

BIOTECH
BRIEFINGS

An illustration in a comic book style showing three people and a robot in a starting crouch on a track. The track is blue with white and red lane markings. The background is a teal gradient with a halftone dot pattern. The robot is a small, blue, mechanical creature with yellow joints and a single eye. The people are a man in a white shirt and red tie, a woman in a white shirt and blue skirt, and a man in a green suit and red tie. They are all leaning forward with their hands on the ground, ready to start a race.

A Race against Time

How medicines are made. A guide
for the rare disease community.

Cléa Stémitsiotis, MSc

James A. Levine, MD, PhD, Professor



Authors for correspondence:

Cléa Stémitiotis, MSc

James A. Levine, MD, PhD, Professor

Fondation Ipsen

65 Quai Georges Gorse, 92100 Boulogne Billancourt, France

Cléa Stémitiotis holds a Bachelor's degree in Management from the London School of Economics and a Master's degree in Economics and Business from Sciences Po Paris. She works on the impact evaluation of Fondation Ipsen and innovative finance for rare diseases.

James A. Levine, MD, PhD, Professor, is President of Fondation Ipsen. He is a serial entrepreneur, scientist and physician, trained in business at Harvard Business School.



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Introduction

Making medicines is complex and, requires meticulous research, innovative thinking, and unwavering dedication. In the realm of rare diseases, this journey is even more complex because the illnesses are so rare. Even rare disease experts often do not know how to help their patients. We need more treatments because 90% of people living with rare disease do not have an effective treatment.

This book explores the steps involved in making medicines. It is our response to requests from the rare disease community. There is an urgent need to understand how medicines are created so that patients and those who care for them can advocate with greater clarity and louder voices. We hope you find this book useful.

How to use this guide

The purpose of this guide is to explore the steps involved during the rare disease medicine development process. It is not a comprehensive science textbook but rather a 'quick read'. Each chapter is short and designed to be read in 5-10 minutes.

Summary

Rare diseases, also known as orphan diseases, are a diverse group of medical conditions that affect a small number of individuals within the population. In the European Union, a disease is considered rare when it affects fewer than 1 in 2,000 people. In the United States, a disease is considered rare when it affects fewer than 200,000 people in the country. These diseases are often characterized by a combination of complex, debilitating, and life-threatening symptoms. Due to their low prevalence, rare diseases pose unique challenges in terms of diagnosis, treatment, and research efforts.

The development of medicines for rare diseases presents unique challenges due to the limited patient population, complex disease mechanisms, and often high unmet medical needs. These rare diseases, affecting a small percentage of the population, are financially unattractive for pharmaceutical companies. However, thanks to advancements in scientific research and regulatory incentives, there has been progress in creating medicines specifically tailored to address rare diseases.

This book explores the specialized journey of developing medicines for rare diseases, highlighting some key aspects and considerations involved in this process. The dimensions below will be explored in the following chapters:

1. Understanding Rare Diseases

Developing medicines for rare diseases begins with a deep understanding of the disease itself. Rare diseases encompass a wide range of conditions, each with its own unique characteristics and challenges. Scientific research focuses on unraveling the underlying mechanisms of these diseases, including genetic, molecular, and cellular aspects. This understanding provides insights into potential targets for therapeutic intervention.

2. Target Identification and Medicine Discovery

In this stage, researchers identify specific biological targets that play a crucial role in the rare disease. Once the target is identified, the next step is to discover potential medicine candidates, also known as hits, that interact with the target and show promising biological activity: High-Throughput Screening (HTS) and Virtual Screening are employed to identify potential compounds or molecules that interact with the target and show promising biological activity. Techniques such as structural biology provide insights into the three-dimensional structure of the target, aiding in rational medicine design.

3. Medicine Design and Development

Researchers utilize various strategies to develop medicine candidates. For traditional medicines, this may involve medicinal chemistry, structural optimization, and formulation development. However, medicine discovery for rare diseases often requires innovative approaches due to limited knowledge and understanding. Researchers may explore repurposing existing medicines, developing gene therapies, utilizing RNA-based therapeutics, or applying advanced technologies like gene editing and cell therapy to target the specific rare disease.

4. Preclinical Testing

Preclinical testing is a critical step in the development of medicines for rare diseases before advancing to human trials. It involves rigorous laboratory testing using in vitro and in vivo models to assess the safety, efficacy, and pharmacokinetic properties of the medicine candidates. Animal models, such as genetically modified mice or other organisms, are used to simulate the disease condition and evaluate the medicine's therapeutic potential. These studies provide essential data to support the progression of promising medicine candidates to clinical trials.

5. Focus on the Orphan Drug Designation

To incentivize the development of medicines for rare diseases, regulatory authorities around the world, such as the Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA) in Europe, provide orphan drug designation. This designation grants certain benefits to pharmaceutical companies, including extended market exclusivity, regulatory fee waivers, and access to research grants. Orphan drug status encourages investment in research and development efforts for rare diseases.

6. Clinical Trials

Clinical trials are research studies conducted with human participants to evaluate the safety and efficacy of medicines or treatments. Clinical trials involving rare disease medicines face unique challenges due to the limited number of eligible patients related to patient recruitment, outcome measures and trial design. Researchers often rely on collaborations, natural history studies, and adaptive trial designs to address these challenges and advance clinical research for rare diseases.

7. Regulatory Approval and Post-Marketing Considerations

Following successful clinical trials, the pharmaceutical company submits an application for regulatory approval to the relevant regulatory authorities. In the case of rare diseases, regulatory agencies often offer incentives and expedited pathways to encourage the development of treatments for these conditions. Once approved, the medicine can be marketed and made available to patients. Post-marketing surveillance continues to monitor the medicine's safety and effectiveness in a broader patient population.

8. Patient Access and Support

Ensuring patient access to medicines for rare diseases is a critical aspect of the medicine development process. Pharmaceutical companies, patient advocacy groups, and healthcare providers collaborate to raise awareness, improve diagnosis, and facilitate access to the medicine for affected individuals. Support programs, patient assistance programs, and reimbursement mechanisms are often implemented to assist patients in accessing and affording these specialized treatments.

9. Focus on Milestones of Medicine Development for Rare Disease Companies, Relationships with Regulators, and Investors

Companies focused on rare diseases undergo a challenging journey to develop medicines for rare diseases, from the early stages of research and development all the way to patients getting access to the medicine. Companies engage with regulatory authorities throughout the medicine development process, including IND submissions, during the NDA review process, and post-marketing. Different types of investors step in during the company's life to provide the necessary funding to complete each milestone.

1

Understanding Rare Diseases

Developing medicines for rare diseases begins with a deep understanding of the disease itself. Rare diseases encompass a wide range of conditions, each with its own unique characteristics and challenges. Scientific research focuses on unraveling the underlying mechanisms of these diseases, including genetic, molecular, and cellular aspects. This understanding provides insights into potential targets for therapeutic intervention.

1. Gathering Information about Rare Diseases

Gaining knowledge about rare diseases involves **collecting data from various sources**, including scientific literature, clinical observations, patient registries, and international collaborations. **Researchers, healthcare professionals, patient advocacy groups, and regulatory agencies** play vital roles in gathering and sharing information to enhance the understanding of rare diseases.

Sources include:

- **Scientific Literature:** Researchers extensively study published scientific papers, case reports, and clinical studies related to rare diseases. This literature review helps identify key characteristics, disease mechanisms, and potential treatment avenues.
- **Clinical Observations:** Healthcare professionals who encounter patients with rare diseases contribute valuable clinical observations. Through careful documentation and sharing of patient data, patterns, symptoms, and disease progression can be analyzed to uncover underlying causes and develop hypotheses.
- **Patient Registries:** Patient registries serve as centralized databases that collect and store information about individuals affected by rare diseases. These registries provide a comprehensive overview of the disease's prevalence, clinical manifestations, genetic mutations, and treatment outcomes. Researchers can analyze this data to gain insights into the natural history of the disease and evaluate treatment effectiveness.
- **International Collaborations:** Collaborative efforts among researchers and institutions globally foster knowledge sharing and enable a broader understanding of rare diseases. Networks and consortia dedicated to specific rare diseases facilitate the exchange of information, resources, and expertise, leading to advancements in diagnosis, treatment, and research. Examples of international collaborations include:
- **The International Rare Diseases Research Consortium (IRDiRC):** IRDiRC (<https://irdirc.org/>) is a global consortium that brings together researchers, funding organizations, and patient advocacy groups from around the world. Its primary goal is to promote collaboration and coordination in rare disease research. IRDiRC aims to facilitate the sharing of data, resources, and expertise to accelerate the discovery of diagnostics and therapies for rare diseases.

- **European Reference Networks (ERNs):** The European Reference Networks (https://health.ec.europa.eu/european-reference-networks_en) are virtual networks that bring together healthcare professionals and experts from across Europe to improve the diagnosis, treatment, and care of patients with rare diseases. These networks facilitate the exchange of knowledge, best practices, and patient data among specialized centers of excellence.

2. Researchers' Role in Understanding Rare Diseases

Researchers employ a **range of approaches and techniques** to enhance the understanding of rare diseases. Their primary objectives include **unraveling disease mechanisms, identifying genetic mutations, discovering biomarkers, and exploring therapeutic interventions**:

- **Disease mechanisms** refer to the biological processes, pathways, and factors that contribute to the development and progression of a specific disease. They involve understanding the underlying molecular, cellular, and physiological abnormalities or dysfunctions that lead to the manifestation of the disease. Investigating disease mechanisms helps researchers identify key targets for intervention and develop strategies for diagnosing, treating, or preventing the disease.
- **Genetic mutations** are alterations or changes in the DNA sequence of an individual's genes. These mutations can occur spontaneously or be inherited from parents. They can affect the structure or function of proteins, disrupt normal cellular processes, and contribute to the development of various diseases, including rare diseases. Understanding genetic mutations is crucial in unraveling the genetic basis of diseases, identifying disease subtypes, and developing targeted therapies or genetic testing approaches.
- **Biomarkers** are measurable indicators, such as molecules or genetic markers, that provide information about a biological process, disease state, or response to a treatment. They can be found in various bodily fluids, tissues, or cells and are used to assess disease presence, progression, or therapeutic response. Biomarkers play a critical role

in rare disease research by aiding in diagnosis, monitoring disease progression, predicting treatment outcomes, and identifying patient subgroups.

- **Therapeutic interventions** refer to the strategies, treatments, or interventions designed to alleviate, manage, or cure a disease. In the context of rare diseases, therapeutic interventions can include a wide range of approaches, such as pharmacological therapies, gene therapies, cell-based therapies, surgical interventions, dietary modifications, or supportive care measures. The aim of therapeutic interventions is to improve symptoms, slow disease progression, enhance quality of life, or provide a potential cure for individuals affected by rare diseases.

The following are some **common research methods** employed by researchers to understand rare diseases:

Genetic Studies: Genetic research plays a crucial role in understanding rare diseases. Techniques such as DNA sequencing, genome-wide association studies (GWAS), and next-generation sequencing (NGS) help identify genetic variations associated with rare diseases. Researchers investigate the role of specific genes, mutations, or copy number variations to determine their impact on disease development and progression. Techniques associated with genetic studies are described below:

- **DNA sequencing** is a technique used to determine the precise order of nucleotide bases (adenine, thymine, cytosine, and guanine) in a DNA molecule. It allows researchers to read and decipher the genetic information encoded within the DNA. DNA sequencing provides insights into the specific sequence variations or mutations present in an individual's genome. There are different methods of DNA sequencing, including Sanger sequencing (also known as capillary electrophoresis sequencing) and more advanced technologies such as next-generation sequencing (NGS).
- **Genome-wide association studies (GWAS)** are a powerful tool in genetics research that aims to identify genetic variations associated with specific traits, diseases, or conditions. In GWAS, researchers analyze genetic data from large populations to identify common genetic variants that are more prevalent in individuals with a particular trait or disease

compared to those without it. GWAS typically involves genotyping or sequencing many single nucleotide polymorphisms (SNPs) across the genome to identify associations between genetic variants and diseases or traits of interest. GWAS can provide insights into the genetic basis of rare diseases and help identify potential target genes or pathways.

- **Next-generation sequencing (NGS)**, also known as high-throughput sequencing, revolutionized genetic research by enabling the rapid sequencing of large amounts of DNA or RNA. NGS techniques allow for the simultaneous sequencing of multiple DNA fragments or genes, making it more efficient and cost-effective compared to traditional Sanger sequencing. NGS has various applications in rare disease research, such as whole exome sequencing (WES) and whole genome sequencing (WGS), which involve sequencing the protein-coding regions or the entire genome, respectively. NGS facilitates the identification of disease-causing mutations, rare genetic variants, and novel genes associated with rare diseases.

Molecular and Cellular Studies: Researchers explore the molecular and cellular mechanisms underlying rare diseases. This involves analyzing protein functions, signaling pathways, cellular interactions, and metabolic processes, as described below:

- **Protein Functions:** Proteins are large, complex molecules that play crucial roles in the structure, function, and regulation of cells and tissues. Protein functions refer to the specific activities and roles that proteins perform within cells. These functions can include enzymatic activity, transport of molecules, structural support, signaling, and regulation of gene expression. Understanding protein functions is essential in unraveling the molecular mechanisms underlying rare diseases, as abnormalities or dysfunctions in proteins can contribute to disease development and progression.
- **Signaling Pathways:** Signaling pathways are complex networks of molecular interactions within cells that transmit signals and regulate various cellular processes. These pathways enable cells to respond to external stimuli, coordinate their activities, and maintain homeostasis. Signaling pathways often involve the binding of signaling molecules (such as hormones or growth factors) to cell surface receptors, triggering a cascade of molecular events that ultimately lead to specific cellular

responses. Dysregulation or alterations in signaling pathways can contribute to the pathogenesis of rare diseases. Studying these pathways provides insights into the molecular mechanisms underlying these conditions.

- **Cellular Interactions:** Cellular interactions refer to the communication, physical contacts, and collaborations between cells. Cells within tissues and organs interact with each other to carry out specific functions and maintain tissue homeostasis. These interactions involve various cellular processes, including cell signaling, adhesion, migration, and communication through gap junctions or soluble factors. Understanding cellular interactions is crucial in deciphering the mechanisms underlying rare diseases, as disruptions in cellular communication or interactions can contribute to disease pathogenesis.
- **Metabolic Processes:** Metabolic processes encompass the chemical reactions and transformations that occur within cells to convert nutrients into energy, synthesize biomolecules, and regulate cellular activities. Metabolism involves various pathways, such as glycolysis, the citric acid cycle, and oxidative phosphorylation, which generate energy in the form of ATP and provide building blocks for cellular components. Metabolic dysregulation can contribute to the development of rare diseases. Analyzing metabolic processes helps researchers identify specific alterations or imbalances that may contribute to disease pathogenesis and progression.

Advanced techniques, such as transcriptomics, proteomics, and metabolomics provide insights into disease-specific alterations at the molecular level:

- **Transcriptomics:** Transcriptomics is the study of the complete set of RNA transcripts (messenger RNA or mRNA) produced by a cell or tissue at a given time. It provides insights into gene expression patterns, including which genes are turned on or off, their relative levels of expression, and alternative splicing events. Transcriptomics techniques, such as microarray analysis or RNA sequencing, enable researchers to analyze gene expression profiles and identify genes that are differentially expressed in rare diseases. This helps in understanding the molecular changes associated with the condition.

- **Proteomics:** Proteomics is the large-scale study of proteins expressed by a cell, tissue, or organism. It involves identifying, quantifying, and characterizing the entire complement of proteins present in each sample. Proteomics techniques enable researchers to explore protein expression patterns, post-translational modifications, and protein-protein interactions in the context of rare diseases. By studying the proteome, researchers can gain insights into disease-specific alterations at the protein level and identify potential biomarkers or therapeutic targets.
- **Metabolomics:** Metabolomics is the comprehensive study of small molecules, known as metabolites, involved in cellular processes and metabolic pathways. It aims to identify and quantify the complete set of metabolites present in a biological sample. Metabolomics provides insights into the metabolic profile and alterations associated with rare diseases. By studying metabolites, researchers can identify specific metabolic abnormalities or dysfunctions that may contribute to disease pathogenesis and potentially serve as diagnostic or prognostic markers.

Animal Models: To mimic rare diseases and study their pathophysiology, which refers to the study of the functional changes and abnormalities that occur in the body because of a disease or disorder, including the underlying mechanisms and physiological processes involved, researchers develop animal models with genetic modifications or specific phenotypes. These models help investigate disease progression, identify therapeutic targets, and evaluate potential treatments.

Disease Pathway Mapping: Researchers aim to understand the complex networks and pathways disrupted in rare diseases. Pathway mapping involves constructing disease-specific interaction networks and identifying key nodes, proteins, or molecules that contribute to the disease phenotype. This approach aids in unraveling disease mechanisms and identifying potential therapeutic targets.

TAKE AWAY

In summary, understanding rare diseases requires a **multidimensional approach** involving **researchers, healthcare professionals, patient registries, and international collaborations**. By gathering information from **scientific literature, clinical observations, patient registries, and collaborative efforts**, researchers gain valuable insights into the underlying mechanisms, genetic mutations, and treatment options for rare diseases.

Research methods, including **genetic studies** (e.g., DNA sequencing, genome-wide association studies (GWAS), and next-generation sequencing (NGS)), **molecular and cellular studies** (e.g., analysis of protein functions, signaling pathways, cellular interactions, and metabolic processes, as well as advanced methods such as transcriptomics, proteomics, and metabolomics), **animal models** and **disease pathway mappings**, contribute to unraveling the complexities of these diseases.

2

Target Identification and Medicine Discovery

In this stage, researchers **identify specific biological targets** that play a crucial role in the rare disease. Once the target is identified, the next step is to **discover potential medicine candidates**, also known as **hits**, that interact with the target and show promising biological activity. **High-Throughput Screening (HTS)** and **Virtual Screening** are employed to identify potential compounds or molecules that interact with the target and show promising biological activity. Techniques such as structural biology provide insights into the three-dimensional structure of the target, aiding in rational medicine design.

1. Biological Targets

Biological targets are **specific molecules** or cellular components that are **involved in disease processes** and **can be modulated by therapeutic interventions**. These targets may include proteins, enzymes, receptors, genes, or signaling pathways that play a critical role in the development or progression of a particular disease. By targeting these components, researchers aim to restore normal cellular function or disrupt disease pathways, ultimately leading to therapeutic benefits.

2. Target Identification

The process of target identification involves **identifying and selecting specific biological targets that are relevant to a particular disease**. This is often a complex and iterative process that requires a deep understanding of the disease biology and its underlying mechanisms.

Various approaches and technologies are employed to identify potential targets, such as:

- **Genomics:** Genomic studies involve analyzing the entire set of genes (genome) to identify genetic variations associated with a disease. Techniques such as genome-wide association studies (GWAS) compare the genomes of affected individuals with healthy individuals to identify genetic loci or specific genes linked to the disease.
- **Proteomics:** Proteomics focuses on the comprehensive study of proteins in a biological system. It involves the identification, quantification, and characterization of proteins to understand their functions, interactions, and alterations in disease conditions. Mass spectrometry-based techniques, such as liquid chromatography-mass spectrometry (LC-MS), are commonly used in proteomic analysis.
- **Transcriptomics:** Transcriptomics explores the entirety of RNA transcripts (transcriptome) in a specific tissue or cell type. Techniques like microarray analysis and RNA sequencing (RNA-seq) provide insights into gene expression patterns and help identify genes that are differentially expressed in disease states.

3. Hit Discovery

Once the target is identified, the next step is to **discover potential medicine candidates**, also known as **hits**, that **interact with the target and show promising biological activity**.

Several advanced technologies and techniques are employed in hit discovery, such as:

- **High-Throughput Screening (HTS):** HTS allows for the rapid screening of large libraries of chemical compounds against the target. This automated approach enables the testing of thousands to millions of compounds, significantly accelerating the discovery of potential hits. Compounds that show activity against the target are further optimized in subsequent steps.
- **Virtual Screening:** Virtual screening uses computational methods to predict and prioritize potential medicine candidates based on their fit to the target's structure or other molecular characteristics. Molecular docking, molecular dynamics simulations, and machine learning algorithms are utilized to virtually screen large databases of compounds. This approach helps identify hits with a higher likelihood of binding to the target and exhibiting the desired biological activity.
- **Structural Biology:** Structural biology techniques, such as X-ray crystallography, nuclear magnetic resonance (NMR) spectroscopy, and cryo-electron microscopy (cryo-EM), provide three-dimensional structural information about the target protein. These techniques help researchers understand the target's structure, function, interactions, and dynamics. This knowledge aids in rational medicine design and optimization efforts by identifying potential binding sites and guiding the design of molecules that can interact with the target.
- **Combinatorial Chemistry:** Combinatorial chemistry involves synthesizing large libraries of chemical compounds by systematically combining different building blocks. This approach allows for the generation of diverse compound libraries, which can be screened against the target to identify potential medicine candidates. Combinatorial chemistry provides a way to explore a wide range of chemical structures and properties to discover hits with desired biological activity.
- **Pharmacogenomics:** Although not directly associated with hit discovery, pharmacogenomics plays a role in personalized medicine. It involves studying how genetic variations influence an individual's response to medicines. By analyzing the genetic profiles of patients, researchers

can identify specific genetic subgroups that may respond differently to treatments. This information can guide the selection and optimization of medicine candidates for specific patient populations.

Hits with promising activity against the target are further optimized to improve their potency, selectivity, and pharmacokinetic properties. These optimized compounds will move forward in the medicine development pipeline as **lead compounds**, which will undergo further testing and refinement in subsequent stages.

TAKE AWAY

In summary, target identification and medicine discovery involve **identifying specific biological targets** involved in the disease and **discovering potential medicine candidates** that interact with these targets. Advanced technologies such as HTS, virtual screening, structural biology, combinatorial chemistry, and pharmacogenomics are utilized to **identify hits with promising biological activity**, which will be **further optimized** in subsequent steps of the medicine development process.

3

Medicine Design and Development

Researchers utilize various strategies to develop medicine candidates. For traditional medicines, this may involve medicinal chemistry, structural optimization, and formulation development. However, **medicine discovery for rare diseases often requires innovative approaches** due to limited knowledge and understanding. Researchers may explore repurposing existing medicines, developing gene therapies, utilizing RNA-based therapeutics, or applying advanced technologies like gene editing and cell therapy to target the specific rare disease.

1. Traditional Medicine Discovery

In traditional medicine discovery, **lead optimization** is an essential activity that occurs after hit discovery. Once promising hits have been identified, medicinal chemists and pharmaceutical scientists work together to **optimize these compounds to create more potent, selective, and medicine-like candidates**.

- **Potency** refers to the strength or effectiveness of a compound in modulating the target's activity. During optimization, researchers aim to improve the potency of the compound, making it more effective in engaging the target and producing the desired therapeutic effect.
- **Selectivity** relates to the specificity of a compound in binding to the intended target without significantly interacting with other off-target molecules. Researchers strive to enhance the selectivity of the compound to minimize potential side effects or unwanted interactions with unrelated targets.
- **Pharmacokinetic properties** refer to how a compound is absorbed, distributed, metabolized, and eliminated within the body. Optimization involves improving these properties, such as enhancing the compound's bioavailability, stability, and half-life, to ensure it can reach and persist at effective concentrations in the target tissues.

Lead optimization involves several key activities:

- **Medicinal Chemistry:** Medicinal chemists use their expertise in organic chemistry to modify the chemical structure of the lead compounds obtained from hit discovery. Through strategic modifications, they aim to improve the compounds' potency, selectivity, solubility, stability, and other pharmacokinetic properties. This iterative process involves synthesizing and testing analogs and derivatives of the lead compounds to identify improved versions.
- **Structure-Activity Relationship (SAR) Studies:** SAR studies help establish the relationship between the structural features of the compounds and their biological activity. By systematically modifying specific regions of the lead compounds, researchers can understand the impact on their activity. This knowledge guides the design of new compounds with enhanced potency, selectivity, and other desired properties.

- **Formulation Development:** As lead compounds are optimized, formulation development becomes important. Pharmaceutical scientists focus on developing appropriate dosage forms such as tablets, capsules, injections, or topical preparations. These formulations ensure the stability of the medicine, effective delivery to the target site, and patient compliance.

2. Strategies for Developing Medicine Candidates for Rare Diseases

In the context of rare diseases, medicine discovery may require innovative approaches due to the limited understanding of disease mechanisms. The following strategies can be employed:

- **Repurposing Existing Medicines:** Given the time and resource constraints in developing entirely new medicine candidates, researchers explore the repurposing of existing medicines or medicine candidates that have shown promise in other diseases. This approach leverages existing knowledge about medicine safety, pharmacokinetics, and potential mechanisms of action to expedite the development process.
- **Gene Therapies:** For rare diseases caused by specific genetic mutations, gene therapies hold promise. These therapies involve introducing functional copies of the mutated gene or modifying the patient's own genes to correct the genetic defect. Techniques like viral vectors, antisense oligonucleotides, and gene editing technologies (e.g., CRISPR-Cas9) can be employed for targeting and modifying genetic material.
- **RNA-Based Therapeutics:** Targeting RNA molecules involved in disease mechanisms is the focus of RNA-based therapeutics. Techniques such as RNA interference (RNAi) and antisense oligonucleotides are used to reduce the production of disease-causing proteins or restore the function of specific RNA molecules.
- **Advanced Technologies:** Other advanced technologies like cell-based therapies (e.g., stem cell transplantation, CAR-T cell therapy) or personalized medicine approaches may be utilized in the development of targeted therapies for rare diseases. These technologies address the specific mechanisms and genetic components of rare diseases.

During lead optimization, researchers carefully **refine and modify the lead compounds** to improve their medicine-like properties and enhance their therapeutic potential. The iterative process involves synthesizing and testing analogs and derivatives, considering structure-activity relationships, and optimizing the compounds' pharmacokinetic and pharmacodynamic properties. This stage aims to **select the most promising medicine candidates** to move forward into **pre-clinical testing**.

TAKE AWAY

In summary, the medicine design and development stage involves a combination of **innovative approaches, optimization of lead compounds, formulation development**, and the exploration of **advanced technologies** to create **effective and targeted medicines** for rare diseases. Researchers collaborate closely with **experts from various disciplines** to design and develop medicine candidates that have the potential to address the specific disease mechanisms and provide therapeutic benefits for patients with rare diseases.

4

Preclinical testing

Preclinical testing is a critical step in the development of medicines for rare diseases **before advancing to human trials**. It involves rigorous laboratory testing **using in vitro and in vivo models** to assess the **safety, efficacy, and pharmacokinetic properties** of the medicine candidates. **Animal models**, such as genetically modified mice or other organisms, are used to **simulate the disease condition** and evaluate the medicine's therapeutic potential. These studies provide **essential data** to support the progression of promising medicine candidates to **clinical trials**.

1. Overview of Preclinical Testing

Preclinical testing refers to the **evaluation of medicine candidates in laboratory and animal models** before they are tested in human clinical trials. The main objectives of preclinical testing are to assess the medicine's **safety, efficacy, pharmacokinetics**, and **mechanism of action**. It plays a crucial role in providing valuable data that guides the decision to proceed with clinical trials.

2. Importance of Preclinical Testing in Rare Diseases

In the context of rare diseases, preclinical testing is particularly important due to the following reasons:

- **Limited Patient Population:** Rare diseases often affect a small number of individuals, making it challenging to conduct clinical trials with statistically significant sample sizes. Preclinical testing provides an opportunity to gather preliminary data on the medicine's efficacy and safety, which can guide the decision to proceed with clinical trials.
- **Limited Understanding:** Rare diseases are often characterized by complex and poorly understood mechanisms. Preclinical testing allows researchers to investigate the medicine's mechanism of action, assess its impact on disease pathways, and gain insights into potential therapeutic effects.
- **Safety Assessment:** Preclinical testing helps evaluate the safety profile of the medicine candidate. It provides data on potential adverse effects, toxicities, and dose-dependent responses, enabling researchers to establish safe starting doses for clinical trials.

3. Preclinical Testing Process

The preclinical testing process typically involves the following key steps:

- **In Vitro Studies:** In this initial stage, the medicine candidate is tested in controlled laboratory settings using various in vitro (outside the living organism) assays and models. The purpose is to assess the medicine's

interactions with target molecules, its mechanism of action, and its effects on cellular processes. These studies help researchers understand the medicine's pharmacological properties, efficacy, and potential toxicity.

- **Animal studies**

- **Acute Toxicity Studies:** These studies evaluate the immediate toxic effects of the medicine candidate on animals. Different doses are administered, and the animals are closely monitored for any adverse reactions or systemic effects. These tests help determine the medicine's safety profile and establish the maximum tolerated dose.
- **Sub Chronic and Chronic Toxicity Studies:** These studies involve the administration of the medicine candidate to animals for an extended period, usually ranging from several weeks to several months. Researchers monitor the animals for any long-term toxic effects, changes in organ function, or other adverse reactions.
- **Pharmacokinetics and Pharmacodynamics:** Animal studies are conducted to assess the medicine candidate's absorption, distribution, metabolism, and excretion (ADME) properties. This helps determine the medicine's bioavailability, how it is processed in the body, and its duration of action. Pharmacodynamic studies investigate the medicine's effects on the target molecules or biological processes in animals.
- **Safety Pharmacology Studies:** These studies evaluate the potential impact of the medicine candidate on vital organ systems such as the cardiovascular, respiratory, and central nervous systems. The goal is to identify any unwanted or off-target effects that may affect the safety and tolerability of the medicine.
- **Genotoxicity and Carcinogenicity Studies:** Genotoxicity studies assess whether the medicine candidate has the potential to cause DNA damage or mutations. Carcinogenicity studies examine the medicine's potential to induce the development of tumors in animals over prolonged exposure.

- **Formulation Refinement:** During pre-clinical testing, formulation scientists continue to optimize the medicine's formulation to ensure

stability, appropriate dosage form, and effective delivery to the target site. The goal is to develop a formulation that maintains the medicine's integrity, enhances its bioavailability, and supports its therapeutic efficacy.

- **Data Analysis and Safety Assessment:** The data obtained from the pre-clinical studies are analyzed and assessed to determine the medicine candidate's safety and potential risks. Researchers consider factors such as toxicity, pharmacokinetics, pharmacodynamics, and efficacy data to make informed decisions about advancing the candidate to clinical trials.
- **Regulatory Submissions:** Pre-clinical data, along with detailed study reports, are compiled and submitted to regulatory authorities for review and approval. This submission is part of the process to obtain regulatory clearance to proceed with human clinical trials.

4. Regulatory Considerations in the Context of Rare Diseases

Preclinical testing in the context of rare diseases may involve specific regulatory considerations:

- **Orphan Drug Designation** (please refer to Chapter 6): Regulatory agencies provide orphan drug designations to encourage the development of treatments for rare diseases. This designation grants incentives, such as extended exclusivity periods, tax credits, and regulatory assistance, to facilitate the development of medicines for rare diseases.
- **Safety and Efficacy Data Requirements:** Regulatory authorities require sufficient preclinical safety and efficacy data to support the initiation of clinical trials. However, considering the challenges associated with rare diseases, they may be more flexible and open to considering alternative preclinical testing approaches and data sources.
- **Translational Considerations:** Researchers aim to establish the relevance and predictive value of preclinical models for rare diseases, ensuring that the data generated can be effectively translated to the clinical setting. This involves selecting appropriate animal models, biomarkers, and study endpoints that closely mimic the disease characteristics observed in humans.

TAKEAWAY

In summary, preclinical testing is a crucial step in medicine development that involves **in vitro studies**, **pharmacokinetics** and **toxicity evaluations**, and **animal studies**. In the context of rare diseases, preclinical testing plays a vital role in establishing initial **efficacy**, understanding the **medicine's mechanism of action**, assessing **safety profiles**, and informing decision-making regarding the **progression to clinical trials**. **Regulatory considerations**, such as orphan drug designations and flexible data requirements, recognize the **unique challenges** associated with rare diseases and aim to facilitate the development of treatments for these conditions.

5

Focus on the Orphan Drug Designation

To incentivize the development of medicines for rare diseases, regulatory authorities around the world, such as the **Food and Drug Administration** (FDA) in the United States and the **European Medicines Agency** (EMA) in Europe, provide **orphan drug designation**. This designation grants certain benefits to pharmaceutical companies, including extended **market exclusivity**, regulatory **fee waivers**, and access to **research grants**. Orphan drug status encourages **investment** in research and development efforts for rare diseases.

1. Definition of Orphan Medicine

An orphan medicine is a **pharmaceutical product** developed to **treat a rare disease or condition**. In the United States, a rare disease is defined as a condition that affects **fewer than 200,000 individuals**, while in the European Union, it is defined as a condition that affects **fewer than 5 in 10,000 individuals**. Orphan medicines are specifically developed to address the unmet medical needs of patients with rare diseases.

2. Orphan Drug Designation

Orphan Drug Designation is a **regulatory status** granted by health authorities to **medicines or therapies intended for the treatment, diagnosis, or prevention of rare diseases**. This designation provides certain **incentives** and **benefits** to facilitate and encourage the development of medicines for rare diseases. The specific process and criteria for orphan drug designation may vary across different countries or regions, but the overarching goal remains the same. To qualify for orphan drug designation, the medicine candidate must **demonstrate a potential therapeutic benefit for the rare disease**, and the sponsor (typically the pharmaceutical company or researcher) must **submit supporting data and evidence** to the regulatory agency.

3. Benefits and Incentives of Orphan Drug Designation

Obtaining orphan drug designation provides several benefits and incentives for medicine developers, including:

- **Market Exclusivity:** One of the key incentives is market exclusivity, which grants the medicine developer a period of exclusivity during which no similar medicine for the same indication can be approved. In the United States, orphan medicine exclusivity provides seven years of market exclusivity, while in the European Union, it is ten years.
- **Financial Incentives:** Orphan drug designation may provide financial incentives to support the development of medicines for rare diseases.

These incentives can include tax credits for research and development expenses, reduced fees for regulatory submissions, and grants for clinical trials.

- **Protocol Assistance:** Regulatory agencies may provide guidance and assistance to medicine developers throughout the development process, including assistance in designing clinical trials, optimizing study protocols, and navigating regulatory requirements.
- **Priority Review:** Orphan medicines may be eligible for accelerated or priority review by regulatory agencies, which expedites the assessment process and reduces the time to market approval.
- **Access to Orphan Drug Designation Database:** Medicines with orphan drug designation are included in a public database, which facilitates collaboration and knowledge sharing among researchers, drug developers, and patient advocacy groups.

4. Orphan Drug Designation Process

The process of obtaining orphan drug designation typically involves the following steps:

- **Application Submission:** The drug developer submits an application for orphan drug designation to the relevant regulatory agency, such as the U.S. Food and Drug Administration (FDA) in the United States or the European Medicines Agency (EMA) in the European Union. The application includes scientific data and information about the disease, the medicine's mechanism of action, preclinical data, and a rationale for the medicine's potential to address the unmet medical need.
- **Review and Evaluation:** The regulatory agency reviews the application to assess the eligibility of the medicine for orphan designation. This includes evaluating the prevalence of the rare disease, the potential benefit of the medicine in treating the condition, and the lack of available alternative therapies.
- **Decision and Designation:** Based on the review, the regulatory agency makes a decision on granting orphan drug designation. If approved, the medicine is designated as an orphan drug for the specific rare disease or condition.

Once granted, orphan drug designation typically does not require renewal if the medicine development continues and the criteria for orphan status are maintained. However, medicine developers are required to provide periodic updates on the progress of the medicine development, clinical trials, and any changes that may affect the eligibility for orphan drug designation.

TAKEAWAY

In summary, **orphan drug designation** is a **regulatory status** granted to medicines intended for the **treatment of rare diseases**. It provides **incentives and benefits**, such as **market exclusivity**, **financial incentives**, **protocol assistance**, **priority review**, and access to a designated **database**. The process involves application submission, review and evaluation by regulatory agencies, and the decision to grant orphan drug designation. These incentives and benefits aim to **encourage** and support the development of medicines for rare diseases, addressing the unmet medical needs of patients with these conditions.

6

Clinical trials

Clinical trials are research studies conducted with **human participants** to evaluate the **safety** and **efficacy** of medicines or treatments. Clinical trials involving rare disease medicines face **unique challenges** due to the limited number of eligible patients related to **patient recruitment**, **outcome measures** and **trial design**. Researchers often rely on **collaborations**, **natural history studies**, and **adaptive trial designs** to address these challenges and advance clinical research for rare diseases.

1. Clinical Trials Overview

Clinical trials are research studies conducted with **human participants** to evaluate the safety, efficacy, dosage, and potential side effects of a medicine or treatment. They follow a systematic and rigorous process to gather scientific evidence and determine whether a medicine is safe and effective for use in patients.

- **Phase I:** Phase I trials are the initial stage of clinical testing and primarily focus on assessing the **safety, dosage, and potential side effects** of a new medicine or treatment. These trials usually involve a **small number of (healthy) participants**, typically ranging from 20 to 100 individuals. The main objective of Phase I trials is to determine the **maximum tolerated dose (MTD)** or the highest dose that can be given without causing unacceptable toxicity. Phase I trials also provide valuable information about the medicine's pharmacokinetics and pharmacodynamics.
- **Phase II:** Phase II trials follow Phase I and aim to evaluate the medicine's **effectiveness** and further assess its **safety**. These trials involve a **larger number of patients**, typically ranging from 100 to 300 individuals. The specific number of participants may vary depending on the rarity of the disease and the availability of eligible patients. Phase II trials provide **preliminary data** on the medicine's efficacy in treating the target disease and help researchers select appropriate **dosing** regimens for further study.
- **Phase III:** Phase III trials are **large-scale trials** that involve a **significantly larger number of patients**. These trials aim to confirm the medicine's **efficacy**, assess its overall **risk-benefit profile**, and compare it to existing standard treatments or placebos. The number of participants in Phase III trials can range from **several hundred to several thousand**, depending on factors such as disease prevalence, statistical power requirements, and regulatory considerations. Phase III trials aim to provide robust evidence to support the medicine's approval and marketing authorization.
- **Phase IV:** Phase IV trials, also known as **post-marketing studies**, occur after the medicine has received regulatory approval and are conducted to **gather additional information** about the medicine's long-term safety, efficacy, and optimal use in a larger patient population. These trials typically involve thousands of patients, and the specific number of participants may vary depending on the purpose and scope of the post-marketing study. Phase IV trials provide valuable **real-world data** on the

medicine's performance and safety in a broader patient population over an extended period.

2. Clinical Trials for Rare Diseases

Clinical trials for rare diseases face **specific challenges** due to the **limited patient population** and **unique disease characteristics**. Here are some considerations that differentiate clinical trials for rare diseases:

- **Patient Recruitment:** The limited number of patients with a specific rare disease makes patient recruitment more challenging. Researchers often collaborate with patient advocacy groups, specialized clinics, and international networks to identify and recruit eligible participants.
- **Natural History Studies:** Natural history studies are conducted to understand the disease progression, variability, and natural course of the rare disease. These studies provide critical data for trial design, selection of appropriate endpoints, and identification of suitable patient populations.
- **Endpoint Selection:** Selecting appropriate clinical endpoints is essential in rare disease trials. Traditional clinical endpoints, such as overall survival or disease progression, may be impractical or take a long time to measure in rare diseases due to the slow progression or limited availability of validated surrogate endpoints. Therefore, alternative endpoints, such as biomarkers, patient-reported outcomes, or disease-specific measures, are often utilized to assess the treatment's efficacy and impact on patients' lives.
- **Adaptive Trial Designs:** Traditional clinical trial designs may not be suitable for rare diseases. Adaptive trial designs, which allow for modifications and adjustments during the trial based on accumulating data, are frequently employed. These designs enable flexibility in sample size, treatment arms, endpoints, and statistical analyses, ensuring that the trial can efficiently adapt to emerging information and evolving knowledge about the rare disease.
- **Expanded Access Programs:** Expanded Access Programs, also known as compassionate use programs or named patient programs, provide access to investigational treatments outside the clinical trial setting for patients with serious or life-threatening diseases who do not meet the eligibility criteria for ongoing trials. These programs offer a pathway for patients with rare diseases to access potentially beneficial treatments when no approved alternative is available. Expanded access programs require careful ethical considerations and regulatory oversight.

- **Global Collaboration:** Due to the rarity of the diseases, international collaboration among researchers, clinicians, patient organizations, and pharmaceutical companies is critical for rare disease clinical trials. Sharing knowledge, resources, and patient data across borders facilitates the recruitment of an adequate patient population and enhances the statistical power and generalizability of the trial results. Initiatives such as international rare disease research consortia and patient registries play a significant role in fostering collaboration and advancing rare disease clinical research.
- **Regulatory Considerations:** Regulatory agencies recognize the unique challenges associated with rare diseases and have implemented specific regulatory pathways and incentives. Orphan Drug Designation, as mentioned before and described in Chapter 6, provides benefits and incentives to encourage the development of treatments for rare diseases. Regulatory agencies may also offer flexibility in trial design, endpoints, and data requirements to accommodate the limited patient population and the unique characteristics of the rare disease.

TAKE AWAY

In summary, clinical trials are essential for evaluating the **safety** and **efficacy** of medicines or treatments. Clinical trials for rare diseases face **challenges** related to **patient recruitment**, **outcome measures**, and **trial design**. Researchers often rely on **collaborations**, **natural history studies**, and **adaptive trial designs** to address these challenges and advance clinical research for rare diseases. Additionally, **expanded access programs** provide a means for patients to access investigational treatments outside of clinical trials in specific circumstances.

7

Regulatory Approval and Post-Marketing Considerations

Following **successful clinical trials**, the pharmaceutical company submits an application for **regulatory approval** to the relevant regulatory authorities. In the case of rare diseases, regulatory agencies often offer **incentives** and **expedited pathways** to encourage the development of treatments for these conditions. Once approved, the medicine can be marketed and made available to patients. **Post-marketing surveillance** continues to monitor the medicine's safety and effectiveness in a broader patient population.

1. Regulatory Approval Process

Upon completion of clinical trials, the medicine developer **compiles and analyzes the trial data** to demonstrate the **safety** and **efficacy** of the medicine candidate. This data, along with additional documentation, is submitted as part of a regulatory approval application to the appropriate **regulatory agency**, such as the **U.S. Food and Drug Administration (FDA)** and the **European Medicines Agency (EMA)**. The agency reviews the data, assesses the **risk-benefit profile of the medicine**, and determines whether to **grant marketing authorization** for the treatment of the rare disease.

Regulatory approval involves a **rigorous evaluation process** that considers the clinical trial results, safety data, manufacturing practices, labeling information, and overall benefit to patients. The agency may also consult external expert committees or advisory panels to obtain independent evaluations and recommendations. If approved, the medicine can be marketed and made available to patients with the rare disease.

For rare diseases, regulatory agencies **acknowledge the unique challenges** faced by these conditions and have implemented specific measures to facilitate the development and approval of treatments. Here are some considerations:

- **Orphan Drug Designation:** As described in Chapter 6, orphan drug designation provides regulatory incentives and benefits to support the development of medicines for rare diseases. It streamlines the regulatory review process and can grant market exclusivity, financial incentives, and protocol assistance.
- **Adaptive Regulatory Pathways:** Regulatory agencies may adopt flexible and adaptive approaches to accommodate the specific needs of rare diseases. This can include accelerated approval pathways, breakthrough therapy designations, or conditional approvals, allowing earlier access to potentially life-saving treatments.
- **Small Patient Populations:** Regulatory agencies recognize the challenges of conducting large-scale clinical trials in rare diseases due to limited patient populations. In certain cases, they may accept smaller clinical trials with fewer patients as long as the evidence of safety and efficacy is robust.

- **Real-World Evidence:** In some instances, regulatory agencies may consider real-world evidence (RWE) or data from expanded access programs, compassionate use, or patient registries to support regulatory decision-making for rare diseases. RWE can provide valuable insights into the long-term safety and effectiveness of treatments in real-world settings.

2. Post-Marketing Considerations

Once a medicine is approved and enters the market, post-marketing considerations come into play. These considerations are relevant for both rare diseases and more common conditions. Key aspects include:

- **Pharmacovigilance:** Continuous monitoring of the medicine's safety profile is essential. Post-marketing surveillance systems are in place to detect and evaluate adverse events, side effects, and long-term safety concerns associated with the medicine.
- **Risk Evaluation and Mitigation Strategies (REMS):** In certain cases, regulatory agencies may require the implementation of REMS for medicines used in rare diseases. REMS are designed to ensure the safe and appropriate use of the medicine, particularly when there are specific safety concerns or requirements.
- **Expanded Access Programs:** As mentioned earlier, expanded access programs provide a pathway for patients with rare diseases to access investigational treatments outside of clinical trials. These programs continue to be available even after regulatory approval to ensure continued access for eligible patients.
- **Post-Marketing Studies:** Post-marketing studies, including Phase IV trials, are conducted to gather additional data on the medicine's long-term safety, effectiveness, and optimal use. These studies help refine the understanding of the medicine's risk-benefit profile in a larger patient population and may uncover new insights or indications.

3. Collaboration and Engagement

Regulatory agencies actively engage with stakeholders, including patient advocacy groups, researchers, healthcare professionals, and industry representatives, to facilitate the development and approval of treatments

for rare diseases. Collaborative efforts aim to streamline regulatory processes, gather patient perspectives, promote scientific exchange, and ensure the availability of safe and effective treatments for rare diseases.

TAKE AWAY

In summary, once clinical trials are completed, pharmaceutical companies **compile the data and submit applications for regulatory approval**. Regulatory authorities evaluate the safety, efficacy, and benefit-risk profile of the medicine based on the available evidence. Special regulatory pathways, such as accelerated approvals and conditional marketing authorizations, may be available for rare disease medicines to expedite their availability to patients with unmet medical needs.

Post-marketing surveillance remains crucial for rare disease medicines to continuously monitor safety and effectiveness. Long-term follow-up studies, patient registries, and real-world evidence contribute to a better understanding of the medicine's performance in a larger patient population. Continued collaboration among healthcare professionals, regulatory agencies, and patient communities ensures ongoing assessment and improvement of rare disease therapies.

8

Patient Access and Support

Ensuring patient access to medicines for rare diseases is a critical aspect of the medicine development process. Pharmaceutical companies, patient advocacy groups, and healthcare providers collaborate to **raise awareness, improve diagnosis, and facilitate access** to the medicine for affected individuals. **Support programs, patient assistance programs, and reimbursement mechanisms** are often implemented to assist patients in **accessing** and **affording** these specialized treatments.

1. Patient Access

Here are some important dimensions to consider to facilitate access to medicines for patients living with a rare disease:

- **Reimbursement and Insurance Coverage:** Obtaining reimbursement and insurance coverage for rare disease treatments is often a significant challenge due to the unique nature of these conditions and the associated high costs of specialized therapies. Pharmaceutical companies work closely with healthcare systems, payers, and insurance providers to secure adequate reimbursement and coverage for the approved treatments. This includes demonstrating the treatment's value, cost-effectiveness, and the significant unmet medical need it addresses in the rare disease population.
- **Patient Assistance Programs:** Pharmaceutical companies often establish patient assistance programs to support individuals with rare diseases in accessing the approved treatments. These programs may provide financial assistance, such as copay or deductible assistance, to eligible patients who face financial barriers in obtaining the treatment. Patient assistance programs also offer guidance and support to navigate the complexities of insurance coverage, reimbursement, and accessing specialized healthcare services.
- **Expanded Access Programs:** In situations where approved treatments are not yet widely available or accessible to all eligible patients, expanded access programs, also known as compassionate use, or named patient programs, may be established. These programs allow patients with severe or life-threatening rare diseases, who have exhausted all other treatment options, to access investigational therapies outside of clinical trials. Expanded access programs involve a careful evaluation of the potential risks and benefits and require regulatory oversight and ethical considerations.

2. Patient support

Here are some dimensions to consider regarding patient support:

- **Patient Education and Support:** Rare disease patients often face unique challenges, including limited understanding of their condition, lack of

available information, and limited support networks. Patient education and support programs play a crucial role in empowering patients and their families with knowledge about the disease, available treatments, and self-management strategies. These programs may include educational materials, online resources, support groups, counseling services, and patient advocacy organizations that provide a platform for patients to connect, share experiences, and access support networks.

- **Transitioning from Pediatric to Adult Care:** Many rare diseases manifest in childhood and require ongoing care and management throughout a patient's lifespan. Transitioning from pediatric to adult care can be a complex process, involving changes in healthcare providers, treatment plans, and support systems. Ensuring a smooth and coordinated transition is essential to maintain continuity of care and support the unique needs of patients as they transition to adult healthcare settings.
- **Patient Registries and Natural History Studies:** Patient registries and natural history studies continue to be valuable resources in the post-marketing phase. These initiatives collect and analyze data from patients with rare diseases over an extended period to better understand disease progression, treatment outcomes, and long-term effects. Patient registries serve as a repository of information and contribute to ongoing research, enabling healthcare providers, researchers, and regulatory authorities to make informed decisions regarding patient care, treatment guidelines, and the development of future therapies.
- **Advocacy and Policy Development:** Patient advocacy groups play a vital role in raising awareness, advocating for the needs of individuals with rare diseases, and influencing policy development. These groups work collaboratively with patients, healthcare providers, researchers, and policymakers to advocate for improved access to treatments, increased research funding, and the development of policies that support individuals with rare diseases. They also contribute to shaping regulatory frameworks, reimbursement policies, and legislation that promote equitable access to approved treatments.

TAKE AWAY

In summary, **patient access** and **support** are essential considerations in the medicine development process for rare diseases. They require **collaboration** among pharmaceutical companies, healthcare systems, payers, patient advocacy groups, and regulatory authorities to ensure that patients can **access** and **benefit from the approved treatments**. By addressing the unique challenges and needs of individuals with rare diseases, this step aims to **enhance patient outcomes**, improve quality of life, and foster a supportive ecosystem for the rare disease community.

9

Focus on Milestones for Rare Disease Companies, Relationships with Regulators, and Investors

Companies focused on rare diseases undergo a challenging journey to develop medicines for rare diseases, from the early stages of research and development all the way to patients getting access to the medicine. **Companies engage with regulatory authorities** throughout the drug development process, including IND submissions, during the NDA review process, and post-marketing. **Different types of funders** step in during companies' lives to provide the necessary funding to complete each milestone.

Milestones for Companies to Develop Rare Disease Medicines

The milestones for a company to develop a medicine for rare diseases may include the following:

- **Founding and Early Stage:** The company is founded with a mission to address a specific rare disease. This includes assembling a team of experts, securing initial funding, and establishing research and development infrastructure.
- **Research and Development:** The company conducts intensive research and development to identify potential therapeutic approaches, validate drug targets, and develop candidate compounds or therapies. This involves in vitro and in vivo studies, target identification, and optimization of medicine candidates.
- **Intellectual Property Protection:** Patents and intellectual property rights are obtained to protect the company's innovations and potential medicine candidates.
- **Funding and Partnerships:** Companies focused on rare diseases often require substantial funding due to the complex nature of research and development. Obtaining funding from venture capital firms, angel investors, government grants, and partnerships with pharmaceutical companies or patient advocacy groups is crucial to support ongoing research efforts.
- **Preclinical Development:** Once promising medicine candidates are identified, preclinical development begins. This stage involves extensive testing in laboratory settings and animal models to assess safety, efficacy, pharmacokinetics, and toxicity profiles of the drug candidates.
- **Clinical Trials:** Companies initiate clinical trials to evaluate the safety and effectiveness of their medicine candidates in human subjects. The company designs and conducts Phase 1, Phase 2, and Phase 3 trials, adhering to regulatory guidelines and obtaining necessary approvals.
- **Regulatory Interactions:** The company engages with regulatory authorities throughout the medicine development process, including for Investigational New Drug (IND) Application submissions or the New Drug Application (NDA) review process.

- **Market Approval:** If the clinical trials are successful and regulatory approval is granted, the company can gain access to the market and commercialize the medicine for the specific rare disease and negotiate reimbursement and pricing strategies with healthcare payers.
- **Manufacturing and Distribution:** The company establishes manufacturing capabilities and distribution channels to produce and deliver the medicine to patients in need.
- **Post-Market Activities:** After the launch of the medicine, the company continues to monitor its safety and efficacy, conduct post-marketing studies, and gather real-world evidence. The company may also engage in additional clinical trials to explore expanded indications, combination therapies, or pediatric applications.
- **Market Expansion and Patient Access:** Companies strive to expand market access and ensure patient access to their medicines. This involves seeking additional regulatory approvals in different countries, navigating reimbursement processes, and collaborating with patient advocacy groups to raise awareness and improve patient access to the treatment. It may also include exploration of additional indications or expansions into other rare diseases to maximize the therapeutic impact and reach a broader patient population.

It is important to note that these milestones can be complex and time-consuming, often taking several years to accomplish. Additionally, the specific milestones and timelines may vary depending on the nature of the rare disease, the complexity of the drug development process, and regulatory requirements in different countries.

Interactions with Regulators

Regulatory interactions play a vital role in the medicine development process for rare diseases. Companies and medicine developers must engage with regulatory agencies to obtain approval for their therapies. Here is an overview of the key regulatory interactions during this process:

- **Orphan Drug Designation:** Before starting clinical trials, medicine developers can seek orphan drug designation from regulatory agencies such as the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA).
- **Investigational New Drug (IND) Application:** Before conducting clinical trials, medicine developers must submit an IND application to the regulatory agency. The IND provides detailed information about the drug's preclinical data, manufacturing processes, proposed clinical trial protocols, and safety plans. The regulatory agency reviews the IND to ensure the proposed clinical trials are safe for human participants.
- **Clinical Trial Approvals:** Each phase of clinical trials (Phase 1, Phase 2, and Phase 3) requires regulatory approval before it can commence. The medicine developer submits detailed study protocols and safety data to the regulatory agency for evaluation. The agency assesses the proposed trials' design, safety measures, and ethical considerations before granting approval.
- **End-of-Phase 2 Meetings:** After completing Phase 2 trials, drug developers can request an end-of-Phase 2 meeting with regulatory agencies to discuss the results and the planned Phase 3 trial design. This meeting allows the regulator to provide feedback on the data and trial plans, helping to optimize the Phase 3 study design.
- **New Drug Application (NDA) or Marketing Authorization Application (MAA):** Once the clinical trials are completed, the medicine developer submits an NDA (in the case of the FDA) or an MAA (in the case of the EMA) to seek marketing approval. The application includes comprehensive data from preclinical studies, clinical trials, safety assessments, and manufacturing information. The regulatory agency reviews the application and may conduct on-site inspections to ensure compliance with good manufacturing practices.
- **Advisory Committee Meetings:** In some cases, regulatory agencies may convene advisory committee meetings to seek external expert opinions on the medicine's safety and efficacy data. The committee provides non-binding recommendations, which can influence the agency's final decision on approval.
- **Conditional Approvals and Accelerated Pathways:** Regulatory agencies may grant conditional approvals or use accelerated approval pathways for therapies that address unmet medical needs. Conditional approvals may require post-marketing studies to confirm the medicine's clinical benefit fully.

- **Post-Approval Commitments:** After approval, medicine developers are often required to fulfill post-marketing commitments, such as conducting further studies, updating safety information, or monitoring long-term efficacy and safety data.

Throughout the medicine development process, continuous communication and collaboration between medicine developers and regulatory agencies are essential. Early engagement with regulators can provide valuable guidance, potentially leading to more efficient medicine development and expedited approvals for therapies that address rare diseases with high unmet medical needs.

Relationships with Investors: Which Funders Step in, and When?

Investors can step in at various stages of a company's development, depending on factors such as the company's progress, the stage of medicine development, and the funding needs. The types of investors involved in supporting biotech companies focused on rare disease include:

- **Government Grants and Non-Profit Organizations:** Companies focused on rare diseases can secure funding through government grants and contracts. These grants are often provided by agencies with a focus on healthcare and research, such as the **National Institutes of Health (NIH)** in the United States or the **European Commission's Horizon Europe Program**. Non-profit organizations and disease-specific foundations also offer grants or support for research and development in rare diseases.
- **Seed Stage Investors:** At the early stages of a company, often referred to as the seed stage, seed investors may provide initial funding. These are typically early-stage investors who provide initial funding to support the company's foundational research, proof-of-concept studies, and early development. Seed investors can include **angel investors, friends and family, and early-stage venture capital firms**. They are typically seeking high-risk, high-reward opportunities and may invest based on the potential of the company's technology, team, or early preclinical data.

- **Venture Philanthropists (VP):** Venture philanthropy is another significant player in supporting biotech companies focused on rare diseases. Unlike traditional philanthropy, which involves donating funds to charitable organizations, venture philanthropy takes a more strategic approach by investing in companies and projects with the potential for social impact. Venture philanthropy organizations often provide not only financial support but also strategic guidance, mentorship, and access to networks. By aligning social and financial objectives, venture philanthropy aims to catalyze the development of therapies for rare diseases and accelerate their journey to market.
- **Venture Capitalists (VC):** As the company progresses, it may seek funding from venture capital firms specializing in life sciences and healthcare. These firms provide capital to support the company's research, development, and clinical trials. VC firms often invest at various stages, such as Series A, B, and C funding rounds, providing capital to fuel growth and advance the company's pipeline.
 - **Series A Financing:** Once a company has made progress in its research and development, it may seek Series A financing. At this stage, investors, including venture capital firms and sometimes strategic investors, provide funding to support further preclinical research or the initiation of clinical trials.
 - **Series B and C Financing:** As the company advances through clinical development, it may require additional funding for larger and more expensive clinical trials. Series B and C financing rounds involve larger investments from venture capital firms, institutional investors, and sometimes corporate investors who see the potential value of the company's pipeline and drug candidates.
- **Strategic Investors/Pharmaceutical Partnerships/ Licensing deals:** Pharmaceutical companies or large biotechnology firms may invest in or form partnerships with smaller companies focused on rare diseases. These strategic investors provide funding, expertise, and resources, such as access to specialized technologies, regulatory guidance, and commercialization support. Strategic investors may also collaborate on research and development projects or co-develop certain assets. These partnerships can provide upfront payments, milestone payments tied to development and commercialization achievements, and royalties on product sales.

- **Public Markets and Initial Public Offerings (IPOs):** An IPO is a significant milestone for a company, where it becomes a publicly traded entity by offering shares to the public. This allows the company to raise substantial capital from the public markets, including institutional investors, mutual funds, and retail investors. The IPO proceeds can be used to fund late-stage clinical trials, manufacturing scale-up, commercialization efforts and expansion plans. Publicly traded biotech companies can access additional funding through subsequent public offerings and attract institutional investors.
- **Late-Stage Financing:** In some cases, companies may require additional funding for late-stage clinical trials, regulatory interactions, or market launch preparations. Late-stage financing can involve **private equity firms**, **crossover funds**, or even partnerships with pharmaceutical companies looking to invest in or collaborate on a promising medicine candidate.
- **Merger and Acquisition (M&A) Deals:** Another avenue of investment is through mergers and acquisitions. Larger pharmaceutical or biotech companies may acquire smaller biotech companies focused on rare diseases to gain access to promising drug candidates, technology platforms, or specialized expertise. M&A deals can provide a significant financial return to the company's investors.

It is worth noting that the **timing** and **involvement of investors** can vary greatly depending on the company's specific stage of development, circumstances, and the prevailing market conditions. Some companies may attract investors early on, while others may secure funding at later stages when they have achieved significant milestones or obtained positive clinical trial results. Different types of investors have **varying risk appetites**, **investment strategies**, and **desired returns**. **Biotech companies often rely on a mix of funding sources** throughout their development journey to support their research, clinical trials, and commercialization efforts.

TAKE AWAY

Companies focused on rare diseases undergo a challenging journey starting from research and development, through preclinical studies and clinical trials, to regulatory approval and market access. These milestones can be complex and time-consuming, taking several years to accomplish.

Regulatory interactions during the medicine development process for biotech companies working on rare diseases are essential and involve obtaining orphan drug designation, submitting IND applications for clinical trials, seeking approvals for each trial phase, submitting NDAs/MAAs for marketing approval, and engaging in advisory committee meetings, all while maintaining continuous communication and collaboration with regulatory agencies to address unmet medical needs effectively.

At each stage of the company's development, different types of investors play crucial roles in supporting the company's progress. These include, for example, government grants, non-profit organizations, seed investors, venture philanthropists, venture capitalists, strategic investors, public markets, late-stage financing, and mergers and acquisitions. The timing and involvement of investors can vary greatly depending on the company's specific stage of development, circumstances, and the prevailing market conditions.

Conclusion

Creating medicines for rare diseases presents unique challenges due to the limited patient population and complex disease mechanisms. Rare diseases often lack effective treatments, leaving patients with unmet medical needs and limited options. However, advancements in scientific research, innovative drug design approaches, and regulatory incentives have provided a glimmer of hope for patients and their families affected by these conditions. Creating medicines for rare diseases is a challenging but vital pursuit. Collaboration among researchers, patient advocacy groups, pharmaceutical companies, and regulatory authorities is crucial in driving progress. By focusing on rare diseases, we can provide hope and improved healthcare outcomes for patients and families living with rare diseases.

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Making medicines is complex and, requires meticulous research, innovative thinking, and unwavering dedication. In the realm of rare diseases, this journey is even more complex because the illnesses are so rare. Even rare disease experts often do not know how to help their patients. We need more treatments because 90% of people living with rare disease do not have an effective treatment.

This book explores the steps involved in making medicines. It is our response to requests from the rare disease community. There is an urgent need to understand how medicines are created so that patients and those who care for them can advocate with greater clarity and louder voices. We hope you find this book useful.

How to use this guide

The purpose of this guide is to explore the steps involved during the rare disease medicine development process. It is not a comprehensive science textbook but rather a 'quick read'. Each chapter is short and designed to be read in 5-10 minutes.



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