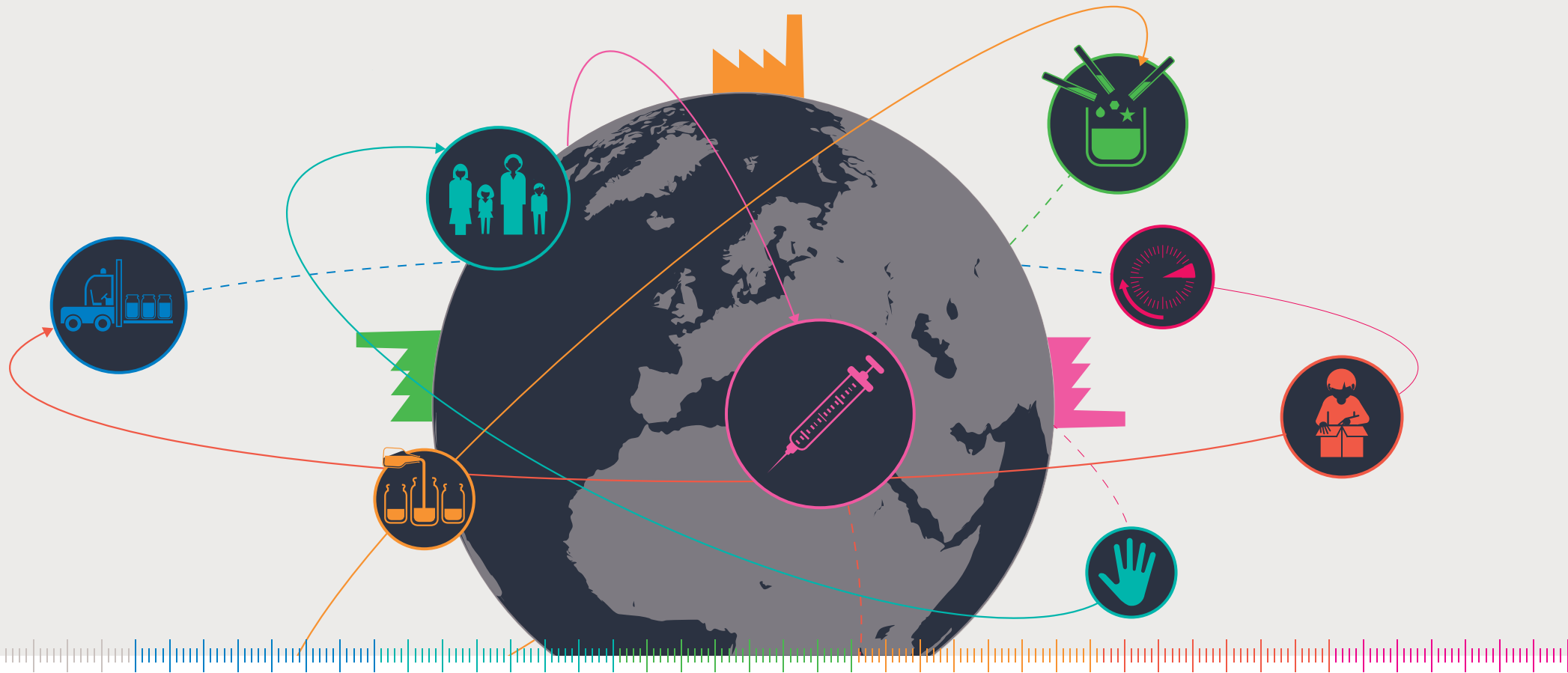


# THE COMPLEX JOURNEY OF A VACCINE – PART III

## The Steps Behind Developing a New Vaccine



## A Short Overview of the Clinical Development of a Vaccine

Vaccines continue to revolutionize our ability to prevent diseases, save lives, and improve health. The scientific community, including our own researchers, are driven by a shared purpose to improve vaccine technologies and bring the benefits of immunization to everyone, regardless of where they live. With every technological advance, our members are uniquely placed to bridge the gap between breakthrough discoveries and revolutionary vaccines, and to provide better protection from life-threatening and debilitating infectious diseases. However, developing new vaccines is a complex process, and the benefits from these advancements will not be fully realized unless there is also significant progress in areas such as regulatory convergence and harmonization.

This brochure explains why the regulatory environment is critical to allow timely development of vaccines by answering the following questions:

- ➔ *Why is developing a vaccine so complex? How does clinical development impact availability of novel vaccines to patients?*
- ➔ *What could be done to speed up innovative vaccine development and consequently faster access to life saving products?*

The development of novel vaccines is a long endeavor. It takes usually between 10 to 15 years to develop a novel vaccine, as well as establishing its quality, safety and efficacy. There are three major factors that contribute to these long timelines:

### 1 Vaccine Development Complexities

Vaccines are complex biological products which are given to healthy people. Safety is therefore paramount; vaccine development often entails large, time-consuming and resource-intensive studies in order to detect rare safety issues and to establish vaccine efficacy.

### 2 Globalized Clinical Development

Data from different countries/regions is often requested for regulatory approval purposes. However, many countries have divergent clinical labelling requirements as well as varying timelines, which adds further complexity to the process of conducting clinical trials across the globe.

### 3 Divergent Regulatory Requirements

Regulatory requirements for clinical trials (both Chemistry, Manufacturing, and Controls, or CMC, nonclinical and clinical) also vary significantly between countries and regions. Consequently, this may result in significant delays in the development of novel vaccines.

# 1 Vaccine Development Complexities

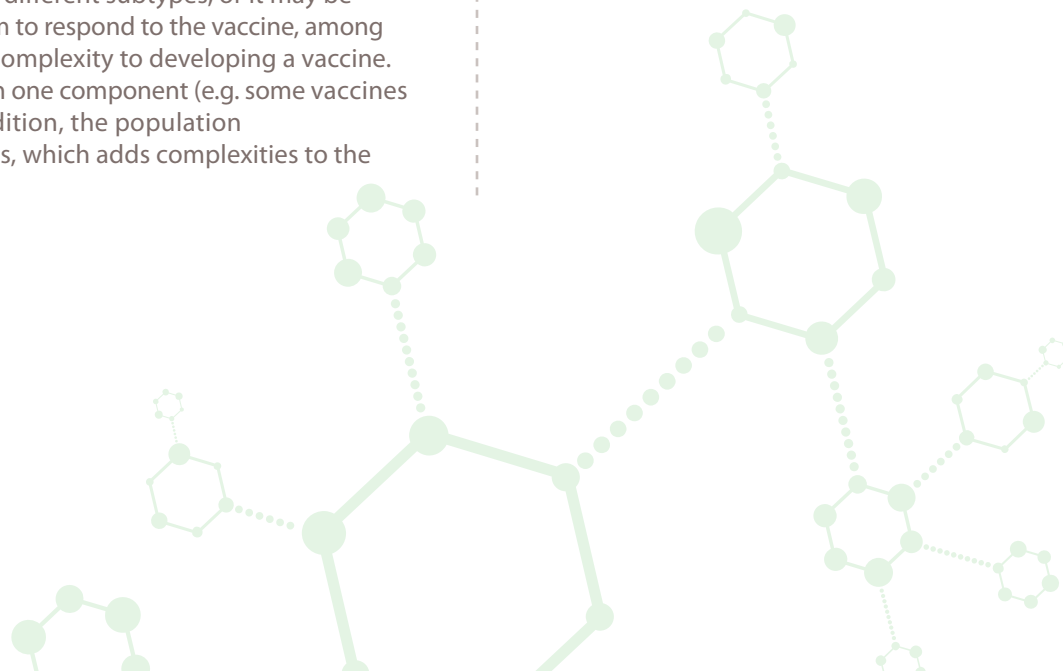
Vaccines are primarily intended for use in healthy individuals as a preventive measure. They are complex biological products which are developed to prevent;

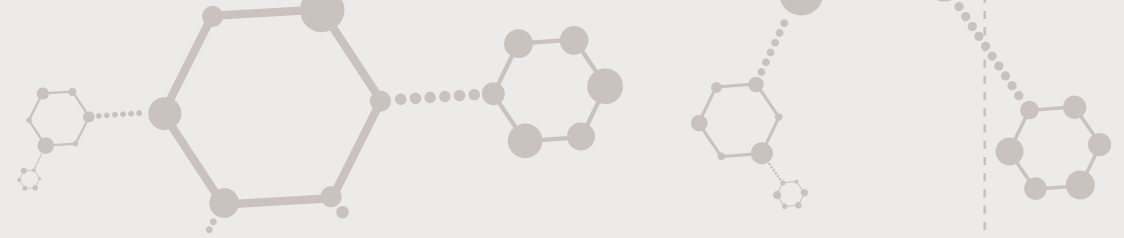
- ➔ *Infections by current or emerging infectious disease agents (pathogens such as viruses, bacteria, and parasites).*
- ➔ *Infections against diseases where classical medicinal products don't work any longer (e.g. against antibiotic resistant bacteria).*

Their development is a complex and lengthy process and it significantly differs from the development of conventional drugs, which makes their regulatory assessment also more technically challenging. For instance, some pathogens can mutate, or have different subtypes, or it may be difficult to activate the immune system to respond to the vaccine, among other issues; that adds considerable complexity to developing a vaccine. Also, some vaccines include more than one component (e.g. some vaccines contain 23 different antigens). In addition, the population being targeted is often healthy infants, which adds complexities to the vaccine development.

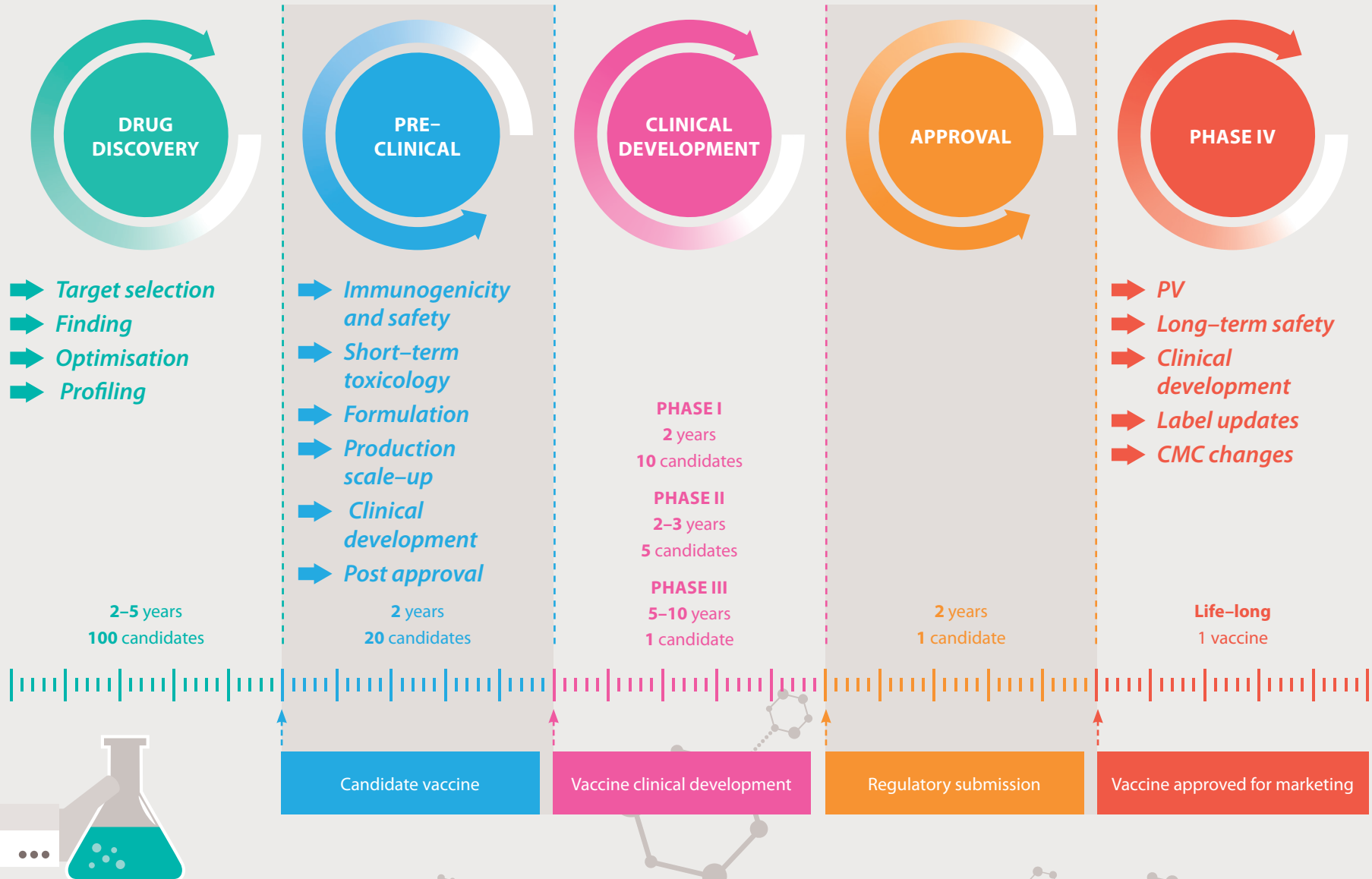
In contrast to classical medicinal products that treat a disease in sick people, the intention of a vaccine is to prevent an infection and/or a disease in a healthy population. Since vaccines are given to healthy people throughout life, from childhood to older age, it is necessary to establish a very large safety database, by carrying out many studies involving thousands of participants, before a vaccine can be licensed. Ultimately, the benefit of the vaccine must significantly outweigh any risks.

Before a vaccine is licensed and brought to the market, it undergoes a long and rigorous process of research, followed by many years of clinical testing. The overall development of a vaccine consists generally of a discovery phase, a pre-clinical phase, the clinical development phase (phases I to III) and the post licensure phase (phase IV), and it takes on an average about 10 to 15 years.





**Figure 1: Overview of the Development of a Medicine or Vaccine**



## Pre-Clinical Trials

In vaccine development, the first step is to identify a vaccine candidate. It is the pre-clinical development stage which determines a vaccine's ultimate safety profile. During this stage the researchers will carefully select the antigen and appropriate technologies, and both in vitro and in vivo tests will be performed. The information collected from these studies will be vital to proceed with the following clinical trials in humans.

## Phase I Vaccine Studies

This first attempt to assess the candidate vaccine in humans involves a small group, usually between 20-80 subjects. The candidate vaccine will be tested for the first time in humans in order to evaluate its safety, determine a dosage range that is safe and that provides optimal immune response, and identify any vaccine-related side effects. If the vaccine is intended for children, researchers will first test adults, and then gradually step down the age of the test subjects until they reach their target age.

The goals of Phase 1 testing are to assess the safety of the candidate vaccine and to determine the type and extent of immune responses that the vaccine induces.

If results from the Phase 1 study are positive, the vaccine will progress to the next stage.

## Phase II Vaccine Trials

The goals of Phase II are to study the candidate vaccine's safety, immunogenicity, proposed doses, schedule of immunizations, and method of delivery. These trials are randomized and well controlled, and include a placebo group; some of the individuals may belong to groups at risk of acquiring the disease.

A larger group of several hundred individuals participate in Phase II testing. This phase aims at evaluating in more detail the dose and administration schedule compared to Phase I.

## Phase III Vaccine Trials

Based on the success of Phase II, the candidate vaccines move on to further research and studies, enrolling from three to tens of thousands of people.

The key objective of Phase III is to assess vaccine safety and efficacy in a significantly large group of people and specifically those for which the vaccine is aimed for. In this phase, concomitant administration with other vaccines can also be tested.

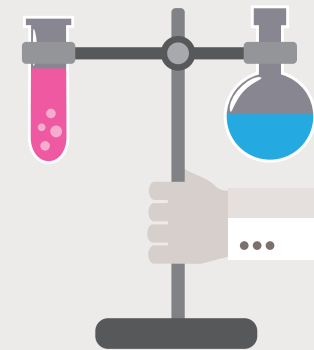
## Approval and Licensure

After a successful Phase III trial, the vaccine researcher will submit a dossier to the national competent authority which will undergo review and approval.

After licensure, the national competent authority will continue to monitor the production of the vaccine, inspect facilities and review the manufacturer's testing processes involved in the vaccine development.

## Phase IV or Pharmacovigilance

Once on the market, the vaccine manufacturer will perform pharmacovigilance activities in order to continuously assess the vaccine's safety and detect any risk of adverse event following the use of the vaccine. These studies, also called "post-marketing studies", have the objective of determining the evidence of protection given by the vaccine is long-lasting, and also to investigate new indications (or a different schedule, for instance).



## 2 Globalized Clinical Development

Infectious diseases know no borders, and the clinical testing of vaccines is a vital process to ensure safety, efficacy, and quality for all populations across the world. The globalization of clinical development requires conducting multi-country clinical trials in settings with varying maturity levels of infrastructure and regulatory capacity.

Other additional considerations for manufacturers, regulators, clinical trial sites and institutions include:

- ➔ *In some countries official quality control testing is required, making it necessary to transfer assays to governmental laboratories, which often leads to significant delays in starting the study.*
- ➔ *The vaccine supply chain for clinical trials can be quite complex, as many vaccines must be transported and stored refrigerated. In some instances, the required cold chain infrastructure needs to be set up before clinical materials can be shipped to the clinical sites. In the case of large clinical trials, vaccine studies are typically run in many different countries, which adds to the logistical complexity.*

- ➔ *Many countries and regions have divergent clinical labelling requirements, including specific requirements on the primary container (e.g. shelf-life, trial numbers, country-specific warnings etc.). This leads to multiple versions of a candidate product, which (at least in the early phases of development) is often manufactured in limited quantities; this can lead to difficulties in supplying sufficient quantities of candidate vaccines in a timely manner.*
- ➔ *Differences in approval timelines often adversely impact the overall process of study organization. It can lead to a significant delay in collecting relevant clinical data and planning study staff and number of sites, which poses challenges and often lead to a waste of resources, and may even lead to sites never being able to start the studies at all.*
- ➔ *For multinational trials, clinical study samples are often analyzed in a central laboratory for both logistical reasons and to ensure the data is collected in a consistent way, and is therefore more reliable. However, in several countries, exportation of clinical samples can be a significant challenge due to local regulatory and administrative hurdles.*

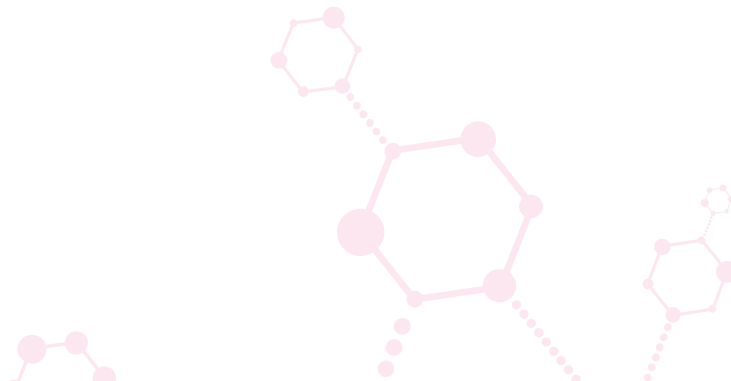


Figure 2: Regulatory Approval Timelines for Clinical Trials Globally

	Studies	EC approval average time (days)	Regulatory approval average time (days)	Overall average time (days)
Benchmark*	931	53	53	69
Country 1	37	61	36	46
Country 2	10	26	65	84
Country 3	17	58	5	90
Country 4	4	12	68	91
Country 5	36	88	61	99
Country 6	12	72	67	105
Country 7	4	48	82	117
Country 8	16	73	121	128
Country 9	34	37	58	139
Country 10	12	83	51	141
Country 11	18	83	136	146
Country 12	32	33	98	157
Country 13	16	59	55	162
Country 14	18	36	195	168
Country 15	15	30	100	191
Country 16	1	–	205	205
Country 17	27	107	132	221
Country 18	1	163	105	281
Country 19	5	261	174	300
Country 20	3	139	311	323
Country 21	1	365	172	365
Country 22	1	329	346	484
Country 23	9	14	673	1093
<b>Sum</b>	<b>329</b>			

\*Benchmark: ICH founding members, N=931 Clinical Trial Applications

Depicted Countries: N=329 Clinical Trial Applications

Even if the above challenges are overcome, there is still a high variability and uncertainty around the approval times to start the clinical trials; those can have different causes and may include the following:

- ➔ *The documentation review cycle by the regulatory authorities and ethics bodies may be slow due to a lack of resources and expertise;*
- ➔ *The review involves several different ethics committees and regulatory authorities, sometimes in a sequential process (i.e. need to wait for the ethics committee's approval before submission to the regulatory authority);*
- ➔ *Often there is no possibility to interact with ethics committees and regulatory authorities prior to submission of the Clinical Trial Application (CTA), which would otherwise help in a better mutual understanding of requirements and product specifics ahead of the submission;*

➔ *Genetically modified organisms (GMOs) are often regulated by different departments/ministries (e.g. Ministry of Agriculture), while CTAs are often handled by the Ministry of Health; there is typically no alignment between the different ministries, both in terms of submission windows as well as approval timelines. Also, ministries in charge of overseeing GMOs often lack knowledge about clinical trials with medicinal GMO products, which leads to additional challenges causing delays.*





## Differences Between Vaccines and Medicines:



*Wide variety of vaccination schedules*



*Wide variety of co-administrations*



*Rare side effects sometimes mandating a Phase III of >80000 individuals*



*Rare diseases endpoints mandating large studies*



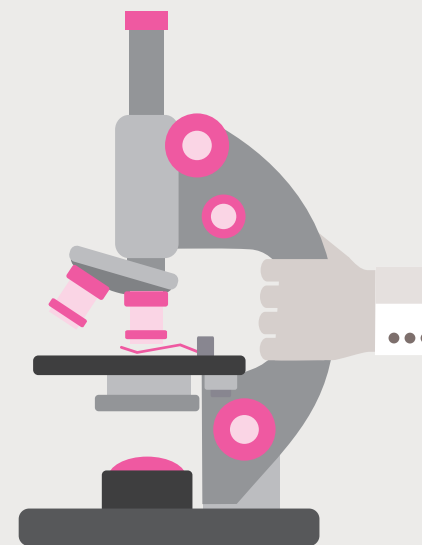
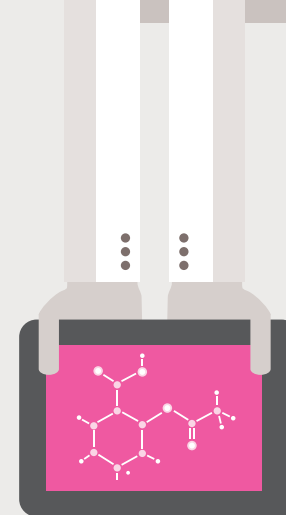
*Cold chain maintenance*



*Community-based rather than hospital-based*



*Long manufacturing lead times for clinical trial lots*



### 3 Increasingly Complex Regulatory Requirements

While regulatory authorities perform a vital role to ensure quality, safety and efficacy of a vaccine, the regulatory requirements and regulatory processes are not converging, potentially impacting the timely clinical development and availability of novel vaccines to patients. For example:

- ➔ *The review timelines can vary greatly from country to country; in some countries, certain regulations (e.g. for GMOs) can even vary from province to province. Clinical trial approvals can take from 30 days to several months - and sometimes even more than a year. In some countries, although generally limited to emergency situations, accelerated approval pathways are becoming available.*
- ➔ *In many countries, there is a sequential process of (sometimes multiple) ethics and biosafety committees ahead of the submission to the national regulatory authority, which leads to additional delays without an evident benefit in most cases.*
- ➔ *In many instances, there are no clear regulations or guidance available describing the requirements for clinical trials ahead of submission. Sometimes guidance documents are indeed available, but often those are only partially applied, or not at all. This includes both Chemistry, Manufacturing and Controls (CMC), non-clinical and clinical elements necessary*

*for the initial CTA application. This often implies unnecessary waiting periods to respond to queries which could have been handled in the initial CTA phase, thus resulting in a waste of resources, both on the sponsor and regulatory authority/ethics committee side, and ultimately causing an additional delay in the approval of the trial.*

- ➔ *There is also no global standard with regards to both the dossier content and its format, with many countries having introduced country-specific, unique requirements. In some instances, CTA applications are in a harmonized format, while in other instances country specific formats are applicable. Some countries and regions require electronic submissions, whereas others request paper submissions. This can mean that, for a single study, many different dossiers must be prepared, adding to the complexity to run global, multinational clinical trials.*
- ➔ *As mentioned before, for GMOs the applicable requirements are often focused on agricultural products and processes which not applicable to clinical trial products, including vaccines. In such circumstances, the GMO application approval often takes longer than the CTA application itself.*

## It Is Time To Act – Healthy People Are (Done) Waiting

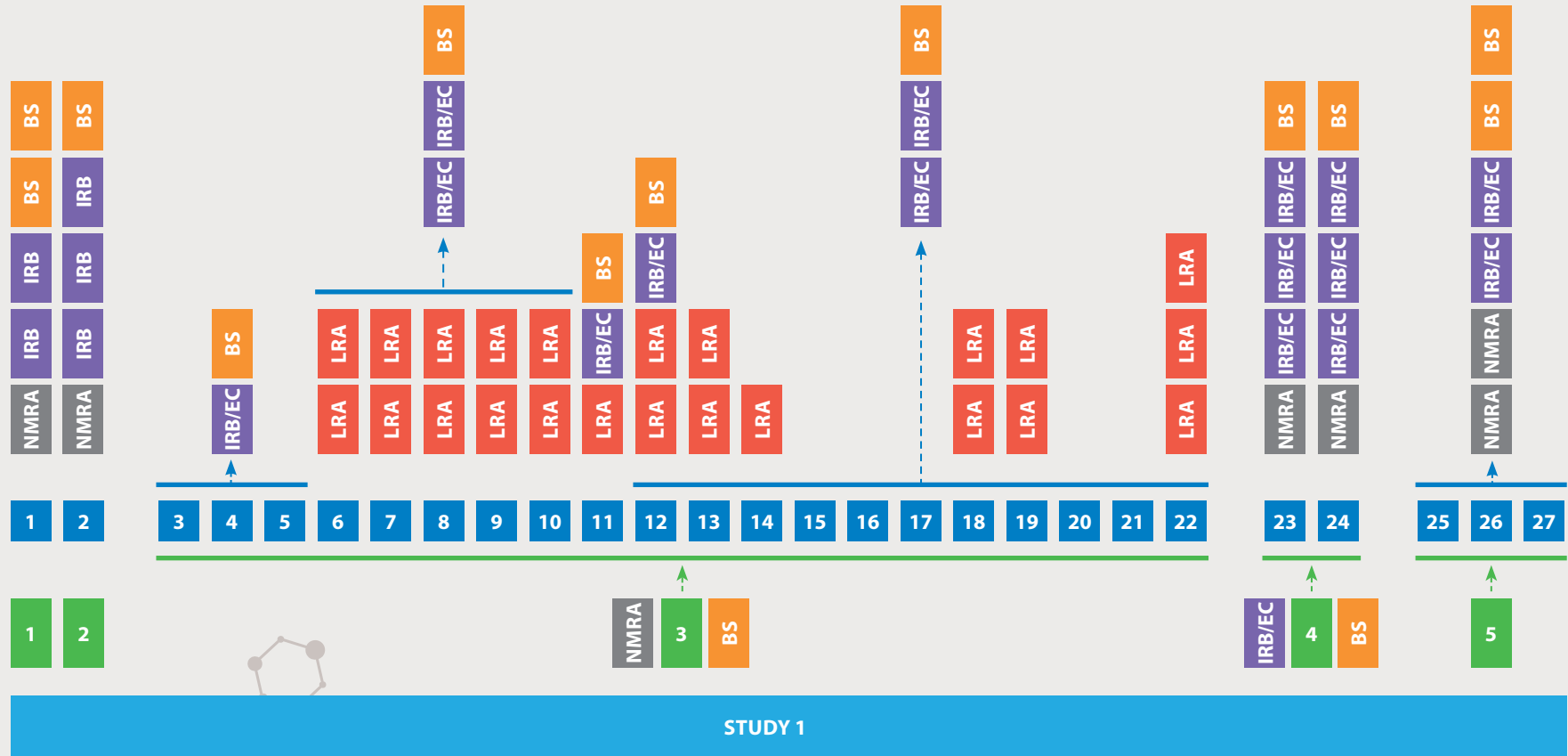
The current complexity of global regulatory processes for CTAs is a threat to innovation, and is likely to slow down access to innovative products. As for the development of a novel vaccine, three development phases are needed. It is estimated that delay in CTA approval delayed possibility to license of more than three years. Considering that, for a disease such as HIV, a 50% effective vaccine could prevent 2500 healthy people getting infected every day, any unnecessary delay to having a vaccine approved entails a human cost.

All medicinal products, including vaccines, must go through three phases of development - each with sometimes multiple clinical trials - before the product can be licensed. For each of these a CTA has to be filed to the Health Authority in each of the participating countries. In addition, multiple ethics and biosafety bodies are usually involved in the review of the study at each of the participating clinical study sites. During the development of a vaccine multiple and large clinical trials have to be conducted and consequently, the generally lengthy CTA approval process has a significant impact on the overall development timeline. For many new vaccines, development is global and clinical trials are conducted across different countries and regions. The current complexity, divergence and lack of a coordinated approach to regulate CTAs may impede innovation and ultimately slow down access to innovative vaccines.



Figure 3: Multiplicity of Approvals

Real world information from a multiregional trial



**STUDY**

**COUNTRY**

**SITE**

**NRA** National Reg Authority

**LRA** Local/Provincial Reg Authority

**BS** Biosafety

**IRB/EC** Ethics committee

**Country Approvals**

The countries above have achieved the indicated study approvals. Their site specific approvals are indicated on the right.

- ➔ 1 Trial
- ➔ 5 Countries
- ➔ 27 sites
- ➔ Ca. 65 Approvals

➔ ***Need to establish a common, global set of requirements for CTAs as per the phase of development***

Need for a guidance document issued by WHO, the International Conference on Harmonization (ICH) or other unifying bodies.

➔ ***Need for a one-dossier-fits-all for CTA***

Like the calls for convergence and harmonization towards standardized registration procedures for new marketing applications and post approval changes, there is an urgent need to establish a common and global set of requirements for CTAs. This could be driven by global bodies such as WHO or ICH. The objective is to allow applicants to use a common dossier for applications to Ethical committees and regulators in different countries. For these reviewers the added benefit is to receive standardized information irrespective of the originator which facilitates reviews.

➔ ***Parallel ethics committee and national regulatory review rather than sequential reviews will be more beneficial and time saving***

Too often, the ethics committee and the national regulatory authority applications are required to be submitted in a sequential way. This unnecessarily lengthens the time to obtain approval to start a clinical trial, as shown from the data in Figure 3. A coordinated and simultaneous application to ethics committees and national regulatory authorities could considerably shorten development timelines.

➔ ***Clear and transparent assessment timelines***

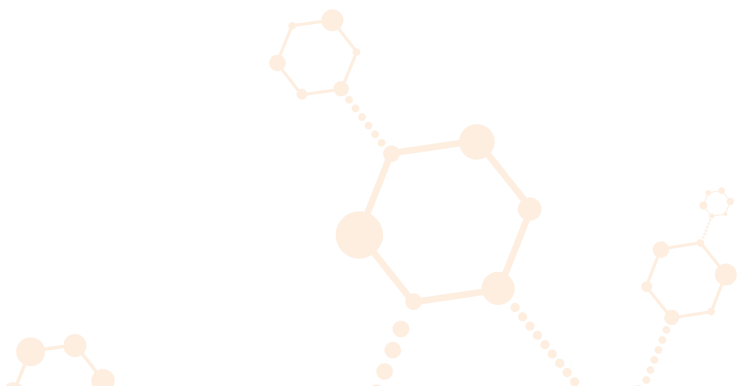
Timelines for approvals vary considerably between regions and between either ethics committees and national regulatory authorities. Other (regulatory) applications for, such as; products variations or renewals, target timelines are recommended and implemented by WHO and many other authorities. Having clear and transparent timelines and adherence to these will result in predictability for applicants and more efficiency.

➔ ***Transparency, consistency and predictability in regulatory outcomes and decision making***

The outcomes of the ethics committees and national regulatory authorities' reviews, as well as established timelines, should be shared in a transparent and safe manner such as to facilitate subsequent applications and reviews. This will also contribute considerably towards building mutual trust, which is paramount to reliance.

➔ ***Closer harmonization and specialization of NRAs, where possible, leading to reliance and potential mutual recognition***

Reliance is increasingly being considered and used for regulatory processes and reviews related to new product applications, as well as life cycle management or post approval changes. Using converging guidelines and considering joint reviews between regulatory authorities or ethics committees is an efficient way forward. Given the complexities of modern clinical development, reliance and joint reviews will also allow certain committees and authorities to specialize in particular diseases or technologies without having to spread resource too widely in order to review every single application. An interesting example of a joint review of vaccine CTA applications is the one carried out by African Vaccine Regulatory Forum (AVAREF).



➔ ***Expedited approval of certain CTAs that are of significant benefit to the healthy population***

There are public health emergencies (e.g. Ebola outbreak) or medical needs which could require expedited approval pathways. These circumstances could result in a different risk benefit ratio and thus mandating a more urgent action. These expedited pathways can potentially provide quicker access to certain vaccination options or provide developers with insight early on, to help steer development in the right direction.

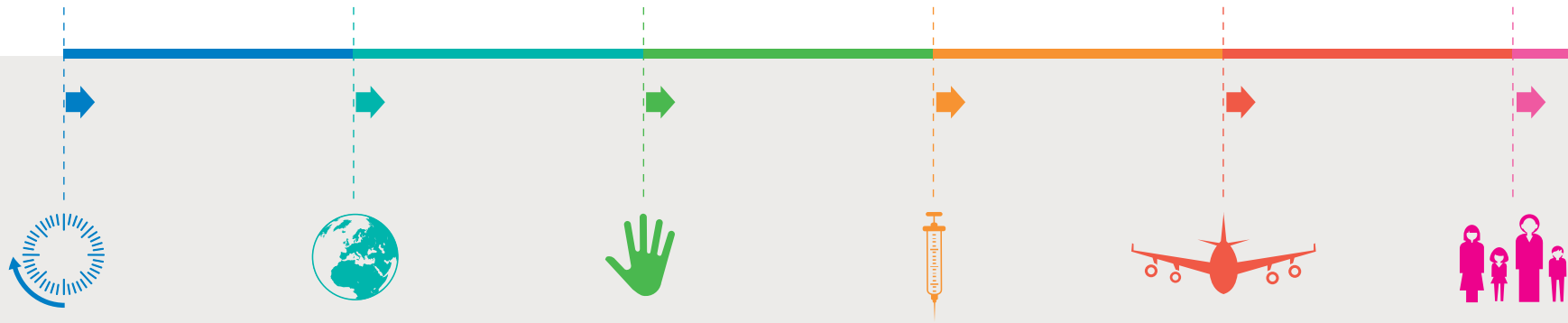
➔ ***Focus on reducing overall regulatory burden for national regulatory authorities, ethics committees and study sponsors***

Convergence and Harmonization of CTA Requirements, Reliance and Mutual Recognition of CTA Approvals can save precious development time, potentially saving millions of lives. It is time to act...





The regulatory processes during the clinical development of a vaccine are necessary to safeguard healthy people but at the same time these require resources and time from all stakeholders (national regulatory authorities, ethics committees and study sponsors). It is in the overall interest of patients that these regulatory processes enable robust and timely clinical development and not become a barrier. Therefore, convergence towards common global standards for CTA requirements, reliance and ultimately mutual recognition of CTA approvals, will result in enabling this robust and timely development of much needed vaccines.



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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.

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.

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