The Drug Development Process

A guide to understanding how new therapies are created (with a special focus on rare diseases)

Approved medicines are not yet available to treat many of the approximately 7000 rare diseases that have been identified to date. Because of this, the development of new drugs is of special interest for many individuals and families who are living with a rare disease.[1,2]

There are numerous reasons for all of these unmet medical needs. One is that developing new medicines for any condition is a very lengthy and expensive process[3]:

- Many years—often 10 or more—of research in the laboratory and in animals (preclinical testing), testing in human beings (clinical testing), and careful regulatory review are required before a new medicine can be approved
- These strict scientific and regulatory requirements help protect patients by ensuring that new medicines are well-tolerated and effective, but the process can be very expensive: according to a 2016 study, the average total cost of bringing a single new medicine to the market is £2 billion, or approximately €2.3 billion[3]

Another important reason is that developing new medicines for rare diseases in particular involves additional special challenges. By definition, rare diseases affect very small patient populations,[a] and as you will see, that simple fact may complicate the development process of the medicine in many ways.[1]

This leaflet describes the typical stages that a medicine goes through from laboratory to medicine cabinet.

It highlights special considerations for medicines that are being developed to treat a rare disease (also known as an orphan medicine or orphan drug.[b])

[a]Note that exactly how rare diseases or disorders are defined may differ slightly in different parts of the world. For example, in Europe, a disease or disorder is designated as rare if it affects fewer than 1 in 2000 persons, whereas in the United States, rare diseases or disorders are defined as those affecting fewer than 200,000 Americans at any given time.[2,4]

[b]Although the term "orphan drug" may be used in a broad sense to refer to medicines developed for use in a rare disease, the precise definition of the term involves some complexities that may vary by locality and other factors.[1]

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Medicine development: How new medicines travel from discovery to approval and beyond

The timeline on the next few pages describes the long road all potential medicines must follow to become available to patients as new therapies. Only a tiny percentage of compounds (an estimated 1 out of every 5000-10,000 screened) actually make it from discovery—the starting line—to that hoped-for destination. The medicines that do make it through the rigorous approval process have the potential to transform the lives of patients and their families.[5]

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Discovery

5000-10,000 substances screened[5] (based on averages)

The discovery phase of medicine development involves two stages[6]:

Target discovery–identifying processes or sites within the body (such as genes or proteins) that are linked to a disease

Medicine discovery–looking for chemical or biological compounds that may have an impact on those targets

When a promising substance is identified, it moves to the next stage of the journey: preclinical testing.[6]

Preclinical Testing

250 investigational medicines undergo preclinical testing[5]

Preclinical testing is done first in the laboratory and then in animals to learn about the substance (at this point called an investigational medicine). These early experiments are conducted to evaluate [6]:

Safety–including the possibility that the substance could cause serious harm (ie, toxicology)

Mechanism of action–how the substance might work in the body

Potential dosages–ranging from the lowest amount of the substance that may be needed to create a therapeutic effect, to the highest amount that can be tolerated or taken safely

If the results of preclinical trials show the investigational medicine might be well-tolerated and effective, an application is filed for approval to begin clinical testing.[6]

MILESTONE:
Preclinical Data Review

Before clinical testing (trials done in humans[4]) can begin, data from preclinical trials must be reviewed and approved by the regulatory agency of the region or country where the clinical trial will take place.

These preclinical data are sent to the appropriate regulatory agency as part of a formal application process. Different names may be used for this process in different areas—for example, Clinical Trial Applications (CTAs) in the EU[7] and Investigational New Drug Applications (INDs)[8] in the US—but the application and approval procedures are similar.[4–8]

The health and safety of trial participants is also protected. This is overseen by ethics committees and regulatory authorities such as the European Medicines Agency (EMA) in the EU[7,9] and the Food and Drug Administration (FDA) and Institutional Review Boards (IRBs) in the US.

If the application is approved, the investigational medicine moves to the next stage.[6]

Clinical Testing

5 investigational medicines are approved for clinical testing[5]

Clinical trials evaluate the safety and efficacy of medicines in human beings.[6] They usually take place in three phases leading up to market approval:

Phase 1 trials focus mostly on overall safety and determining dosages. They are usually (although not always) conducted in healthy volunteers.[5,6,10]

Phase 2 trials are larger, and although they still focus on safety, they also evaluate efficacy. They enrol people who have been diagnosed with the disease the medicine is intended to treat.[5,6,10]

Phase 3 trials are even larger studies, involving many more participants and study sites. They may be placebo-controlled and usually have a much longer duration. Phase 3 studies are intended to confirm the safety and longer-term efficacy of the investigational medicine.[5,6,10]

If the results of all three phases meet certain strict, specific scientific, clinical, and statistical standards, an application for approval of the investigational medicine is submitted for regulatory review.[6]

MILESTONE:
Comprehensive Data Review

An application for a license for a medicine is called different things around the world. In the EU, the application for market approval of a new medicine is called the Marketing Authorisation Application (MAA).[11] In the US, it is called a New Drug Application (NDA).[6]

These applications must include comprehensive information about the investigational medicine's manufacturing processes as well as its preclinical and clinical trial results.[6]

If the regulatory agency determines that the investigational medicine is well-tolerated, effective, and that its potential benefits outweigh its risks, the application is approved.[4]

Approval

1 new medicine is approved[5]

After regulatory and reimbursement coverage approval, the new medicine may be launched commercially and become widely available for prescription.

Certain new medicines may also become available to some patients before approval through arrangements known as Early or Expanded Access Programmes, or EAPs (sometimes also called 'compassionate use' programmes). These programmes vary by country, but they are generally intended for people who have life-threatening diseases for which no approved (or no suitable) treatment is available. The FDA and EMA provide regulations and recommendations for compassionate use, and each EU member state has developed its own specific rules and regulations.[12,13]

In the past, participating in a clinical trial was the only way to access new medicines prior to regulatory approval. However, some patients cannot meet the enrolment criteria of these trials, and participation in a clinical trial may be difficult for patients with chronic, seriously debilitating, or life-threatening rare diseases. EAPs have generated alternative channels for such patients.[13]

Post-Marketing

Surveillance and trials for additional uses

Regulatory agencies continue to monitor medicines after approval to gather long-term safety information and watch for unexpected side effects or other problems not seen during earlier clinical trials (which are by nature shorter in duration). In some cases, a type of trial called a post-marketing surveillance study (also known as a Phase 4 trial) may be done to gather more data about the medicine.[6,10]

The medicine may also undergo additional trials designed to test it for safety and efficacy in other patient populations (such as paediatric patients) or for the treatment of other diseases.

3-6 years[5] | **6-7 years[5]** | **6 months-2 years required for review[5]** | **Ongoing**

NOTE: This timeline is generally what happens but each case may be different.

★ Special considerations in rare diseases: natural history data

- The natural history (how a disease develops and progresses over time) of most rare diseases is not very well understood. This is because only a small number of people are affected by each rare disease, and because these diseases may manifest very differently in different patients[1]
- This relative lack of data is a problem, because the scientific understanding of the natural history of a disease plays a central role in determining the focus of research[1]
- Because of this, natural history studies are an essential part of the development process for rare diseases. They help keep research on the right path and increase the chances that new therapies will be successfully developed[1]

Ways to help:
- Join a patient registry
- Help raise awareness and advocate for research
- Enrol in a natural history study

★ Special considerations in rare diseases: clinical testing

- Small patient populations mean that fewer patients are available to participate in trials. Further, the few who are available may live far away from each other and from potential study locations, which may pose logistical difficulties
- Well-defined ways to measure how well an investigational medicine works (known as end points, outcome measures, or biomarkers) are lacking for many rare diseases, which can complicate trial design[1]
- It may be more difficult to attain the high level of statistical proof of safety and efficacy required for approval with trials involving small numbers of people

Ways to help:
- Enrol in a clinical study
- Help spread the word about clinical research and the importance of advancing disease knowledge
- Share information about clinical study recruitment with your community

★ Special considerations in rare diseases: review and approval

- Investigational medicines intended to treat rare diseases or other serious diseases with few or no other treatment options may be reviewed via special, faster pathways and become available to patients sooner. (However, it's important to be aware that these faster pathways still require medicines to meet high standards of safety and efficacy.)[14]

Ways to help:
- Advocate for appropriately modified regulatory review processes for medicines used to treat rare diseases
- Communicate with regulatory agencies to help them understand and evaluate the risks and benefits of investigational medicines for rare diseases

★ Special considerations in rare diseases: approval and beyond

- Many people with rare diseases face significant challenges in accessing medicines they need to treat their conditions. Uninsured or underinsured patients are at special risk, but even those who have insurance may find that their coverage for rare diseases has important limitations.
- Many patient advocacy organisations, such as European Organisation for Rare Disorders (EURORDIS) and National Organization for Rare Disorders (NORD), may offer financial and other assistance to help secure access to treatments for patients in need

Ways to help:
- Advocate for the repurposing of approved medicines
- Work with patient advocacy organisations and medicine companies to help secure better patient access to medicines

The Path Ahead

Developing new medicines—especially medicines used to treat rare diseases—is often a lengthy, scientifically demanding, logistically complex, and very expensive process.[3] However, the good news is that the rare disease community now has more reasons than ever to feel optimistic about new treatments becoming available for the conditions that affect them. Many progressive changes in legislation and regulatory processes have been made over recent decades that have encouraged and facilitated development of medicines for rare diseases, with the result that more are becoming available every year.

And there's more good news: you can help! People with rare diseases and their families have played an important role in making those positive changes happen. Over time, the relationships among patient advocacy organisations and the scientists who study rare diseases, the companies that develop new therapies, and the government agencies responsible for regulatory processes have evolved into true collaborative partnerships. These partnerships are unparalleled in other areas of medical research, and they've helped transform the lives of many people touched by rare diseases. However, there's still much work to be done. We hope that learning more about how new medicines are developed will inspire and empower you to get involved and help make a difference.

Glossary

Clinical Trial Application (CTA) in the EU or Investigational New Drug (IND) in the US: Documents that describe the results of preclinical studies of investigational medicines. They must be submitted to the European Medicines Agency or US Food and Drug Administration for approval before clinical testing (studies in humans) can begin.

Early Access to Medicines Scheme (EAPs): Also sometimes called compassionate use programmes, EAPs are special regulatory programmes that can allow patients to gain access to investigational treatments intended to treat serious diseases before they are approved for general use.

Investigational medicine: A compound or other potential treatment that is in preclinical or clinical testing but has not yet been approved by a regulatory agency.

Marketing Authorisation Application (MAA) in the EU or New Drug Application (NDA) in the US: Applications for approval of an investigational medicine by the European Medicines Agency or US Food and Drug Administration. It provides comprehensive information about the investigational medicine, including preclinical and clinical study results and manufacturing information.

Natural history: The course a disease takes without treatment from its beginning until its eventual resolution through recovery or death.

Orphan drug: A medicine developed to treat a rare disease (also called an orphan medicine).

Placebo-controlled: A term used to describe a method of research in which a *placebo*—an inactive substance made to be physically indistinguishable from the treatment being studied—is given to one group of participants, while the investigational treatment (usually a medicine or vaccine) being studied is given to another group. The results obtained in the two groups are then compared to see if the investigational treatment is more effective than the placebo.

Post-marketing surveillance: The ongoing monitoring of the safety of a medicine by regulatory agencies after market approval.

Registry: A collection of information about individuals who share a specific characteristic, such as a particular condition or diagnosis.

Toxicology: A scientific discipline involving the examination of adverse effects of chemicals or other substances on living organisms.

For more information:

European Medicines Agency
EU government agency responsible for the evaluation and supervision of medicinal products; also provides information about medicines, medical research, and the regulatory process for the general public

European Organisation for Rare Disorders (EURORDIS)
A non-governmental, patient-driven alliance of patient organisations representing 862 rare disease patient organisations in 70 countries

EveryLife Foundation for Rare Diseases
An organisation dedicated to advancing the development of treatment and diagnostic opportunities for patients with rare diseases through science-driven public policy

Global Genes
An organisation dedicated to connecting, empowering, and inspiring the rare disease community

National Organization for Rare Disorders (NORD)
A patient advocacy organisation dedicated to individuals with rare diseases and the organisations that serve them

US Food and Drug Administration
US government agency responsible for protecting public health by ensuring the safety, efficacy, and security of human and veterinary medicines, biological products, and medical devices; also provides information about medicines, medical research, and the regulatory process for the general public

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