

Development  
process of  
**Orphan**  
Medicinal  
Products



**efpia**

**EuropaBio™**

The European Association for Bioindustries

# Did you know that...

A rare disease is officially defined as a life-threatening or chronically debilitating condition that affects no more than **5 in 10,000**

There is **very little knowledge** about the underlying disease mechanism for a large majority of these conditions.

Only **1 out of the 5,000 to 10,000 substances** initially tested gets through to the marketing authorisation phase.

The EU has **a dedicated piece of legislation** for orphan medicinal products (OMPs) – Regulation No 141/2000 of 16 December 1999 on Orphan Medicinal Products.

Prior to the creation of the EU's Orphan Medicinal Products Regulation, just **8 products** had been authorised for treating such diseases. The European Commission subsequently formally identified these as "Orphan-like" products. Almost 15 years after its entry into force, more than **90 orphan medicinal products** were approved to treat rare diseases .

It is estimated that between **6,000 and 8,000 distinct rare diseases** exist today.

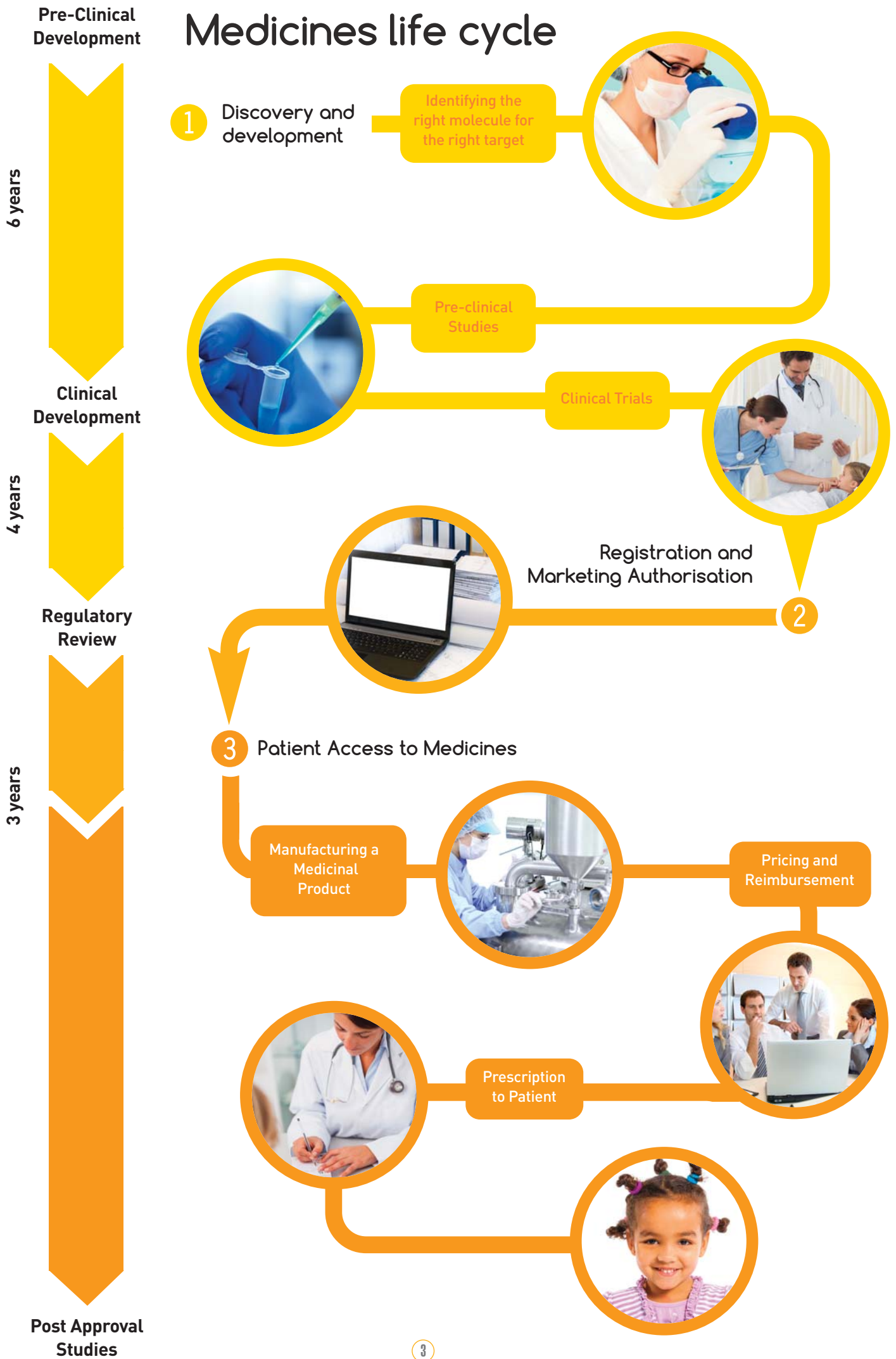
It takes on average **10 to 12 years and 1,1172 million EUR** to develop and bring a new treatment to the market.

Overall, employment in all departments of companies working in the area of orphan drugs more than doubled between 2000 and 2008 increasing from about **2,000 in 2000** to more than **5,000 in 2008**.

**80% of rare diseases** have a genetic cause. Other rare diseases are due to degenerative and proliferative causes.



# Medicines life cycle



# MEDICINES LIFE CYCLE

## 1 Discovery and Development

### Identifying the Right Molecule for the Right Target

Decisions to develop a medicinal product for a certain disease are based on outcomes of fundamental research, the identification of an unmet medical need or a corporate strategy.

### Testing the Molecule

**Pre-clinical Studies:** Before any testing in human beings, the candidate medicine is tested to assess the preliminary efficacy and toxicity levels. Studies are carried out in vitro and in vivo in the laboratory and, if they indicate that the molecule is not toxic or does not cause any harmful effects, the molecule is declared a candidate medicine.

### Clinical Development

#### • Clinical Development Phase I:

The active ingredient is tested on a small population (20 to 100) of healthy human volunteers to assess the safety, tolerability and other effects in a human body.

#### • Clinical Development Phase II:

The treatment is tested on a higher number of people (100 to 300), this time patients who are suffering from the condition and who volunteer to receive the new candidate medicine. A proportion of them will receive the active treatment that is being tested, while another proportion, called a control group, receives a placebo. This "control" group is important, because it precludes subjective results.

#### • Clinical Development Phase III:

The treatment is tested on larger patient population (300 to 3,000), who are also given either the new medicine or a control treatment. This phase aims to define the final efficacy and toxicity profiles of the medicinal product before the application for marketing authorisation to the relevant regulatory authorities.

### Pharmaceutical Development

Selected molecules will be turned into medicines that can be used by patients. This process will determine how to make the active ingredients, how to make an actual dosage form (tablet, capsule or injection), how to test it for purity and how to ensure that the dosage form consistently delivers safe and effective drug levels.

## 2 Registration and Marketing Authorisation

When a developer has demonstrated efficacy, safety and quality of its potential new medicine through the required analytical and clinical tests, it may

apply for a marketing authorisation at national or European level. Certain kind of medicines (e.g. biologicals, cancer treatments, and certain other

categories including orphan medicines) can only be authorised through the European centralised procedure.

## 3 Patient Access to Medicines

### Manufacturing a Medicinal Product

The holder of a marketing authorisation must manufacture medicinal products in a way that ensures they are fit for their intended use, and that they comply with the requirements of the marketing authorisation in terms of safety, quality and efficacy. This manufacturing process is also subject to regulatory authorisation.

### Pricing and Reimbursement

After a marketing authorisation is granted, either by the national competent authorities, or by the European Commission, the manufacturer has to apply to the countries or regions to start pricing

and reimbursement discussions. It is the decision of each EU Member State – or, sometimes, even each region in a country – to decide if it will grant reimbursed patient access to new treatments. Increasingly, countries and regions are subjecting new treatments to Health Technology Assessments, before granting access to the new treatment. This assessment can include cost-effectiveness evaluations as well as other elements. So, this additional step can require large and complex data sets beyond the clinical outcomes that demonstrate safety and efficacy of newly approved treatment, and if missing these data will need to be generated in post approval studies.

### Prescription to Patient

Medicines may be sold or made available to patients with a valid prescription from a physician. Prescription medicines are usually dispensed by a retail or hospital pharmacist.

### Pharmacovigilance (Safety Monitoring)

Once the medicine has been authorised, it may be prescribed by doctors. Doctors, manufacturers and authorities are required by law to continue to watch out for possible side effects. If a pattern emerges, this is further investigated and, if new findings come to light, the instructions for use are updated, or products may even be withdrawn.

# SPECIFIC FEATURES OF ORPHAN MEDICINES

## 1 Discovery and Development

Research and development of orphan medicinal products is complex and time-consuming, due to the specificities of rare diseases. These are due to the small number of patients and the heterogeneity of the conditions – one rare disease may show a wide variety of different symptoms. The chronicity or severity of the disease, the lack of scientific knowledge and the lack of alternative treatment can all influence the medicine development.

### Testing the Molecule

#### • Pre-clinical Studies:

A poor understanding of the biology and pathophysiology of a disease will

mean that there are no, or few animal models or computer simulations, since there will be limited science to guide the selection and/or development of such models.

### Clinical Trials

Orphan medicinal products development faces many challenges, such as study design and execution, and patient recruitment. Small, geographically spread patient populations are often under- or misdiagnosed, and the scarcity (or absence) of “centers of expertise” adds to the difficulty in finding enough eligible patients for a rare disease clinical trial. Placebo

controlled arms can be an ethical issue in patient populations without valuable treatment options. As a result, clinical trials for orphan medicinal products are expensive and complicated to conduct successfully. Furthermore, a very small patient population in clinical trials means that “traditional” clinical trial designs and statistical data analysis methods are essentially not feasible for these conditions. Alternative trial design is often essential but this requires thorough discussion with regulators on the acceptability of data from such trials, which is a challenge for those developing new medicines for rare diseases.

## 2 Registration and Marketing Authorisation

Marketing authorisations for orphan medicinal products are only granted at European level since the new pharmaceutical legislation adopted in 2004. Orphan medicinal products are

complex issues and their clinical assessment requires a solid expertise, which is often difficult to find, even amongst regulators. This can lead to lengthy discussions with the regulator

as all those involved in the evaluation of the rare disease and its treatment seek to understand the best approach for the patients who could potentially benefit from a new treatment.

## 3 Patient Access to Medicines

### Pricing and Reimbursement

Because of the uncertainties related to rare diseases’ rarity, severity and lack of alternative treatments, some Member States have amended their HTA systems to support access to orphan medicinal products. However, in many cases conventional HTA systems are not adapted to the characteristics of orphan medicinal products.

Because of the restricted number of patients affected by rare diseases, the overall budget impact of OMPs is limited and sustainable. In fact, even 15 years after the EU OMP legislation these represent 3-4% of the pharmaceutical budget.

### Patient Access and Prescription

Access to orphan medicinal products differs greatly from one European country to another in terms of availability on the market and the time it takes to get reimbursed patient access. Specific conditions may apply to the prescription of orphan medicinal products depending on the European country. In some countries for example, prescription of orphan medicinal products is the exclusive responsibility of a specialist physician. In other countries, a second opinion is required before a patient may receive an orphan treatment for a rare disease. The lack of specific treatment guidelines can also make patient access more complicated.

### Pharmacovigilance (Safety Monitoring)

#### • Throughout post-marketing authorisation: Registries

Orphan medicinal products are often approved by regulators on a “conditional basis”, clinical trials are small and trial designs can be non-traditional. This is due to the rarity of the condition. The decision to grant approval may be based on the recognition of the unmet medical need and the conditional authorization will be linked to commitments to learn more about the disease and the effects of the treatment after the marketing authorization. Companies will then invest in setting up registries and conduct post approval studies to fulfill the regulatory commitments.

# Orphan Medicinal Products Regulation Glossary

**Newborn screening:** Genetic rare diseases are severe, chronic and degenerative. Symptom onset can occur during childhood and for many conditions, symptoms may not appear in the first days or months following birth, even though irreversible damage may have already happened. In these instances, it is important to make the right diagnose early in life to treat at the right moment and ultimately achieve better health outcomes for the child. New born screening could support this goal. Newborn screening policies of Member States vary significantly with respect to the conditions screened for, and the processes and criteria by which new conditions are added to their screening panels. The number of conditions screened for varies from one or two to more than twenty conditions.

**Committee for Orphan Medicinal Products (COMP):** The Committee for Orphan Medicinal Products at the European Medicines Agency (EMA), comprised of experts from the Member States, is responsible for examining whether a medicine may be granted the status of orphan medicinal product at an early development phase. If the European Commission agrees with the vote of the COMP, the product is entered in the Register of designated orphan medicinal products. The product has then to go through the evaluation for safety, quality and efficacy that all medicines have to follow, carried out by the Committee for Human Medicinal Products (CHMP) at the EMA.

**Orphan Designation & Community Register:** If a medicine meets the criteria defined under the EU's Orphan Medicinal Products Regulation, it may be officially designated as an orphan. These are listed on the official Community Register. The orphan medicinal products that have received a Marketing Authorisation via the EU's centralised procedure are also indicated on this Register.

**Incentives at European level:** To support the development and authorisation process of orphan medicinal products, EU legislators have adopted a series of incentives, namely 10-year marketing exclusivity, protocol assistance (scientific advice provided by the EMA during the product development phase), and a reduction/waiver of fees.

**Conditional Approval:** Before a medicinal product is authorised, it generally has to undergo extensive studies to ensure that it is safe, of high quality and effective for use in the target population. In the case of certain categories of medicinal products, however, in order to meet unmet medical needs of patients and in the interests of public health, it may be necessary to grant marketing authorisations on the basis of less complete data than is normally the case. This is a 'conditional marketing authorisation'. These medicinal products are granted a marketing authorisation but with the obligation to complete studies afterwards, aiming at confirming that the risk-benefit balance is positive.

**Registries** have, in some cases, been set up to describe the natural history of a specific rare disease. These can have a variety of functions, including determining the clinical effectiveness of an orphan medicinal product, monitoring its safety, supporting further research, collecting clinical outcomes and even monitoring its cost-effectiveness. In some cases, industry establishes and funds these registries. However, the Registries are overseen by independent, governing bodies.



# Joint EUROPABIO–EFPIA Task Force on Rare Diseases and Orphan Medicinal Products

EFPIA (European Federation of Pharmaceutical Industries and Associations) and EuropaBio (European Association for Bioindustries) have established a joint EuropaBio-EFPIA Task Force on Rare Diseases and Orphan Medicines, comprising companies that have either developed or intend to develop orphan medicines under European Regulation No 141/2000. Together, members of the Joint Task Force represent a large proportion of orphan medicines currently available on the EU market.



European Federation of Pharmaceutical  
Industries and Associations

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the pharmaceutical industry operating in Europe. Through its direct membership of 33 national associations and 40 leading pharmaceutical companies, EFPIA is the voice on the EU scene of 1,900 companies committed to researching, developing and bringing to patients new medicines that will improve health and the quality of life around the world. It has two specialized groups, EBE (European Biopharmaceutical Enterprises) and Vaccines' Europe.

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The European Association for Bioindustries

EuropaBio's mission is to promote an innovative and dynamic biotechnology-based industry in Europe. EuropaBio (the European Association for Bioindustries) has 55 corporate members, 15 associate members and Bio regions, and 17 national biotechnology associations, who in turn represent more than 1800 small and medium sized biotech companies in Europe. Members of EuropaBio are involved in research, development, testing, manufacturing and commercialisation of biotechnology products and processes. Our corporate members have a wide range of activities: human and animal health care, diagnostics, bio-informatics, chemicals, crop protection, agriculture, food and environmental products and services.

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