IFPMA

DCVMN

THE DEVELOPMENT AND MANUFACTURE OF VACCINES TO PROTECT GLOBAL HEALTH

01

THE LONG JOURNEY OF BRINGING A VACCINE TO MARKET

KEY STAGES AND TIMELINE TO BRING VACCINES TO MARKET

The successful accelerated development and manufacturing of COVID-19 vaccines was an exceptional achievement enabled by various factors such as intense international collaboration among various stakeholders, rapid sharing of pathogens and data, reliance on innovative technology platforms, and use of regulatory agilities and convergence. 1. Adjuvants: Ingredients of some vaccines that help to promote a better immune response; they can also reduce the amount of virus needed for the vaccine production. 2. However, extensive previous research and insights around vaccines and possible diseases that could cause a pandemic were leveraged during this time. GMP: Good Manufacturing Practice.

				STANDARD timeline to bring a vaccine to market: 10-15 years on average	**ACCELERATED** timeline to bring COVID-19 vaccines to market: 1-2 years
1	**RESEARCH & ANTIGEN DISCOVERY**	◆ Intensive research around the antigen	◆ Vaccine candidate is evaluated for safety and efficacy using in vitro and in vivo testing	**1-5 years**	**6 months[2]**
2	**PRE-CLINICAL DEVELOPMENT**	◆ Safety studies are conducted (laboratory and animal models)	◆ No testing on humans in this phase ◆ Adjuvant(s)[1] selection/consideration	**1-4 years**	**6 months**
3	**CLINICAL DEVELOPMENT**	◆ Human clinical trials ◆ Small-scale process development: - Process system definition and - First GMP-level batches tested for safety	◆ Testing in human clinical trials in 3 phases: i Small # of people ii Larger # of people iii Thousands of people	**5-7 years**	**1.5 years**
4	**REGULATORY REVIEW & APPROVAL**	◆ Document regulatory submission, evaluation for approval	◆ The regulatory authority may conduct its own testing/evaluation	**1-2 years**	**6 months**
5	**MANUFACTURING SCALE-UP**	◆ The manufacturing processes is established and optimized—for commercial scale	- Regulatory & GMP requirements - Large scale production of enough vaccine doses for NIPs	**+/-24 months**	**3-6 months**
6	**POST-LICENSE MONITORING & QUALITY CONTROL**	◆ Following its market entry, the product is tracked and monitored ◆ Post-marketing safety and efficacy are monitored during a vaccine's whole life ◆ Phase IV trials may be conducted	◆ Long term impact & safety of the vaccine is monitored ◆ Monitoring of side effects or issues reported following vaccination	**Throughout the entire lifecycle**	**Throughout the entire lifecycle**

HIGH INVESTMENT IN VACCINE R&D

Vaccine R&D is a lengthy and capital-intensive process, accompanied by substantial risk of failure for any candidate under development.

High investment in vaccine R&D

- R&D investment for vaccines can range from $200 million to $1 billion+
- High degree of innovation goes into the early stages of discovery (from antigen design to selection of formulation and dose optimization)
- Low success rate: 6% probability of market entry from preclinical stage
- Lack of competitive vaccine markets for diseases most prevalent in lower-income countries

High investment in vaccine R&D

PARTNERSHIPS CAN HELP DRIVE INNOVATION

- Collaborative innovation models, including product development partnerships (PDPs) can support the development of, and expand access to, vaccines tackling neglected diseases and addressing unmet needs in endemic countries
- PDPs are successful models to undertake R&D in diseases which would otherwise lack commercial interest; avoiding a single entity having to bear the full cost and risk of R&D
- PDPs may leverage partnerships with industry, public and private actors, but also philanthropic entities
- Innovating funding mechanism, such as Advance Market Commitments (AMC) can secure access to innovative vaccine where the demand is uncertain

TECHNOLOGY PLATFORMS

Depending on the target pathogen (bacteria / virus) various technology platforms can be used to create a vaccine and initiate an immune response.

TRADITIONAL PLATFORMS:

- **Live-attenuated vaccines:** contain a live pathogen from a bacterium/ virus that has been attenuated/weakened
- **Inactivated vaccines:** contain an inactivated/killed pathogen from a bacteria /virus which creates an immune response
- **Subunit, recombinant, polysaccharide, and conjugate vaccines:** contain a piece of a pathogen (like its protein, sugar or capsid-a casing around the germ) not the whole organism
- **Toxoid vaccines:** contain inactivated toxins (proteins) to target the toxic activity created by the pathogen, rather than targeting the pathogen itself

DIVERSITY

Different technology platforms may offer different advantages and hurdles depending on the pathogen, desired immune response, and people's needs.

INNOVATIVE PLATFORMS:

- **Viral vector vaccines:** use a harmless virus - the vector - to deliver the genetic code of the antigen (that the immune system should fight) to the host cells, triggering an immune response
- **Nucleic acid vaccines:** use genetic material (DNA or RNA), from a virus/bacterium, used by the host cells to produce a protein from the pathogen, recognized by the immune system as foreign (antigen), triggering an immune response
  - **mRNA vaccines:** introduce messenger RNA, containing genetic instructions for the cells to produce the vaccine antigens and generate an immune response
  - **DNA vaccines:** use small DNA molecules (plasmids). DNA vaccines are currently under research and no DNA vaccine has been approved to date

Diversity

VALUE OF DIVERSE VACCINE PLATFORMS:

- Widens vaccine choice for people (who may have different needs and preferences)
- May facilitate access globally (given countries' different infrastructures and resources)
- Can facilitate supply reliability and decrease risk of shortages
- Can accelerate vaccine development during an emergency

The shortlist of the VIS 2024 (final decision in June 2024) includes the below pathogens, to be made available to countries as a part of the Gavi support programme:

Endemic diseases prevention:

- TB
- GBS
- Shigella
- Dengue

Epidemic-prone diseases:

- Hepatitis E vaccine

Vaccines considered are currently both licensed or in pipeline and **rely on various technology platforms.**

VIS: Vaccine Investment Strategy; TB: Tuberculosis; GBS: group b streptococcus

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THE SUCCESSFUL DEVELOPMENT & MANUFACTURING OF COVID-19 VACCINES

UNPRECEDENTED EFFORTS AND RESULTS

The global vaccine industry, together with the global community, successfully responded to the COVID-19 pandemic with unprecedented speed and scale.

EXTRAORDINARY RESULTS WERE ACHIEVED

- Record time for vaccine development: 326 days from genome sequencing to an approved vaccine
- The industry quickly scaled-up manufacturing, with 11 billion doses produced in 2021
- Since 2021, more than 13 billion vaccine doses administered globally during the COVID-19 PHEIC

USE OF INNOVATIVE VACCINE PLATFORMS

COVID-19 vaccines were rolled out based on both traditional platforms and groundbreaking technology platforms which can also be used as a springboard to develop new ones.

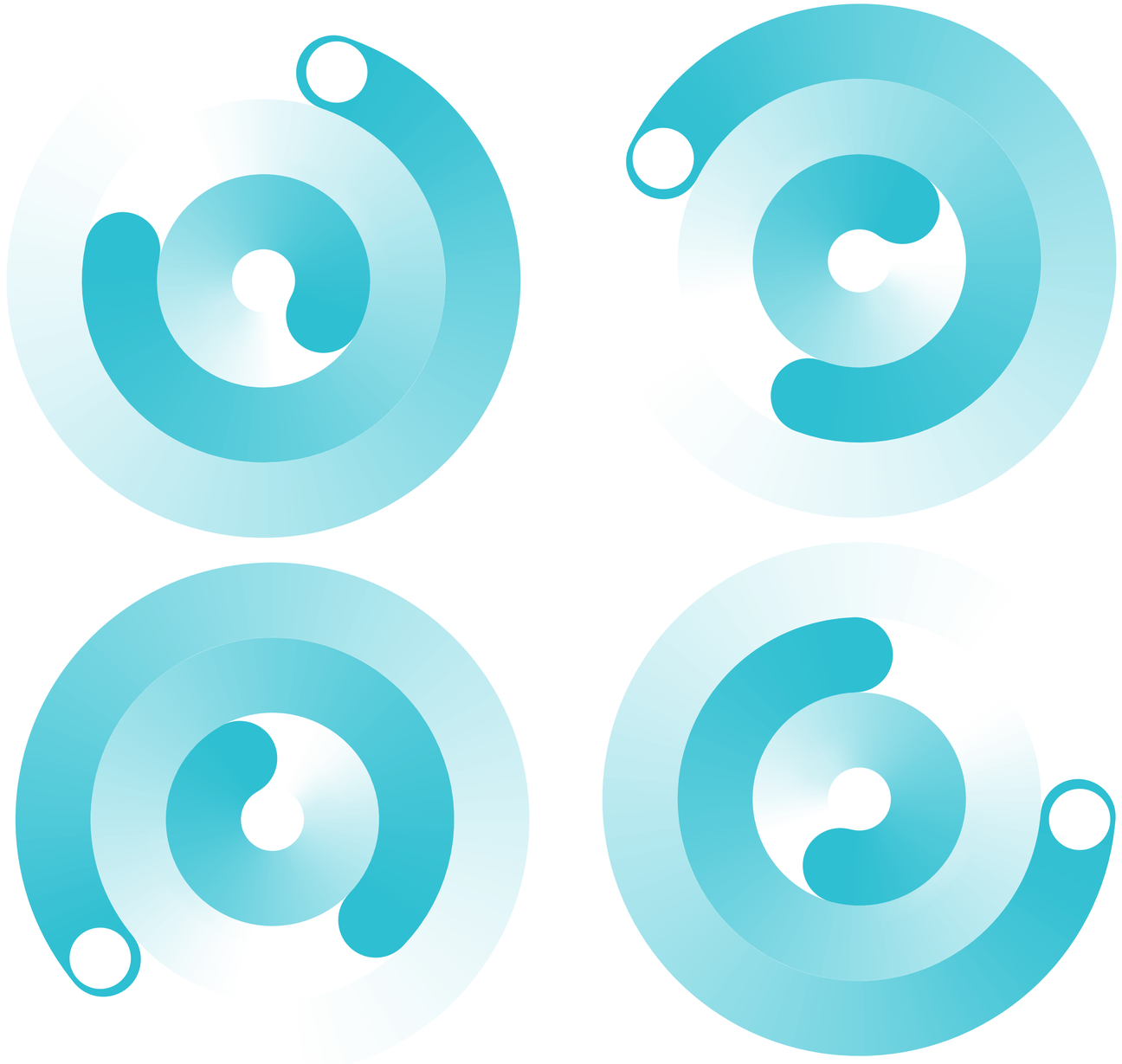
Use of innovative vaccine platforms

FACTORS THAT ALLOWED THESE ACHIEVEMENTS INCLUDED:

- Pre-existing insights on pathogens and technology platforms
- Rapid detection and open sharing of pathogens and their information on emerging infectious diseases
- Overlapping vaccine development stages
- Highly coordinated and collaborative multistakeholder global effort
- Regulatory convergence and agilities granted by regulators
- De-risking mechanisms to support R&D, scale up manufacturing, and procurement agreements
- Investments made by industry (i.e., in technology platforms and manufacturing facilities)
- Effective voluntary partnerships, including voluntary licensing partnerships, technology transfers, or approaches, underpinned by intellectual property

Even with these unprecedented timelines and results, hurdles such as sub-optimal clinical trial results, regulatory delays in different countries and difficulties scaling manufacturing were still present.

PACs: post-approval changes; PHEIC: public health emergency of international concern; mRNA: messenger ribonucleic acid



CONSIDERATIONS MOVING FORWARD

The extraordinary achievements of the COVID-19 pandemic may not be replicable for all future and new-generation vaccines for endemic and epidemic-prone diseases; however, we can still learn from this experience.

The pandemic highlighted the importance of…

- **Using innovative technologies**
- Pathogen **surveillance** and information sharing
- **Regulatory convergence and agilities** to streamline regulatory processes
- **Diversity of voluntary partnerships** that accelerate R&D and manufacturing
- **Effective planning**, at global and local levels (defining priority populations based on epidemiology and avoiding wastage)
- **Life cycle management** expertise for the continuous improvement of vaccines
- **Durability** (as well as efficacy) of candidate vaccines
- Compatibility of vaccine **formulations** with resource-limited settings
- Investing in countries' **readiness for deploying and delivering** vaccines

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COMPLEX AND CAPITAL-INTENSIVE VACCINE MANUFACTURING PROCESS

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A FOCUS ON THE MANUFACTURING CHAIN

- Vaccine manufacturing involves 6 key steps, potentially each step can be performed in different sites in different countries.
- A vaccine typically travels through several different sites before being ready for shipment.
- A vaccine undergoes up to several hundred quality control tests during its manufacturing journey.
- Quality control represents up to 70% of the full manufacturing time

Raw material reception

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

Bulk antigen manufacturing

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

Formulation

The active ingredient is mixed with other ingredients (such as stabilizers, preservatives, adjuvants) to improve the immune response and ensure product stability.

Filling

The vaccine is filled into the final container (a vial or a prefilled syringe).

Packaging

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

Lot release

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

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Manufacturing scale-up

- Testing is done by different stakeholders:
  - Manufacturers
  - Exporting country
  - Importing country

R&D: Research and development; PDPs: Public-private product development partnerships

VACCINE MANUFACTURING IS A COMPLEX AND DEMANDING PROCESS

Vaccine manufacturing processes (upstream, downstream, fill-and-finish) are lengthy, capital-intensive and complex.

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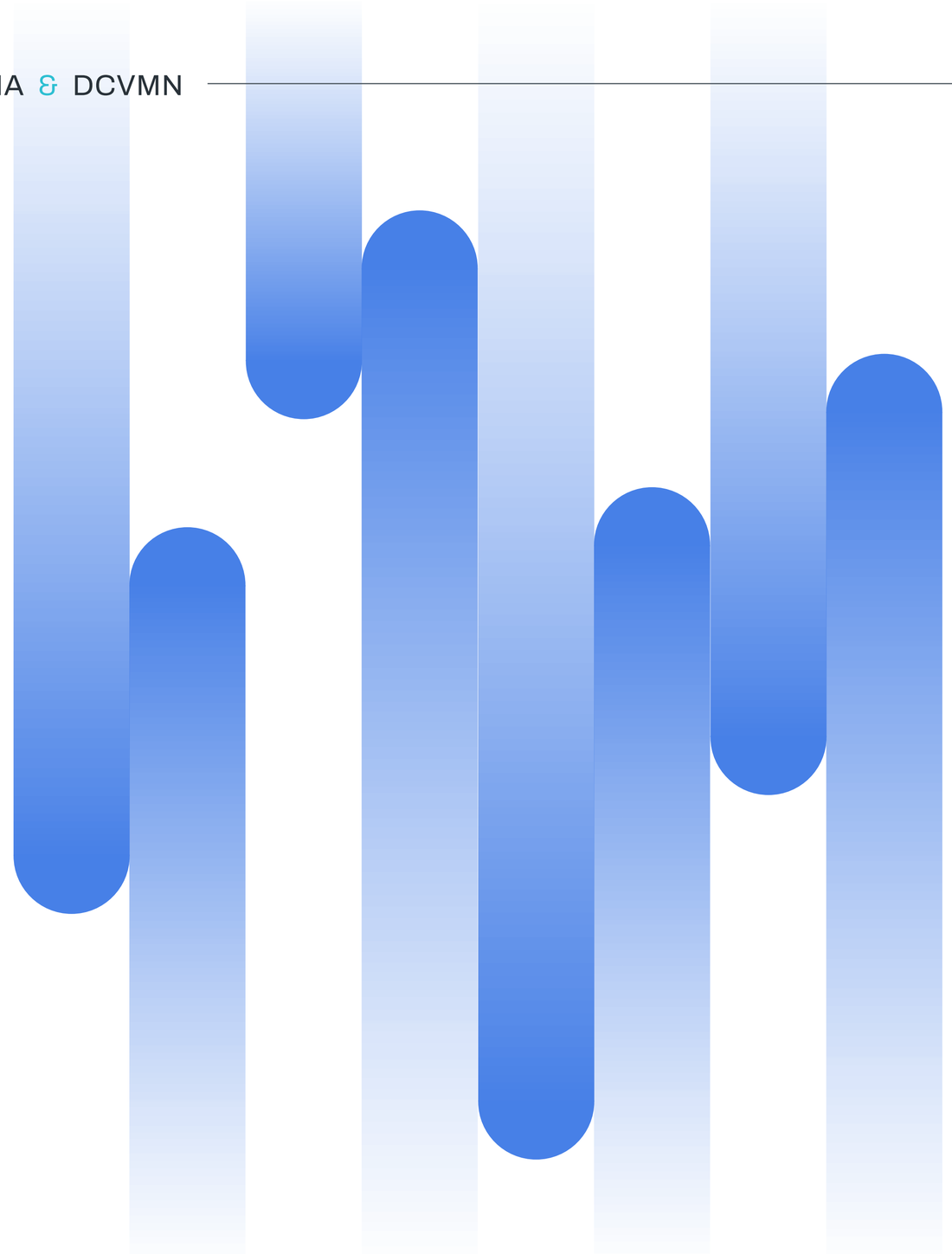
COMPLEX AND CAPITAL-INTENSIVE VACCINE MANUFACTURING PROCESS



Vaccine manufacturing is a complex and demanding process

ESTABLISHING A NEW PRODUCTION FACILITY REQUIRES:

- Considerable costs for upscaling production and regulatory updates
  - Upfront investment of $10 million to more than $100 million
  - High fixed and ongoing maintenance costs
  - 5-10 years for new facilities to be built and certified
  - 18-30 months to transfer production to other sites or manufacturers

Vaccine manufacturing is a complex and demanding process

SPECIALIZED PROCESS REQUIRING SPECIFIC KNOW-HOW:

- Complex and closely regulated manufacturing stages
- Strict quality standards to be met

TO KEEP THE PROCESS CONSISTENT AND ENSURE SUPPLY SECURITY:

- Tightly control the source and nature of starting material
- Use process controls to assure predictable manufacturing outcomes

LIMITED FLEXIBILITY FOR CHANGE :

- Once in production, it is difficult to make PACs
- Manufacturing changes may affect living systems used to produce biologics, including:
  - The nature of the finished biologic
  - How it functions in the body

PACs: post-approval changes

HIGHLY SPECIALIZED EQUIPMENT AND PERSONNEL

Vaccine manufacturing is a highly specialized process, involving cutting-edge science and technologies.

NEED FOR HIGHLY SPECIALIZED EQUIPMENT:

- Across platforms, such as bio reactors, filtration and chromatography
- In designated areas, such as filling and lyophilization
- Appropriately classified to ensure product safety
- Qualified through testing

HIGHLY SKILLED PERSONNEL TO ENSURE:

- Autonomy
- Ability to reproduce consistent manufacturing processes
- Quality control

COMMON CHALLENGES

Can be overcome via collaborative innovation models.

- Need for multidisciplinary knowledge and expertise to develop fit-for-purpose next-generation vaccines
- Need for highly specialized equipment
- Need for highly skilled personnel
- Difficult and time-consuming technology transfers
- Management of complex international supply chains frequently involving more than 100 components (often sourced from different countries)
  - Risk of shortages of equipment and raw materials; the lack of a single component can stall production and delay supply
  - Need for specific input for a certain technology platform (i.e., raw materials, consumables, equipment)

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TECHNOLOGY TRANSFERS

VACCINES SKILLS AND TECHNOLOGY TRANSFER PROCESS OVERVIEW

Stages Align with the Major Manufacturing Process Steps and Advance Upon Achieving Certain Milestones

TECHNOLOGY TRANSFERS

- A technology transfers is a complex and long process, but important to improve public health, expand capabilities and economic development of the recipient country
- Government in recipient countries can help to create the conditions to attract technology

Technology transfers

DIFFERENT ELEMENTS ARE INVOLVED:

- **Physical objects & materials** such as production equipment
- **Human skills** and trainings
- **Techniques** related to knowledge, information, and technology (in the form of a technology license)
- Organizational and procedural **knowledge to operate a technology**

SOME ENABLERS FOR SUCCESSFUL VOLUNTARY TECHNOLOGY TRANSFERS:

- Rule of law is established and enforced
- Political stability and transparent economic governance
- A trusted partner adhering to high ethical standards
- A viable, and accessible local market
- Appropriate capital markets
- Innovation-friendly environment with sound intellectual property rights
- Proper access to information
- Adherence to high regulatory standards
- Highly skilled personnel
- Clear economic development priorities

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REGULATORY AND POST-MARKETING APPROVAL CHANGES

REGULATORY APPROVAL PROCESS

Vaccines undergo rigorous and lengthy regulatory evaluation processes in different countries.

Regulatory approval process

THE VACCINE PROCESS FROM CONCEPT TO LICENSURE CAN TAKE 10 TO 30 YEARS, INCLUDING:

- Comply with diverging local and international regulations
- Apply for registration with different regulatory authority (which may require in country clinical trials)

VACCINE REGULATORY APPROVAL IS BASED ON THE SUBMISSION TO REGULATORY AUTHORITIES OF:

- Chemistry, manufacturing and controls information (processes and analytics)
- Preclinical and clinical trial results
- Proposals for post-licensure effectiveness and safety data collection

Convergence of requirements and use of regulatory reliance in decision-making can help to save resources, and facilitate timely approval and access to vaccines.

POST-APPROVAL CHANGES (PACS)

The complexity of PACs highly affects the ability of a manufacturer to supply vaccines globally and can lead to insufficient amount of vaccines to supply tender bids of countries.

PACS CAN CAUSE DELAYS IN VACCINE SUPPLY:

- Long PAC approval timelines, as PACs can take up to 4 years to be globally approved
- A simple change (e.g., a filter of chromatography) can add 2-4 years to process
- Manufacturers need to navigate complex and different regulations on approval timelines, reporting, and data requirements which can differ by country

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- Increasing regulatory harmonization and reliance can support timely vaccine supply
- The WHO Prequalification process can be used to manage PACs and reduce the long lead time for approvals

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MARKET CERTAINTY, DEMAND PLANNING, AND PROCUREMENT

LONG-TERM DEMAND PLANNING TO SECURE PROCUREMENT

- Collaboration and early dialogue with manufacturers can help align Gavi's goals with industry strategic planning
- Long-term planning and flagging vaccine demand early is important to inform investments and planning of manufacturing and supply. Inaccurate plans can result in shortages or waste

Long-term demand planning to secure procurement

TIMELY VACCINE DEMAND IS IMPORTANT BECAUSE:

- It takes 3-5 years to expand capacity with existing facilities
- It can take 5-10 years to build and qualify a new production facility
- Regulatory processes (including registration), vary by country and can require 2-4 years for approval

Long-term demand planning to secure procurement

VACCINE PROCUREMENT AIMS TO SECURE VACCINES:

- At the right time
- In the correct quantities
- At a price favorable to public markets and manufacturers

TO SIGNAL DEMAND, MANUFACTURERS LOOK TO PROCURERS TO PROVIDE:

- Accurate, accessible short-term (1-2 years) and long-term (4+ years) forecasting plans
- Demand estimates based on target population, previous consumption, and size of immunization sessions
- Relevant national procurement and regulatory requirements
- Good plans and forecasting are data driven and informed by production and delivery timelines

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THANK YOU

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