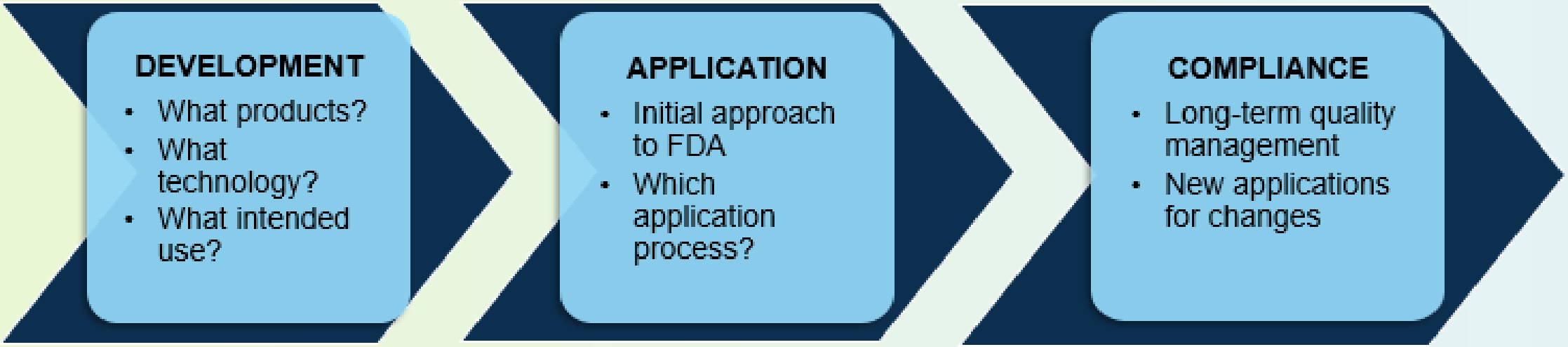
Drug Regulatory Case Study
ChroKi Biosciences

Regulatory Overview

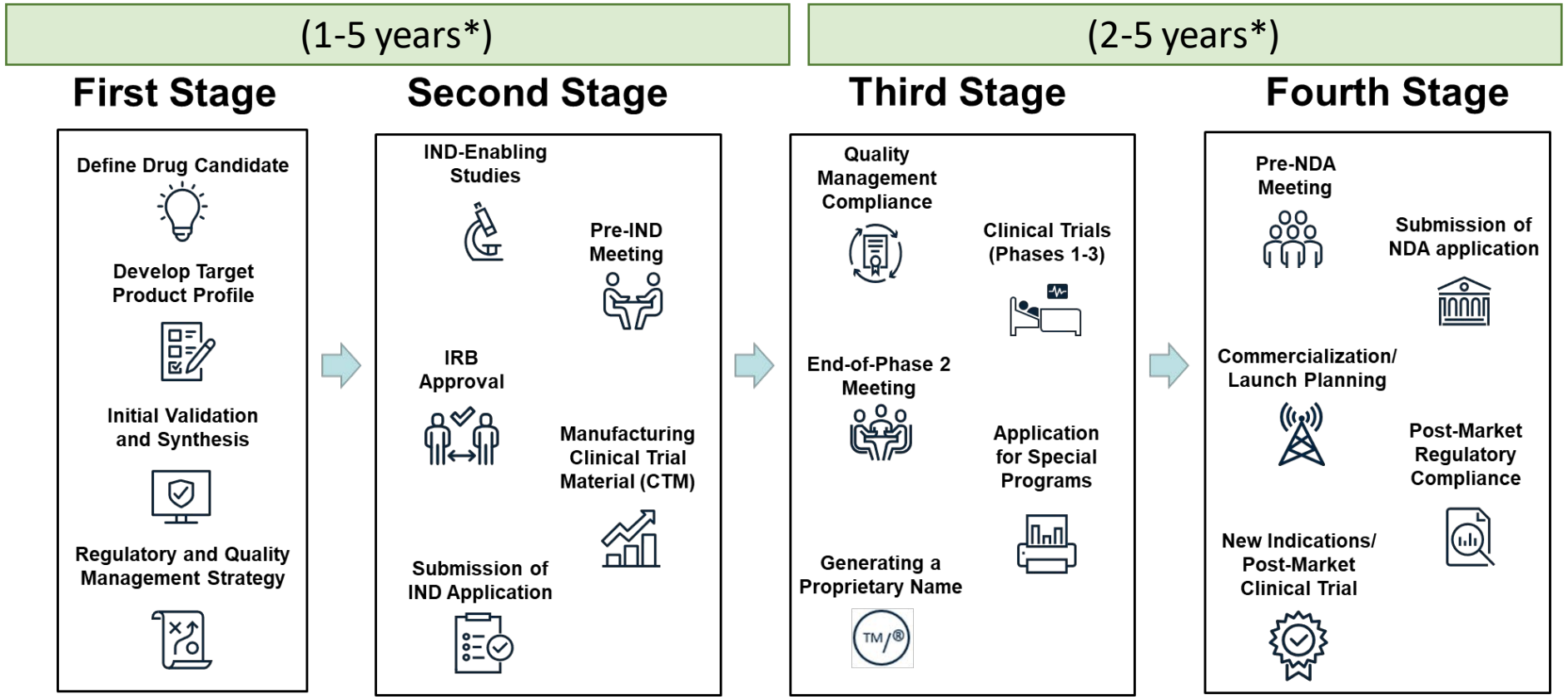
To bring a medical product to market an innovator needs to understand the entire commercialization process and manage multiple tasks related to early-stage research and development, clinical trials, regulations, and reimbursement. The goal of receiving Food and Drug Administration (FDA) approval is a 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 that they can successfully navigate the approval process.

Key Elements of a Regulatory Strategy



Regulatory Strategy Activities Roadmap

This case study breaks down the process described in our *Regulatory Knowledge Guides*. It will take you step-by-step through a process innovators may follow to develop a strategy for FDA market authorization. Drug development, testing, and market authorization is a lengthy process, and likely taking several 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.

Story Characters

ChroKi Biosciences

Headquarters: Boston, MA

Employees: 150

Develops drug candidates for kidney diseases

ChroKi CEO

Name: **Stephan Olrig**

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

Principal Investigator

Name: **Amara Akintola, PhD**

Leads all technical activities, meetings, and regulatory development for the lead drug candidate at Chroki Biosciences. 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: **Brent Myehrs**

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 drug manufacturing and development.

NIH Program Official

Name: **Linh Yen, PhD**

Scientific and programmatic contact at NIH.

Introduction to ChroKi Biosciences

Stephan Olrig is the CEO of ChroKi Biosciences , a small research company in Boston, Massachusetts. ChroKi has made scientific discoveries with small-molecule inhibitors and is starting to expand its landscape of anti-FGFR therapies. Stephan has a fibroblast growth factor receptor (FGFR) inhibitor for the treatment of chronic kidney disease (CKD) that has a novel mechanism of action in comparison to existing CKD therapies. Stephan is interested in approaching steps for regulatory approval candidate drugs. He appoints Amara Akintola, a principal investigator at ChroKi, to lead the effort.

What will ChroKi need to do to navigate regulatory requirements and legally market the new drug?

Here's some background.

Research Description:

- ChroKi previously investigated the role of growth factor receptors and their inhibition in CKD.
- ChroKi intends to identify a targeted therapy to improve kidney function and quality of life for patients with CKD.
- ChroKi has sufficient funding to support all activities up to Phase 1 clinical trials, including outsourced activities.

Why CKD?

- CKD is a serious condition involving gradual loss of kidney function over time, which could progress to end-stage kidney failure, heart disease, stroke, or other health problems.
- According to the CDC, more than 15% of adults (37 million Americans) are estimated to have CKD.
- In 2019, treating Medicare beneficiaries with CKD cost $87.2 billion and treating people with ESRD cost an additional $37.3 billion.

First Stage

First Stage

- Define Drug Candidate
- Develop Target Product Profile
- Initial Validation and Synthesis
- Regulatory and Quality Management Strategy

Second Stage

- IND-Enabling Studies
- Pre-IND Meeting
- 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
- Application for Special Programs
- Generating a Proprietary Name

Fourth Stage

- Pre-NDA Meeting
- Submission of NDA application
- Commercialization/ Launch Planning
- Post-Market Regulatory Compliance
- New Indications/ Post-Market Clinical Trial

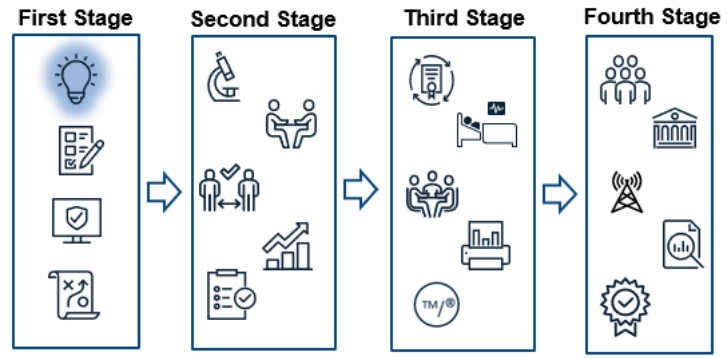
First Stage: Define Drug Candidate

Early on, Amara's team conducted studies on discovery and early-stage development for a candidate drug targeting FGFR, a novel target for treating CKD. These pre-regulatory activities focused on optimizing synthesis of, and further defining, the drug candidates.

With a focus on kidney diseases, Chroki first identifies the potential therapeutic target's function and its role in CKD. The Chroki team aligns efforts to the therapeutic target, FGFR, based on prior screenings and published data on its role in CKD progression. The team then uses low-throughput target validation assays to demonstrate FGFR's involvement in pathways associated with CKD progression.

A screening assay is used to test their compound library for impact to biological activity. The team developed an assay using TGF-β1-stimulated AARGH23 cells, followed by monitoring the expression of α-smooth muscle actin (α-SMA), a marker for pathologic fibroblasts. This assay identified a potent drug candidate, demonstrating *in vitro* inhibition of AARGH23 cells toward fibrosis.

The team further confirmed the drug candidate's activity through biochemical and cellular assays, defining the structure activity relationships, determining efficacy in mice, and establishing synthetic feasibility of the drug candidate. Because the drug candidate's mechanism of action is unique compared to existing therapies and products, they decide to pursue the drug candidate (PIX-003) as a novel drug, to be designated as a first-in-class drug or a new molecular entity (NME).



Key questions:

- What are considered pre-regulatory activities?
- How is the drug candidate defined?

First Stage: Develop a Target Product Profile

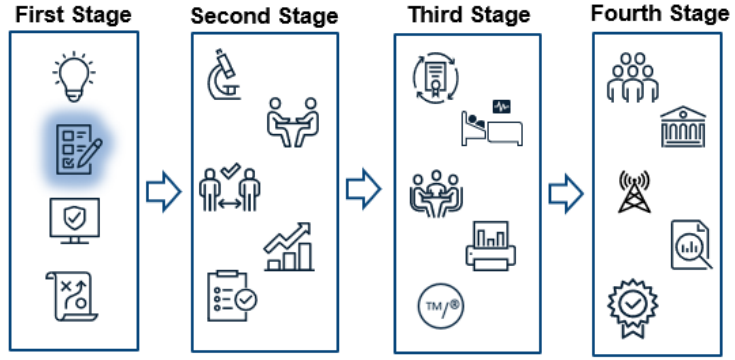
After identifying the lead compound, PIX-003, Amara's team starts to develop a Target Product Profile (TPP). Stephan hears that the TPP is not necessary. Bringing this information to Amara, Stephan learns that although the TPP is not mandated, it is strongly recommended by the FDA and will likely save time and result in more streamlined interactions.

Amara discovers an NIH example TPP and realizes that the TPP is a planning tool that outlines drug characteristics that help guide product research and development. After watching the TPP webinar, they realize items such as intended use, target populations, and other desired attributes of products (including safety, and efficacy-related characteristics) should be included.

Feeling more informed, Amara and her team meet to discuss what to include in the TPP. They decide on:

- Target identification and candidate development (i.e., primary indication, target class, patient population)
- Nonclinical development and efficacy (i.e., efficacy standards)
- Dosage and formulation (i.e., dosage form, dose/strength, schedule, delivery mode)

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



Key questions:

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

First Stage: Develop a Target Product Profile

Attribute	Minimum TPP	Optimal TPP
Product class	Small molecule drug: IM parenteral delivery	Small molecule drug: Oral
Clinical Study Endpoints	Primary endpoints: Provides greater clinical benefit over competitor Secondary endpoints: Equivalent to competitor	Primary endpoints: Far greater clinical benefit over competitor Secondary endpoints: Better than competitor
Safety and Tolerability	No major safety concerns or side effects; acceptable tolerability	No major safety concerns; no side effects
Pharmacology and Toxicology	IM Parenteral dose has satisfactory PK/PD and toxicology	Oral dose has satisfactory PK/PD and toxicology
Manufacturing/Purity	≥ 98% pure and all impurities present at ≥ 0.1% controlled and characterized	≥ 99% pure and all impurities present at < 0.1%
Dosage Regimen/Schedule	Quarterly	Once per year
Storage Requirements	To be shipped at 2-8°C for transport and storage – cold chain required; sub-optimal end user suitability	No special transport or storage requirements; end user suitability

- The team creates a draft TPP.

Note: Presented TPP shows selected attributes. Full example TPPs can be found within the Example Target Product Profile-Small Molecule Drug or the NIH CREATE Bio Example

- While entering in specific sections, it becomes clear that regular updates are needed to assess whether the required product development and critical quality attribute goals are being met.

First Stage: Initial Validation and Synthesis

With PIX-003 as the lead drug candidate, Amara's team must now conduct additional pharmacological and biological testing to confirm its activity.

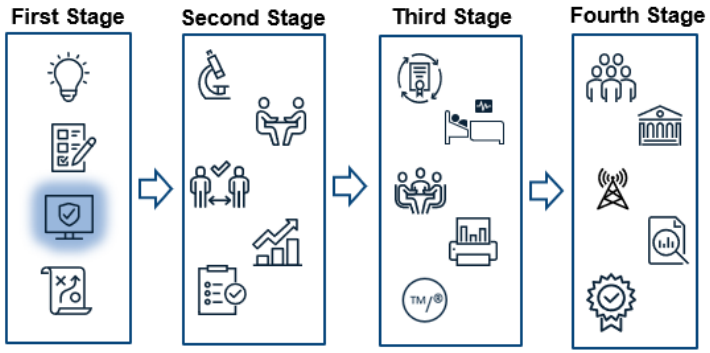
With *in vitro* assays identifying the lead candidate and the TPP now developed, the team discusses how to evaluate the candidate's biological activity and other vital characteristics. They develop additional assays to further confirm the lead candidate in order to establish pharmacodynamic endpoints.

The team designs studies focused on:

- Establishing the mechanism of action
- Defining metabolic stability
- Confirming cellular pathways
- Optimizing formulation for stability and efficacy
- Identifying process-related impurities and characterize ≥ 0.1%
- Synthesis

The team also conducts dose-escalating studies in rats, which led to no significant side-effects at up to 50 times the effective dose. However, results from the animal data support parenteral delivery, due to high doses needed, and liquid formulation, which impacts the initial entries in their TPP. The research team is still excited about pursuing approval of PIX-003, and Amara finds an overview of the FDA Drug Approval Process, to better understand key steps and expectations.

TPP *Amara updates the Pharmacology and Toxicology section of the TPP*



Key questions:

- What should be the focus of confirmation studies?
- Are there any product or process impurities of concern?

First Stage: UPDATED Target Product Profile

Attribute	Minimum TPP	Optimal TPP
Product class	Small molecule drug: IM parenteral delivery	Small molecule drug: Oral
Clinical Study Endpoints	Primary endpoints: Provides greater clinical benefit over competitor Secondary endpoints: Equivalent to competitor	Primary endpoints: Far greater clinical benefit over competitor Secondary endpoints: Better than competitor
Safety and Tolerability	No major safety concerns or side effects; acceptable tolerability	No major safety concerns; no side effects
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Dosage Regimen/Schedule	Quarterly	Once per year
Storage Requirements	To be shipped at 2-8°C for transport and storage – cold chain required; sub-optimal end user suitability	No special transport or storage requirements; end user suitability

- The TPP is updated to reflect animal data, which demonstrated that significantly higher amounts of drug needed is needed for an oral dose.
- An updated TPP refines the minimal/ideal profile based on generated results.

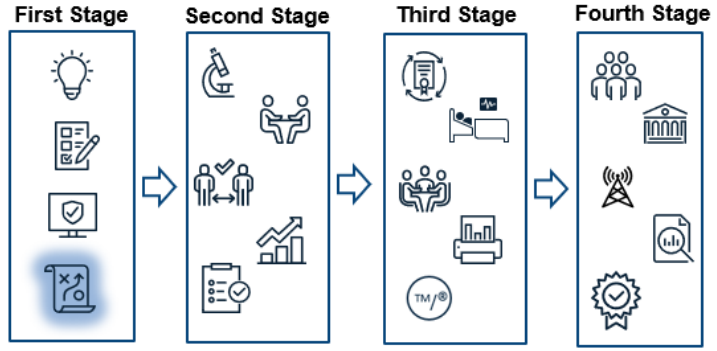
First Stage: Regulatory and Quality Management Strategy

The *in vitro* and small-scale *in vivo* studies provided confidence for promising results with PIX-003. The team starts to identify ways to develop their regulatory strategy.

Without anyone on the team having extensive experience in the drug development process, they find the FDA CDER Small Business and Industry Assistance (SBIA) office website and the FDA CDER Small Business and Industry Assistance (SBIA) Learn repository helpful. They decide to hire a regulatory consultant for additional guidance. As an NIH-funded innovator, Amara consults with the NIH SEED Office and applies to the TABA Program for help in finding one. She works with Stephan to outline the statement of work that they need to identify the right consultant.

Amara searches for a regulatory consultant with experience in first-in-class small molecule drug approvals for assistance. She asks potential consultants if they have experience with the Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN) within the Office of New Drugs, which is the office that reviews drugs like PIX-003. She finds Brent Myehrs, a regulatory consultant who can begin working with her and her team to develop their quality and regulatory strategy. Brent will assist Amara and her team with identifying:

- Quality management considerations
- Regulatory documentation



Key questions:

- How does FDA regulate small molecule drugs?
- What should be the scope of work of the regulatory consultant?

Second Stage

First Stage

- Define Drug Candidate
- Develop a Target Product Profile
- Initial Validation and Synthesis
- Regulatory and Quality Management Strategy

Second Stage

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Fourth Stage

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Second Stage: IND-Enabling Preclinical Studies

Prior to advancing to human testing, Brent notes that Amara and her team must first conduct IND-enabling studies. These studies should ultimately identify the safety, toxicity, and dosing of their lead candidate, PIX-003, in animal models.

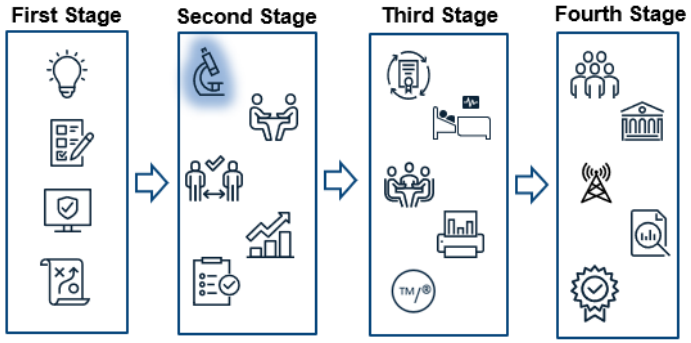
Brent suggests meeting with the FDA prior to conducting the IND-enabling preclinical studies, but due to time constraints and to keep momentum, Amara decides to move forward prior to seeking FDA guidance. The team finalizes formulation for PIX-003 use in the IND-enabling preclinical studies.

Amara's team designs IND-enabling studies in an C57BL/6J mouse model to:

- Validate the drug-target interaction
- Assess the lead candidate's impact on the disease state
- Predict the drug pharmacology, pharmacokinetics, and pharmacodynamics
- Predict therapeutic efficacy and dose
- Identify potential toxicity/safety/tolerability concerns

The team decides to also use animals with progressively more severe renal disease with longer follow-ups. Realizing the scale and scope of their study is too large for their location, they identify a Contract Research Organization (CRO) to conduct the studies under Good Laboratory Practices (GLP).

Study results were all optimal, apart from the tolerability data, where results of local tolerance testing indicated acceptable levels of irritation at the injection site.



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 *Amara updates the Safety and Tolerability section of the TPP*

Second Stage: UPDATED Target Product Profile

Attribute	Minimum TPP	Optimal TPP
Product class	Small molecule drug: IM parenteral delivery	Small molecule drug: Oral
Clinical Study Endpoints	Primary endpoints: Provides greater clinical benefit over competitor Secondary endpoints: Equivalent to competitor	Primary endpoints: Far greater clinical benefit over competitor Secondary endpoints: Better than competitor
Safety and Tolerability	No major safety concerns or side effects; acceptable tolerability	No major safety concerns; ~~no side effects~~
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Manufacturing/Purity	≥ 98% pure and all impurities present at ≥ 0.1% controlled and characterized	≥ 99% pure and all impurities present at < 0.1%
Dosage Regimen/Schedule	Quarterly	Once per year
Storage Requirements	To be shipped at 2-8°C for transport and storage – cold chain required; sub-optimal end user suitability	No special transport or storage requirements; end user suitability

- The TPP is updated to reflect additional animal data demonstrating irritation at the injection site.
- An updated TPP reflects the removal of "no side effects" due to the minimal/ideal profile based on generated results.

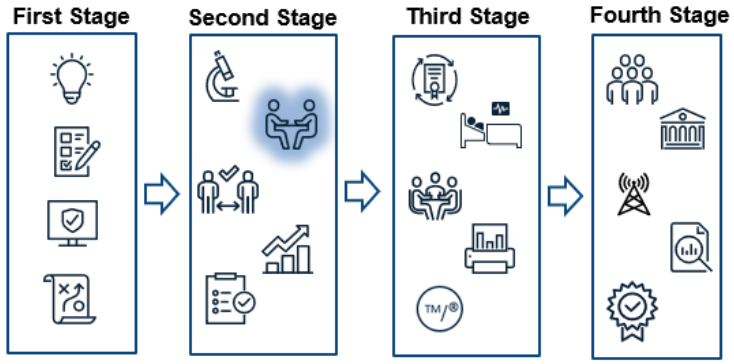
Second Stage: Preparing for Pre-IND Meeting (1 of 2)

With the initial validation complete and IND-enabling studies underway*, Amara must plan for the next major step, clinical testing. Considering their limited experience with clinical activities, both Amara and Stephan decide to get assistance in preparing for human studies.

To start clinical trials, Amara knows an IND application must be submitted, which must include a clinical trials strategy and plans to manufacture additional lead drug candidate. Amara looks for a clinical research organization (CRO) and a contract development and manufacturing organization (CDMO) to:

- Help with clinical strategy development following their promising IND-enabling pre-clinical studies (CRO)
- Assist with manufacturing plans for clinical trial scale-up (CDMO)

*Ideally, the IND-enabling studies are conducted after receiving FDA input on the nonclinical study plans. The NIH SEED team recommends having the pre-IND meeting prior to conducting IND-enabling studies. This helps avoid costly revisions to work that may be required to address FDA's feedback.



Key questions:

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

Second Stage: Preparing for Pre-IND Meeting (2 of 2)

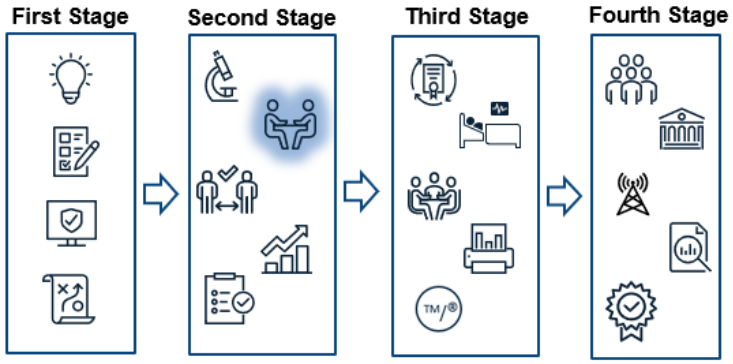
Stephan helps Amara with identifying topics to note in the pre-IND meeting that will be applicable later in the development process, to include approval programs.

Amara prepares the meeting request for the pre-IND meeting, based on the consult and Frequently Asked Questions on the Pre-Investigational New Drug (IND) Meeting. Brent and Amara to gather the following key items in advance of the meeting:

- Plans for GLP animal studies
- Manufacturing information
- Clinical protocols (study plans) and Investigator Information

Brent reviews special programs with Amara using the Expedited Programs for Serious Conditions Guide, which outlines four FDA programs intended to facilitate and expedite development and review of new drugs. Brent notes that if PIX-003 demonstrates substantial improvement over available therapy on clinically significant endpoint(s) during their clinical trials, they should consider Breakthrough Therapy. Additionally, Brent emphasizes that with PIX-003 having a novel mechanisms of action that offer a new therapeutic approach to treating CKD, Amara should mention PIX-003 being considered a first-in-class drug during the pre-IND meeting.

Since ChroKi received NIH National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) funding for exploring FGFR inhibitors, their NIH Program Official, Linh Yen, recommended they have a regulatory consult with the NIH SEED office to help them review their pre-IND meeting request questions.



Key questions:

- What information is collected in advance of the pre-IND meeting?
- What expedited programs exist?
- When should expedited programs be mentioned to FDA?
- What support does the NIH SEED Office provide?

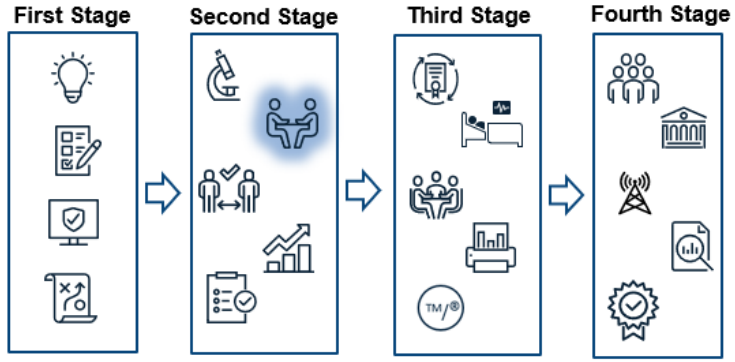
Second Stage: Pre-IND Meeting

After receiving a pre-IND meeting confirmation, Amara arms herself with the nonclinical study data, the clinical trials strategy and manufacturing plans. She feels ready to share the proposed path forward for their lead candidate, but also prepares questions on their strategies to get the FDA's insight that will help avoid any future challenges or delays.

Amara would like the FDA meeting outcomes to be confirmation that their studies provide useful information, FDA support for their proposed clinical strategy, confirmed adequacy of CMC information, and additional regulatory insight. She uses additional IND Meetings for Human Drugs and Biologics Guidance to prioritize talking points and questions.

They first discuss scientific and regulatory aspects of the drug relative to safety. Considering the promising nonclinical study data, the FDA noted the use of only a C57BL/6J mouse model in their preclinical studies gave cause for concern. Specifically, they noted that more studies in a larger animal species would make their data more robust and would be favorable during the IND review.

Considering the developments with the animal studies, Amara quickly reviews their clinical trial design to assess whether the initial-phase trials will expose subjects to unnecessary risks. The FDA acknowledges that the CMC information is adequate. However, the FDA notes that more information should be provided to justify the proposed dose in draft study protocol. Without this information, there may be a delay in initiating the clinical trial, as a "clinical hold" might be issued by FDA.



Key questions:

- What is the intent of a pre-IND meeting?
- What should the team expect during a pre-IND meeting?

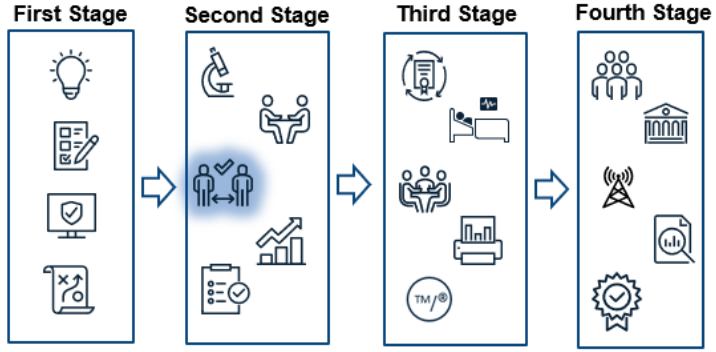
Second Stage: IRB Approval

The CRO working with Amara and Stephan also provides Institutional Review Board (IRB) support. This is ChroKi's first clinical trial, and without an internal or previously used IRB, they must obtain IRB approval to initiate clinical studies.

With the pre-IND meeting complete, the CRO reaches out to Amara and Stephan to discuss IRB approval. They note that although having a successful pre-IND meeting, an IND submission won't be possible without commitments to obtain informed consent from the research subjects and obtaining review of the study by an IRB.

Although the CRO can easily assist with the IRB, Amara and Stephan still 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. Amara also reviews the Institutional Review Board (IRB) Written Procedures: Guidance for Institutions and IRBs, to confirm their submission aligns with FDA's written procedures for the IRB.

Amara and Stephan call a meeting with the CRO to review the IRB plans. Once they agree on the strategy, the CRO submits for IRB approval. Amara also coordinates with their NIH program officer to ensure the study is registered and that 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 (CTM)

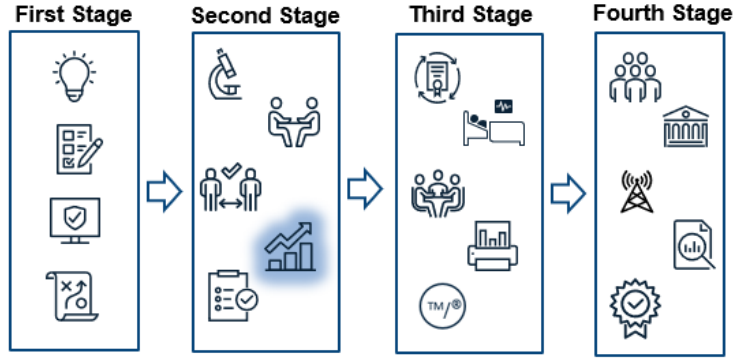
Up to this point, Amara's team produced quantities of the lead candidate sufficient for the necessary studies, but they must scale-up production of the material for clinical trials. Amara and Stephan relies on the CDMO to assist with the manufacturing strategy and provide manufacturing services, as well as comply with current good manufacturing practices (cGMP).

In a meeting with the CDMO, they note that key elements for scale-up production include:

- Manufacturing enough drug product for clinical trials (identifying amount of drug product material required)
- Establishing certificate of analysis (CoA) with specifications for physical, chemical, and quality attributes among all batches
- Retaining samples for bridging and stability studies
- Implementing cGMP practices

During the meeting, the CDMO offers guidance that producing excess material is recommended, with companies typically manufacturing 130% of their need. Additionally, they warn not to exceed scale-up by a factor of 10, in order to avoid product variability. Amara notes this for their strategy and reviews a comprehensive compliance policy guide. During scale-up, there are increases in total process-derived impurities. However, no impurity was present ≥ 0.1%, so further characterization and control is not needed.

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



Key questions:

- What are the scale-up manufacturing requirements?
- How does the CDMO support manufacturing scale-up?
- How much scale-up is sufficient?
- Do you need to update your TPP to reflect changes in manufacturing process and/or impurity profiles?

Second Stage: Target Product Profile Review

Attribute	Minimum TPP	Optimal TPP
Product class	Small molecule drug: IM parenteral delivery	Small molecule drug: Oral
Clinical Study Endpoints	Primary endpoints: Provides greater clinical benefit over competitor Secondary endpoints: Equivalent to competitor	Primary endpoints: Far greater clinical benefit over competitor Secondary endpoints: Better than competitor
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Dosage Regimen/Schedule	Quarterly	Once per year
Storage Requirements	To be shipped at 2-8°C for transport and storage – cold chain required; sub-optimal end user suitability	No special transport or storage requirements; end user suitability

- The TPP reflects the new impurity data available. Slightly increased impurities, but within the optimal target limits.

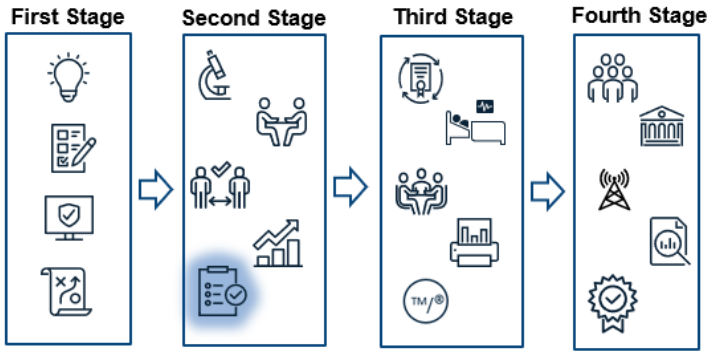
Second Stage: Submission of IND Application

Amara needs to provide information supporting why she believes the lead drug candidate will be effective in an initial clinical protocol. She provides this information in an Investigational New Drug (IND) application.

Brent takes the lead in preparing the IND application, which includes sections summarizing preclinical development, detailed manufacturing information, and clinical investigations.

Brent and Amara 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. Amara also reviews the IND Forms and Instructions for submission templates and details. Amara learns that the FDA has 30 days to review the application for safety concerns

After submission, Amara receives notice from the FDA of an IND tracking number, indicating receipt of her application. Thirty days after submission, Amara hasn't received an FDA response or authorization letter. This is an indicator that Amara and her team can proceed with their proposed clinical study.



Key questions:

- What are the contents of an IND application?
- How long does it take for FDA review of an IND application?

Third Stage

First Stage

- Define Drug Candidate
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- Initial Validation and Synthesis
- Regulatory and Quality Management Strategy

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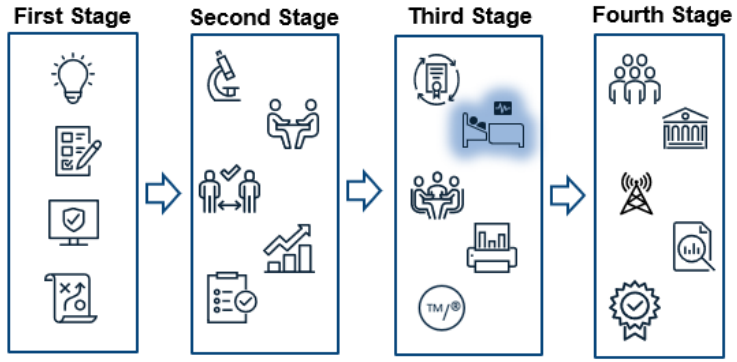
Third Stage: Preparing for the Initiation of the Clinical Study

With no flags raised by the FDA, Amara prepares to move forward with the clinical study. The framework for clinical trials and clinical monitoring will be critical as the clinical study begins – Amara coordinates heavily with the CRO and CDMO in advance.

Amara calls a joint meeting with the CRO, Brent, and Stephan to review clinical study plans, their potential outcomes and the impact to the desired regulatory approval. The CRO, having previously worked with similar-sized companies in the CKD space, emphasizes its network of specialized trial sites and clinical development experience for data-driven approaches to accelerate proof of concept.

As the CDMO has fill-finish manufacturing capabilities, it will provide the drug in a 5 mL multi-dose vial, to yield four 1 mL doses + 20% overage. Each dose is 100mg/mL. Amara confirms with the CDMO that they will also make placebo for the clinical study. Before shipping to the clinical trial sites, the CDMO will perform a shipping validation study to ensure PIX-003 can be transported without loss of potency.

Although a syringe is needed for administration, the CDMO recommends against a pre-filled syringe, to avoid being regulated as combination product by FDA. Amara agrees, and although not to be provided with the shipped materials, she decides a luer lock syringe will be provided for the healthcare site to use during clinical trials.



Key questions:

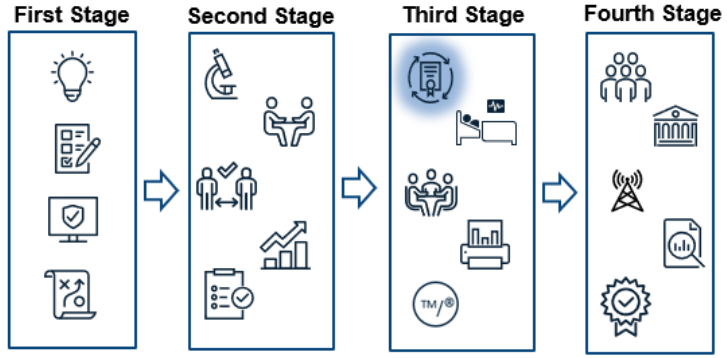
- Who assists with clinical study initiation?
- What should be reviewed prior to executing the clinical study?

Third Stage: Compliance to Quality Management Systems

To support Phase 1 clinical trials, the CDMO will scale-up production of clinical trial material following current GMP guidelines, and the CRO will adhere to regulations that ensure integrity of clinical data.

Good clinical practice (GCP) includes ethical and scientific quality requirements for conducting clinical trials, and it is relevant for pharmaceutical companies, the contract research laboratories and clinics involved. Good manufacturing practice (GMP) includes guidelines for quality assurance in product production, regulates standard operating procedures, documentation requirements, the management of deviations and changes in processes, qualification of systems and validation of methods. Responsibilities for GCP lie with the CRO conducting the clinical trials, whereas GMP practices aligns with the CMDO manufacturing the drug.

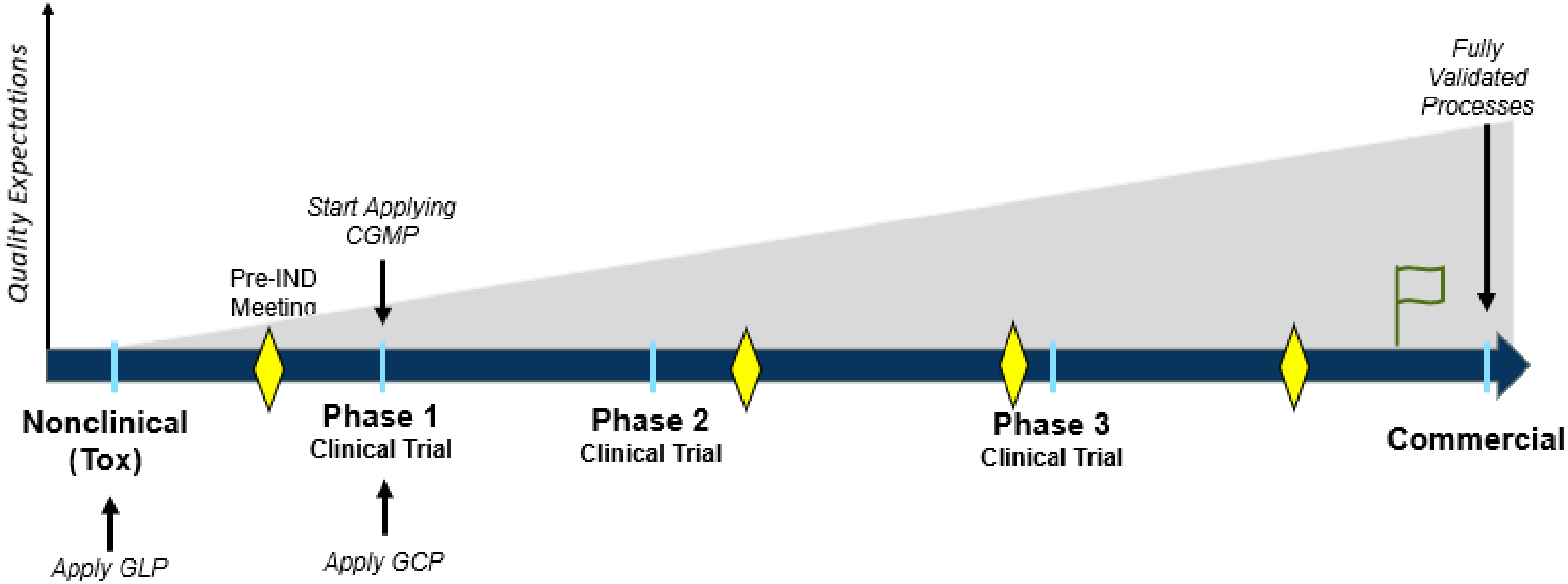
The CDMO emphasizes compliance with an established quality management system (QMS) – procedures and practices set in place to ensure consistent product quality. They note the essential nature of the QMS, which contributes to product quality and safeguards that the final product meets customer & regulatory requirements the manufacturer is obliged to follow.



Key questions:

- What is GCP and GMP?
- Who has responsibilities for GCP and GMP?
- What is a QMS?

Quality Expectations Increase as Program Progresses



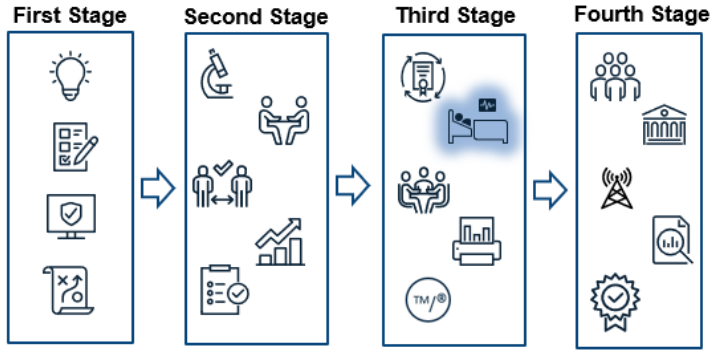
Third Stage: Clinical Trials (Phase 1)

The CRO initiates Phase 1 trials in healthy volunteers, where the drug is tested for safety, side effects, and dose. At this stage, Amara and Stephan will also be responsible for reporting requirements and requesting a generic drug name.

Brent notes that the *process of naming drugs* typically occur during Phase 1 or 2 trials, where investigators can submit a United States Adopted Name (USAN) request for an established drug name. Brent refers Amara to the FDA Established Names Supplemental Policy, which outlines the requirements, types and sources of names used for human and animal drug preparations. Amara confers with Stephan, apply for a name, and are assigned the generic name chrokitinib.

During the clinical trial, Amara and Stephan are responsible for the Safety Reporting Requirements and Safety Assessment. Although the CRO will manage this, the ultimate responsibility lies with ChroKi, based on the signed contract with the CRO.

Reporting requirements apply for serious and unexpected suspected adverse reactions during trials. During the Phase 1 trial with chrokitinib, no adverse events or issues of concern were noted. Additionally, the biodistribution (PK/PD) were consistent with animal models (IND-enabling studies) and dosing.



Key questions:

- What occurs in Phase 1 clinical trials?
- When and how do you request a drug generic name?
- Who is responsible for reporting requirements?

Third Stage: Clinical Trials (Phase 2)

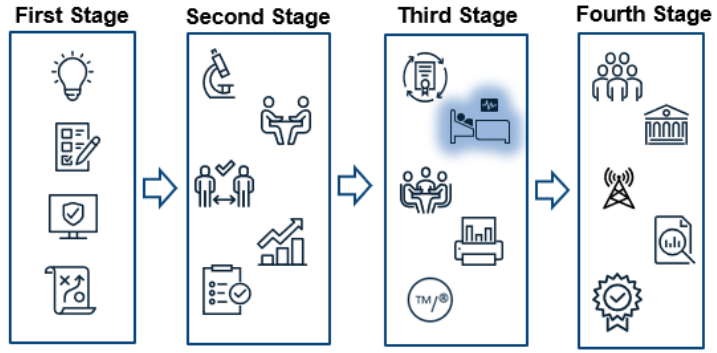
With completion of Phase 1, the CRO initiates Phase 2 trials in CKD patients, where measures of efficacy and side effects are critical. As a first-in-class drug, Brent recommends Amara request an End-of-Phase 2A (EOP2A) meeting with FDA.

To continue with clinical studies for chrokitinib, Chroki received investments for Phase 2 trials based on achieved milestones from Phase 1. The CRO first proceeds with Phase 2A trials, where the focus is on exposure response in patients.

The EOP2A meeting is an opportunity for Amara to seek guidance related to clinical trial design employing clinical trial simulation and quantitative modeling with existing data, designing trials for better dose response estimation and dose selection, and other related items. In preparation for the meeting, Amara reviews End-of-Phase 2A Guidance to learn about meeting objectives, potential topics for discussion, preparing a EOP2A meeting package, and how to make a EOP2A meeting request.

At the End of Phase 2A meeting, Amara and the FDA discuss the Phase 2A data. The result of the Phase 2A study suggest that a higher dose is needed in humans than estimated from animal models. The FDA requested exploring a broader dose range than proposed in Phase 2B, the patient dose-ranging trial.

The CRO designed a Phase 2B/3 trial to save time and resources to allow a smooth transition from the dose-finding stage to the confirmatory stage of the trial. This type of trial can be beneficial when there is strong preliminary evidence of a drug's effectiveness and a need for expedited development, such as in the case of severe diseases.



Key questions:

- What occurs in Phase 2 clinical trials?
- What is discussed at an EOP2A meeting?

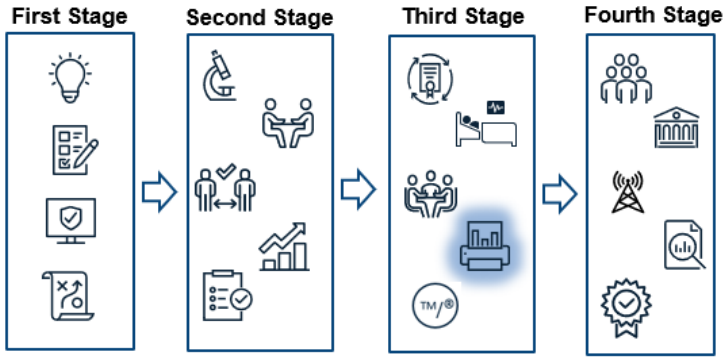
Third Stage: Application for Special Programs

Many of the FDA special programs are intended to speed up the development and review of drugs and biologics that address unmet medical needs. With the clinical study data strengthening chrokitinib becoming as a first-in-class drug, Stephan and Amara review appropriate special programs for accelerating approval.

Phase 1 and Phase 2 studies demonstrated safety and a high therapeutic effect seen through improvements in estimated glomerular filtration rate (eGFR), a surrogate endpoint. Brent notes the preliminary clinical evidence meets the criteria for Breakthrough Therapy and Accelerated Approval by demonstrating *substantial improvement over available therapies* and *addressing an unmet medical need in the treatment of a serious or life-threatening condition.*

After reviewing the FAQ for Breakthrough Therapies, Amara works with Brent to submit a request for Breakthrough Therapy designation as an amendment to the IND before their planned EOP2 meeting. Within 60 days, ChroKi receives a letter from the FDA that chrokitinib has been granted Breakthrough Therapy designation.

Amara reads that the FDA can rely on a drug's effect on a surrogate endpoint as a basis for Accelerated Approval. Her application for accelerated approval includes evidence that the used surrogate endpoint is reasonably likely to predict chrokitinib's intended clinical benefit.



Key questions:

- How many Special Programs exist, and what are they?
- What is the criteria for obtaining Breakthrough Therapy designation?
- What is the criteria for an Accelerated Approval Pathway?
- What is the process for making a Breakthrough Therapy request?

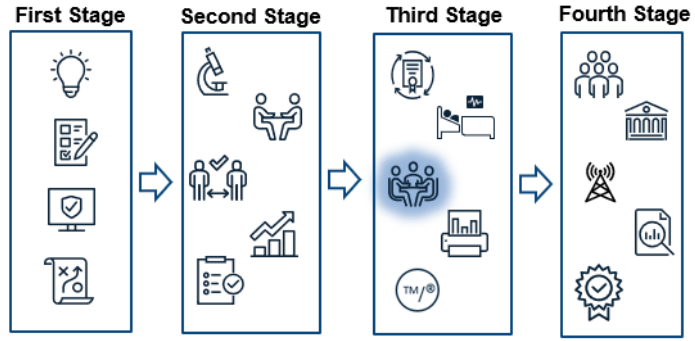
Third Stage: Preparing for End-of-Phase 2 Meeting

With the Phase 2 trials complete, Amara 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.

Amara desires to get FDA agreement with the planned Phase 3 trials and knows this can occur during the EOP2 meeting. In preparation for the meeting, Amara 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 looks over an FDA End of Phase 2 Meeting resource for potential topics and questions.

Amara works with the CRO on modeling of Phases I and II data to simulate results to inform the design parameters of subsequent trial and dosage regimen choice(s). They modeled dose response, disease change over the likely duration of the trial, effects in the placebo group including time-course, and patient baseline data. Amara, Brent and the CRO work together to incorporate data and models into the EOP2 meeting package, which is due at least 50 days before the meeting.

Amara also intends to present the plans for Phase 2B/3 trials, which will incorporate an interim analysis that allows a transition that is more exploratory and dose-finding in nature (Phase 2B) to focus on clinical efficacy and adverse effects (Phase 3) without the need for a pause to analyze data and set up a separate Phase 3 trial. The design and execution of these trials are complex and require careful planning, sophisticated statistical analysis methods, and adjustment of Phase 3 sample size.



Key questions:

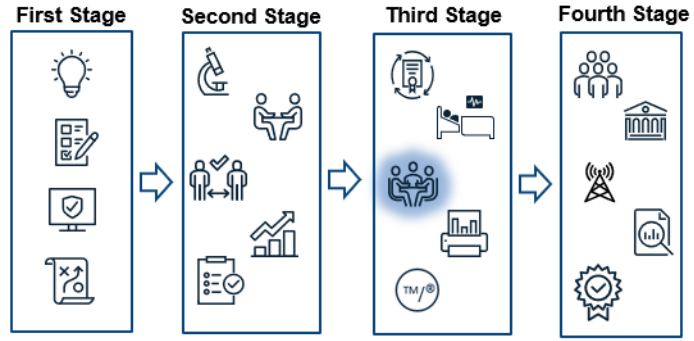
- What is the significance of the EOP2 meeting?
- What resources are available to prepare for EOP2 meeting?
- What types of data can be included in the EOP2 meeting package?

Third Stage: End-of-Phase 2 Meeting

FDA responded to Amara's EOP2 meeting package submission with several clarifying questions. Amara and Brent prepare answers and bring them to the EOP2 meeting.

Prior to the meeting, the FDA raised concerns about increasing production from pilot scale to market scale. Amara and Brent reach out the CDMO for specific CMC information that will help address FDA's concerns. The CDMO provides evidence from previous drug manufacturing runs demonstrating their capacity to achieve the required commercial manufacturing scale plus the recommended 20% overage. The CDMO also confirms their capacity to produce three consecutive manufacturing lots and perform quality checks to verify purity, strength, etc.

Amara and Brent bring their prepared answers and new evidence to the FDA's questions in response to their EOP2 submission package. They know to only discuss topics/issues included in the pre-meeting materials and FDA's response. During the meeting, the FDA asks Amara and the CRO to increase patient size for Phase 3 to confirm correct dosage. Increasing the participant size requirement for their Phase 3 trial is disappointing, however is within the manufacturing capacity of their CDMO and recruitment potential of their planned sites. The team takes notes during the meeting and submits them to FDA as meeting minutes.



Key questions:

- Based on FDA's written feedback before the meeting, what is the best use of time for the face-to-face discussion?
- Is further clarification from FDA needed?

Third Stage: Creating a Proprietary Name

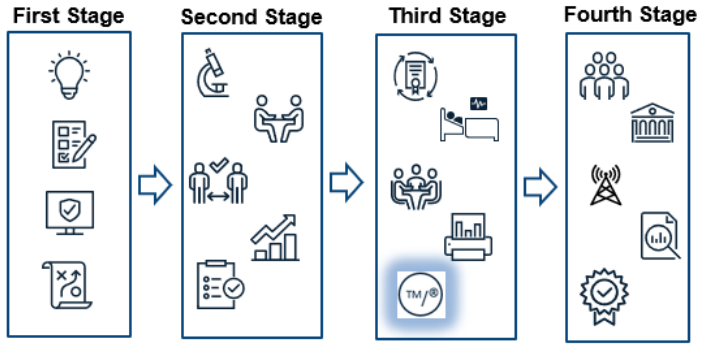
Creating a brand or proprietary name for a new drug involves various legal, marketing, and regulatory considerations, and Best Practices in Developing Proprietary Names exist. Amara and her team are ready for a trade name but must first go through the brand name and Trademark Registration process.

Brent notes to Amara that the trade name should effectively communicate the drug's efficacy and uses and be easy to pronounce and remember. Additionally, Brent notes to Amara that creating a brand name requires multiple steps: Research & Development, Preliminary Screening, Legal Clearance, Linguistic & Cultural Testing, Market Research, and Regulatory Approval.

Brent reminds Amara that the FDA's role is to ensure that the proposed name for a drug aligns with its guidelines by reviewing and approving a drug's brand name to prevent medication errors and misrepresenting its efficacy. However, 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 with the specified goods or services. Therefore, both agencies play distinct roles in naming and protecting drug brand names in the US.

USPTO registration and FDA approval are independent processes that typically follow different timelines. Since Amara doesn't don't know exactly how long it will take to receive approval, Brent recommends she register a trademark with an intent-to-use (ITU) filing basis. She is encouraged to file a new ITU application as early as possible to claim the filing date to establish trademark rights.

FDA granted Chroki the brand name Nephrolix, and the USPTO registered the trademark.



Key questions:

- What are the roles of FDA and USPTO, and are their processes dependent on the other?
- What is an ITU, and when should it be used?

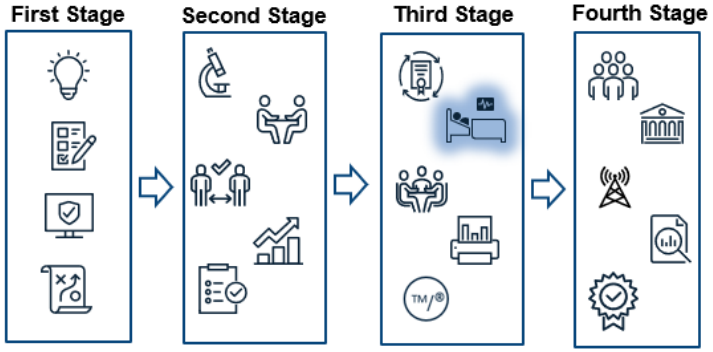
Third Stage: Clinical Trials (Phase 3)

After a successful EOP2 meeting with FDA, ChroKi initiates Phase 3 trials in collaboration with the CRO and CDMO. The primary clinical endpoint, which was discussed with FDA in the EOP2 meeting and 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 in adult patients with chronic kidney disease (CKD). Phase 3 also includes manufacturing of large-scale clinical trial material (CTM), also called pivotal clinical material manufactured using GMP-level quality measures.

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, ChroKi needs to have data demonstrating that chrokitinib provides better patient outcomes than existing treatment options. For patients, this means they either live better or live longer. In Phase 3 trials, the primary composite clinical endpoint is time to "worsening kidney function," defined as >50% sustained decline in eGFR or onset of end-stage kidney disease. Also in Phase 3, the dosing frequency was confirmed as once a year.

Since the trials are only for one indication, the CRO notes that only one pivotal trial is needed. However, since Nephrolix will be considered a new molecular entity-NME, a long-term (12 month) follow-up within Phase 3 is incorporated as part of the study design.



Key questions:

- What occurs during Phase 3 clinical trial?
- What data is required to provide evidence of efficacy and safety?
- Is dose and dosing frequency confirmed?

Fourth Stage

First Stage

- Define Drug Candidate
- Develop a Target Product Profile
- Initial Validation and Synthesis
- Regulatory and Quality Management Strategy

Second Stage

- IND-Enabling Studies
- Pre-IND Meeting
- IRB Approval
- Manufacturing Clinical Trial Material
- Submission of IND Application

Third Stage

- Quality Management Compliance
- Clinical Trials (Phases 1-3)
- End-of-Phase 2 Meeting
- Application for Special Programs
- Creating a Proprietary Name

Fourth Stage

- Pre-NDA Meeting
- Submission of NDA application
- Commercialization/ Launch Planning
- Post-Market Regulatory Compliance
- New Indications/ Post-Market Clinical Trial

Fourth Stage: Pre-NDA Meeting

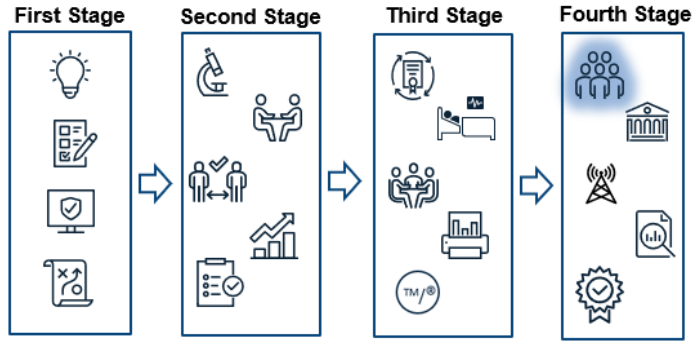
The outcomes of Phase 3 clinical trials are critical for gaining regulatory approval, and Amara will need to gather data for presentation at a pre-NDA meeting as an opportunity to address important or outstanding issues with the FDA before submitting the NDA. As a regulatory expert, Brent works with Amara to complete the NDA.

Amara reviews Guidance for Formal Meetings Between the FDA and Sponsors or Applicants to prepare herself for how to set up the meeting. The meeting is a chance, prior to market authorization, to receive FDA feedback and clarification on the acceptability of:

- Key clinical data, including data that might become available for submission during NDA review
- Chemistry, manufacturing, and controls (CMC) information

Amara works with Brent, the CRO and CDMO to gather all clinical studies data. During the pre-NDA meeting, discussions with FDA include the proposed label, package insert wording, and efficacy of the drug. Upon review of the prepared package, the FDA does not note any major unresolved problems.

However, the FDA suggests having an Advisory Committee Meeting to invite leaders in the field to provide input on whether the clinical data demonstrates the safety and effectiveness of the first-in-class drug.



Key questions:

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

Fourth Stage: NDA Application

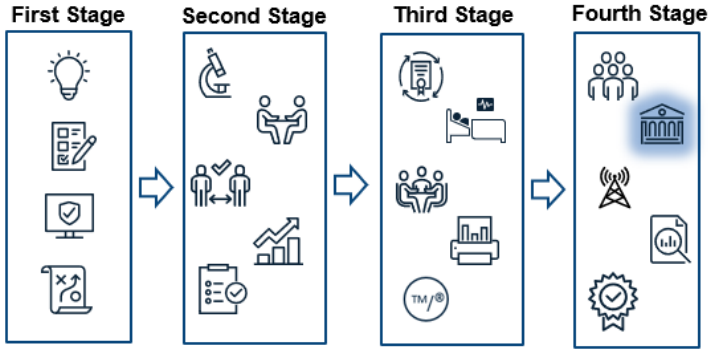
After addressing FDA concerns during the pre-NDA meeting, Amara is ready to submit an NDA Application. The NDA application it is how drug innovators formally propose the FDA approve a new pharmaceutical for sale and marketing in the U.S.

Brent directs Amara to the FDA NDA website, where she can find Resources for NDA Submissions, such as Guidance Documents and NDA forms. Specifically, Amara reviews the guidelines for Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs, guidelines for Formatting, Assembling and Submitting, guidance on Pharmacology/Toxicology and Human Pharmacokinetics and Bioavailability.

As with the IND application, Brent takes the lead in preparing the NDA application, which includes sections for Applicant Information, Product Description, and Application Information. He meets with Amara to review the pre-NDA meeting notes. Because of his , he knows the FDA will expect pre-NDA notes to be included in the application package. In the CMC section, the CDMO helps Amara to focus on demonstrating commercial scale and having readiness to launch.

Within 14 days after submitting the NDA, Amara was informed there were no filing review issues. With the good news, Amara continues to wait to hear from the FDA, which can take up to 60 days from the time of NDA receipt.

Although not part of the application, Amara and Brent start to outline the processes for commercialization and launch. This will help give them a head start, if the NDA application is approved.



Key questions:

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 999999

NDA APPROVAL

GW Research, Ltd.
Attention: Stephan Olrig
ChroKi Biosciences
54321 Bioscience Drive
Boston, MA 27709

Dear Mr. Olrig:

Please refer to your New Drug Application (NDA), dated and received June 2, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Nephrolix (chrokitinib) 100 mg/mL intramuscular solution for the treatment of Chronic Kidney Disease (CKD) in patients eighteen years of age and older.

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

Nephrolix Fictional Approval Letter

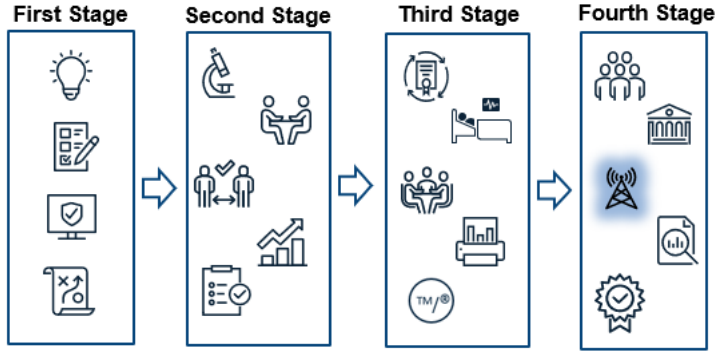
Fourth Stage: Commercialization and Launch

Stephan and Amara work on the commercialization and launch of Nephrolix. Much of this involves when and how to generate the acceptable label, which is initiated in parallel with the process of preparing the NDA application. The label for Nephrolix is critical, without it, there is no launch.

In preparation for generating a label, Amara learns about the FDA Office of Prescription Drug Promotion (OPDP). OPDP ensures the accuracy of drug promotion through research and education, as well as enhancing communication of label and promotion information to consumers and healthcare providers.

When trying to learn more about requirements for labeling, Amara turns to the OPDP Frequently Asked Questions (FAQs). She learns that generally, FDA pre-approval of promotional materials is not required; however, since Nephrolix received accelerated NDA approval, there is a pre-submission requirement. Amara works with Brent to gather and submit to the FDA all promotional materials prior public advertising.

Brent also points Amara to other resources focused on Product Labeling Guidance, Labeling Information, and Presenting Information in Direct-to-Consumer Promotional Labeling Guidance, which shares how to communicate the product risks to consumers.



Key questions:

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

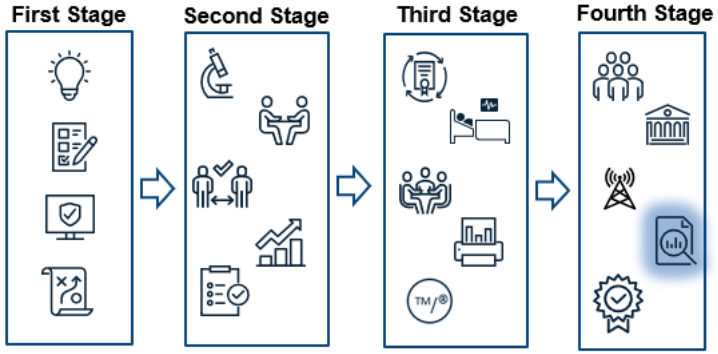
Fourth Stage: Post-Market Regulatory Compliance

After receiving approval, there are continuous product reviews and reporting that the FDA oversees. This is part of the FDA Post-Market Drug Safety Monitoring.

After Nephrolix approval, Amara realizes there will be Postmarketing Clinical Trials. Also called post-marketing surveillance, these trials are conducted after a drug has received regulatory approval and launched in the market. These trials provide valuable insights into a drug's performance beyond the controlled environments of earlier phase trials, informing usage recommendations and ensuring continued risk-benefit balance.

Amara and ChroKi continue to receive data and reporting on adverse events, known as pharmacovigilance. Using pharmacovigilance processes, Amara monitors and collects data on the drug's safety, efficacy, and adverse reactions. This real-world data identifies the need for a minor change to the drug's contraindications, which helps maintain the drug's safety profile and minimize patient risks. Amara reviewed the FDA guidance on Changes to an Approved NDA and FAQs and works with Brent on the submission to the FDA.

Amara must report adverse events in the NDA's required Annual Report, in accordance with the Postmarket Requirements and Commitments. She learns more about these requirements by reviewing the FAQs. Amara also learns that the FDA will annually publish a report on the status of postmarketing studies in the Federal Register and make basic information about the status of each available online.



Key questions:

- What is the purpose of postmarking clinical trials?
- Can changes be made after NDA approval?
- Are there reporting requirements?

Nephrolix Press Release

**The following is a fictional portrayal of what success for Nephrolix may look like*

For Immediate Release

ChroKi Bioscience's Nephrolix Receives FDA Approval for Treatment of Chronic Kidney Disease

Boston, MA, June 2, 2023 –

Today, the U.S. Food and Drug Administration (FDA) has approved for Nephrolix, a first-in-class fibroblast growth factor receptor (FGFR) inhibitor, for use in patients with chronic kidney disease. Nephrolix demonstrated significant improvement over existing comparators in clinical trials involving more than 10,000 adult patients with chronic kidney disease (CKD) and requires only a once-a-year dosing. FDA's Cardiovascular and Renal Drugs Advisory Committee voted unanimously to confirm the clinical benefit of Nephrolix to patients at their most recent meeting.

"Today's announcement is a major step for better therapeutic options for patients suffering from serious kidney complications, such as chronic kidney disease," said Stephan Olrig, ChroKi Bioscience's CEO. "Nephrolix will contribute to reducing the risk of kidney function decline, kidney failure, and end-stage kidney disease. It is also the first and only FGFR inhibitor to have such great outcomes, and we are excited to be part of bring this new therapy to people with this condition."

Fourth Stage: New Indications/Post-Market Clinical Trial

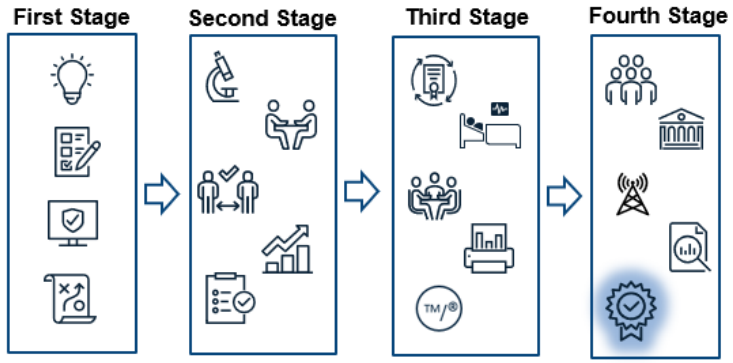
After approval for chronic kidney disease, ongoing research for ChroKi suggested it might be useful for additional indications. Amara looks to Brent for more information on this, as reporting of Nephrolix effects may require a post-market clinical trial for approval as a new indication.

Amara receives reporting of patients with diabetes, with CKD, who are taking Nephrolix experiencing significant improvement of their diabetes. Nephrolix use by patients with diabetes would be considered a new indication based on patient use, and a clinical trial will be required by the FDA. Additionally, whenever a sponsor seeks approval of a new indication for an already-approved drug, the FDA requires a supplemental new drug application (sNDA) with the same quality and content as the drug's original new drug application.

An sNDA is an application to allow a company to make changes to a product that already has an approved new drug application. The sNDA is submitted for an approved NDA for any changes in packaging, labeling, dosages, ingredients, or new indications. With proposed used by diabetes patients, Nephrolix's pharmacokinetics, pharmacodynamics, and interactions with other drugs must be well understood as a standalone agent and in combination therapies.

Even though the Nephrolix mechanism of action is well-known and its effectiveness was proven in earlier controlled trials, a pivotal clinical trial is designed to establish a more thorough clinical examination of Nephrolix pharmacodynamics and unique tissue-specific mechanisms. The safety data for use in diabetic patients closely resemble those from the original indication, indicating the drug behaves comparably in both contexts. These results improve the chance of an sNDA approval. Following the trials, Amara and Stephan submit a sNDA to the FDA, which can take several months to a year for complete review and a decision.

Nephrolix received approval for use in Type 2 diabetes, in addition to CKD, primarily due to the similar safety profiles detected in both conditions.



Key questions:

- What is an sNDA, and when is it required?
- What is the focus of clinical trials for a new indication?
- What improves chances of sNDA approval?

SUMMARY

Summary: By Stage

First Stage

- Define Drug Candidate: Pre-regulatory activities focused on optimizing synthesis, identifying the potential therapeutic target, and testing for biological activity
- Develop a Target Product Profile: Defining the TPP as a planning tool that outlines drug characteristics to guide product research and development
- Initial Validation and Synthesis: Evaluating pharmacological and biological activity to further confirm the lead candidate
- Regulatory and Quality Management Strategy Consultant: Enlisting a regulatory for assistance with developing quality and regulatory strategy

Second Stage

- IND-Enabling Studies: Process of identifying the safety, toxicity, and dosing of the lead candidate
- Pre-IND Meeting: Preparation and expectations for pre-IND meeting, to include including the correct vendors (CRO and CDMO)
- 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: Scaling-up production of clinical trial material following GMP guidelines
- Clinical Trials (Phases 1-3): Purpose and outcomes of clinical trial Phases
- End-of-Phase 2 Meeting: Preparation for, and expectations of, EOP2 meeting
- Application for Special Programs: Identifies FDA special programs intended to speed up the development and review of drugs that address unmet medical needs
- Generating a Proprietary Name: Process for generating a brand name and the role of FDA versus USPTO

Fourth Stage

- Pre-NDA Meeting: Preparation and expectations for pre-NDA meeting
- Submission of NDA Application: Preparing and submitting application for official drug approval
- Commercialization/Launch Planning: Developing a communications plan
- Post-Market Regulatory Compliance: Continuous product reviews and reporting to FDA post-NDA approval
- New Indications/Post-Market Clinical: Additional applications for an approved drug can lead to a new indication

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