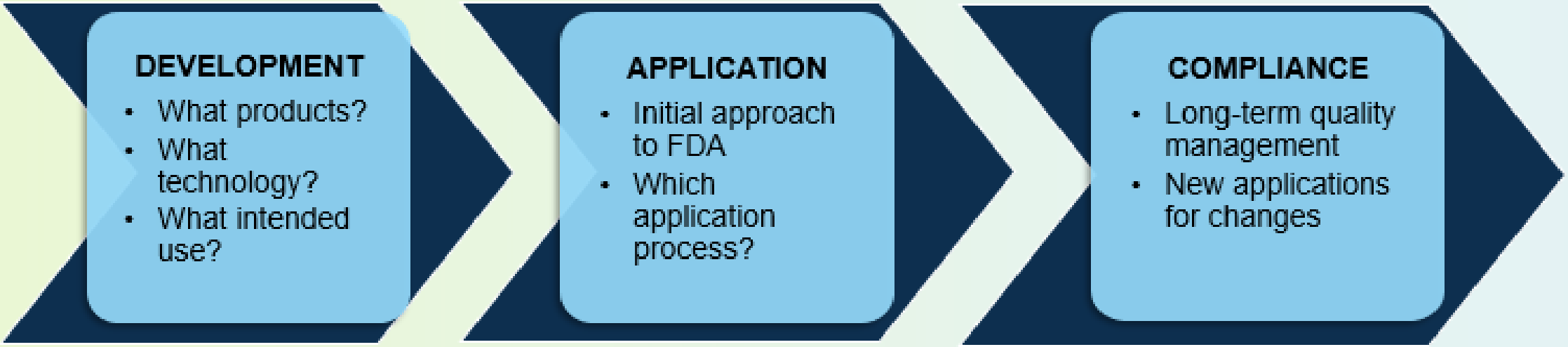
Vaccine Regulatory Case Study
EndemicEase Biotech

Regulatory Overview

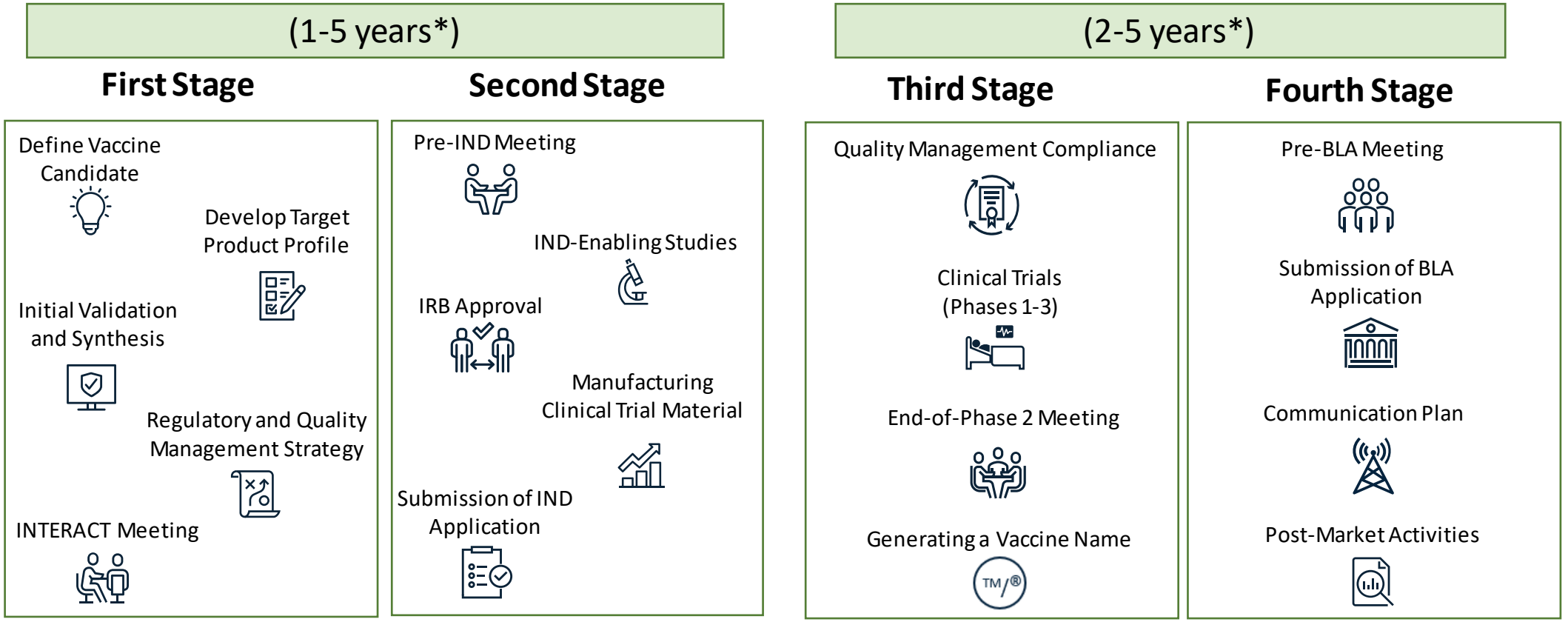
To bring a medical product to market an innovator needs to understand the entire commercialization process and manage multiple tasks related to early-stage research and development, clinical trials, regulations, and reimbursement. The goal of receiving Food and Drug Administration (FDA) approval is a major milestone in leading a new technology to commercial success. Innovators developing new medical products need to become familiar with the regulatory processes that may be applicable to their drug, device, or biologic; so, they can successfully navigate the approval process.

Key Elements of a Regulatory Strategy



Regulatory Strategy Activities Roadmap

This case study breaks down processes described in our *Regulatory Knowledge Guides*. It will take you through the steps innovators may follow when developing and executing a strategy to gain FDA market authorization. Drug development, testing, and market authorization is a lengthy process, typically taking multiple years. We'll walk through each step from the innovator's point of view, with each slide presenting one aspect within a stage of the process. Aspects of the process may be conducted together, roughly in tandem.



*Timeframes represent estimates. Completion of Stages will be variable and may be longer or shorter than noted, dependent on the vaccine platform and disease targeted.

Story Characters

EndemicEase Biotech

Headquarters: Rocky Mount, NC

Employees: 70

Specializes in respiratory viruses R&D

EndemicEase CEO

Name: **Carolyn Rilean**

Oversees all company activities. Responsible for business decisions, activities and outcomes.

Principal Investigator

Name: **Leia Parmore, PhD**

Leads all technical activities, meetings, and regulatory development for the lead vaccine candidate at EndemicEase Biotech. Responsible for all decisions, activities and outcomes.

Primary coordinator and contact with regulatory consultant, Contract Development and Manufacturing Organization (CDMO), Contract Research Organization (CRO) and NIH Program Official.

Regulatory Consultant

Name: **Kai Kekoa, PhD**

Coordinates development of the best regulatory pathway and provides regulatory solutions and expertise.

CRO

Conducts preclinical studies. Contributes knowledge, capabilities, processes and procedures for developing and conducting clinical trials.

CDMO

Provides services related to vaccine development and manufacturing.

NIH Program Official

Name: **Spencer Leyes, PhD**

Scientific and programmatic contact at NIH. Works with multiple awardees developing inhaled and injectable vaccines.

Introduction to EndemicEase Biotech

Carolyn Rilean is the CEO of EndemicEase Biotech, a small biotech company in Rocky Mount, North Carolina. EndemicEase made previous scientific discoveries with antivirals for respiratory viruses and is starting to expand its landscape into vaccine development. Carolyn has an adjuvanted virus-like particle (VLP) vaccine to immunize against Human Metapneumovirus (HMPV), a leading global cause of respiratory illnesses. Because vaccine development can be more challenging than developing small molecule drugs or monoclonal antibodies, Carolyn knows she'll need a better understanding of the steps required for regulatory approval of the vaccine candidate. She appoints Leia Parmore, a principal investigator at EndemicEase, to lead the effort.

What will EndemicEase need to do to navigate regulatory requirements and legally market a new vaccine?

Here's some background.

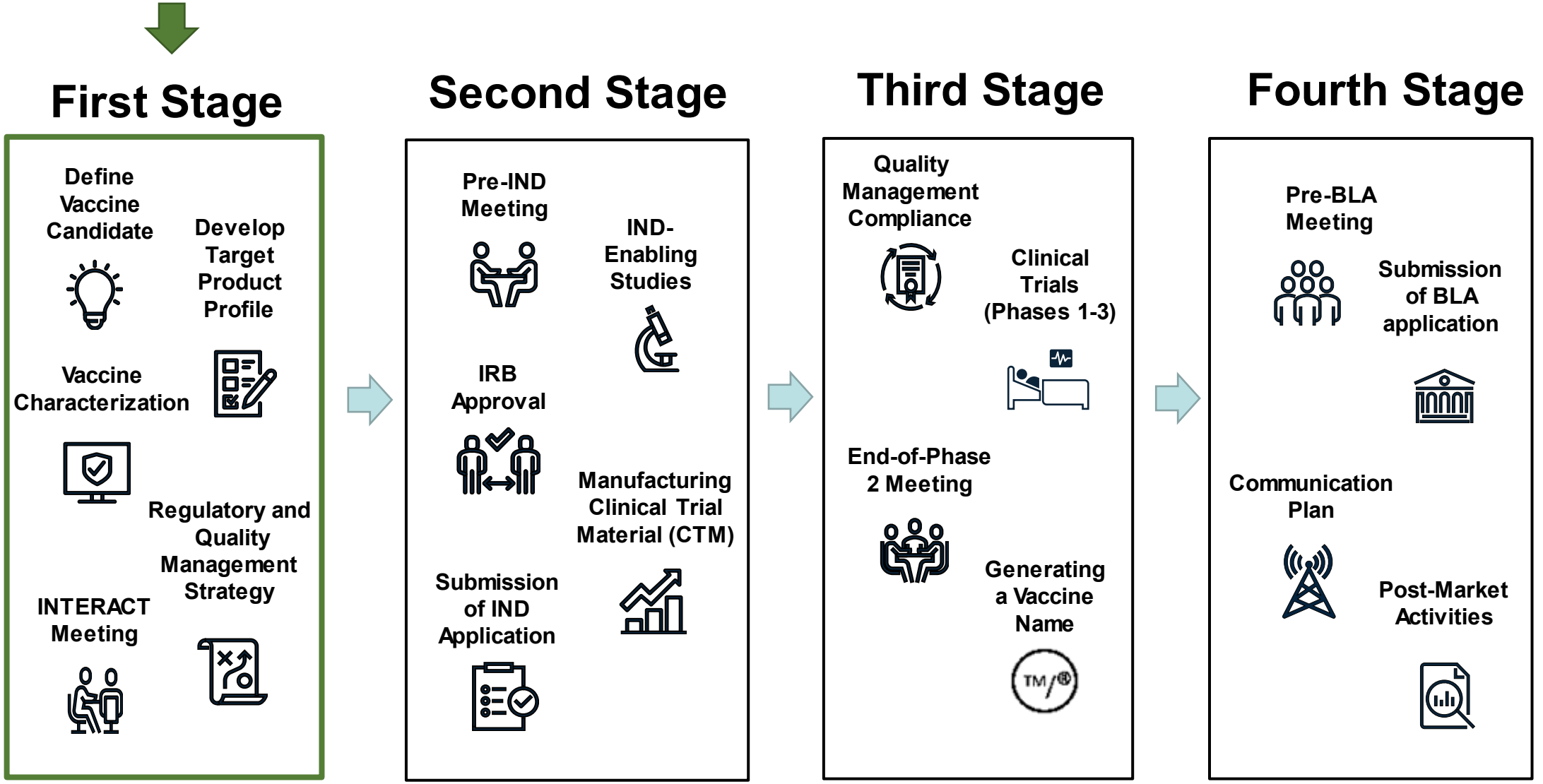
Research Description:

- EndemicEase previously investigated respiratory viruses for antiviral therapies.
- The primary hurdles in developing vaccines arise from the inherent biological complexity of the targeted pathogens. In this case, the new VLP vaccine is being developed for prevention of HMPV disease in infants, children, adolescents, and adults.
- EndemicEase has sufficient funding to support all activities up to Phase 1 clinical trials, including outsourced activities.

Why HMPV?

- HMPV is a significant worldwide cause of respiratory illnesses. While symptoms are often mild, some patients with HMPV develop a lower respiratory tract infection like pneumonia.
- There is no specific antiviral therapy for HMPV treatment and no vaccine for HMPV prevention. Medical care is supportive.

First Stage


First Stage
Define Vaccine Candidate
Develop Target Product Profile
Vaccine Characterization
Regulatory and Quality Management Strategy
INTERACT Meeting
Second Stage
Pre-IND Meeting
IND-Enabling Studies
IRB Approval
Manufacturing Clinical Trial Material (CTM)
Submission of IND Application
Third Stage
Quality Management Compliance
Clinical Trials (Phases 1-3)
End-of-Phase 2 Meeting
Generating a Vaccine Name
Fourth Stage
Pre-BLA Meeting
Submission of BLA application
Communication Plan
Post-Market Activities

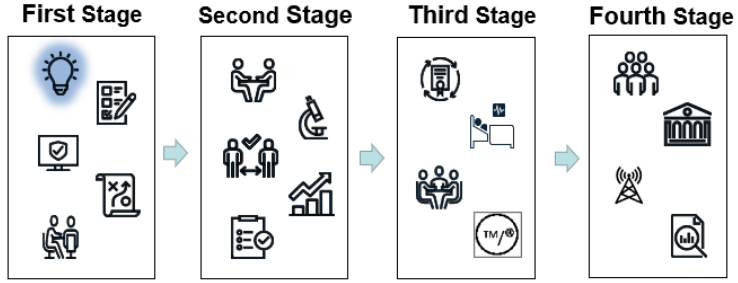
First Stage: Define the Vaccine Candidate

Developing vaccines is a more challenging process than other drug development efforts because of the inherent complexity of the targeted pathogens. Production of a HMPV vaccine involves cell culture of genetically engineered host cells to express a recombinant capsid protein, followed by harvesting the secreted protein. Researchers must test the vaccine candidate's components to ensure their safety and efficacy, which will be evaluated by the FDA's Center for Biologics Evaluation and Research (CBER).

The recombinant capsid protein of HMPV was selected to optimize protection against HMPV because it contains neutralizing epitopes. The recombinant capsid protein is expressed in a novel baculovirus-insect cell system (H5). EndemicEase's new H5 platform offers higher protein expression levels, ease of scale-up, and simplified cell growth for large-scale expression.

Leia's team decides to use a virus-like particle (VLP) approach, as VLPs are highly immunogenic and able to elicit cell- and antibody-mediated immune response. Production of this vaccine candidate, rHMPV-VLP, will involve clarification, chromatographic purification, and VLP formation. Additionally, detailed analysis of the VLP structure and function will be integrated into its characterization.

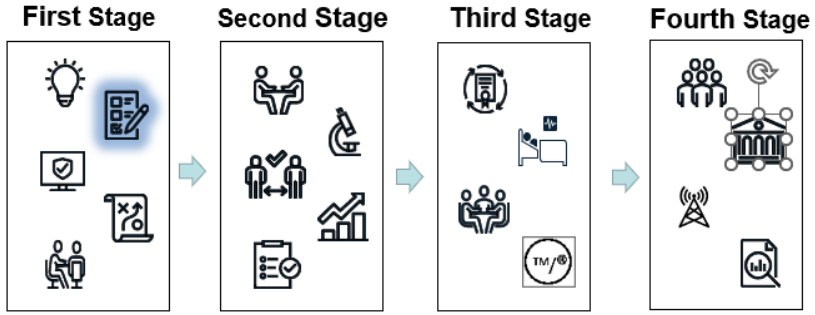
The vaccine candidate includes an adjuvant, that will target specific components of the body's immune response, intended to strengthen protection against HMPV and to elicit longer lasting protection. The team understands, when using a novel adjuvant, that additional studies will be needed to demonstrate safety. Early studies demonstrated HMPV protection in a BALB/c mouse model with and without adjuvant. This early animal data is used support the development of the Target Product Profile (TPP).



Key questions:

- What are considered pre-regulatory activities?
- How is the vaccine candidate defined?
- If the vaccine uses an adjuvant, how will that impact the regulatory process?

First Stage: Develop a Target Product Profile



After identifying the adjuvanted vaccine, rHMPV-VLP, the team develops a TPP. The TPP is a document used to plan and track new vaccine development activities and its use is strongly recommended by the FDA.

A TPP is an especially valuable tool in vaccine development, offering a comprehensive and cohesive roadmap that integrates scientific, clinical, regulatory, and commercial considerations. By defining the desired attributes and guiding the development process, a TPP helps align efforts across various teams, facilitate strategic planning, and enhance communication with stakeholders.

Leia is excited to discover a vaccine TPP example. She watches this TPP webinar which helps her understand specific attributes to include in the TPP, such as safety and efficacy-related characteristics. Her team meets and decides the TPP should include:

- Target identification and candidate development (e.g., target class, patient population)
- Clinical endpoints
- Dosage and regimen (i.e., dosage form, dose/strength, schedule, delivery mode)
- Safety and tolerability (including impurities and stability)

Key questions:

- What is included in a TPP?
- How often is the TPP updated?

TPP *The TPP is a living document and should be continually updated throughout development.*

First Stage: Develop a Target Product Profile

Attribute	Minimum TPP	Optimal TPP
Patient population	Adults ≥20 yrs	Adults ≥20 yrs, infants <1 yr, children 1-10 yrs and adolescents 11-19 yrs
Primary Endpoints	Prevent 70% of HMPV-related illnesses in adults ≥20 yrs, and reduce infection and transmission rates by at least 50%	Prevent 85% of HMPV-related illnesses in optimal patient population, and reduce infection and transmission rates by >70%
Interference	Demonstrate favorable safety and immunologic non-interference upon co-administration of other vaccines	Demonstrate maximum safety and immunologic non-interference upon co-administration of other vaccines
Safety and Tolerability	No major safety concerns or side effects; acceptable tolerability	No major safety concerns; no side effects
Dosing	Single ≤15.0 mcg in 1.0 mL dose (adults ≥20 yrs)	Single ≤15.0 mcg in 0.5mL dose (children ≤19 yrs); Single ≤15.0 mcg in <1.0 mL dose (adults ≥20 yrs)
Dosage Regimen/Schedule	Initial vaccination of 2 doses, 8 weeks apart, followed by an annual booster shot	Single vaccination, with no annual booster shot
Stability	1-year shelf life at 2-8 °C, 3-month stability at room temperature	2-year shelf life at 2-8 °C, 6-month stability at room temperature
Process-derived impurities	15-30ng/mL HCP impurities	≤15ng/mL HCP impurities

- The team creates a draft TPP. The TPP targets were extrapolated from efficacy studies in animal models. **Note:** Presented TPP shows selected attributes for a vaccine. Full vaccine TPPs can be found within the NIH SEED example, WHO Vaccine example or the BARDA example.
- Regular TPP updates are needed to assess whether required product development and critical quality attribute goals are being met.

First Stage: Initial Validation and Formulation (slide 1 of 2)

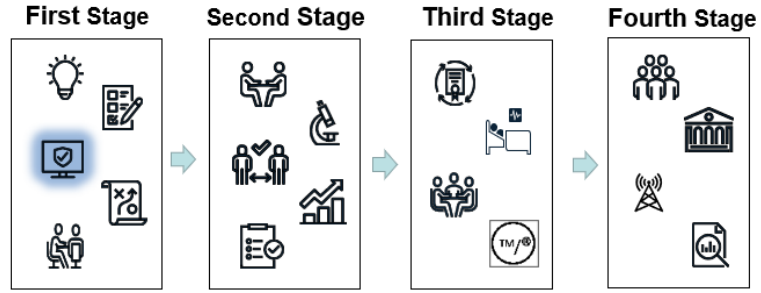
Leia's team identifies the appropriate vendors to assist with their early development studies.

With *in vitro* assays identifying the lead candidate and the TPP now developed, the team discusses how to evaluate the vaccine's activity and the adjuvant's ability to target immune components. Carolyn and Leia search for a Clinical Research Organization (CRO) who can assist with both preclinical studies and future clinical trial development.

For complicated biologics, such as vaccines, "the process is the product." Any manufacturing process adjustments can result in a fundamental change to the biological molecule, impacting the product and its performance, safety, or efficacy. For these reasons, they also hire a Contract Development and Manufacturing Organization (CDMO) for future manufacturing services, select assay development, and bioprocess development.

The team designs multiple studies that will be conducted by either the CDMO or CRO.

- Host cell protein assay (HCP) for vaccine purity (CRO)
- Correlate *in vitro* antigenicity with *in vivo* immunogenicity (CRO)
- Adjuvant safety and efficacy (CRO)
- Potency assay (CDMO or CRO, depending on format)
- VLP characterization (CDMO)
- Optimizing formulation for stability and efficacy (CDMO)

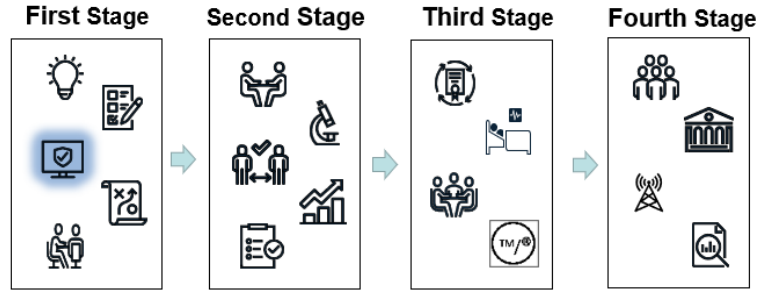


Key questions:

- What vendors can assist during vaccine validation and formulation?
- What study designs are key for vaccine development?

First Stage: Initial Validation and Formulation (slide 2 of 2)

As vaccine development programs are unique and complex, the CRO and CDMO develop assays that will characterize the key components of the lead vaccine candidate rHMPV-VLP.



Analytical development occurs through refining methods for demonstrating purity, identity, potency, and characterizing the VLP structure. The team works with the CDMO to develop characterization tests to understand the structure, assembly, and stability of the VLP in different conditions. The team agrees upon mass spectrometry to confirm VLP identity, cryogenic electron microscopy (CryoEM) for VLP assembly, size distribution and integrity. For the *in vitro* potency-indicating assay, the team develops an enzyme-linked immunosorbent assay (ELISA) to assess antigenicity. The potency assay is a regulatory requirement, as potency is a stability indicator for vaccine products.

Separately, the CRO develops a platform-specific HCP assay to characterize and quantify HCPs, which represent a heterogeneous pool of contaminant proteins. The CRO optimizes unique immunoassays (ELISA) and mass spectrometry methods for measuring and characterizing HCPs. HCP impurity values came out at minimum range of ≤15ng/mL, and the team updates the TPP based on this outcome.

Key questions:

- Are there any product or process impurities of concern?
- What vaccine release tests & characterization methods are expected for this vaccine candidate?
- How are HCP impurity levels incorporated into the TPP?

TPP *Leia updates the Process-derived impurities section of the TPP.*

First Stage: UPDATED Target Product Profile

Attribute	Minimum TPP	Optimal TPP
Patient Population	Adults ≥20 yrs	Adults ≥20 yrs, infants <1 yr, children 1-10 yrs and adolescents 11-19 yrs
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Process-Derived Impurities	~~15-30ng/mL HCP impurities~~	≤15ng/mL HCP impurities

- The TPP is updated to reflect measurement and characterization of HCPs.
- An updated TPP reflects the removal of "15-30ng/mL HCP impurities" due to achieving the optimal profile based on generated results.

First Stage: Regulatory and Quality Management Strategy

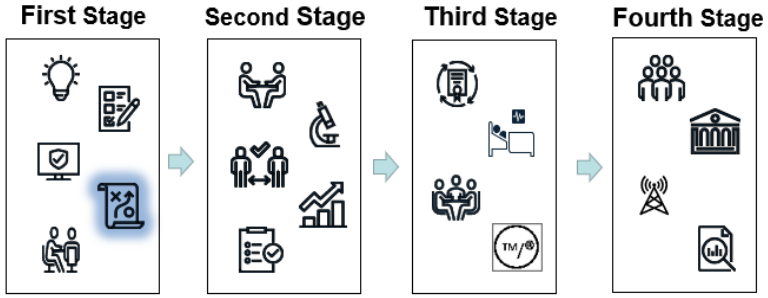
Results of *in vitro* and small-scale *in vivo* studies provide confidence in rHMPV-VLP which is now assigned a lead identifier EEB-001. The team begins to develop their regulatory strategy.

Leia and her team find FDA's Vaccine Development 101, which describes the FDA's process. As an NIH-funded innovator, Leia has frequent interactions with her NIH Program Officer, Spencer Leyes. Spencer puts Leia in contact with the NIH SEED Office for requesting a regulatory consult to help with the development and preliminary confirmation of EndemicEase's regulatory plan.

During her consultation, Leia receives a recommendation to find a regulatory consultant who can assist with her regulatory and quality management strategies. The SEED Office team provides Leia with information on Selecting a Regulatory Consultant. Leia interviews several candidates and hires Kai Kekoa, PhD, a regulatory consultant with experience in vaccine development and extensive interactions with the FDA's Center for Biologics Evaluation and Research (CBER), the center that regulates vaccines. Kai has helped bring five vaccine candidates through the process of approval. Kai will assist Leia and her team with identifying:

- Quality management considerations
- Regulatory documentation

As Leia and her team are still in early product development (i.e., prior to filing of an Investigational New Drug (IND)) and have not yet met with the FDA, Kai immediately recommends Leia request an INitial Targeted Engagement for Regulatory Advice on CBER/CDER ProducTs or INTERACT meeting.

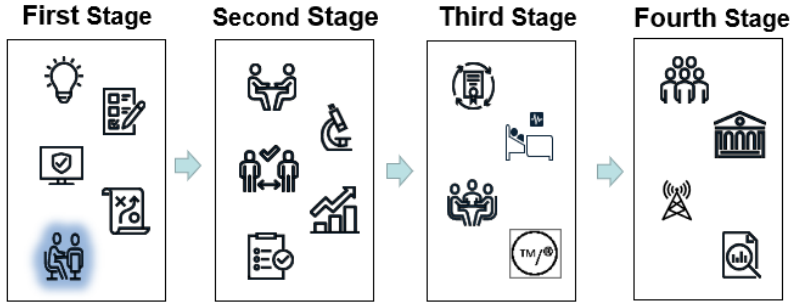


Key questions:

- How does FDA regulate vaccines?
- How can you prepare for engagement with FDA CBER?
- What consultation resource is available to NIH-funded innovators?

First Stage: INTERACT Meeting

The INTERACT meeting is intended to cover novel questions and unique challenges in early product development prior to a pre-IND meeting. This is the first of several meetings Leia will have with FDA, and she uses the Guide for Regulatory Meetings for Drugs and Biological Products to help her prepare.



While not required, the INTERACT meeting will provide valuable input. As the focus of the INTERACT meeting is to discuss unique early development challenges, Leia wants to use the meeting to seek FDA input on her preclinical models and adjuvant safety.

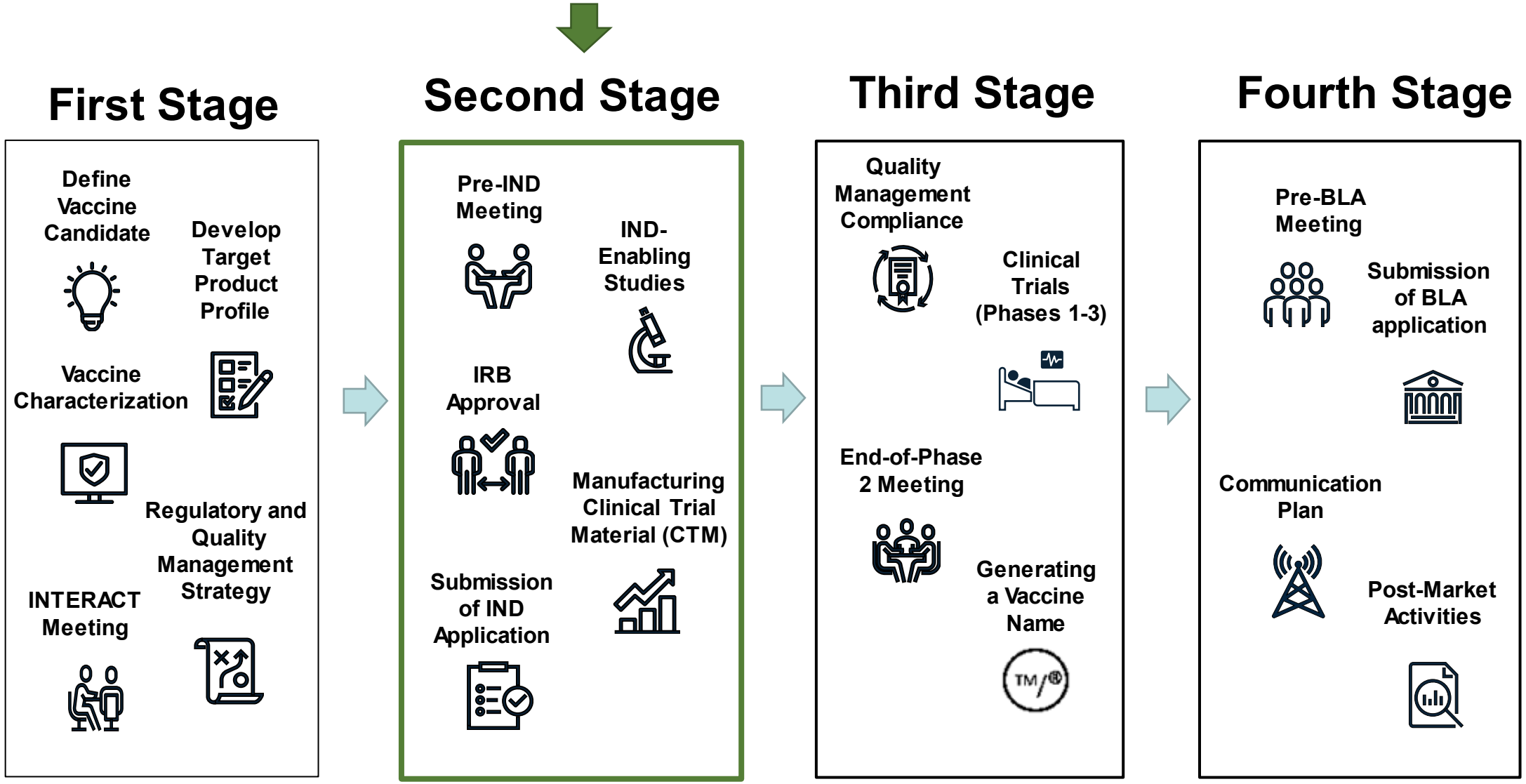
Leia sends a request for the INTERACT meeting, to be held within 75 days of her initial request and includes a meeting package with a set of questions. After receiving a response from the FDA granting the meeting, Leia meets with Kai to further prepare.

In the INTERACT meeting, Leia outlines the challenges of limited preclinical models for HMPV and the semi-permissive replication in models for human Respiratory Syncytial Virus, which is similar in clinical syndrome. Despite this, Leia shares that her team picked the cotton rat models based on available HMPV studies. She also notes the strategy to use chimpanzees in the IND-enabling studies. The FDA agrees their preclinical models should provide information about protective efficacy and outlines the need for safety studies, especially with the novel adjuvant, in the upcoming IND-enabling studies.

Key questions:

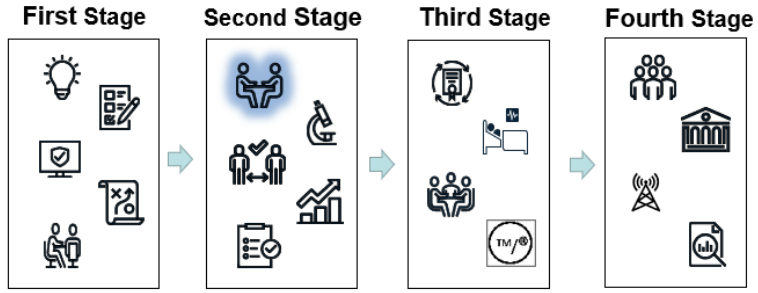
- What resources exist for learning criteria for an INTERACT meeting?
- When should the INTERACT meeting occur?
- What is the focus of the INTERACT meeting?

Second Stage



Second Stage: Preparing for a Pre-IND Meeting

Leia's team conducts efficacy studies in the cotton rat model. They generate positive efficacy data and are excited to implement their strategy of using chimpanzees in the IND-enabling studies. Before conducting GLP studies, the team decides to seek input from the FDA on their proposed IND-enabling studies and other aspects of vaccine development. Working with Kai, they identify questions for the pre-IND meeting to ensure their plans are sufficient to demonstrate vaccine safety and efficacy, and ultimately their IND filing will be accepted by FDA CBER.



Kai notes a pre-IND meeting is an opportunity to get FDA feedback on the team's plans for the IND-enabling studies and product manufacturing, along with a chance to demonstrate readiness for clinical trials following such studies. Leia works with the CRO to get information on the bioassays for serology measurements that will be used for both preclinical and clinical studies, as well as the high-level clinical strategy for upcoming trials. Leia also works with the CDMO to get CMC plans for demonstrating lot-to-lot consistency of vaccine production in both IND-enabling studies and their first-in-human clinical trial.

Leia prepares the pre-IND meeting request, using FDA's FAQ's on Pre-IND Meetings. With the candidate being an adjuvanted vaccine, Kai points Leia to Regulatory Consideration in the Safety Assessment of Adjuvants and Adjuvanted Preventive Vaccines, as well as an FDA recording on vaccine adjuvants. Kai and Leia gather plans for GLP animal studies, manufacturing information, clinical protocols (study plans) and Investigator Information for the meeting. They use the IND Meetings for Human Drugs and Biologics Guidance to prioritize talking points and questions.

Key questions:

- What development activities can be outsourced?
- Who can assist with clinical strategy development and scale-up manufacturing plans?

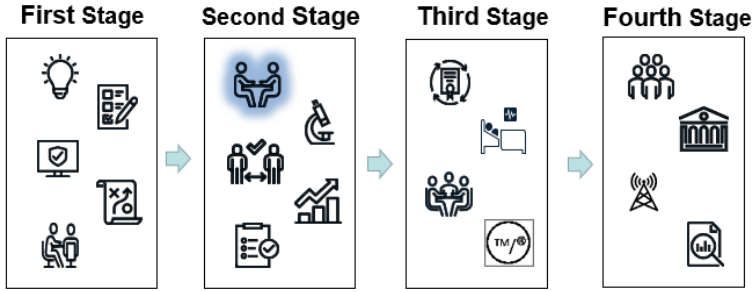
Second Stage: Pre-IND Meeting

After receiving a pre-IND meeting confirmation, Leia collects the nonclinical study data, the clinical trials strategy and manufacturing plans. She also prepares questions to solicit FDA's feedback on their development plan to help avoid any future challenges or delays.

At the meeting, Leia discusses EndemicEase's CMC plans including their approach for lot-to-lot consistency of manufacturing and the potency assay's measure of vaccine-induced biological activity. Leia's questions around manufacturing are addressed, and the FDA considers the relevance of the *in vitro* potency assay to the expected immune response.

Leia describes her plans to use chimpanzees in the IND-enabling studies, and the FDA concurs. The FDA also recommends emphasizing, in the IND submission, the head-to-head comparison in the preclinical studies of the immune response to the antigen with and without adjuvant. Such data will support including the adjuvant in this vaccine candidate.

Leia revises the clinical strategy to include the number and type of subjects, serology measures, and clinical endpoints. She shares that their clinical trial design assesses whether the initial-phase trials will expose subjects to unnecessary risks, especially with the adjuvant. FDA emphasizes safety considerations for the adjuvant, and there must be satisfactory evidence that the adjuvant does not adversely affect the vaccine's safety or potency in the clinical trials.

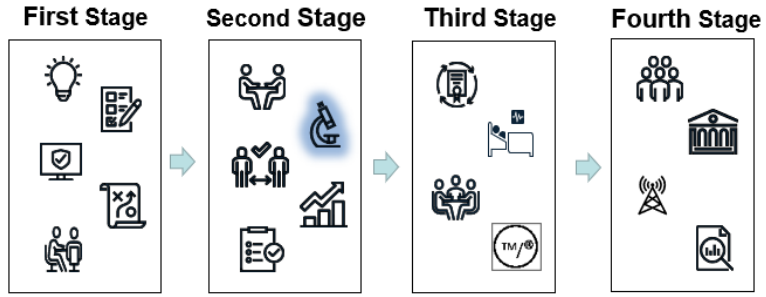


Key questions:

- What is the intent of a pre-IND meeting?
- What guidance is available for pre-IND meeting preparation?
- How is a pre-IND meeting for a vaccine different?

Second Stage: IND-Enabling Preclinical Studies

From their pre-IND meeting, the team has clarity about the IND-enabling studies needed to identify safety, toxicity, and dosing considerations of EEB-001.



Leia's team conducts IND-enabling studies in two models: cotton rat and chimpanzees. In part, these studies include identifying potency in their animal model – which requires measurement of both neutralizing antibodies and cellular immune responses as a surrogate marker for decreased efficacy of the vaccine over time. They also study safety factors for their proposed adjuvant. They note that when immunized animals were challenged with HMPV, protection was observed in 75% of the chimpanzee population, within the range of confirmation for human vaccines.

As part of the comprehensive IND-enabling studies, Leia's team also establish the vaccine's dose-dependency and identify potential toxicity/safety/tolerability concerns to include in the Investigator's Brochure (IB), a compilation of nonclinical and clinical data relevant to the clinical trials. The IB helps facilitate understanding the rationale for, and compliance with, many critical features of the clinical protocol, as well as insight into clinical management of study subjects during the trial.

Key questions:

- What is the focus of IND-enabling preclinical studies?
- What types of experiments are performed?
- How are IND-enabling preclinical study outcomes incorporated into the TPP?

TPP *Leia updates the Primary Endpoints section of the TPP*

Second Stage: UPDATED Target Product Profile

Attribute	Minimum TPP	Optimal TPP
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Process-derived impurities	~~15-30ng/mL HCP impurities~~	≤15ng/mL HCP impurities

- IND-enabling preclinical data demonstrates HMPV prevention below the optimal range. The team notes this observation but does not need to change their TPP prior to clinical data outcomes.

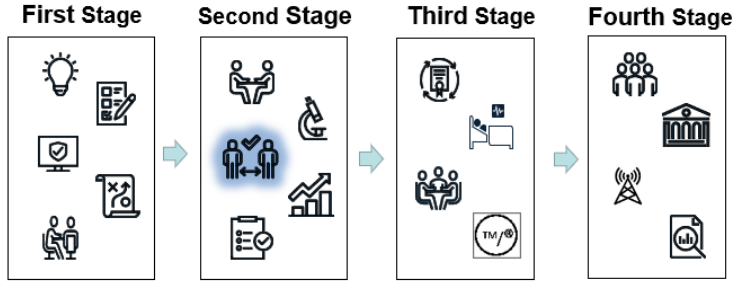
Second Stage: Institutional Review Board Approval

The CRO working with Leia and Carolyn also provides Institutional Review Board (IRB) support. This is EndemicEase's first clinical trial, and they must obtain IRB approval to before beginning. Because vaccines are given to healthy people, there is a more stringent safety standard. As a result, vaccine clinical trials require more participants and extended monitoring.

Following the pre-IND meeting, the CRO reaches out to Leia and Carolyn to discuss IRB approval, noting that without getting informed consent from the research subjects and review of the study by an IRB an IND submission won't be possible.

The CRO has expertise that allows them to easily assist with the IRB. However, Leia and Carolyn also look for resources to learn more about the IRB approval process. As their clinical trial is funded in part through their NIH award, they review Clinical Trial Requirements for Grants and Contracts and Single IRB Policy for Multi-Site or Cooperative Research resources for insight. Leia also reviews the IRB Written Procedures: Guidance for Institutions and IRBs, to confirm their submission aligns with FDA's written procedures for the IRB.

After their research, Leia and Carolyn meet with the CRO to review the IRB plans. Agreeing on the strategy, the CRO submits all required documentation for IRB approval. Leia ensures the study is registered and clinicaltrials.gov information is up-to-date.



Key questions:

- What is needed for IRB approval?
- How is IRB approval achieved?

Second Stage: Manufacturing Clinical Trial Material

Leia's team must now scale-up production of the vaccine for clinical trials. Leia and Carolyn rely on the CDMO to assist with the manufacturing strategy and provide manufacturing services, in compliance with current good manufacturing practices (cGMP).

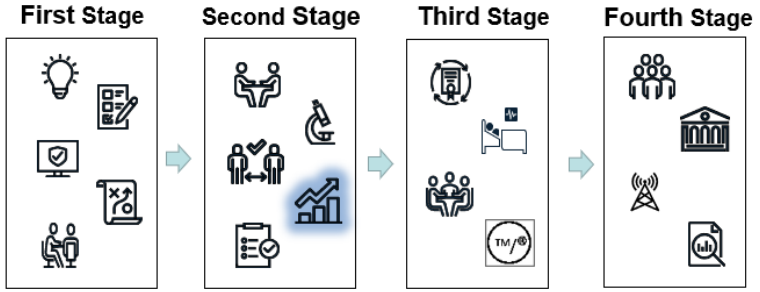
Carolyn and Leia discuss the chemistry, manufacturing and controls (CMC) activities and bioprocesses for EEB-001 with the CDMO. The CDMO indicates the Guidance on Chemistry, Manufacturing and Controls for a vaccine product will be used to support the scale-up for clinical trials. Since the same CDMO will manufacture the clinical trial material, there is no need for technology transfer for assays or bioprocesses because the CDMO developed them.

These key elements help scale-up production by guiding design for the larger scale bioprocess:

- Novelty of the biologic product
- Upstream expressed/harvest titers
- Downstream processed biologic product yield (product loss during purification)
- Final concentration to achieve the therapeutic/clinical dose
- Nature and extent of clinical study (number of doses, number of participants, etc.)

As part of the scale-up production for clinical trials, the CDMO also notes they will need specifications for novel host cell impurities, which was identified in the TPP based on earlier HCP characterization studies.

TPP *Leia reviews the Manufacturing/Purity section of the TPP*

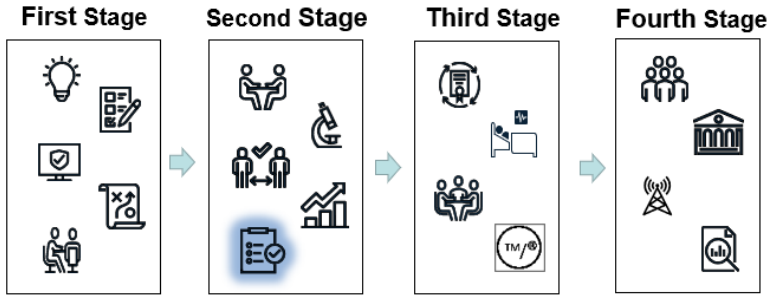


Key questions:

- What CMC guidance is available for a vaccine product?
- How does the CDMO support manufacturing scale-up?
- What are some key elements for vaccine scale-up production?

Second Stage: Submission of IND Application

Leia provides information supporting why EEB-001 is expected to be safe, well tolerated, and effective in clinical studies in an IND application. Demonstrating the data's reproducibility is critical for the IND filing for biologic therapies, especially with vaccines.



Kai leads the IND application preparatory work. He includes sections summarizing preclinical development, emphasizing the positive safety assessment from the adjuvant studies. Kai also includes detailed information on manufacturing and clinical investigations in the IND application. For the CMC section, he outlines lot release and stability data for the adjuvant and includes information on the degree and completeness of absorption.

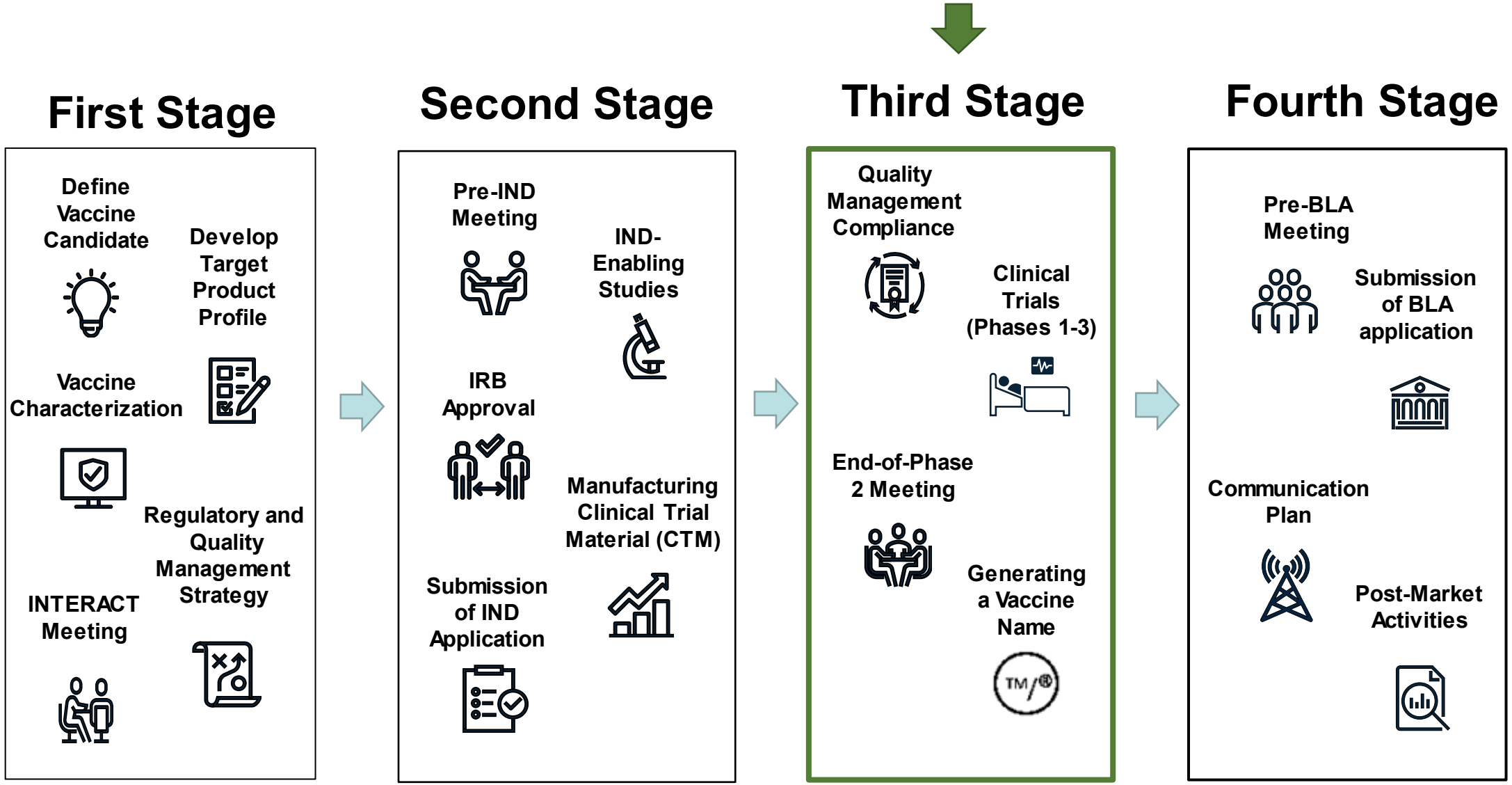
Kai and Leia refer to the pre-IND meeting notes, the Investigator-Initiated Investigational New Drug (IND) Applications table and the IND Applications for Clinical Investigations: Regulatory and Administrative Components guide, which provides explanations and supplemental information for IND application elements. Leia also reviews the IND Forms and Instructions for submission templates and details. Leia learns that the FDA has 30 days to review the application for safety concerns

After the IND submission, Leia receives notice from the FDA of an IND tracking number, indicating receipt of her application. Leia recalls in her reading that no response from the FDA within 30 days means allowance of the IND application. After not receiving a response within 30 days, the team moves forward with their clinical study.

Key questions:

- What are the contents of an IND application?
- What are notification and timeline expectations following submission?

Third Stage

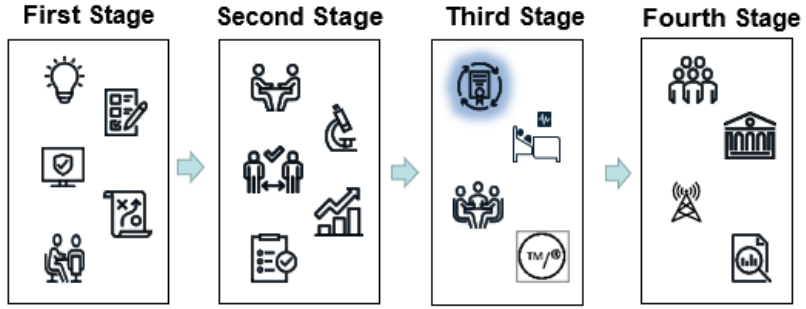

First Stage
Define Vaccine Candidate
Develop Target Product Profile
Vaccine Characterization
Regulatory and Quality Management Strategy
INTERACT Meeting
Second Stage
Pre-IND Meeting
IND-Enabling Studies
IRB Approval
Manufacturing Clinical Trial Material (CTM)
Submission of IND Application
Third Stage
Quality Management Compliance
Clinical Trials (Phases 1-3)
End-of-Phase 2 Meeting
Generating a Vaccine Name
Fourth Stage
Pre-BLA Meeting
Submission of BLA application
Communication Plan
Post-Market Activities

Third Stage: Preparing for the Initiation of the Clinical Study

Unlike most drugs that treat illnesses, vaccines are provided to healthy individuals to prevent diseases. This necessitates a stringent safety standard, requiring vaccine clinical trials to have many participants and extended trial durations to confirm safety and effectiveness.

A key difference in vaccines versus drugs are their primary endpoints. For example, primary endpoints for a vaccine will include characterizing the intended immune response in participants. Another distinction between vaccines and drugs are the dose response curves. For vaccines, the dosing is typically a small amount with a longer lasting response. Also, adjuvants are frequently used in vaccines to achieve a protective immune response using the smallest effective dose.

Leia knows that clinical trials require preparation through extensive coordination with the CRO and CDMO to establish the framework for the clinical trials and clinical monitoring. She initiates meetings with both the CDMO and CRO to better understand their roles in the clinical study.



Key questions:

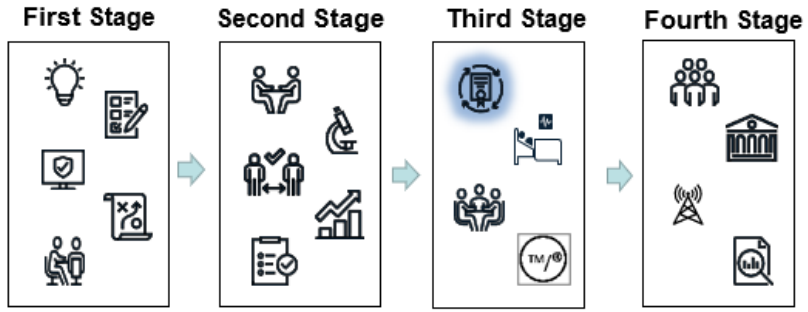
- What are unique characteristics of vaccine clinical development?
- What is the role of the adjuvant?
- Who is involved in clinical study preparation?

Third Stage: Quality Management Systems Compliance – CDMO

Prior to Phase 1 clinical trials, the CDMO will scale-up production of clinical trial material following current GMP guidelines.

The CDMO adheres to GMP practices, which includes quality assurance in product production. The CDMO must emphasize compliance with an established quality management system (QMS), as well as procedures and practices to ensure consistent product quality. To ensure compliance, the CDMO is audited on a yearly basis. Prior to the initiation of clinical trials, the CDMO working with Leia and Carolyn passed their most recent audit, confirming the validity of their QMS.

The CDMO has fill-finish manufacturing capabilities, which will occur as an aseptic process in an ISO 5 environment. Data from the IND enabling studies led to the selection of three vaccine doses: 5, 10 and 15 mcg. With its manufacturing capabilities, the CDMO will provide each vaccine in a single-dose vial for an adult formulation. In a meeting with the CDMO, Leia confirms that a placebo will also be made for the clinical study. Before shipping to the clinical trial sites, the CDMO will perform a shipping validation study to ensure EEB-001 can be transported without loss of potency.



Key questions:

- What is GMP and who has responsibility for it?
- What is a QMS and how is it different between vaccines vs drugs?
- What does the CDMO need to produce before clinical trials can begin?

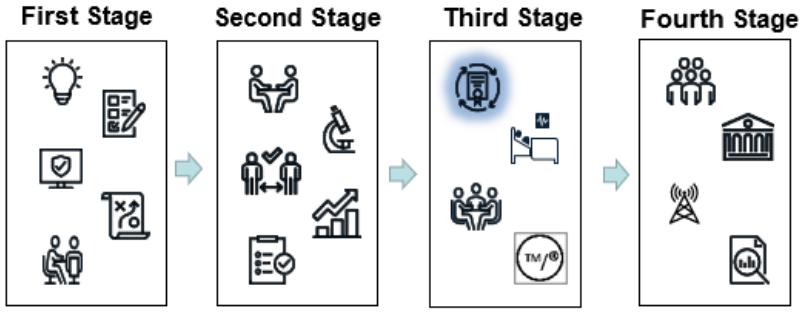
Third Stage: Quality Management Systems Compliance – CRO

Among many other responsibilities for the administration and monitoring of the clinical trials, the CRO also adheres to regulations that ensure integrity of clinical data (GCP).

Good clinical practice (GCP) includes ethical and scientific quality requirements for conducting clinical trials. Responsibilities for GCP lie with the CRO conducting the clinical trials. The CRO, Kai, Leia and Carolyn meet to review clinical study plans, their potential outcomes and impact toward the desired regulatory approval. The CRO notes the trial design will cover all age groups, initially starting with adults and gradually expanding to infants.

A major difference between the production of vaccines versus drugs is the development, and use, of a potency assay. Leia's team was able to identify potency through an observed correlation between *in vitro* potency and immune responses in their animal models. Within the clinical trials, they hope to establish the same potency correlation in humans.

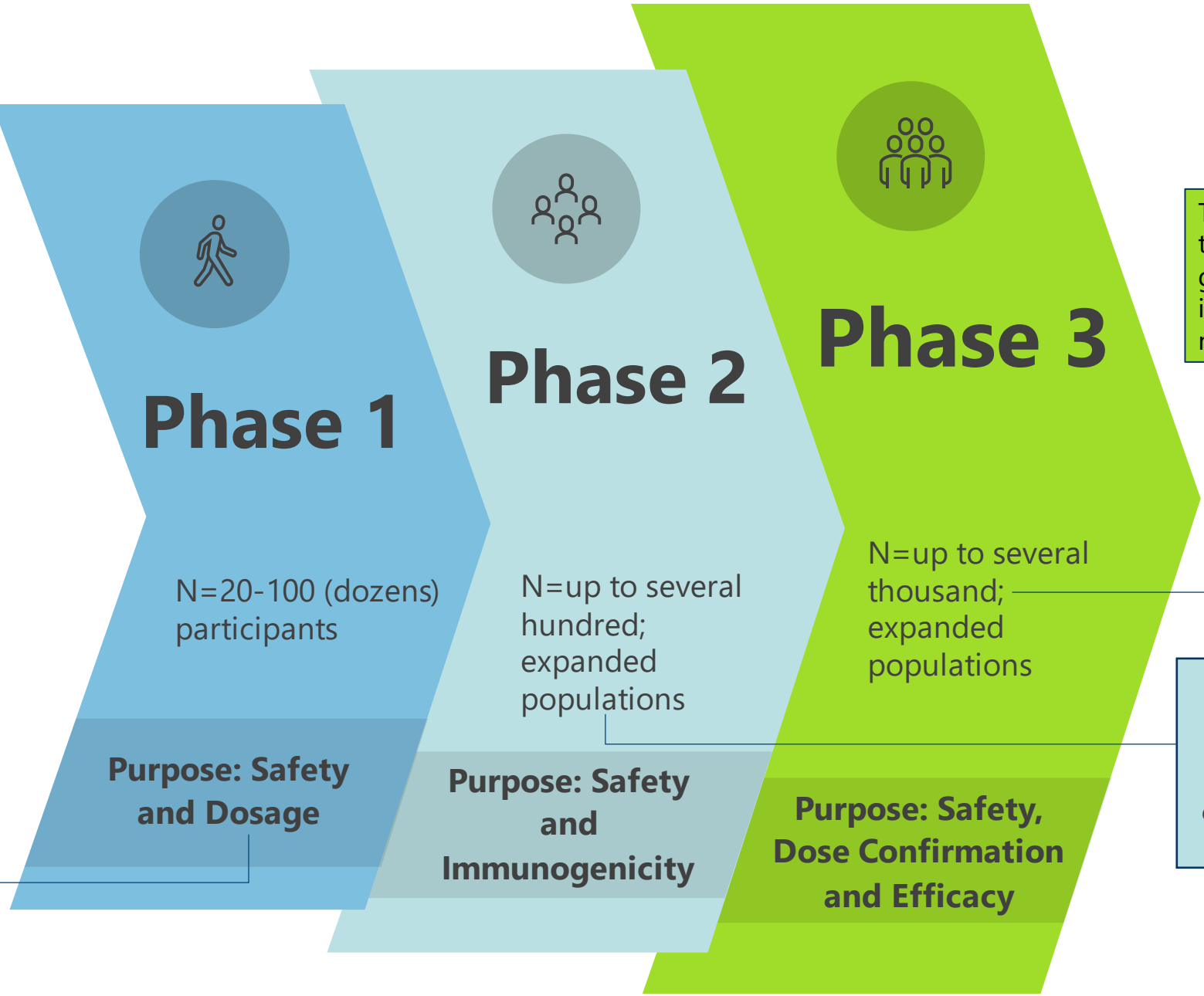
Prior to clinical trial initiation, Leia meets with the CRO to go over their study plan for Phases 1-3.



Key questions:

- What is GCP?
- Who has responsibilities for GCP and GMP?
- What is a QMS and how is it different between vaccines vs drugs?

Clinical Study Phases



The three selected vaccine doses will be initiated here.

The CRO designs the study for gradual increases in participant numbers

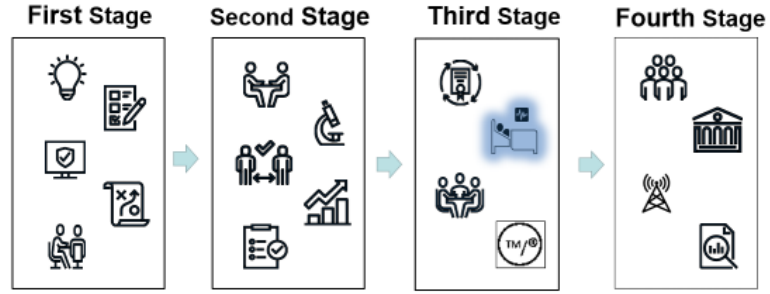
Where the study extends age groups beyond adults to older children, toddlers, and infants

Third Stage: Phase 1 Clinical Trial

The CRO initiates the Phase 1 trial to establish the safety and immunogenicity of the EEB-001 vaccine in healthy adults. At this stage, Leia and Carolyn are also responsible for reporting requirements.

As part of the clinical trial design, in Phase 1, three doses are tested to determine the optimal dose that is safe and can generate a potent immune response (e.g., neutralizing antibody response). The team also assesses short-term safety and tolerability (e.g., injection site soreness, fever, muscle aches). As data becomes available, Leia follows the Submitting Study Datasets for Vaccines Guidance which provides detailed information and specifications for the content of datasets submitted to the FDA.

Leia learns there are reporting requirements for serious and unexpected suspected adverse reactions during trials. Since the adverse events in the Phase 1 trial were mild and transient, such reporting requirements were not applicable. However, Leia and Carolyn are responsible for the Safety Reporting Requirements and Safety Assessment that occur during the clinical trial. Although the CRO will manage this, the ultimate responsibility lies with EndemicEase.

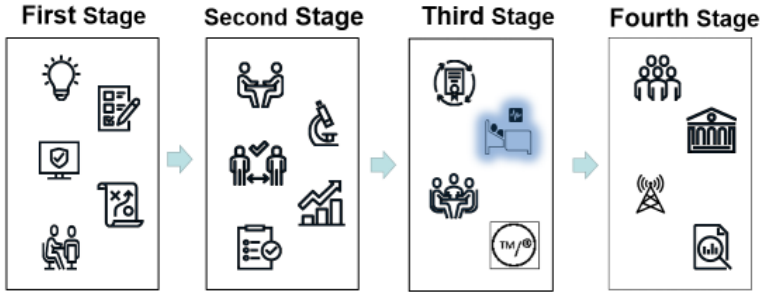


Key questions:

- What guidance is available for submitting clinical data to the FDA?
- Who is responsible for reporting requirements?

Third Stage: Phase 2 Clinical Trials (1 of 2)

In Phase 2, the team plans to include an expanded population, where measures of dosing and validation of potency are critical.



Because the adjuvanted vaccine was well tolerated in Phase 1, the Phase 2 participant population was expanded to include older children, toddlers, and infants. The CDMO manufactures three doses of pediatric/adolescent formulation to identify which has the best dose response. Given the multiple target ages, considerations were given to the formulation of the vaccine for easy administration and tolerability, especially in the pediatric population.

A critical part of Phase 2 is validating the potency assay, which is used for lot release as a predictor of vaccine stability and a correlator with vaccine efficacy. The team begins work to validate their ELISA in Phase 2 to understand this correlation. Early data shows a robust immune response that is characterized as a neutralizing antibody response with little to no cellular response.

Key questions:

- What occurs in Phase 2 clinical trials?
- When can expanded populations be explored for vaccine clinical trials?

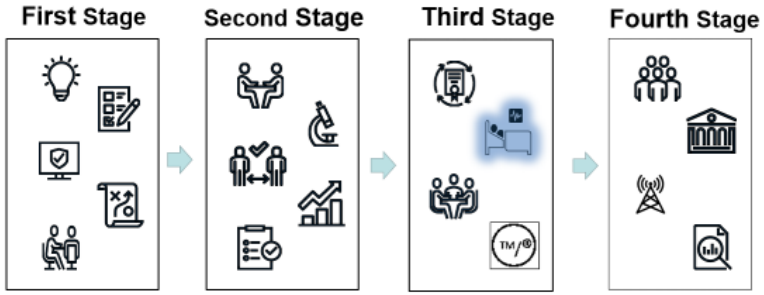
Third Stage: Phase 2 Clinical Trials (2 of 2)

Additional measures of dosing, safety, efficacy and side effects are critical during Phase 2, especially for the additional groups.

Safety, efficacy, immunogenicity, and optimal dosing were assessed in each population. The generic batch-release assays used in the early process development as measures for safety, potency, and immunogenicity were also implemented.

Although the IND-enabling preclinical study results showed protection in 75% of the chimpanzee population, the Phase 2 data demonstrates HMPV prevention at 85% within adult, children, toddlers and infant populations. This higher response aligns with the optimal Primary Endpoint profile noted in the TPP.

Overall, the Phase 2 trial further demonstrated the adjuvanted vaccine was well tolerated and safe, inducing a strong neutralizing antibody response in study participants.



Key questions:

- What can be demonstrated with Phase 2 clinical trials?
- What factors are assessed in varying populations for Phase 2 clinical trials?

TPP *Leia returns to the Primary Endpoints section of the TPP*

Second Stage: UPDATED Target Product Profile

Attribute	Minimum TPP	Optimal TPP
Patient Population	Adults ≥20 yrs	Adults ≥20 yrs, infants <1 yr, children 1-10 yrs and adolescents 11-19 yrs
Primary Endpoints	~~Prevent 70% of HMPV-related illnesses in adults ≥20 yrs, and reduce infection and transmission rates by at least 50%~~	Prevent 85% of HMPV-related illnesses in optimal patient population, and reduce infection and transmission rates by at least 70%
Interference	Demonstrate favorable safety and immunologic non-interference upon co-administration of other vaccines	Demonstrate maximum safety and immunologic non-interference upon co-administration of other vaccines
Safety and Tolerability	No major safety concerns or side effects; acceptable tolerability	No major safety concerns; no side effects
Dosing	Single ≤15.0 mcg in 1.0 mL dose (adults ≥20 yrs)	Single ≤15.0 mcg in 0.5mL dose (children ≤19 yrs); single ≤15.0 mcg in <1.0 mL dose (adults ≥20 yrs)
Dosage Regimen/Schedule	Initial vaccination of 2 doses, 8 weeks apart, followed by an annual booster shot	Single vaccination, with no annual booster shot
Stability	1-year shelf life at 2-8 °C, 3-month stability at room temperature	2-year shelf life at 2-8 °C, 6-month stability at room temperature
Process-derived impurities	~~15-30ng/mL HCP impurities~~	≤15ng/mL HCP impurities

- Phase 2 outcomes support the optimal profile. The team notes this observation but does not need to change their TPP.
- An updated TPP reflects the removal of the minimum profile of "Prevent 70% of HMPV-related illnesses in adults ≥20 years and reduce infection and transmission rates by at least 50%."

Third Stage: Preparing for End-of-Phase 2 (EOP2) Meeting

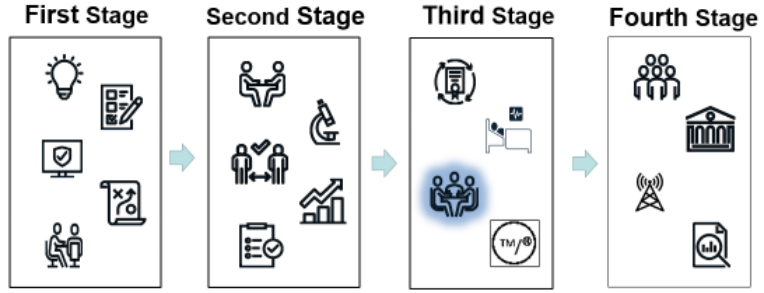
With the Phase 2 trials complete, Leia requests an EOP2 meeting with the FDA. This is her team's opportunity to confirm that the planned Phase 3 clinical trials will support the market authorization application.

In her preparation, Leia reviews Code of Federal Regulations Title 21 and Guidance for Industry IND Meetings for Human Drugs and Biologics to learn EOP2 meeting expectations. She also reviews an FDA EOP2 Meeting resource for topics and questions ideas.

Leia prepares materials on the validated product-specific assays. She highlights their potency assay, where a correlation between in vitro potency and immune responses in their animal models were validated with observed neutralizing antibody responses from Phase 2 study participants. Leia also plans to speak to their characterization assays, used to validate VLP structure, assembly, and stability.

The CDMO provides Leia with information demonstrating their capabilities for large-scale manufacturing processes, product characterization, and lot-to-lot consistency (generating three consecutive lots) in Phase 3. Leia plans to note that Phase 3 vaccine production will initially be at commercial scale with their current CDMO, with plans for tech transfer to a different CMO site.

Leia, Kai and the CRO work together to incorporate data and plans into the EOP2 meeting package, to include modeling of Phases 1 and 2 data to inform Phase 3 design parameters. They modeled dose response, HMPV protection over the likely duration of the trial, patient baseline data, and effects in the placebo group.



Key questions:

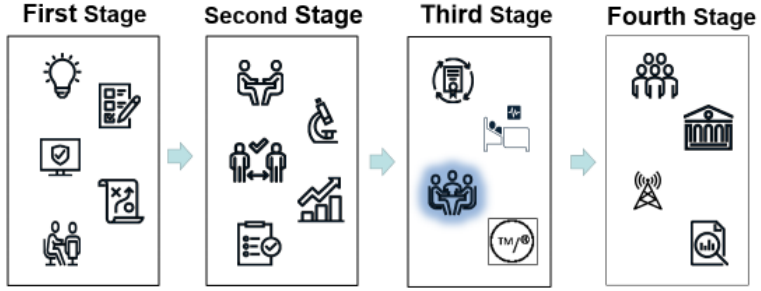
- What is the significance of the EOP2 meeting?
- What resources are available to prepare for EOP2 meeting?
- What types of data can be included in the EOP2 meeting package?

Third Stage: End-of-Phase 2 Meeting

After reviewing the EOP2 meeting package submission, FDA responds with a list of questions.

Prior to the meeting, FDA raised concerns about increasing production from pilot scale to market scale. Leia and Kai reach out the CDMO who provides evidence from previous vaccine manufacturing runs demonstrating their capacity for commercial manufacturing scaled up by more than a factor of 5 to 10. The CDMO also confirms its consistency in quality of product with its capacity to produce three consecutive manufacturing lots with quality checks to verify purity, strength, etc.

In response to Leia's Phase 1 and 2 data, including their lot release and characterization assay information, the FDA requests additional characterization testing prior to Phase 3. Although they are currently using mass spectrometry, the FDA requests confirmation through other assays. Leia and the team note their access to CryoEM, as well as differential scanning calorimetry (DSC), which give direct indications of structure and provide orthogonal evidence of batch-to-batch consistency.



Key questions:

- Based on FDA's written feedback before the meeting, what is the best use of time for the face-to-face discussion?
- Can FDA make additional requests during the EOP2 meeting?

Third Stage: Phase 3 Clinical Trials

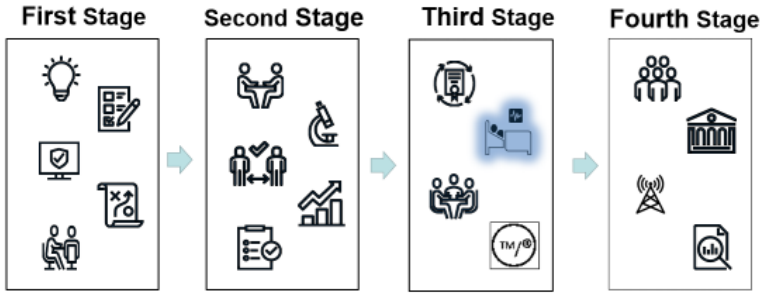
With the help of the CRO and CDMO, Leia initiates Phase 3 trials which focus on the vaccine's efficacy in a large population. The primary clinical endpoint, specified in Phase 3 clinical trial protocols, must be met to demonstrate efficacy.

The CRO leads the Phase 3 randomized, double-blind, placebo-controlled, multicenter clinical study. The Phase 3 clinical trials are designed to test the efficacy of the planned dosages and to accumulate data on any adverse reactions. To move forward, data needs to demonstrate that EEB-001 protects from acquiring HPMV. The primary endpoints are:

- Prevention of ≥85% of HMPV infection
- Reduction in transmission by ≥70%
- Reduction of severe symptoms in those infected

The pivotal Phase 3 study includes manufacturing of commercial-scale clinical trial material (CTM).

In this Phase, the number of HMPV cases in the vaccinated group is compared to the number in the control group to understand if the vaccine reduces the HMPV incidence. The Phase 3 trial demonstrated efficacy against HMPV infection, including reduction of symptoms, lower infection rates, and decreased transmission.



Key questions:

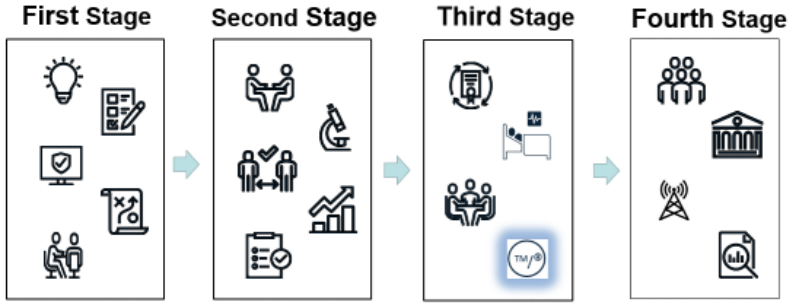
- What occurs during Phase 3 clinical trial?
- What data is required to provide evidence of efficacy and safety?
- What population groups are compared to understand vaccine effectiveness?

Third Stage: Generating a Vaccine Name

Kai shares with Leia the greater flexibility in creating a vaccine name versus a drug name. After determining a name, they should register it for trademark purposes.

Leia, Carolyn and their research team meet to discuss the vaccine's name. Leia researched other existing names and learned that many of them are a combination of their vaccine components or function. In thinking about the origin and components of this vaccine, the team focuses on the recombinant nature of the vaccine, that it includes a recombinant capsid protein, and its intended use to "shield" its users from HMPV. The team ultimately lands on the name RecombiShield-HMPV.

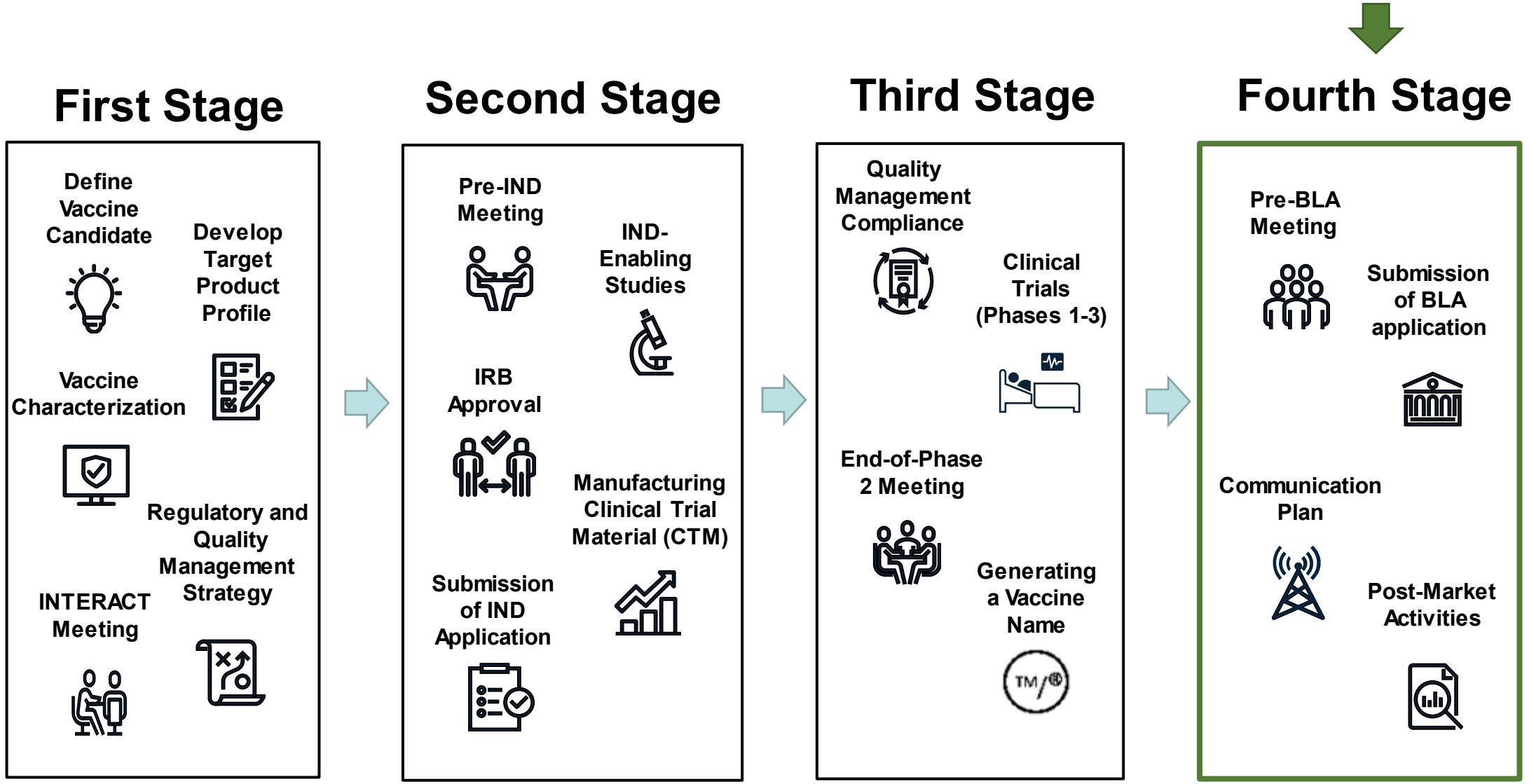
After the team agrees on a name, Leia searches an online to ensure "RecombiShield" or RecombiShield-HMPV isn't already taken. She is pleased to find no use of the name and moves forward with trademark registration. Leia first searches the USPTO Trademark database to confirm RecombiShield isn't already trademarked. She then reviews the Trademark process prior to filing a trademark application. The US Patent and Trademark Office (USPTO) grants the actual trademark registration for the name, providing exclusive rights to the trademark holder for its use.



Key questions:

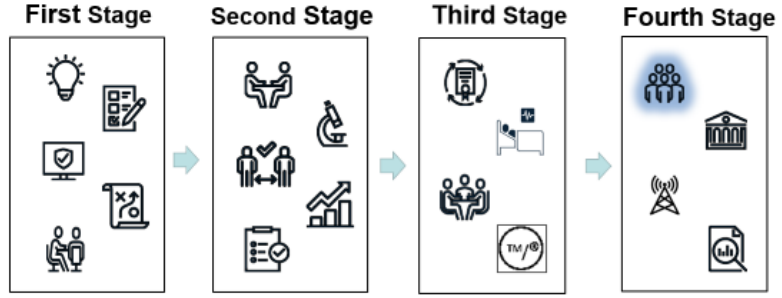
- What steps should occur to ensure a vaccine name isn't already in use?
- How do you register a trademark for a vaccine?

Fourth Stage



Fourth Stage: Preparing for Pre-Biologics License Application (BLA) Meeting

Understanding how critical Phase 3 data is for gaining regulatory approval, Leia focuses on gathering outcomes to present to the FDA. She works with Kai to develop a presentation, emphasizing key clinical data and CMC progress.



Kai directs Leia to the FDA's Office of Therapeutic Products, where she finds information on the intent of, and submission details for, the pre-BLA meetings. Leia also reviews Guidance for Formal Meetings Between the FDA and Sponsors or Applicants to get information on how to set up the meeting. Kai notes this meeting is the opportunity, prior to market authorization, to receive FDA feedback and clarification on the acceptability of:

- Key clinical data, to include dosing outcomes and other data that might become available for submission during BLA review
- Chemistry, manufacturing, and controls (CMC) information

In gathering data, Leia also reviews FDA Guidance for Submitting Study Datasets for Vaccines. Kai recommends to Leia that during the pre-BLA meeting, they should suggest having an Advisory Committee Meeting for input from leaders in the field on whether the clinical data truly demonstrates the vaccine safety and effectiveness. He notes the Vaccines and Related Biological Products Advisory Committee (VRBPAC) is appropriate for their vaccine.

Kai also recommends Leia and Carolyn hire a consultant to provide a labeling template, as labeling will be mentioned during the pre-BLA meeting.

Key questions:

- What is the purpose of a pre-BLA meeting and when does it occur?
- What items can be discussed during a pre-BLA meeting?
- What guidance is available in preparation for the pre-BLA meeting?

Fourth Stage: Pre-BLA Meeting

The pre-BLA meeting serves as an opportunity to address important or outstanding issues with the FDA before submitting the BLA.

At the pre-BLA meeting, Leia informs the FDA of the clinical outcomes from their studies, as well as the CMC readiness for a BLA. Specifically, Leia highlights their clinical data in expanded populations which demonstrated that the vaccine was safe, effective against HMPV infection and decreased transmission.

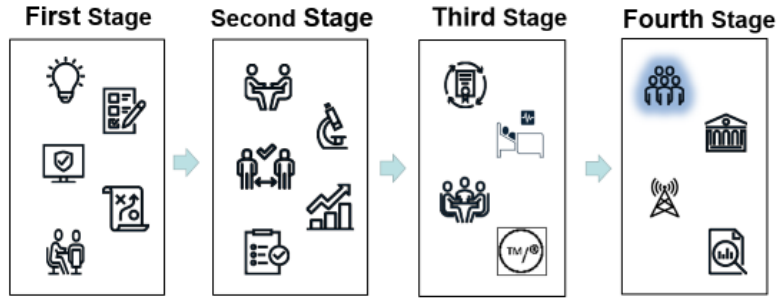
Based on the dose responses within the clinical trials, Leia aims to confirm the dose with as a one-time, single 5 mcg dose IM injection in the following volumes:

- 0.5 mL dose (infants <1 yr, children 1-10 yrs and adolescents 11-19 yrs);
- 1.0 mL dose (adults ≥20 yrs)

FDA agrees for the recommended dosing range of the two populations.

After presenting the clinical data, Leia discusses CMC information, emphasizing their lot-to-lot consistency (generating three consecutive lots).

Leia also mentions the benefit of having an Advisory Committee Meeting with VRBPAC, which the FDA agrees is necessary. Discussions with the FDA then transition to topics of proposed label, package insert wording, and identifying best approaches for data presentation and formatting in the marketing application.



Key questions:

- When does a pre-BLA meeting occur?
- What items can be discussed during a pre-BLA meeting?
- What is the purpose of a pre-BLA meeting?
- What guidance is available in preparation for the pre-BLA meeting?

Fourth Stage: BLA Application

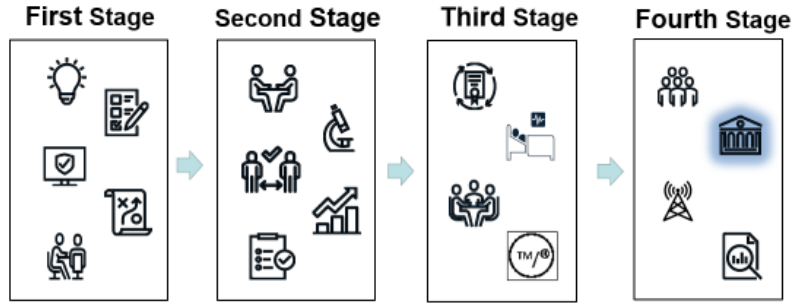
After the pre-BLA meeting, Leia starts the process for submitting a BLA Application. By submitting the BLA, EndemicEase is seeking approval to distribute and market RecombiShield-HMPV.

Kai directs Leia on how to get information about the FDA BLA process, where she can access resources for BLA Submission.

As with the IND application, Kai takes the lead in preparing the BLA application. He directs Leia to Form 356h, which serves as the application and includes sections for Applicant Information, Product Description, and Application Information.

Kai meets with Leia to review the pre-BLA meeting notes for inclusion in the application package. Other than including the expected clinical data and CMC information, Kai tells Leia that within the application, they will also need to present preclinical data, draft or final printed labeling, validation of important processes and assays for manufacturing, the manufacturing facility description, and any case report forms for tabulations and serious events.

Although not part of the application, Leia and Kai start to outline the processes for commercialization and launch. This will give them a head start if the BLA application is approved.



Key questions:

- Where can I find guidance for preparing the BLA application?
- What key items go in the BLA application?
- How does the pre-BLA meeting align with the BLA application?

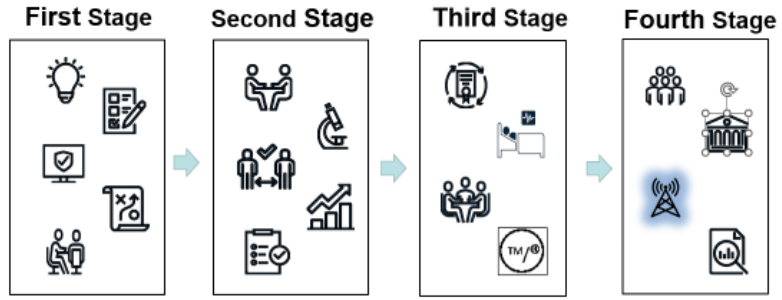
Fourth Stage: Communication Plan

Although RecombiShield-HMPV is not yet FDA-approved, Leia anticipates there will be some public hesitation about using the vaccine after FDA approval. She develops a communication plan about the benefits of the vaccine to gain support for its use.

Based on previous vaccine approvals, Leia knows there will be individuals and groups who oppose RecombiShield-HMPV's use. Anticipating interactions with vaccine-hesitant groups in open forum meetings, Leia hires a Public Relations (PR) consultant to assist with messaging for RecombiShield-HMPV.

The goal is to have a communications plan that effectively communicates the vaccine, which will be given to healthy individuals, is safe and effective. Leia works with the PR consultant to develop targeted messaging for:

- **Healthcare Providers and Professional Medical Societies**: Sharing the benefits of RecombiShield-HMPV through educational materials. Developing talking points about its value especially to children.
- **Vaccine-Hesitant Groups:** Developing materials outlining evidence of the vaccine's safety as well as risk-to-benefit information.
- **Advisory and Review Committees:** Emphasizing the clinical trials data demonstrating RecombiShield-HMPV safety and efficacy.



Key questions:

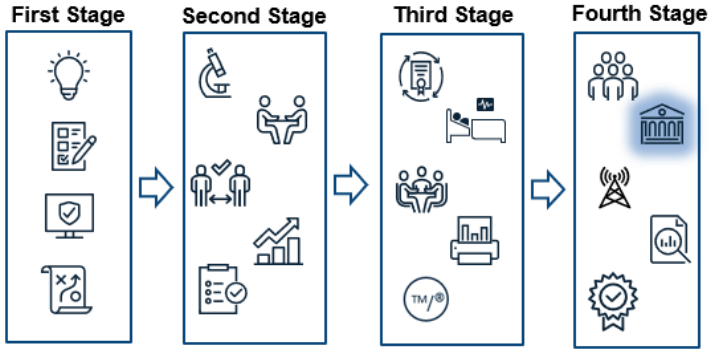
- What outside assistance is available for developing a vaccine communications plan?
- What are potential group targets for communicating vaccine efficacy and safety?

Fourth Stage: FDA Advisory Committee Meeting

With the BLA submitted and in review, the FDA schedules a discussion of RecombiShield-HMPV at an upcoming VRBPAC meeting.

With VRBPAC meeting nearly eleven times a year, there is a near-term opportunity for RecombiShield-HMPV to be discussed. Leia learns there will be a range of presentations on topics including HMPV virology, immunity, and surveillance measures by various laboratory groups within academia and the Centers for Disease Control and Prevention (CDC). There will also be a presentation by the FDA on the benefit of the HMPV vaccine, to include its efficacy and safety BLA review based on CMC and clinical data. Leia learns during the "Sponsor Presentation" session she will be able to give a talk, followed by a Q&A session. Leia gathers materials and data she's developed over the last few months and calls a meeting with her PR consultant to assist with overall messaging to non-scientific audiences. The PR consultant encourages Leia to place emphasis on the risk-benefit ratio, stating that with vaccination, a lower risk of HMPV was observed compared to placebo and there was a lower risk of hospitalization in patients who contracted HMPV.

During the meeting, the committee takes a vote on the safety and effectiveness of RecombiShield-HMPV based on the presented data.



Key questions:

- What is the role of an FDA advisory committee?
- What is an appropriate committee for vaccines?
- When is it appropriate to have an advisory committee meeting?

BL 125999/1

BLA APPROVAL
January 31, 2024

EndemicEase Biotech
Attention: Carolyn Rilean
3426 Winding Road Rocky
Mount, NC 27801

Dear Mrs. Rilean:

Please refer to your Biologics License Application (BLA) received April 3, 2023, submitted under section 351(a) of the Public Health Service Act (PHS Act) for Human Metapneumovirus vaccine.

LICENSING

We have approved your BLA for Human Metapneumovirus Vaccine effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Human Metapneumovirus Vaccine under your existing Department of Health and Human Services U.S. License No. 1111. Human Metapneumovirus Vaccine is indicated for active immunization for the prevention of Human Metapneumovirus in infants <1 yr, children 1-10 yrs, adolescents 11-19 yrs) and adults 20 yrs and older.

This approval letter contains information on:

- MANUFACTURING LOCATIONS
- DATING PERIOD
- FDA LOT RELEASE
- LABELING
- ADVERSE EVENT REPORTING

RecombiShield-HMPV Fictional Approval Letter

RecombiShield-HMPV Press Release

**The following is a fictional portrayal of success for RecombiShield-HMPV*

For Immediate Release

EndemicEase Biotech's RecombiShield-HMPV Receives FDA Approval for Prevention of Human metapneumovirus (HMPV)

Rocky Mount, NC, January 31, 2024 –

Today, the U.S. Food and Drug Administration (FDA) has approved for RecombiShield-HMPV, a one-time single dose intramuscular vaccine for active immunization to prevent HMPV. RecombiShield-HMPV demonstrated up to 85% prevention of HMPV-related illnesses in all patient populations and reduced transmission by 70%.

Safety and effectiveness were demonstrated in clinical trials involving more than 10,000 participants, including adults, adolescents, children and infants. FDA's Vaccines and Related Biological Products Advisory Committee voted 12 - 3 to confirm the clinical benefits of RecombiShield-HMPV to patients at their most recent meeting, which outweighed the minor risks that may be associated with the vaccine.

"Receiving FDA approval of RecombiShield-HMPV as the first and only immunization against HMPV is a significant milestone for public health and the scientific community," said Carolyn Rilean, EndemicEase Biotech's CEO. "We anticipate that RecombiShield-HMPV will contribute to reduced infection and transmission of HMPV, a significant worldwide cause of respiratory illnesses."

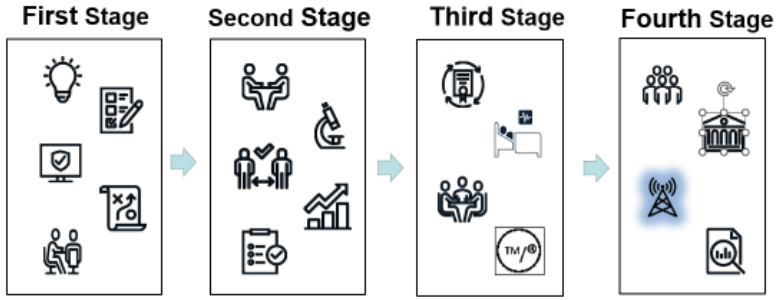
Fourth Stage: Commercialization and Launch

Stephan and Leia work on the commercialization and launch of RecombiShield-HMPV. Much of this involves generating an acceptable label, which is initiated in parallel with the process of preparing the BLA application. The label for RecombiShield-HMPV is critical, without it, there is no launch.

In preparation for generating a label, Leia reviews FDA Guidance for Industry on Vaccine Labeling, which covers the labeling pre-approval review and post-approval surveillance.

When trying to learn more about requirements for labeling, Leia finds information from the FDA on Labeling for CBER-Regulated Products and discovers CBER's instructions for Submitting Biologics Advertising & Promotional Labeling. Through her reviews, Leia learns what descriptions are necessary for the contraindications and warning sections of the label. Additionally, she notes that changes to vaccine labeling will require a BLA supplement (BLS).

Kai also points Leia to another resource focused on Presenting Information in Direct-to-Consumer Promotional Labeling and Advertisements, which shares how to communicate the product risks to consumers. Leia again works with her PR consultant to advertise these materials.



Key questions:

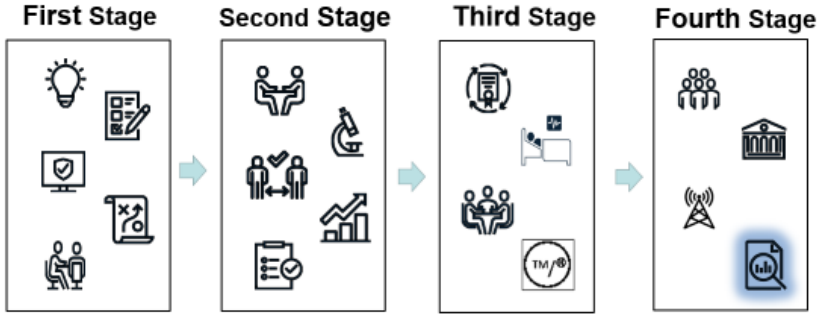
- What labeling guidance is available?
- Is there pre-approval requirement for promotional materials?
- How does an accelerated BLA approval impact labeling requirements?

Fourth Stage: Post-Market Regulatory Compliance

After receiving approval, there are continuous product reviews and reporting to maintain FDA's awareness of the status and safety of RecombiShield-HMPV.

As part of RecombiShield-HMPV's approval, FDA requires Postmarketing Clinical Trials. Also called post-marketing surveillance, these trials are conducted after a vaccine has received regulatory approval and launched in the market. These trials provide valuable insights into a vaccine's performance beyond the controlled environments of earlier phase trials, informing usage recommendations and ensuring continued risk-benefit balance.

Leia reviewed the FDA guidance on electronic submissions of Postmarketing Safety Reports for Vaccines and Changes to an Approved BLA. Leia must submit an Annual Report, in accordance with the Postmarket Requirements and Commitments, each year within 60 days after the anniversary date of BLA approval. She learns more about reporting requirements through Guidance on How to Complete the Vaccine Adverse Event Reporting System Form (VAERS-1). Leia also learns that the FDA will publish an annual report on the status of post-marketing studies in the Federal Register and make basic information about the status of each post-marketing study available online.



Key questions:

- What is the purpose of postmarking clinical trials?
- Can changes be made after BLA approval?
- What are some vaccine reporting requirements?

Fourth Stage: Post-Market CDC Advisory Meeting

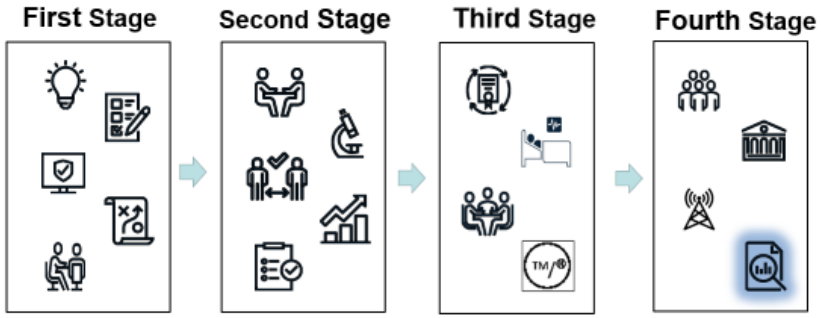
Although RecombiShield-HMPV is FDA-approved, additional U.S. government recommendations are needed to gain support for its general use. These recommendations give healthcare providers confidence that the vaccine is safe and effective.

Leia learns that the CDC's Advisory Committee on Immunization Practices (ACIP) develops recommendations for U.S. immunizations, including who should get a vaccine and when, and precautions and contraindications. ACIP recommendations are reviewed and adopted by the CDC to protect and improve the nation's health.

The safety and efficacy data for RecombiShield-HMPV is reviewed for:

1) Benefits and harms
2) Preferences of people affected
3) Quality of evidence
4) Health economic analysis

Community impact and health equity are also considered, and public input is accepted. At the ACIP meeting, there is much discussion during the public comment period. Ultimately, the ACIP approves the recommendation, which is followed by CDC Director approval. With the director's approval, CDC publishes its recommendation for the use of the RecombiShield-HMPV vaccine in U.S. With this approval, the CDC emphasizes that vaccine safety monitoring systems exist and should be advertised to patients for their use, if needed.



Key questions:

- Where can I find guidance for preparing the BLA application?
- What key items go the BLA application?
- How does the pre-BLA meeting align with the BLA application?

SUMMARY

Summary: By Stage

First Stage

- Define Vaccine Candidate: Pre-regulatory activities focused on vaccine candidate production and testing of its components
- Develop a Target Product Profile: Defining the TPP as a planning tool that outlines vaccine characteristics to guide product research and development
- Vaccine Characterization: Conducting initial validation and formulation studies for the vaccine candidate, to include vendor assistance (CRO and CDMO)
- Regulatory and Quality Management Strategy Consultant: Enlisting assistance with developing a quality and regulatory strategy
- INTERACT meeting: Preparation for, and engagement with FDA in, meeting geared towards early product development challenges

Second Stage

- Pre-IND Meeting: Preparation and expectations for pre-IND meeting, to include nonclinical study data, the clinical trials strategy and manufacturing plans
- IND-Enabling Studies: Process of identifying the safety, toxicity, and dosing of the lead vaccine candidate
- IRB Approval: IRB strategy, plans, and guidelines
- Manufacturing Clinical Trial Material: Manufacturing strategy and key items for scale-up
- Submission of IND Application: Preparing and submitting application for an Investigational New Drug

Third Stage

- Quality Management Compliance: CDMO scale-up of clinical trial material following GMP guidelines and CRO adhering to regulations ensuring GCP
- Clinical Trials (Phases 1-3): Purpose, planning and outcomes of clinical trial phases
- End-of-Phase 2 Meeting: Preparation for, and expectations of, EOP2 meeting
- Generating a Proprietary Name: Flexibility in vaccine naming and registering the trademark

Fourth Stage

- Pre-BLA Meeting: Preparation and expectations for pre-BLA meeting
- Submission of BLA Application: Preparing and submitting application for official vaccine approval
- Communication Plan: Developing a communications plan, recruiting a public relations consultant for messaging and generating an acceptable label
- Post-Market Activities: Additional advisory meetings for government-wide approval and reporting requirements to FDA post-BLA approval

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