

## Procedural document: data collection and registration of medicinal products intended for rare diseases in Orphanet

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## I. Introduction

### 1 Purpose/objectives

Orphanet intends to improve visibility on therapeutic development in the field of rare diseases. This is why it offers a catalogue of medicinal products at all stages of development for a particular rare disease or a group of rare diseases. This includes all the substances that have been granted an orphan designation for disease(s) considered as rare in Europe or the USA, whether they were further developed to become approved medicinal products with marketing authorisation (MA) or not.

The Orphanet database also includes medicinal products without an orphan designation as long as they have been granted a MA issued by the European Medicines Agency (EMA - centralised procedure) with a specific indication for a rare disease.

Orphanet also registers medicinal products (by their substance and/or trade name) that are/have been tested in a clinical trial performed on a rare disease, even if they do not have a regulatory status.

This document aims to explain the workflow and set of criteria for the selection, registration and update of medicinal products for rare diseases in the Orphanet database.

### 2 Disclaimer

- This procedural document is part of the OrphaNetWork Direct Grant (831390), which has received funding from the European Union's Health Programme (2014-2020).
- The content of this procedural document represents the views of the author only and is his/her sole responsibility; it can not be considered to reflect the views of the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.
- Information in Orphanet is updated on a regular basis. It may happen that there is a delay between the granting of a new designations/approvals and their publication in Orphanet. Professionals are always encouraged to consult the most recent publications before making any decisions based on the information provided.
- Orphanet cannot be held responsible for harmful, truncated or erroneous use of any information found in the Orphanet database.
- Orphanet acknowledges the contribution of the European Medicines Agency (EMA) to the creation of the database on orphan medicinal products in Europe. This project was initiated by the Committee for Orphan Medicinal Products (COMP) at the EMA. Several members of the COMP have individually contributed to the development of the database, which was welcomed by the COMP as a significant tool for all stakeholders.

- The database has been developed entirely and autonomously by Orphanet, using public and private funding and publicly available data; as such, neither the EMA nor the FDA are responsible for the content and management of the database.

### 3 Range of application

The present procedure applies to all medicinal products intended for rare diseases registered in Orphanet. The registration and update of the medicinal products is performed by the Orphanet Coordinating Team (OCT).

### 4 References

- [Orphanet Standard Operating Procedures](#)
- [Community Register of orphan medicinal products for human use of the EU commission](#)
- [Community Register of medicinal products for human use of the EU commission](#)
- [EMA's Orphan designation database](#)
- [EMA's European public assessment reports \(EPAR\)](#)
- [FDA Orphan Drug Product designation and approvals database](#)
- [Regulation \(EC\) N°141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products](#)
- [Electronic Code of Federal Regulations of the United states, title 21, chapter 1 part 316](#)

### 5 Definitions

**Active substance:** The substance responsible for the activity of a medicinal product.<sup>1</sup>

**Anatomical Therapeutic Chemical (ATC) code:** a unique code assigned to a medicine according to the organ or system it works on and how it works<sup>2</sup>. In the ATC classification system, the active substances are classified in a hierarchy with five different levels. The system has fourteen main anatomical/pharmacological groups or first levels. The classification system is maintained by the World Health Organisation (WHO).

**Centralised procedure:** The European Union-wide procedure for the authorisation of medicines, where there is a single application, a single evaluation and a single authorisation throughout the European Union (EU) member states, Iceland, Norway and Liechtenstein. Only certain medicines are eligible for the centralised procedure.<sup>3</sup>

**Committee for Medicinal Products for Human Use (CHMP):** The European Medicines Agency's (EMA) committee responsible for human medicines.

<sup>1</sup> <https://www.ema.europa.eu/en/about-us/about-website/glossary>

<sup>2</sup> <https://www.ema.europa.eu/en/glossary/atc-code>

<sup>3</sup> <https://www.ema.europa.eu/en/glossary/centralised-procedure>

**Committee for Orphan Medicinal Products (COMP):** The European Medicines Agency's (EMA) committee responsible for recommending orphan designation of medicines for rare diseases.

**Clinical trial:** A clinical study in which participants receive one or more interventions (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study protocol<sup>4</sup>. In Orphanet, interventions in clinical trials are limited to medicinal products and medical device assessments in the treatment or prevention of a rare disease or a group of rare diseases, conducted in at least one country of the Orphanet network or funded by an IRDiRC member.

**European Medicines Agency (EMA):** A decentralised agency of the European Union (EU) responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU.

**European public assessment report (EPAR):** A set of documents describing the evaluation of a medicine authorised via the European centralised procedure and including the product information<sup>5</sup>.

**The US Food and Drug Administration (FDA):** An agency within the U.S. Department of Health and Human Services. One of its main missions is to protect the public's health by assuring the safety, effectiveness, quality, and security of human and veterinary drugs, vaccines and other biological products, and medical devices.

**International Nonproprietary Name (INN):** Identifies pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognised and is public property. A nonproprietary name is also known as a generic name.<sup>6</sup> This service is maintained by the World Health Organization (WHO).

**Orphan designation (OD):** A status assigned by the concerned regulatory authority to a medicine intended for use in a rare condition. The medicine must fulfil certain criteria for designation as an orphan medicine so that it can benefit from incentives such as protection from competition once on the market.<sup>7</sup>

**Orphan medicine:** A medicine for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition that is rare (affecting not more than five in 10,000 people in the European Union, or fewer than 200 000 persons for the USA) or where the medicine is unlikely to generate sufficient profit to justify research and development costs<sup>8 9</sup>.

**Orphanet coordinating team (OCT):** US14 Inserm-based team (Paris, France) coordinating the

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<sup>4</sup> <https://clinicaltrials.gov/ct2/about-studies/glossary>

<sup>5</sup> <https://www.ema.europa.eu/en/about-us/about-website/glossary>

<sup>6</sup> <http://www.who.int/medicines/services/inn/en/>

<sup>7</sup> <https://www.ema.europa.eu/en/about-us/about-website/glossary>

<sup>8</sup> <https://www.ema.europa.eu/en/glossary/orphan-medicine>

<sup>9</sup> <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm>

Orphanet Network, producing the English Orphanet nomenclature and its scientific annotations and responsible for coordination of the production of the scientific content and for all Network activities including translation and IT developments.

**Public summary of opinion on orphan designation (PSO):** Represents a summary of knowledge on the medical condition and the medicinal product at the time of opinion following positive and negative opinions by EMA’s Committee for Orphan Medicinal Products on applications for orphan designation.

**Marketing authorization (MA):** Refers to the approval for a medicine to be marketed. MA are granted only when a competent authority (or ‘regulatory authority’) has conducted a scientific evaluation, and is satisfied that a medicine is sufficiently safe and effective, and of high enough quality<sup>10</sup>.

**Medicinal product or medicine:** A substance or combination of substances intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action<sup>11</sup>.

**Rare disease:** A disease that affects less than 5 in 10,000 persons in Europe, as defined by the European Regulation on orphan medicinal products ([Regulation \(EC\) N°141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products](#)). In order to be registered in Orphanet, the disease must be described in at least two independent individuals, confirming that it is not an incidental association of clinical signs. For the US, the Orphan Drug Act (ODA) in [21 CFR 316](#) the definition of a “rare disease or condition” includes any disease or condition that affects fewer than 200,000 persons in the United States.

**Tradename:** Commercial name of the medicinal product.

## 6 Filing and updates

This document is updated by the coordinating team as often as necessary and at least once a year. The most up-to-date version is available on the Orphanet website: [https://www.orpha.net/orphacom/cahiers/docs/GB/medicinal\\_products\\_in\\_Orphanet\\_R2\\_R\\_D\\_Drugs\\_EP\\_06](https://www.orpha.net/orphacom/cahiers/docs/GB/medicinal_products_in_Orphanet_R2_R_D_Drugs_EP_06)

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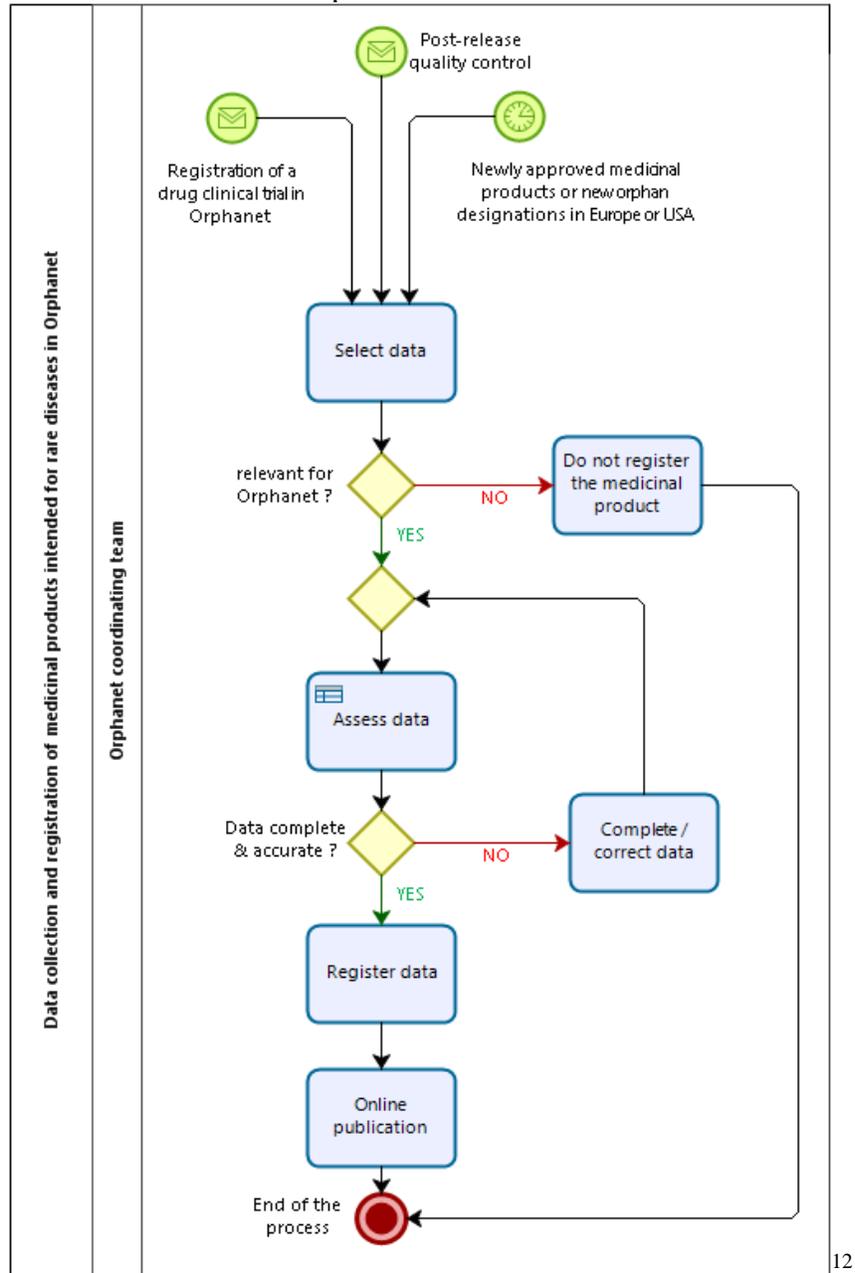
<sup>10</sup> <https://www.eupati.eu/glossary/marketing-authorisation/>

<sup>11</sup> <https://www.ema.europa.eu/en/about-us/about-website/glossary> ([Regulation \(EC\) N°141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products](#))

## II. METHODOLOGY

### 1 Flowchart

The general process for the collection, registration, validation and quality control of data relative to medicinal products for rare diseases is presented below:



## 2 Description

The registration and update of medicinal products for rare diseases is performed by the Orphanet coordinating team (OCT).

The main sources of information for the registration/update of medicinal products in Orphanet are:

- For Europe, the reports of the COMP (Committee for Orphan Medicinal Products) and the CHMP (Committee for Medicinal Products for Human use);
- For the USA, the FDA Orphan Drug Product designation and approvals database;
- All clinical trials registered in Orphanet with a medicinal product being evaluated.

Therefore, the process of registration/update of medicinal products for rare diseases is triggered either by the detection of a medicinal product tested in a clinical trial on rare diseases and not yet registered in the Orphanet database and/or a monthly monitoring of:

- The newly approved medicinal products / extended indications for Europe on EMA's website.
- Orphan designations on EMA's website.
- Orphan designations / Drug approvals on FDA website.

### 2.1 Data selection

#### 2.1.1 Inclusion criteria:

In order to be registered in Orphanet, a medicinal product must meet one of the following conditions:

- Be granted an orphan designation (OD) by the European Commission and / or FDA.
- Be granted a marketing authorisation (MA) by the European Commission (via the centralised procedure) for a rare disease with or without an OD.
- Be granted a marketing authorisation with orphan designation by the FDA.
- Be tested in a clinical trial registered in the Orphanet knowledge base for a rare disease.

#### 2.1.2 Exclusion criteria:

Orphanet does not register a medicinal product if it is:

- A medicinal product with a regulatory status outside Europe or the USA.
- A medicinal product approved in Europe through a procedure other than the centralised procedure.
- A medicinal product not intended for a rare disease.

### 2.2 Data assessment

If the medicinal product complies with the Orphanet inclusion criteria cited above, the OCT analyses the information to check that the mandatory dataset (cf below) is provided and is coherent. In case of inconsistency, or missing information, the OCT may contact EMA or FDA in order to clarify or obtain the supplementary information needed.

#### 2.2.1 Orphanet dataset for active substances

- Common name of the substance in English
- Code name given to the product candidate by pharmaceutical companies during its

- development
- Chemical name or description
  - International Nonproprietary Name (INN)
  - Indication of the type of production: synthetic/extractive chemistry, or biotechnology
  - Indication of the type of substance: Ingredient/substance, cell therapy product, blood-derived drug, gene therapy product, human/animal tissue/organ, other type of health product

### 2.2.2 Orphanet dataset for regulatory status of medicinal products

- Regulatory status (Orphan designation/Marketing authorisation with orphan designation/Marketing authorisation without orphan designation/Compassionate use/Orphan designation withdrawn/ Marketing authorisation withdrawn)
- Geographical zone concerned by the regulatory status (Europe /USA)
- Therapeutic indication or orphan designation
- Disease or group of diseases covered by the therapeutic indication / orphan designation
- Orphan designation (OD) or Marketing authorisation (MA) number
- Date of issue of MA/ Date of decision of OD
- Link to the corresponding Public summary of opinion on orphan designation (PSO) or European public assessment report (EPAR)
- ATC code of the medicinal product
- Main group of the ATC classification
- Name and address of the sponsor of OD or MA holder

## 2.3 Data registration & publication

Once all the necessary information collected and assessed, the medicinal product is registered in the Orphanet database. It becomes then accessible on the Orphanet website and can be retrieved from Orphadata after signing a Data Transfer Agreement (DTA) or service contract. Data on approved medicinal products for Europe is also released within an Orphanet Report Series that is updated every trimester.

## 2.4 Post-release quality control

The post-release quality control for medicinal products for rare diseases consists of quality control projects organised by the coordinating team on a regular basis to check the completeness, uniqueness and consistency of the data compared to the most up-to-date regulatory information

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