

# THE COMPLEX JOURNEY OF A VACCINE

The manufacturing chain, regulatory requirements and vaccine availability



International Federation  
of Pharmaceutical  
Manufacturers & Associations



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Immunization is one of the most successful and cost-effective public health interventions. This brochure explains why the regulatory environment is critical to allow timely access to vaccines by answering the following questions:

- ➔ **Why has the vaccine manufacturing chain become so complex?**
- ➔ **How can some regulatory requirements unnecessarily slow the availability of vaccines to patients?**
- ➔ **What can we do to secure timely vaccine availability to patients?**

The production, quality control and marketing authorization of vaccines have always been complicated, but in recent years, these have become increasingly complex.

The complexity of a vaccine's manufacturing chain is due to three factors:

### 1 VACCINE COMPLEXITY

*Innovative vaccines are complex biological products and therefore require sophisticated equipment and processes to ensure a consistently high product quality.*

### 2 GLOBALIZED MANUFACTURING CHAIN

*Manufacturers both increase their manufacturing capacity and seek to maximize their utilization to better meet patient demand.*

### 3 INCREASINGLY COMPLEX REGULATORY REQUIREMENTS

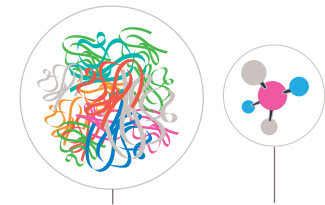
*Regulatory authority expectations and standards have increased.*

*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).*

## 1 VACCINE COMPLEXITY

- ➔ Cutting edge **medical science** and **advanced manufacturing technologies** have led to the development of highly **sophisticated vaccines**.
- ➔ The variability of biological processes requires highly **sophisticated manufacturing** and **testing techniques**.
- ➔ To produce vaccines of **consistent quality**, **specialized manufacturing facilities are required**.

[ **Complex** antigen Vs. **simple** medicine ]\*



ANTIGEN

MOLECULE

\*A vaccine includes an antigen which is typically a large, complex molecule that is difficult to characterize because it is produced via an inherently variable biotechnological process. A traditional medicine contains a small, chemically synthesized molecule with well-defined characteristics (which is much smaller than a vaccine antigen).

## 2 GLOBALIZED MANUFACTURING CHAIN

➔ With globalization, **multiple manufacturing sites may be involved in the production** of the different components of the vaccine. The same manufacturing step may even be performed at different sites in order to maximize production capacity (multi-sourcing).

### *What are the drivers for a globalized manufacturing chain?*

MANUFACTURERS GLOBALIZE PRODUCTION TO:

- ➔ Support better patient access to the vaccine.
- ➔ Use existing in-house or contractor facilities.
- ➔ Take advantage of a skilled global workforce.
- ➔ Respond to country-specific expectations and preferences for local manufacture.
- ➔ Move late stage manufacture closer to the patient. This can reduce lead-times and allow packaging customization to better meet local regulatory requirements and customer preferences.
- ➔ Seek cost containment and manufacturing efficiencies to make vaccines more affordable and therefore more accessible.
- ➔ Better meet the need of a large variety of national vaccination programs and allow differentiation between public and private markets. Support the production of a wide portfolio of vaccine presentations.

### *Globalization and multi-sourcing offer:*

- ➔ Improved security of supply.
- ➔ Improved manufacturing productivity.
- ➔ Faster production and better response to customer needs.
- ➔ Better patient access to vaccines.



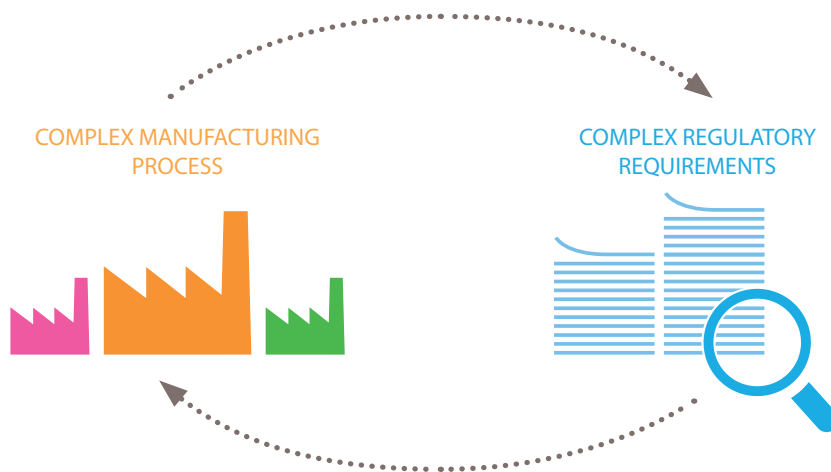
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### 3 INCREASINGLY COMPLEX REGULATORY REQUIREMENTS

- ➔ As vaccines are given to large numbers of healthy individuals there is **a strong focus upon vaccine quality, safety and efficacy in assessing the benefit-risk to public health.**
- ➔ **Advancing scientific knowledge and greater expectations** for public safety continue to drive quality standards higher.

#### *The relationship between regulatory and manufacturing complexity*



- ➔ **There is a direct correlation between the manufacturing complexity and the regulatory standards.**
  - To ensure the control of the manufacturing of innovative and complex products, new regulatory requirements are developed.
  - To meet specific, divergent regulatory requirements and highly demanding standards, multiple manufacturing and testing processes may need to be executed.

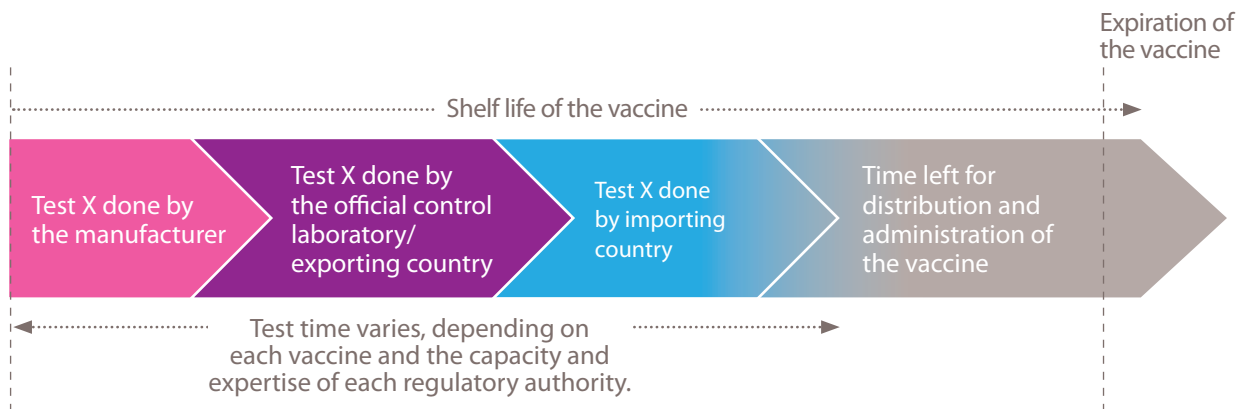
#### *Regulatory challenges inhibiting the timely supply of vaccines to patients*

- ➔ Regulatory authorities resource constraints may limit their ability to quickly review complex regulatory submissions.
- ➔ There is duplication of regulatory reviews, facility inspections and quality control testing, because many countries perform the same evaluation.
- ➔ Scientific and technical progress necessitates continuous updates to manufacturing process and/or testing of product. Most changes require prior approval and review times vary greatly from country to country. While awaiting approval of the change, supply can be delayed or interrupted.

## EXAMPLE REDUNDANT TESTING AND DELAYED ACCESS TO VACCINES

The quality of vaccines is confirmed via the extensive testing that is performed during the manufacturing process. The product is also tested by the official control laboratory in the country of manufacture. The availability of vaccines can be delayed by the need to conduct additional testing in the importing country. Typically, these tests are performed consecutively.

- ➔ **The remaining shelf life of a vaccine is directly affected by the time taken for testing.**
- ➔ **Consequently, prolonged testing means less time for the distribution and administration of the vaccines to patients.**



- ➔ **Regulatory authorities may use a risk-based approach, by assessing regular and satisfactory inspection results of the Quality Control facilities, to determine whether elimination of redundant importation testing is warranted.**

## ➔ **Securing timely patient access to vaccines**

*The foundations of a sustainable regulatory environment should include:*

- *Promoting convergence of standards.*
- *Collaborating with well-resourced regulatory authorities with relevant expertise.*
- *Leveraging appropriate use of WHO Prequalification to accelerate local review and authorization.*
- *Enhancing regional cooperation to leverage complementary expertise.*
- *Making best use of limited review resources while still supporting other essential functions.*

R&D

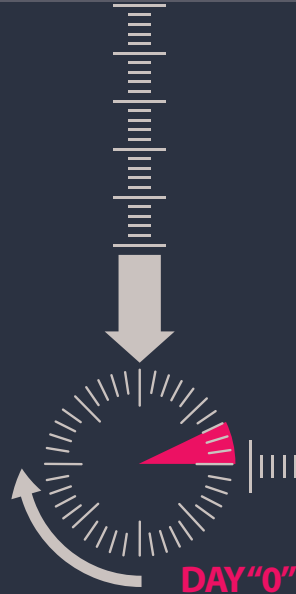


APPROVED SAFE & EFFECTIVE BY A REGULATORY AUTHORITY



# THE COMPLEX JOURNEY OF A VACCINE

MANUFACTURING CHAIN



Vaccine manufacturing involves **6 basic steps**. Each step can be performed in different sites situated in different countries.

- Testing done by the **manufacturer**
- Testing done by the **exporting country**
- Testing done by the **importing country**

## 1 RAW MATERIAL RECEPTION

All incoming raw materials are checked for conformance with the quality specifications.



## 2 BULK ANTIGEN MANUFACTURING

The active ingredient of the vaccine is manufactured. This is the most critical step in the production of high quality, safe and efficacious vaccines.



## 3 FORMULATION

The active ingredient is mixed with other ingredients to enhance the immune response and ensure product stability.



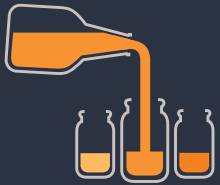
Quality Control represents up to **70%** of manufacturing time.



A vaccine typically travels through **several different sites** before being ready for shipment.

## 4 FILLING

The vaccine is filled into the final container. This could be a vial or a prefilled syringe.



## 5 PACKAGING

The vaccine in the final container is labeled in accordance with regulatory requirements and packed, ready for shipping to the customer.



## 6 LOT RELEASE

Quality assurance confirms that the product has been manufactured and tested in accordance with the correct procedures. The national regulatory authority gives the final authorization to release the product for distribution.



+/- 24 MONTHS



VACCINE OF  
CONSISTENT  
QUALITY

SHIPMENT



DISTRIBUTION



A vaccine undergoes up to **several hundred Quality Control tests** during its manufacturing journey.

### EXAMPLE REGULATORY APPROVAL TIMES AND ACCESS TO VACCINES

#### *Definition of Variations to Vaccine*

After a new vaccine has been approved by regulatory authorities and granted a market authorization, manufacturers may decide to make changes (or regulatory authorities may mandate these changes) to a large variety of elements such as: the manufacturing process, the strategy to control the quality of the product, the information contained in the labeling items...

An extra layer of complexity results from the fact that there are many variations occurring to the same vaccine as most vaccines contain multiple components which each have their own processes and variations.

**There are 4 main reasons for manufacturers to introduce variations:**

- 1.** Introduce a change to improve the quality or clinical performance of the vaccine;
- 2.** Meet new regulatory standards developed by local regulatory authorities;
- 3.** Modify the manufacturing process or the strategy to control product quality to ensure a reliable and sustainable global supply chain;
- 4.** Introduce changes in the labelling to reflect new safety information.

#### *Validation Studies and Regulatory Approval Process of Variations*

As a first step before manufacturers are able to submit a variation for a major manufacturing change to regulatory authorities, extensive validation and stability studies are often needed to provide evidence that the quality and stability of the vaccine are not negatively impacted by the change. The more complex the vaccine is, the more studies may need to be done and the longer it takes.

Once the process validation studies are completed (this can take up to 18-24 months), manufacturers can submit the variation(s) to all the national regulatory authorities where the vaccine is licensed. Regulatory authorities then review and approve the changes prior to allowing any commercial distribution of the "new" vaccine in their respective countries. The approval process is managed on a country by country basis which can result in hundreds of regulatory submissions.

#### *Description of differences of approval times*

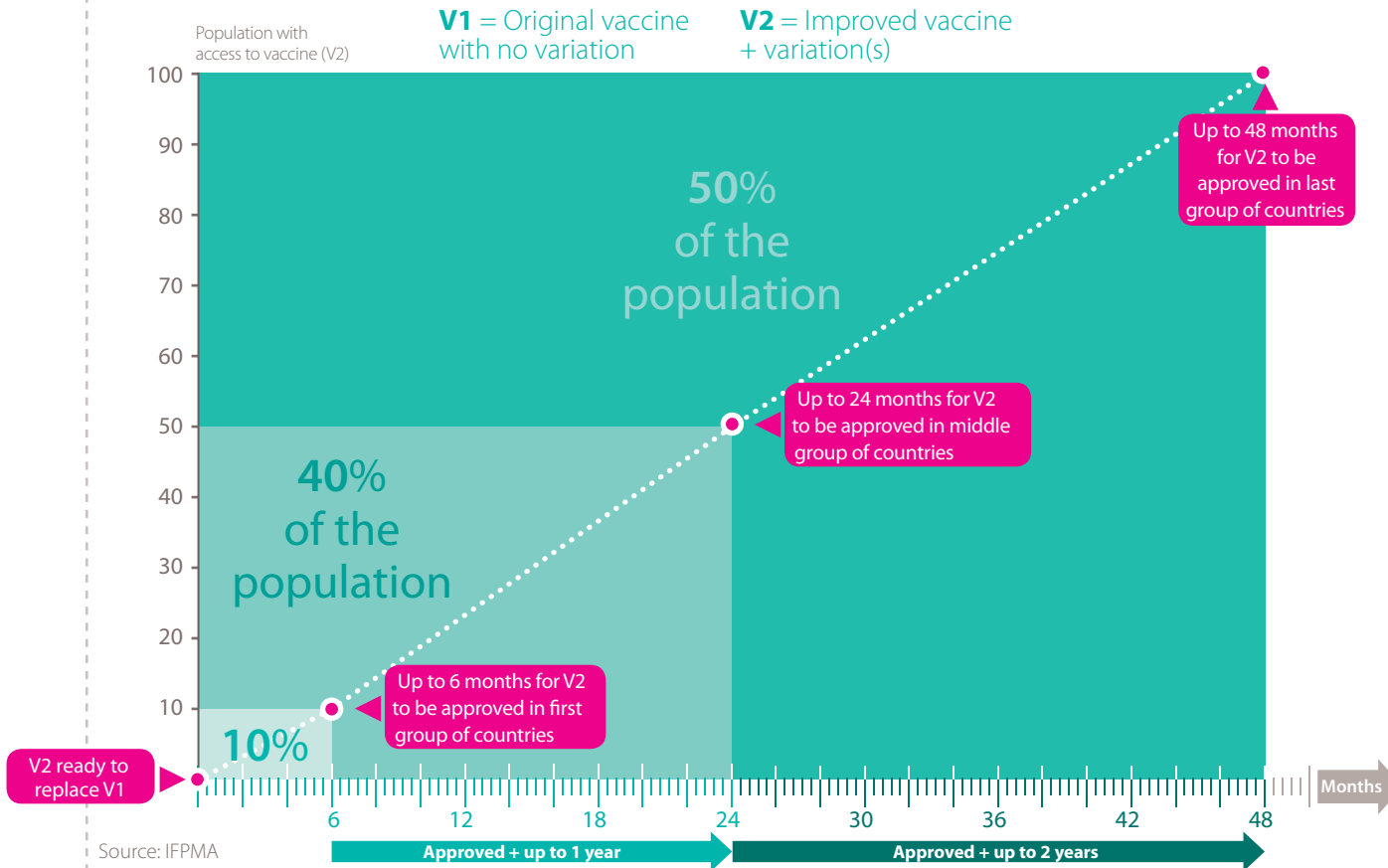
The regulatory requirements are not harmonized and the review time lines can vary greatly from country to country.

After validations studies have been completed and the variations document submitted to regulatory authorities, it takes approximately 2 years to obtain regulatory approvals for manufacturers to be allowed to supply the new version of the vaccine to 50% of the world population. For the other 50% of the world population, involving a considerable percentage of children under 5, regulatory authorities take up to 48 months to grant the approval.

The following graph illustrates the amount of time it takes to complete the approval process worldwide of one single variation for a complex vaccine.



## Differences of Approval Times



### 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.

### The variability in approval times can have different causes:

- ➔ The documentation review cycle by the regulatory authority may be slow due to lack of resources and expertise;
- ➔ The time to approval may be delayed because a manufacturer cannot submit the change request without prior approval in another market (i.e. need to await source country approval before submission);
- ➔ The definition of what is a “major” change (has the potential to impact the Quality, Safety and Efficacy (Q,S,E) of the vaccine) is not harmonized globally. For example, there are changes that are categorized as minor in one country that would be considered as a major change in others. This difference in change categorization has a huge impact upon review times.

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### **Consequences of long approval times on access to vaccines and security of supply**

Differences in approval times can have serious consequences on access and security of supply. Indeed, due to the complexity of the production process and limited production capacity, manufacturers often cannot simultaneously maintain two separate manufacturing processes (one for the original vaccine and one for the improved vaccine with the changes implemented) at the same time.

### **Manufacturers are frequently faced with the following options:**

#### **Option 1:**

Stop production of V1 and implement vaccine V2. Vaccine V2 can only be made available in the countries where it is approved. There is a risk of shortage for people in countries where the variation is not approved when stocks of V1 run out.

- ➔ This option does not support fair and equitable access to vaccines.

#### **Option 2:**

Continue production of V1 until the variation is approved worldwide, even though this means delaying access to an improved vaccine for the entire global population.

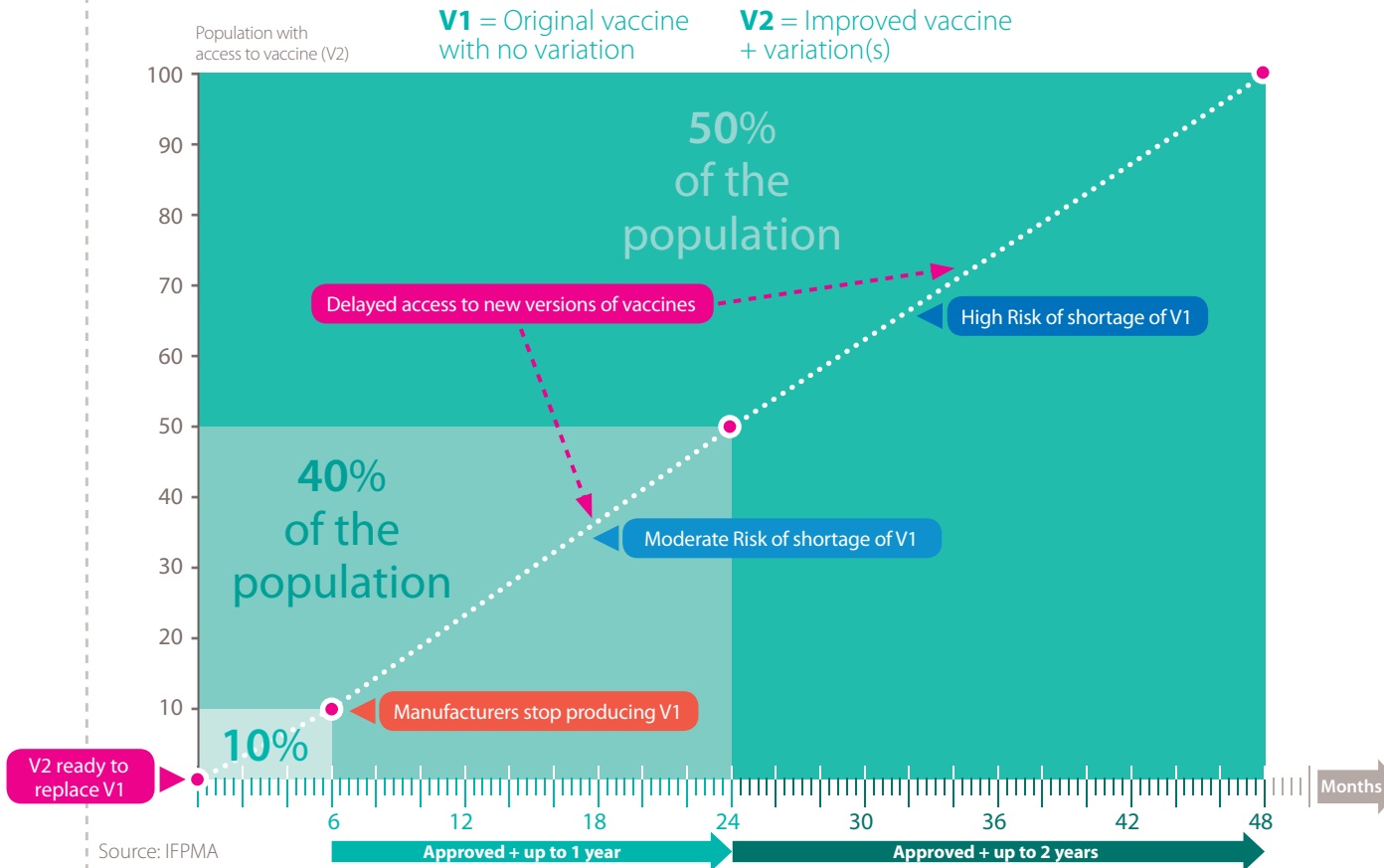
- ➔ Option 2 is not always possible; if the variation has been developed to meet new standards, manufacturers cannot (and are not allowed to) wait for all countries to have approved the variation as they may undergo inspections of their site that will verify that the variation has been implemented.
- ➔ Option 2 is also complicated by regulatory agencies that require the variation be implemented once it is approved in their country.

#### **Option 3:**

Sustain the production of V1 and V2 at the same time.

- ➔ This can put the supply chain at risk due to the increased complexity of maintaining more than one process and the need to restrict V2 to the countries where it has been approved.
- ➔ This option is typically not feasible because manufacturers do not have the capacity to operate two separate production lines.

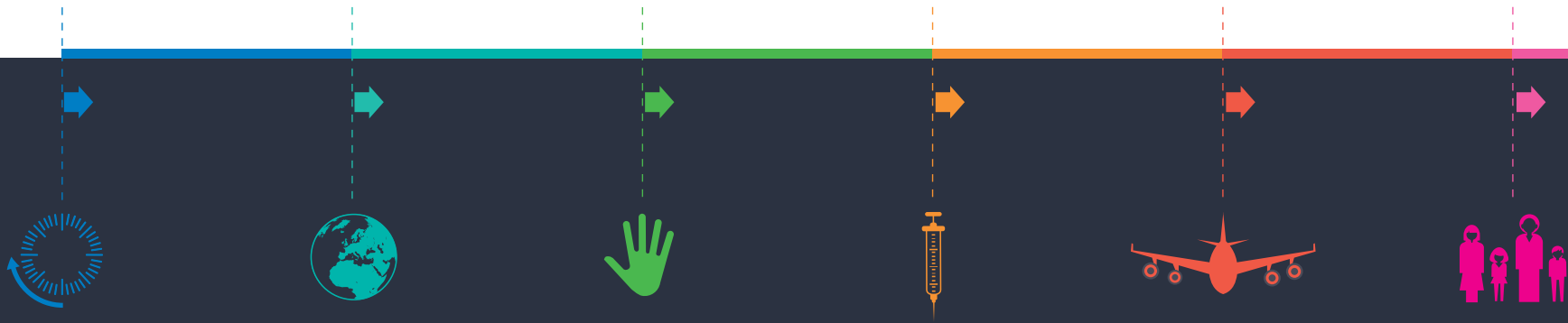
## Approval Times, Risk of Shortage and Inequity



- ➔ Companies usually stop producing V1 shortly after the first group of countries has approved the variation, production of the improved vaccine (V2) commences. This means that the last group of countries will be supplied from stock manufactured with the previous process. The longer the approval takes, the greater the risk of vaccine shortage because stocks are depleted or expired.
- ➔ Differences in approval time also create inequity, a significant part of the population cannot have access to improved vaccine.

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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 1.3 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.

IFPMA manages global initiatives including: IFPMA Developing World Health Partnerships initiative studies and identifies trends for the research-based pharmaceutical industry's long-term partnership programs to improve health in developing countries; IFPMA Code of Practice sets standards for ethical promotion of medicines; IFPMA Clinical Trials Portal helps patients and health professionals find out about on-going clinical trials and trial results.

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