THE COMPLEX JOURNEY OF A VACCINE – PART II

Immunization Supply Chain, Delivery Innovation, and Regulatory Requirements

International Federation
of Pharmaceutical
Manufacturers & Associations

IFPMA

THE IMMUNIZATION SUPPLY CHAIN COMPLEXITY

EXECUTIVE SUMMARY

Vaccines are one of the most effective preventative technologies in the fight against infectious diseases. No other technology has proven to be as instrumental or cost effective in saving lives and averting illness from infectious diseases.

Our members are part of a global community united by a common challenge to save lives and together with our partners, we can provide the latest state-of-the-art vaccines to the richest and poorest communities in the world alike.

As a group of private sector companies, we provide a unique set of skills and resources to this community that allows us to deliver innovation and scale to the supply and development of vaccines, and make a meaningful and sustained contribution to this collective effort to protect people against infectious diseases.

Our new generation vaccines are already making the same kind of public health impact as their pioneering predecessors.

The vaccine technologies that have driven the public health and economic gains from immunization around the world would not be possible without sustained investment in innovation and the unwavering ambition of dedicated scientists working in universities, research institutions, biotechs, and our own companies.

We are continually exploring new technologies and creating new formulations to help vaccines work better and to make it easier to reach people regardless of where they live.

However, the benefits from these advancements will not be fully realized unless there is also progress in the areas of regulatory convergence and harmonization, facilitated approvals, country-level infrastructure upgrading, sustainable supply chain training, and demand forecasting.

No single country, organization, company, or community can meet vaccines delivery challenges alone. Cooperation and coordination are important elements to ensure an effective and rapid response to achieve the above changes.

IFPMA vaccine manufacturers encourage immunization partners to consider the potential long-term impacts of today's policies and standards to address in-country downstream logistical complexities on ongoing investment in R&D, manufacturing capacity, and future vaccine supply.

IFPMA supports the WHO's Global Vaccine Action Plan calling for a shift in approach that will improve the immunization supply chain around the world. Our partnerships enable us to expand access to life-saving vaccines, working together towards an aspiration that every person of any age who can be protected through immunization, is protected by vaccines.

INTRODUCTION

Continuous improvement of the vaccine delivery process is important to ensure that the right vaccine is in the right place, at the right time, and under the right conditions[1]. Improving vaccine delivery from shipment through to administration is a shared concern for all those within the vaccines community, requiring close collaboration between global partners, including UNICEF, national governments, manufacturers, and others.

Vaccine manufacturers are thus committed to help realize the goals of accelerated vaccine delivery, and equitable vaccine uptake and coverage as stated in the Decade of Vaccine (DOV) Global Vaccine Action Plan (GVAP)[2]. Yet, getting life-saving vaccines to the people who need them most cannot happen without a strong Immunization Supply Chain and Logistics (ICSL) systems in place.

This sequel to the "Complex Journey of Vaccine" published in 2014[3] depicts the delivery part of vaccines. This edition examines in details the delivery needs, particularly adapted to remote settings. It also offers some of the solutions that manufacturers are working on to improve vaccine delivery to low-resource settings and highlights the associated regulatory considerations.

- ***What makes vaccine supply delivery chain so complex?***
- ***How can vaccine delivery innovations be deployed expeditiously and not be subjected to protracted delays due to diverse and localized regulatory requirements?***

1 WHO Immunization Supply Chain and Logistics http://goo.gl/DLZZWX

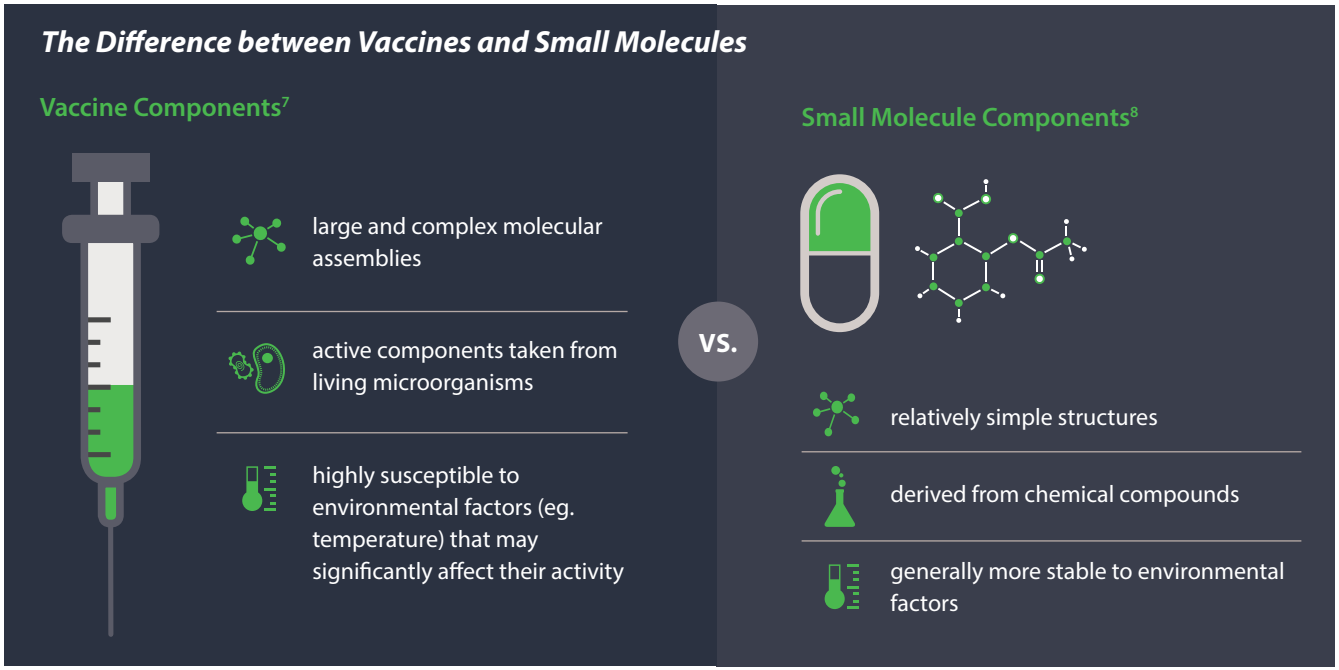
2 WHO Decade of Vaccines Global Vaccine Action Plan 2011-2020, Table 7, Page 70 http://tinyurl.com/oubpszz

3 IFPMA Complex Journey of Vaccine Publication 2014 http://www.ifpma.org/fileadmin/content/Publication/2014/IFPMA_Complex_Journey_Vaccine_Publication_2014.pdf

1 VACCINE SUPPLY CHAIN COMPLEXITY

"The role of the supply chain is to ensure effective vaccine storage, handling, and stock management; rigorous temperature control in the cold chain; and maintenance of adequate logistics management information systems. The ultimate goal is to ensure the uninterrupted availability of quality vaccines from manufacturer to service-delivery levels, so that opportunities to vaccinate are not missed because vaccines are unavailable".[4] To ensure an uninterrupted supply of quality vaccines to patients, the regulatory environment needs to reflect the complexity of new vaccines and Good Manufacturing Practices (GMP).

- Vaccines are complex biological products that often require "cold chain" storage, i.e. temperature control of 2 to 8°C.
- As the Expanded Programme on Immunization (EPI)[5] has been extended to include new vaccines and the number of doses of vaccine required increased, there is mounting pressure to increase performance of national immunization supply chain and logistics systems.
- Adequate supply chain management is critical: failure to store and handle vaccines properly can diminish vaccine effectiveness, consequently leading to inadequate immune responses in patients and poor protection against diseases. The public's trust in vaccination may be eroded if the vaccines people receive have been compromised (for example, exposed to inappropriate conditions/temperatures or simply mishandled).[6]



4 World Health Organization (WHO) Immunization supply chain and logistics (ISCL) http://www.who.int/immunization/programmes_systems/supply_chain/en/

5 Health system cost of delivering routine vaccination in low- and lower-middle income countries: what is needed over the next decade? Patrick Lydon, Gian Gandhi, Jos Vandelaer & Jean-Marie Okwo-Bele. Bulletin of the World Health Organization 2014;92:382-384. doi: http://dx.doi.org/10.2471/BLT.13.130146

6 Conference report "From refrigerator to arm: Issues in vaccination delivery"; L.J.Tan; Vaccine 32 (2014) 2389-2393

7 http://www.who.int/biologicals/vaccines/Annex_3_WHO_TRS_962-3.pdf?ua=1

8 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3564302/

CURRENT IMMUNIZATION SUPPLY CHAIN & LOGISTICS (ISCL) SYSTEMS

New immunization landscape (1980-2013)[9]

- Provide protection against 2.5 times as many diseases, e.g. overview of Gavi, the Vaccine Alliance – global vaccine access initiative.[10]
  - 2014 Japanese encephalitis
  - 2014 Cholera
  - 2013 IPV
  - 2013 Measles rubella
  - 2013 HPV
  - 2011 Meningitis A
  - 2009 Pneumonococcal
  - 2008 Rotavirus
  - 2007 Measles
  - 2006 Pentavalent
  - 2002 Hib
  - 2001 Yellow fever
  - 2001 Hepatitis B
- Immunize populations across the lifespan – from infants to adults.
- Administer 3 times as many doses per child.
- Store and transport 4 times more vaccine volume per fully immunized child.
- Serve a global target population that has doubled in size.

Immunization Supply Chain & Logistics (ISCL) systems challenges

- Inventory unpredictability
- Inadequate cold chain capacity
- Insufficient funding

ISCL systems are struggling, and often failing, to cope with these increased demands – resulting in stock-outs, potential administration of ineffective vaccines (e.g. when potency is lost due to inadequate management), avoidable wastage, and inadequate cold chain capacity.

A recent study of 57 Gavi-eligible countries[11] concluded that less than 25% of countries are operating at the minimum Effective Vaccine Management (EVM) levels for maintenance, stock management, and distribution and that only 30% of countries are meeting minimum standards for temperature control.

Recent findings from Pakistan show a loss of USD 3.7 million in wastage of donated vaccines due to poor storage.[12]

Vaccine Incident Report from WHO Vigibase, by error type, December 2012

Error Type	Incidents	%
Incorrect vaccine administered	4,238	21.6
Administration error	336	1.7
Incorrect does administered	1,473	7.5
Accidental overdose	484	2.5
Incorrect form	184	0.9
Expired vaccine	50	0.2
Other vaccine incident types	14,321	73.0
Total vaccine incidents reports	**19,613**	**100%**

9 WHO Immunization Supply Chain and Logistics http://www.who.int/immunization/call-to-action_ipac-iscl.pdf

10 Comparing the requirements of Immunization Supply Chain & Logistics (ISCL) systems in the 1980's to the present (Source: http://www.who.int/immunization/sage/meetings/2013/november/1_ISCL_Key_Challenges.pdf)

11 Colrain, P. Study of EVM assessments from 57 Gavi-eligible countries, 2012-2013. http://www.who.int/immunization/sage/meetings/2013/november/1_ISCL_Key_Challenges.pdf

12 Hassan, S.R. Pakistan wastes $3.7 million worth of donated vaccine, official says, 2015. http://www.reuters.com/article/2015/03/02/us-pakistan-vaccine-idUSKBN0LY19920150302

2 ELIMINATING ROADBLOCKS ALONG THE DELIVERY ROUTE

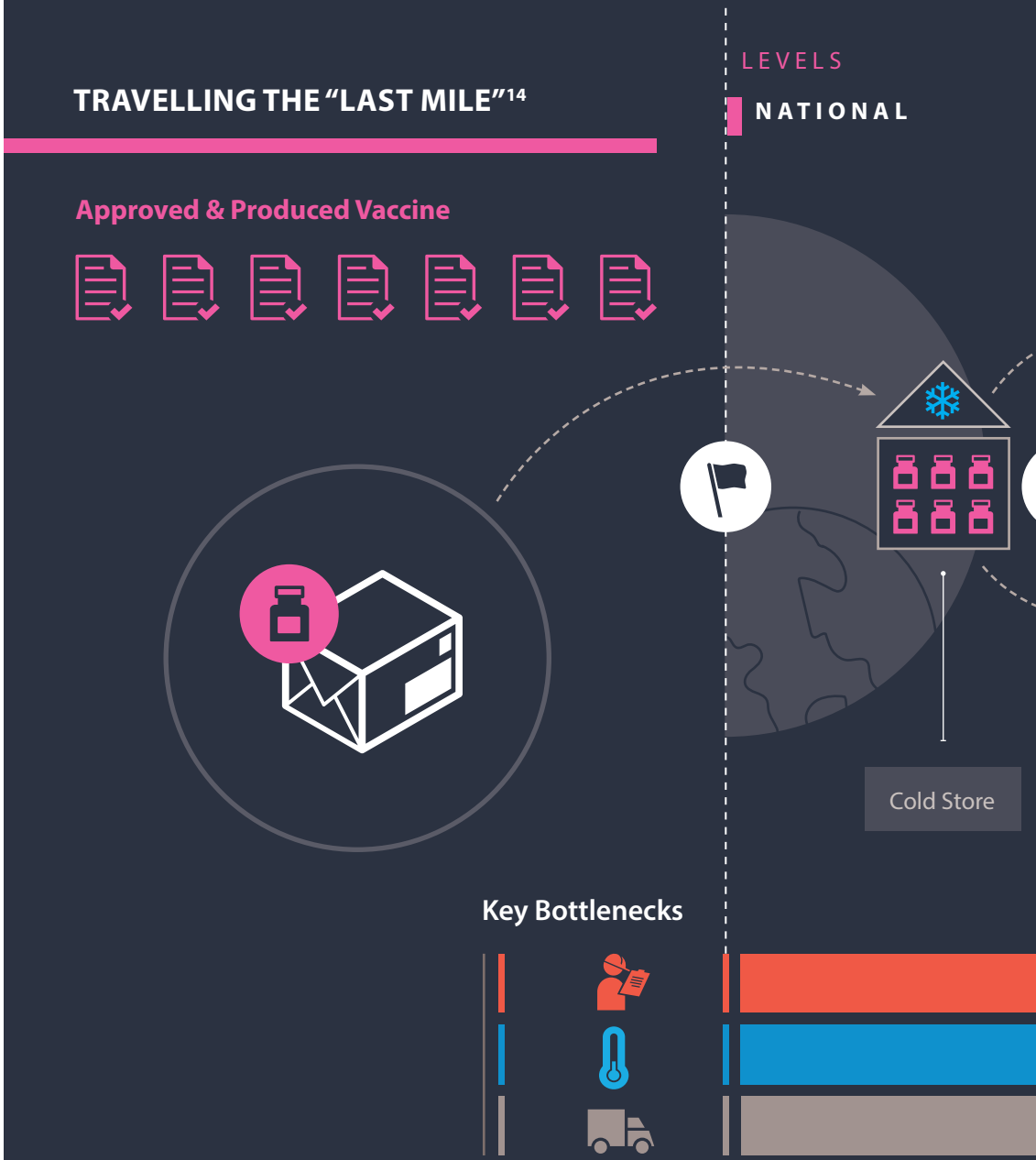
Supply chain experts from the public and private sectors agree that "In an environment with limited resources, protecting every child with lifesaving vaccines may not be possible without also improving the design and presentation of vaccines themselves (…) many supply chain problems can be best addressed at the earlier stages of vaccine development where decisions relating to formulation, packaging, labelling, and presentation can make vaccines more suitable for distribution, storage, and use in low-resource environments."[13]

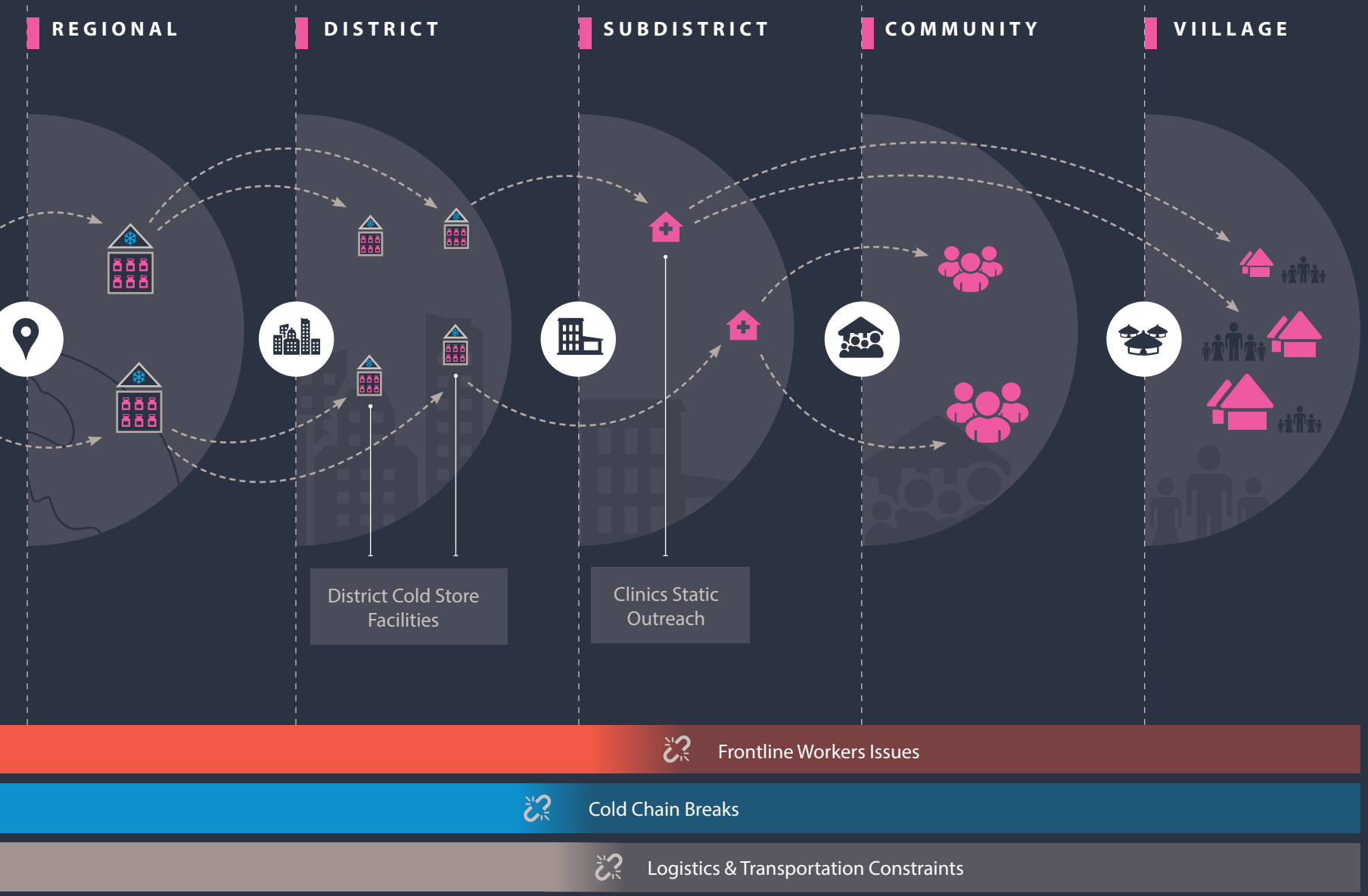
The research-based vaccine manufacturers are working with the public sector to formulate, package, and label vaccines to optimize the usage of existing cold chain capacity, address transportation space concerns, reduce wastage, and secure preparation and administration, particularly in resource-limited settings.[14]

13 Optimize – New Vaccine Presentations ease supply chain pressures http://apps.who.int/immunization_delivery/optimize/Optimize-newsletter-September-2013.pdf

14 IFPMA, Innovation for a Healthier World: How the Research-based Vaccine Manufacturers are contributing to the Decade of Vaccines Global Vaccine Action Plan, 2015. Pages 32-33 http://www.ifpma.org/uploads/media/IFPMA_Innovation_for_a_Healthier_World_-_Vaccines.pdf

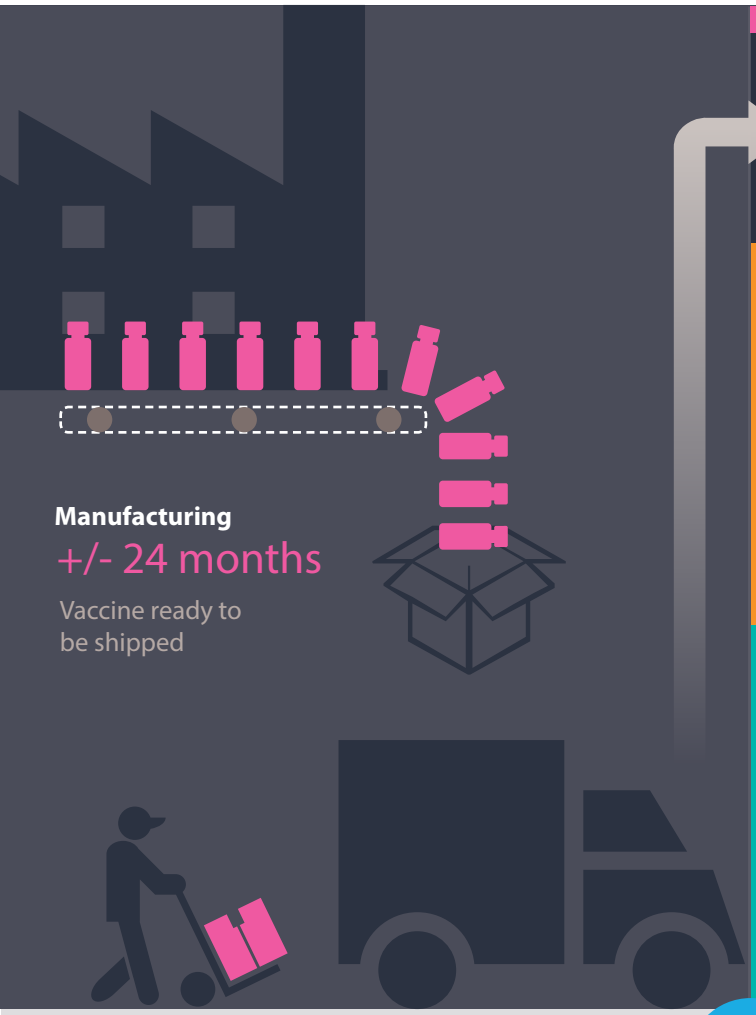
TRAVELLING THE "LAST MILE"[14]




REGIONAL
DISTRICT
SUBDISTRICT
COMMUNITY
VIILLAGE
District Cold Store Facilities
Clinics Static Outreach
How do we facilitate the movement?
How do we prevent missed opportunities?
How do we develop the capacity of the frontline worker?
Frontline Workers Issues
Cold Chain Breaks
Logistics & Transportation Constraints

THE COMPLEX JOURNEY OF A VACCINE[15]

SUPPLY CHAIN DELIVERY



Manufacturing

+/- 24 months

Vaccine ready to be shipped

INTERNATIONAL SHIPPING AND VACCINE ARRIVAL

DISTRICT/REGIONAL STORE

CHALLENGES

- Space and weight of packages
- Cold chain
- Environmental sustainability
- Quantity and quality control check at reception
- Time out of refrigeration

- Storage
- Electricity supply
- Stock management & forecast
- Transportation
- Temperature excursion management
- Shipping solutions, cost, and efficiency

EXAMPLES OF INNOVATION

- Packaging optimization
- E-labeling

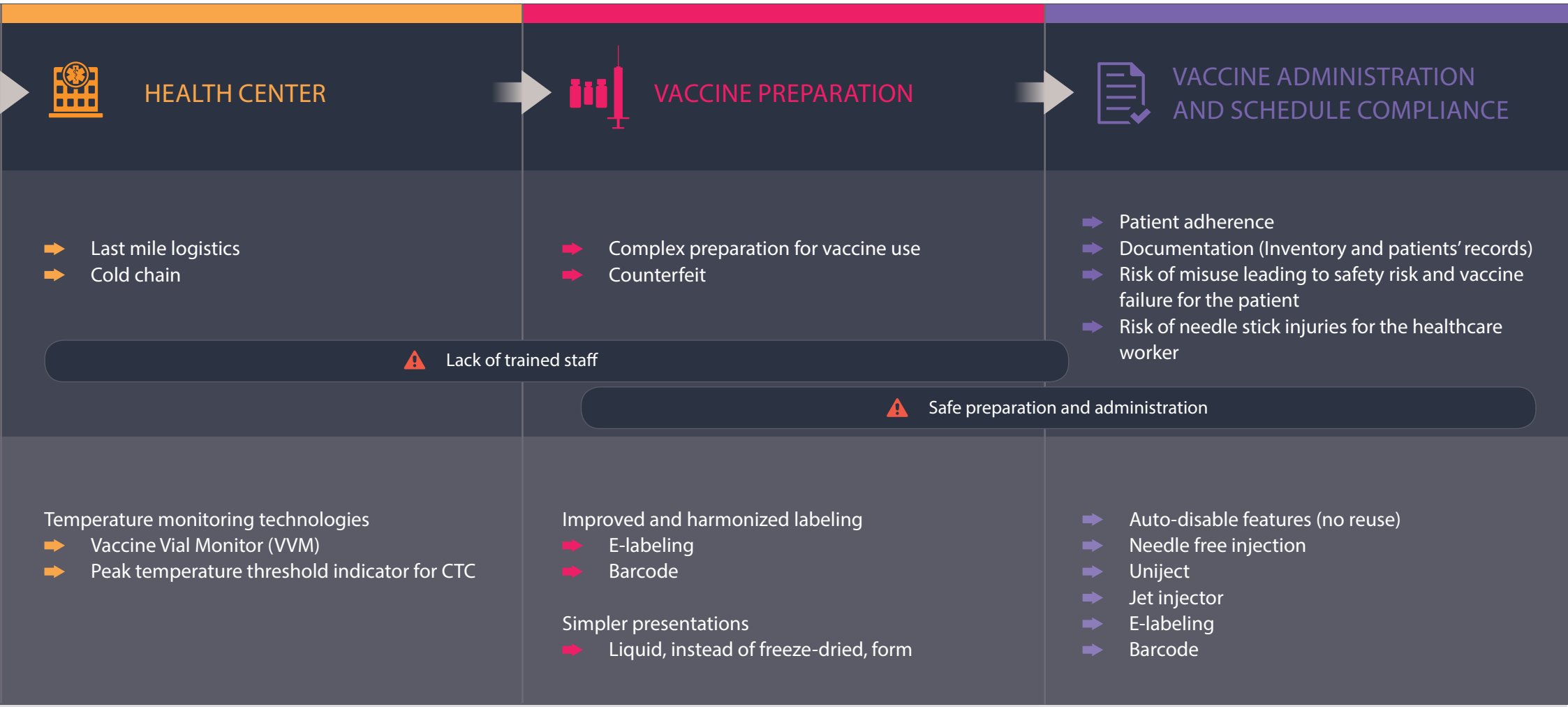
Real time data support over the entire shelf life. New formulations to withstand heat. New refrigeration techniques

- Solar powered refrigerator
- Resistant cold boxes

Temperature control : 2°C / 8°C

Disposal / waste management

15 IFPMA Complex Journey of Vaccine Publication 2014 http://www.ifpma.org/fileadmin/content/Publication/2014/IFPMA_Complex_Journey_Vaccine_Publication_2014.pdf


HEALTH CENTER
VACCINE PREPARATION
VACCINE ADMINISTRATION AND SCHEDULE COMPLIANCE
Last mile logistics
Cold chain
Complex preparation for vaccine use
Counterfeit
Patient adherence
Documentation (Inventory and patients' records)
Risk of misuse leading to safety risk and vaccine failure for the patient
Risk of needle stick injuries for the healthcare worker
Lack of trained staff
Safe preparation and administration
Temperature monitoring technologies
Vaccine Vial Monitor (VVM)
Peak temperature threshold indicator for CTC
Improved and harmonized labeling
E-labeling
Barcode
Simpler presentations
Liquid, instead of freeze-dried, form
Auto-disable features (no reuse)
Needle free injection
Uniject
Jet injector
E-labeling
Barcode

EXAMPLE 1: CONTROLLED-TEMPERATURE CHAIN (CTC)

Research-based vaccine manufacturers are testing the temperature stability of current vaccines for after several days without refrigeration, in addition to long-term storage at recommended temperature conditions. In the longer term, manufacturers are applying similar tests to new technologies and formulations for vaccines in development.

A controlled-temperature chain is defined as the storage and transport temperatures above the traditional 2-8°C, which may allow product exposure to 40°C for 4 days**,** before administration, under monitored and controlled conditions, and as appropriate to the stability of the antigen.[16,17]

Vaccines Cold Chain[18]

Vaccines are kept between 2-8°C (36-46°F). This cold chain requires intense logistics in resource-limited settings.

Challenges when Traveling the Last Mile:

- Lack of large transportation vehicles
- Limited refrigeration

For example: Vaccines against cholera, hepatitis B, human papillomavirus (HPV), malaria, and pneumococcal diseases will be soon available for use in CTC.[18]

What value CTC brings?

- Improved access to vaccines in settings where maintaining the cold chain is not feasible – for example, during the transportation of vaccines from health centres during outreach vaccination campaigns.
- Easier outreach of vaccination campaigns by facilitating local logistics and transportation.
- Lower cost associated with vaccination. Fewer freezers, fewer journeys and less staff time are needed to manage and maintain cold chain requirements.[19]
- Reduce vaccine wastage as a result of accidental freezing of vaccines from cold packs, since many vaccines cannot bear freezing temperatures.

  However, it is important to note that some vaccines are intrinsically unstable when exposed to high temperatures even for short periods of time. Hence, the CTC approach may not work for all vaccines.

16 WHO Controlled Temperature Chain (CTC). http://www.who.int/biologicals/areas/vaccines/controlledtemperaturechain/en/

17 For further information, please also refer to the WHO Film on the Controlled Temperature Chain (CTC) http://www.who.int/immunization/programmes_systems/supply_chain/resources/tools/en/index6.html and https://www.youtube.com/playlist?list=PL9S6xGsoqIBWYg1540xBQ3XFvzz2JRrPT»

18 IFPMA Vaccines Travelling the Last Mile http://www.ifpma.org/uploads/media/IFPMA_Report_Vaccines_Traveling_the_Last_Mile.pdf

19 http://www.who.int/immunization/programmes_systems/supply_chain/resources/WHO_CTC_Infographic.pdf

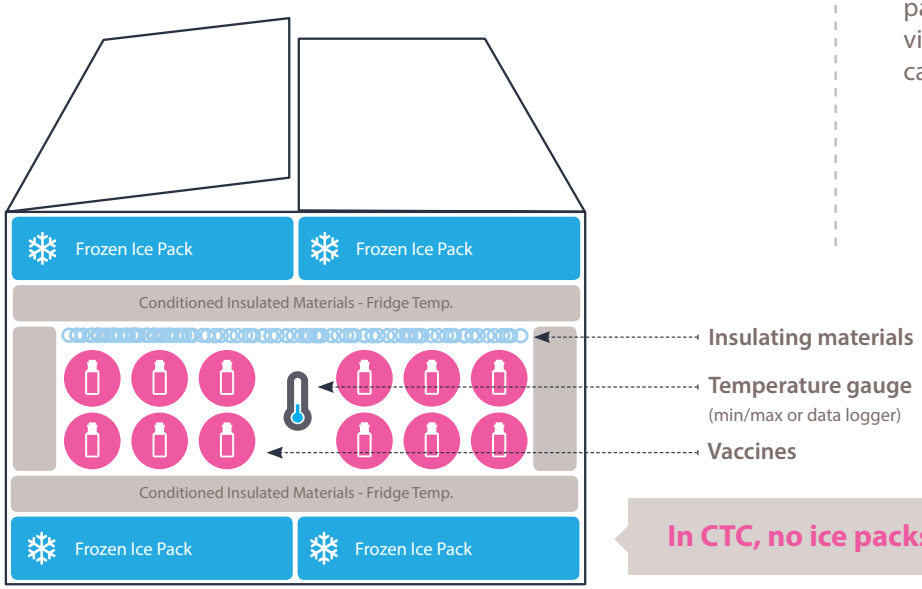
EXAMPLE 2: PACKAGING AND PRESENTATION OPTIMIZATION

What is meant by packaging?

The first level of packaging refers to the vial, ampoule, prefilled syringe, or other container that is in direct contact with the vaccine.

The second level of packaging is what holds the primary container(s) (e.g., cartons containing one or more vials or prefilled syringes of vaccines) and the package insert.

The third level of packaging is the outer box or the shipping box containing multiple secondary packaging.[20]



In CTC, no ice packs are required.

What is meant by presentation?

The pharmaceutical presentation of vaccines refers to the combination of the type of primary packaging (i.e. single-dose vial, multi-dose vial, ampoule, pre-filled syringe) and the type of secondary packaging (i.e. single dose vial assembled by 100 in a carton box).

Manufacturers are addressing packaging size concerns, while remaining mindful of the diverse needs of frontline health care workers for vaccination campaigns. Among other things, manufacturers are converting, when possible, pre-filled syringes, which occupy more volume per dose to single dose vials, reducing and harmonizing the size of primary, secondary, and tertiary containers, as well as developing multi-dose vial presentations and combination vaccines. The aim is to make choices available that are easy to transport and administer. This can help reduce wastage rates and increase vaccination coverage, compliance, and safety, making optimal use of existing cold-chain storage in low-resource settings with limited infrastructure.

20 Adapted from http://www.gov.mb.ca/health/publichealth/cdc/coldchain/protocol7.html

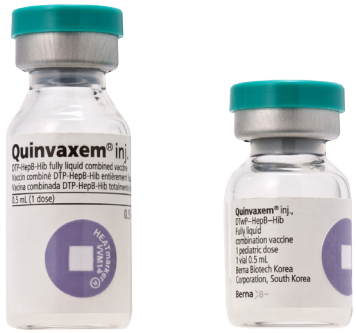
ILLUSTRATIONS OF CHANGES IMPLEMENTED BY MANUFACTURERS TO OPTIMIZE STORAGE & TRANSPORT SPACE AND ULTIMATELY OPTIMIZE COLD CHAIN IMPACT

PREVNAR:

Pfizer changed the pneumococcal vaccine presentation from a prefilled glass syringe to a single-dose vial for use in the developing countries. The change in packaging and presentation reduced the cold chain space per dose required from 55.9 cm^3 to 12 cm^3.

QUINVAXEM:

Crucell (Part of the Janssen Pharmaceutical Companies of Johnson & Johnson) reduced the packaging size of pentavalent vaccine from 13 to 10 cm^3 per dose, allowing an increase of the vial capacity of the tertiary packaging of 17%.

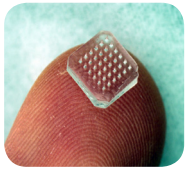


ROTARIX:

GSK's (GlaxoSmithKline) first-generation rotavirus vaccine was lyophilized (freeze-dried) and required to be reconstituted with a supplied diluent. This needed a significant amount of cold storage space. GSK addressed this by changing the lyophilized presentation requiring 156 cm^3 per dose to a ready-to-use liquid presentation in an oral applicator requiring 85.3 cm^3 per dose. GSK then developed a plastic tube presentation requiring only 17.1 cm^3 of space per dose to store and transport.

These examples illustrate that presentation and packaging optimization can deliver significant benefits in the optimal utilization of existing cold-chain storage in low-resource settings with limited cold-chain supply infrastructure.

ILLUSTRATIONS OF PRESENTATION OPTIMIZATION AND INNOVATIVE DEVICE



Intradermal patch[21]

Microneedles[22]

Disposable syringe jet injectors[23]

DIGITAL INNOVATION

Manufacturers are also exploring the development of digital solutions, such as e-labeling to provide clear and legible product and storage information that will improve people's safety. E-labeling could be particularly helpful as product package size is being reduced to optimize the cold-chain footprint.

2D DataMatrix barcoding of vaccines is being explored by our public health partners to optimize vaccine supply chain and stock management in low and middle income countries. Vaccine manufacturers are working collaboratively with a Gavi-funded PATH demonstration project team consisting of vaccine manufacturers, UNICEF, WHO, GS1, and the Tanzania Expanded Programme on Immunization team to demonstrate the technical, user, economic, and regulatory aspects of capturing vaccine product information using 2D bar technology.

By integrating the technical, practical, and user requirements, this demonstration project aims to show how to build an appropriate system to capture and use bar code data located on vaccine packaging to support vaccine management and supply chain decisions.

21 Image courtesy of Jeong-Woo Lee, Laboratory for Drug Delivery, Georgia Institute of Technology in http://www.pnas.org/content/110/25/10049/F1.expansion.html

22 *Microneedles feasible peptide delivery tech, says Merck Director* By Dan Stanton+, 11-Nov-2014 - Photo Credit: Gary Meek, Georgia Tech. http://www.in-pharmatechnologist.com/Drug-Delivery/Microneedles-feasible-peptide-delivery-tech-says-Merck-Director?utm_source=copyright&utm_medium=OnSite&utm_campaign=copyright

23 http://www.3rdstonedesign.com/project/real-mccoy/

3 COMPLEX REGULATORY REQUIREMENTS

Undertaking innovations to overcome supply chain challenges, such as changing the packaging, presentation, and CTC, requires considerable investments in the manufacturing operations and regulatory tasks by vaccines manufacturers.

Our goal is to make choices available that are easy to transport and administer so that we never miss an opportunity to vaccinate.

Overall, any modification after a vaccine has been approved by regulatory authorities must be reviewed by each national regulatory authority before the new vaccine can be distributed in the country, with significant differences in approval times worldwide[24]. Differences in approval times can have serious consequences on vaccine access and security of supply. Due to limited production capacities, manufacturers cannot always simultaneously maintain different lines of production for the multiple approved versions of the vaccine.

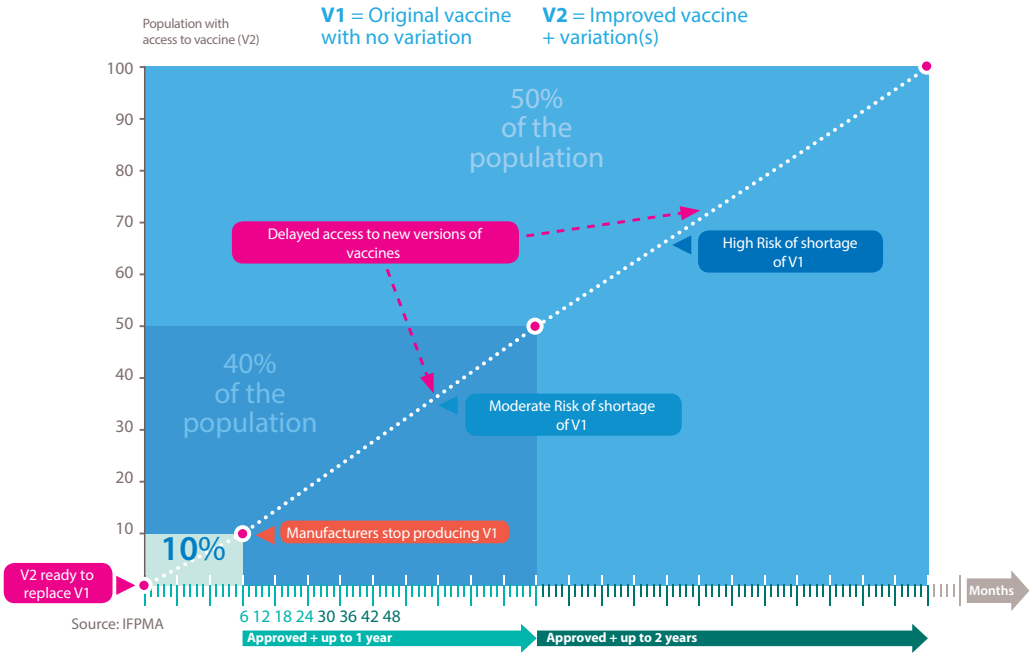
Furthermore, new delivery devices require additional clinical trials to demonstrate that they are equivalent or better in terms of safety and efficacy than the original delivery device. Changes to a vaccine's presentation may require additional approvals by national regulatory agencies that have responsibility for medical devices.

Similarly, once the necessary validation of the CTC has been confirmed (including stability studies and potentially clinical data), the vaccines manufacturers would need to obtain national regulatory approval of the necessary CTC label changes before implementation.

Unfortunately, whilst important to ensure the safety and efficacy of a vaccine, regulatory processes may differ in timelines and requirements among countries, creating a large amount of complexity for global vaccine suppliers. However, IFPMA members remain committed to working with partners to make vaccines available as efficiently and as effectively as possible to those who need them.

24 IFPMA Complex Journey of Vaccine Publication 2014 http://www.ifpma.org/fileadmin/content/Publication/2014/IFPMA_Complex_Journey_Vaccine_Publication_2014.pdf

Approval Times, Risk of Shortage and Inequity



Disclaimer
This graph is intended to help the reader understand the impact of delayed regulatory approvals upon supply and access to vaccines. It is fictionalised, based upon industry experience of managing complex regulatory variations but it does not represent an actual example. Regulatory lead-times are variable and can be influenced by many factors such as medical need.

HOW TO MOVE FORWARD?

- Promote convergence and harmonization of regulatory standards to enable timely vaccine approval, access, and security of supply.
- Collaborate with well-resourced and expert regulatory authorities to leverage their experience.
- Use the WHO Prequalification process to accelerate the local regulatory review and approval, in countries with limited regulatory capabilities.
- Foster dialogue with vaccine manufacturers to align on the development of guidelines on optimal vaccine CTC usage, storage and handling, presentations, and packaging.
- Ensure awareness that CTC does not apply to all vaccines and must be validated before implementation.
- Support the training of healthcare providers on appropriate usage of vaccines with new presentation and CTC label.

We welcome the opportunity to continue working with partners to remove any barriers to vaccinating children, adolescents, and adults.

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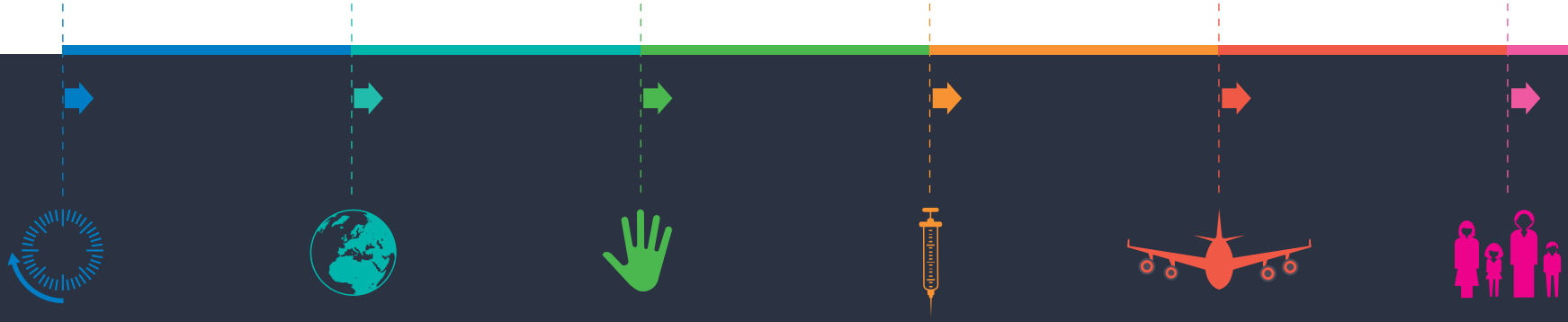

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ABOUT THE IFPMA

IFPMA represents the research-based pharmaceutical companies and associations across the globe. The research-based pharmaceutical industry's 2 million employees research, develop and provide medicines and vaccines that improve the life of patients worldwide. Based in Geneva, IFPMA has official relations with the United Nations and contributes industry expertise to help the global health community find solutions that improve global health.

www.ifpma.org

Our vaccine manufacturers members, together with our partners, are united by a common challenge to save lives, improve health, and ensure long-term prosperity through life-saving vaccines.

ACKNOWLEDGEMENTS

The production of this publication is the fruit of a collective effort between member companies and the secretariat of the IFPMA. The project was managed by Margarita Xydia-Charmanta, in coordination with Sadia Kaenzig.

Layout: messaggio / Inart Design Works, LLC

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ISBN 978-2-940498-23-9