the past. For example, it is unclear which number represents the month and which represents the day in numerical formats (e.g., 02-04-12 = February 4 or April 2). In addition, the use of English abbreviations for the month (e.g., Jun for June and Jan for January) can be confusing for non-English speakers. Standardizing the expiration date format would help to diminish these issues.

Finally, it is important that the vaccine label does not obscure the ability of health workers to view the vial or container contents (for example, to conduct the shake test or ensure that a vial has been fully reconstituted). The VPPAG therefore suggested that it might be valuable to specify a minimum viewing area as part of vaccine labelling specifications; the minimum viewing area may differ by type of vaccine and the number of doses per vial. A smaller vial label may be an option if the information content is reduced.

WHO asked both the Immunization Practices Advisory Committee and the Expert Committee on Biological Standardization to review the recommendations, and both groups endorsed the proposal. WHO is currently updating the Technical Report Series guidelines for primary container labels accordingly. The recommendations below summarize VPPAG's initial recommendations.

Recommendation

For primary container labels

- Minimum requirements could include: Product name, manufacturer, expiry date, batch/lot number, dose volume, and number of doses in the container. Storage conditions and method of administration might also be considered.
- Use of standard, generic names could create consistency and improve correct product use. Brand names could also be included.
- The format of the expiry date: An all numeric format: MM-YYYY should be the standard.^d
- A minimum font size and type should be required for label legibility.
- Specifying a minimum viewing area as part of vaccine labelling specifications could help to ensure the ability of health workers to view the vial or container contents (for example, to conduct the shake test or ensure that a vial has been fully reconstituted). The minimum viewing area may differ by type of vaccine and the number of doses per vial.

Indication of heat damage: vaccine vial monitors

The risk of administering sub-potent vaccines due to heat damage has been reduced for vaccines that are now labelled with VVMs. A VVM signals the cumulative level of heat exposure of the vial or other primary container to which it is attached with a clear indication when the vial has been exposed to excessive heat and should no longer be used. In addition to showing the heat-exposure status of vaccine vials, VVMs can be used to manage stocks, to minimise vaccine wastage, and to allow controlled exposures of vaccines outside the recommended temperature range.

VVMs are currently recommended by both WHO and UNICEF for use on all vaccines; having a VVM is a critical feature in order for a vaccine to be considered for prequalification.⁵⁰ At present there are four types of VVMs, named according to the number of days they can remain at a constant temperature of 37°C before they reach discard point: VVM2, VVM7, VVM14, and VVM30. As part of the WHO prequalification process, WHO works with vaccine producers to identify the VVM type that best matches a specific vaccine's stability profile.⁵¹ In the rare instance where a vaccine has a stability profile that does not match an existing VVM type, WHO can work with the vaccine producer to identify a custom VVM or other type of heat-exposure indicator for use.

Recommendation

Include VVMs on all vaccines, as recommended by WHO and UNICEF.

Secondary carton and tertiary packaging labels

Providing information on multiple faces of a carton or package aids product identification during storage and distribution and helps to minimize product selection errors. It also promotes accuracy during routine stock management activities, such as stock counts.

^d Meaning that the product expires at the end of the month.

Recommendation

It is recommended that secondary and tertiary cartons be labelled on at least two opposing faces, with a preference for three opposing faces, following the design principles set out in *Guidelines for the Labelling of Vaccines: Proposed Amendments to the TRS 822 Document & Requirements for Pre-Qualified Products*. The printed content can consist of static information only. Dynamically applied information such as bar codes and serialization data may be on one face only.

Bar codes

Presently, no effective system exists to monitor vaccine stocks from a country's port of entry to the point of administration. Use of bar codes to enable the capture of data at each step of the process (or supply chain level) provides an opportunity to improve safety through better recordkeeping and to improve supply chain performance resulting in increased vaccine availability and decreased vaccine wastage.

Having stakeholders agree on a system of standards is a first step in taking advantage of the opportunity provided by bar codes. The second step is to agree on the standard set of information contained in the bar codes so that systems can be developed to read and use this information within the recipient country at all vaccine handling levels to the point of administration. The recommendations below were prepared by a working group consisting of WHO, UNICEF, and Gavi as well as VPPAG members in consultation with 15 UN vaccine suppliers.⁵²

Recommendation

Bar codes are recommended on all packaging levels used by manufacturers, with the exception of primary packaging, and should conform to GS1 standards and associated specifications.

Bar code data should include the Global Trade Item Number (GTIN), lot number, and expiry date.

Package inserts

Appropriate labelling and package inserts help to ensure that health workers get the right information to safely administer vaccines. Essential information like product identification (name, batch), administration route (oral, intradermal, intramuscular, subcutaneous), date of expiration, type of VVM, and instructions for handling an opened, multi-dose vial must be accessible to and easily understandable by the service provider at the point of vaccine usage.⁵³

The content and location of package inserts are largely driven by regulatory requirements. At present, the number and location of package inserts included in the secondary packaging of vaccines may not be optimal for developing-country needs. Package inserts can also be bulky and increase secondary packaging and disposal volumes. Both industry and public-sector representatives have expressed interest in reviewing and attempting to improve package inserts for developing countries.

Countries procuring vaccines will find it helpful to have online access to package inserts in all of the UN languages. This will promote a fuller understanding of product characteristics.

The content of the package insert is highly technical and may be printed in a language that the health worker does not understand. A simplified fact sheet (package leaflet) translated into the local language and containing the minimum information relevant to the health worker and the patient is likely to improve knowledge of the product at the grass-roots level and reduce the risk of

administrative error. In addition, the package insert frequently never reaches small health facilities because vaccines are often delivered as individual primary containers. Fact sheets can be beneficial in this situation as well.

Recommendation

It is recommended that all package inserts should be supplied in the standard WHO format. Electronic versions, translated into the appropriate language for the procuring agency (e.g., English, French, Portuguese, and Russian for UNICEF and English and Spanish for the Pan American Health Organization), should be made available for download on the WHO vaccine database.

In addition to the package insert, it is recommended that a simplified single-page fact sheet should be made available for download on the WHO vaccine database so that countries can translate, compile, and distribute the information to health workers.

Annex 1: VPPAG overview

The VPPAG includes representatives from industry (Developing Countries Vaccine Manufacturers' Network and the International Federation of Pharmaceutical Manufacturers & Associations) and the public sector (the Bill & Melinda Gates Foundation, US Centers for Disease Control and Prevention, the Secretariat of Gavi, the Vaccine Alliance, John Snow, Inc., PATH, UNICEF, and WHO). The VPPAG is hosted jointly by WHO and UNICEF, who ensure the administrative and financial support required for the consistent and effective functioning of the group and the execution of its mandate.

While it has no policy-making function, the VPPAG serves as a unique forum for dialogue and consensus-building between industry and public-sector agencies, and it provides (a) input to the WHO processes for setting policy, norms, and standards; and (b) guidance to industry.

The VPPAG provides opportunities for the public sector to share its members' research, field, and policy experience to provide practical guidance to vaccine manufacturers, who in turn are able to share their in-depth knowledge regarding vaccine investment, development, scale-up, manufacturing, regulatory, and commercialization issues. This collaboration between public and private sectors is essential to ensure rapid and effective uptake of vaccines in the developing-country markets as soon as such vaccines become accessible.

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