EURORDIS
THERAPEUTIC REPORT
January 2023
ISSUE 1
UPDATE ON THERAPEUTIC DEVELOPMENT AND PATIENT INVOLVEMENT IN EMA ACTIVITIES

GENERAL NEWS

EMA pilots scientific advice for certain high-risk medical devices

EMA has launched a *pilot* to give *scientific advice* on the intended clinical development strategy and proposals for clinical investigation for certain high-risk medical devices.
The pilot will prioritise certain types of medical devices:

- devices that benefit a small group of patients in the treatment or diagnosis of a disease or condition, such as devices intended for the treatment of a rare condition, known as 'orphan devices', and devices for paediatric use;
- devices addressing medical conditions that are life threatening or cause permanent impairment of a body function and for which current medical alternatives are insufficient or carry significant risks;
- novel devices with a possible major clinical or health impact.

For more information, please read *here.*

PDCO survey on phenylketonuria (PKU)

The Paediatric Committee (PDCO) at the European Medicines Agency (EMA) is currently evaluating a **proposal for a treatment for phenylketonuria (PKU).**

If you have experience with PKU and would like to share your views and perspectives on specific questions and contribute to have a more informed discussion, please fill in the following survey.

Responses should be submitted no later than **24 March 2023.**

IN THIS ISSUE

Did you miss the ***EURORDIS Black Pearl Awards****?*
Watch the recording here!

Orphan medicines in the European Union (EU)

Finding effective treatment for patients with rare diseases can be very difficult. Since the EU orphan regulations entered into force in 2000, it has played a central role in facilitating the development and authorisation of medicines for rare diseases with more than 200 medicines authorized in the EU. **During 2022, 24 orphan medicines were recommended for authorization**, almost 1/3 of the total medicines recommended in 2022.

Development of medicines for rare diseases

The EU offers incentives to encourage companies to research and develop medicines for rare diseases that otherwise would not be developed. To access these incentives, companies can apply for orphan designation for their medicine, provided certain criteria are met.

Orphan Designation

Criteria for orphan designation

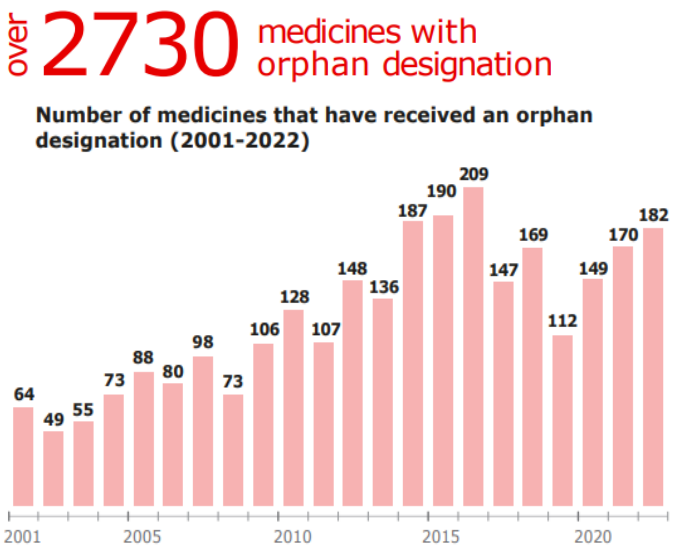
- The medicine must treat, prevent, or diagnose a disease which is life-threatening or chronically debilitating, or it is unlikely that the medicine will generate sufficient returns to justify the investment needed for its development.
- The disease must not affect more than 5 in 10,000 people across the EU.
- No satisfactory method of diagnosis, prevention or treatment exists, or if such a method already exists, the medicine must be of significant additional benefit to those affected by the condition.

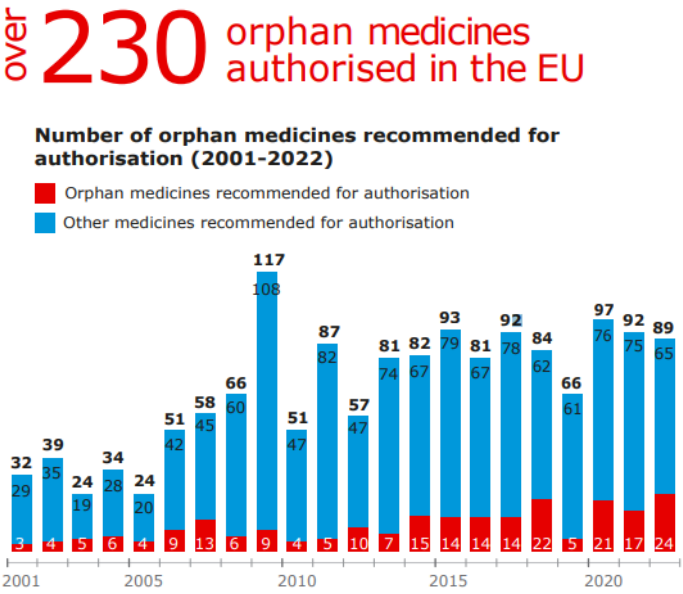
Incentives

During an orphan medicine's research and development, the company can benefit from incentives such as scientific advice on study protocols, various fee reductions and access to EU grants. Orphan-designated medicines that eventually make it to the market, and for which it can be demonstrated that they maintain the criteria for the designation, are **granted 10 years of market exclusivity.**

Not all orphan-designated medicines reach the marketing authorisation application stage. Those that do, are evaluated by EMA's Committee for Medicinal Products for Human Use (CHMP) using the same strict safety and efficacy standards that apply to all medicines evaluated by EMA.

For more information see *infographic here.*





Images adapted from EMA infographic here.

Pharmacovigilance Risk Assessment Committee (PRAC) January 2023

Minutes September 2022
Agenda January 2023
Meeting Highlights January 2023

Zolgensma: fatal cases of acute liver failure

EMA's safety committee (PRAC) informed about fatal cases of acute liver failure in patients treated with **Zolgensma** *(onasemnogene abeparvovec),* a gene therapy medicine for the treatment of spinal muscular atrophy (SMA), a serious rare condition of the nerves that causes muscle wasting and weakness.

This communication informs healthcare professionals of the fatal cases of liver failure and the updated recommendations for monitoring liver function, assessing suspected liver injury after infusion and further advice regarding tapering the corticosteroid treatment.

Healthcare professionals should promptly assess patients with worsening liver function tests and/or signs or symptoms of acute liver illness. **If patients do not respond adequately to treatment with corticosteroids, treating physicians should consult a paediatric gastroenterologist or hepatologist and consider adjustment of the corticosteroid regimen**.

More information is available in *EMA's public health communication.*

Medicines safety resources

- List of medicines under additional monitoring
- EudraVigilance
- Shortages catalogue
- Recommendations on medication errors
- Good Pharmacovigilance Practices
- Patient registries
- Rules of procedure on the organisation and conduct of public hearings at the

Click on the image to get the latest issue of ***QPP Update***, an EMA newsletter with the latest news on EU Pharmacovigilance

Orphan medicines key figures

Since 2000

2757 Orphan designations

272 Orphan designations included in authorised indication

239 Authorised OMPs

95 To be used in children

6 Removed from the market

79 Marketed, but no longer "orphans"

To date

154

Products with a marketing authorisation and an orphan status in the European Union

1 March 2023

CHMP Meeting Highlights January 2023

Minutes December 2022
Agenda January 2023
Meeting Highlights Jan 2023

In January, the CHMP recommended **4 medicines for approval, any orphan medicines**:

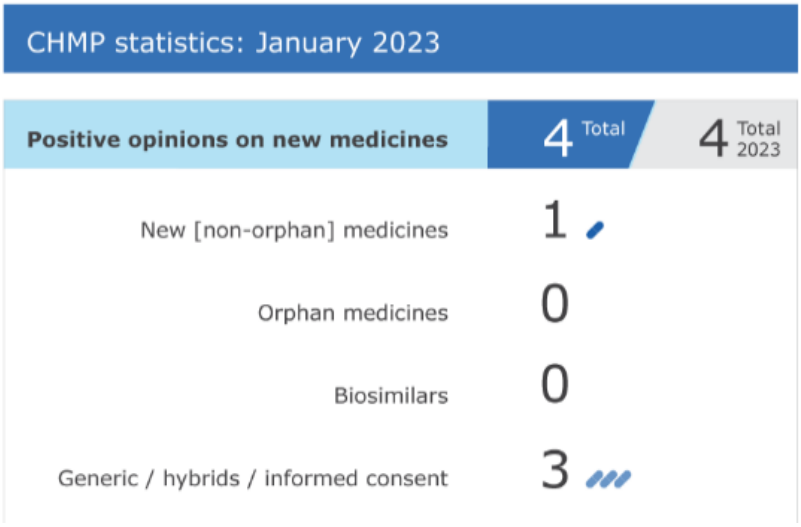
- **Sotyktu** (deucravacitinib), for the treatment of moderate to severe plaque psoriasis in adults, a skin disease causing red, scaly patches.

Three generic medicines:

- **Dapagliflozin Viatris** (dapagliflozin) for the treatment of type 2 diabetes mellitus, heart failure and chronic kidney disease.
- **Sitagliptin/Metformin hydrochloride Sun** (sitagliptin/metformin hydrochloride) for the treatment of type 2 diabetes mellitus.
- **Tolvaptan Accord** (tolvaptan) to treat adults with low blood sodium levels caused by the syndrome of inappropriate antidiuretic hormone secretion.

The CHMP also recommended 7 extensions of therapeutic indication.

For further details, read the full *CHMP meeting highlights*.



Click on the image to get the latest issue of ***Human Medicines Highlights***, a newsletter published by EMA address to organisations representing patients, consumers and healthcare professionals summarising key information on medicines for human use.

COMP September - December to be updated when info available

Minutes May 2022
Agenda July 2022
Meeting July 2022

COMP July 2022 meeting update

During the July plenary, the COMP adopted **21 positive opinions** on the designation of medicines as orphan medicinal products to the European Commission (EC). For further information, please see the *meeting report.* Please find below the list of indications covered in the medicines that were recommended for orphan designation:

- Hutchinson-Gilford progeria syndrome, Global Medical Services Sp. z o.o.;
- Urea cycle disorders , Unicyte S.r.l.;
- Graft-versus-host-disease, MDC RegAffairs GmbH;
- Cryptococcosis, Insight Drug Regulatory;
- Mucopolysaccharidosis type IV A, (Morquio A syndrome), Fondazione Telethon;
- Frontotemporal dementia, Neuroplast B.V.;
- Myasthenia gravis, Pharma Gateway AB;
- Primary sclerosing cholangitis, Amsterdam UMC;
- Prevention of acute liver failure, Egetis Therapeutics AB;
- Nontuberculous mycobacterial lung disease, Regintel Limited;
- Nontuberculous mycobacterial lung disease, Dlrc Pharma Services Limited;
- Amyotrophic lateral sclerosis, Clene Netherlands B.V.;
- Haemophilia A, S-Cubed Pharmaceutical Services ApS;
- Chondrosarcoma, TMC Pharma (EU) Limited;
- Familial adenomatous polyposis, Amsterdam UMC;
- Idiopathic hypersomnia, Propharma Group The Netherlands B.V.;
- Peripheral T-cell lymphoma, Pharma Gateway AB;
- Amyotrophic lateral sclerosis, Novartis Europharm Limited;
- Myelodysplastic syndrome, Syros Pharmaceuticals (Ireland) Limited;
- Osteosarcoma, Hephaistos-Pharma;
- Stargardt's disease, Alnylam Netherlands B.V.

Re-assessment of orphan designation at time of marketing authorisation

When a designated orphan medicinal product receives a positive opinion for marketing authorisation from EMA's Committee for Medicinal Products for Human Use (CHMP), the COMP has the responsibility to review whether or not the medicinal product still fulfils the designation criteria prior to the granting of a marketing authorisation.

The COMP adopted **three** positive opinions at time of CHMP opinion:

- **Roctavian** (valoctocogene roxaparvovec) for treatment of haemophilia A, BioMarin International Limited.
- **Scemblix** (asciminib) for treatment of chronic myeloid leukaemia, Novartis Europharm Limited.
- **Vyvgart** (efgartigimod alfa) for treatment of myasthenia gravis, Argenx.

Summaries of positive opinions on orphan designations are available on the *EMA website*.

Medicinal Product	Marketing Authorisation Holder	Therapeutic Indication	Date of Marketing Authorisation
Hemgenix® *(etranacogene dezaparvovec)*	CSL Behring Gmbh	Haemophilia B	20/02/2023

Please click also on the following links to see:

Orphan medicinal products authorised during 2022

Orphan medicinal products authorised since 2000

As of April 2022 and until further notice, PDCO no longer publishes meeting reports.

Minutes February 2022
Agenda March 2022
Meeting Report March 2022

Boosting the development of medicines for children

In 2017, the European Commission's (EC) *10-year report on the implementation of the Paediatric Regulation* revealed specific challenges. Whereas the report showed an overall increase in medicines being developed for children, it also highlighted that **paediatric development is lagging behind the adult one**, causing a delay in availability of paediatric medicines at patient' bedsides. Another challenge is the development of medicines for which there is no adult indication and are targeted for diseases that exclusively affect children. In order to follow-up on the report's conclusions and to boost the development of medicines for children in Europe, the EC and the European Medicines Agency (EMA) developed a detailed plan of short-term actions that could address the identified shortcomings under the current legal framework. The EMA-EC action plan was published on 2 October 2018 and took into account the suggestions made at a *multistakeholder workshop* convened by the EC and EMA earlier that year.

Progress on all agreed actions has been made through collaboration of all stakeholders. The actions were grouped according to the **five topics areas** highlighted by the Commission in the 10-year report on the implementation of the Regulation:

1. **Identifying paediatric medical needs**
2. **Strengthening of cooperation of decision makers**
3. **Ensuring timely completion of paediatric investigation plans (PIPs)**
4. **Improving the handling of PIP applications**
5. **Increasing transparency around paediatric medicines**

These actions have helped to focus development efforts on areas of high unmet medical need, spared paediatric resources and increased the possibility for earlier availability of new medicines through shorter developments. Administrative steps have been reduced, processes have been simplified and made adaptable to innovative new medicine developments to reduce bureaucracy. Moreover, cooperation among decision makers and stakeholders has been intensified and new lasting working relationships have been created and strengthened.

It is expected that the actions taken will increase the efficiency of paediatric regulatory processes under the current legal framework. Moreover, learnings from the action plan will be translated into the revision of the Paediatric Regulation which is expected to further support the availability of medicines for children.

For more information, please read *here*.

CAT updates are now quarterly

CAT highlights Nov– Jan meeting update

This report provides information on ATMP approvals and extension of indications of authorised ATMPs, as well as statistical data on product-related activities.

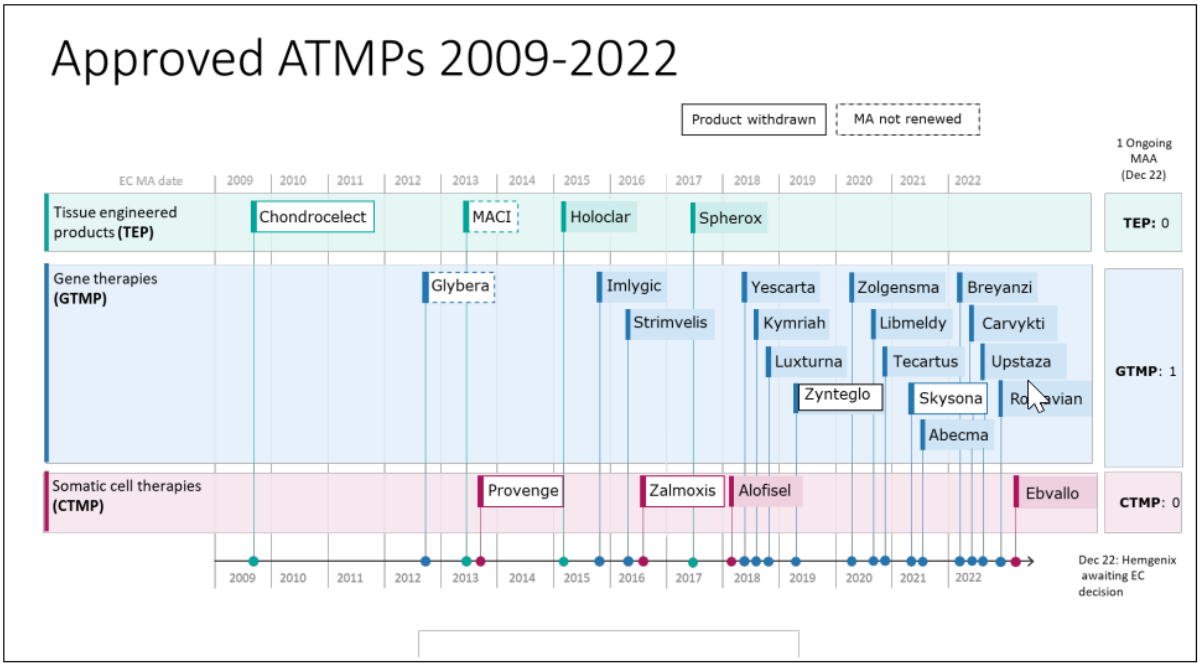
The outcome of these assessments can be found here: *Summaries of scientific recommendations on classification of ATMPs*.

Advanced therapy medicinal products approvals from November 2022-January 2023.

During its plenary meeting of **December 2022,** CAT adopted a positive draft opinion for:

- Conditional marketing authorisation for *Hemgenix ((etranacogene dezaparvovec)* for the following indication: treatment of severe and moderately severe Haemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors.

For more information, see also the *EMA meeting report.*



PATIENTS' AND CONSUMERS' WORKING PARTY

The Patients' and Consumers' Working Party (PCWP), established in 2006, serves as a platform for exchange of information and discussion of issues of common interest between EMA and patients and consumers. It provides recommendations to EMA and its human scientific committees on all matters of interest in relation to medicines.

For more information, see also the *PCWP mandate, objectives and rules of procedure.*

EMA PCWP & HCPWP meeting working parties joint meeting

Last 15th November took place face to face *the Patients and Consumers' (PCWP) and 'Healthcare Professionals' (HCPWP) Working Parties meeting.*

The meeting has focused on different topics. Firstly, the involvement of patient in medicines development and regulation was discussed based on the report from EMA Multistakeholder Workshop on Patient Experience Data and also the CIOMS report on 'Patient involvement in the development, regulation and safe use of medicines'. An update from the Task Force on availability of authorised medicines was given, and later, access to medicines was discussed focusing on the interconnection of regulatory and Health Technology Assessment activities and the role of patients and healthcare professionals. Finally, future activities on antimicrobial resistance have also been presented.

For more information, please see the agenda, presentations and recording *here*.

EMA Glossaries

The EMA just published a *medical terms simplifier* that gives plain-language descriptions of medical terms commonly used in information about medicines.

A *glossary of regulatory terms* that gives definitions for the main terms used on the EMA website and in their documents has also been published.

For more information, please check the *glossaries here.*

GLOSSARY

Accelerated assessment
Rapid assessment of medicines in the centralised procedure aimed at facilitating patient access to new medicines that address an unmet medical need. Accelerated assessment usually takes 150 evaluation days, rather than 210.

Advanced therapies or advanced-therapy medicinal products (ATMPs)
ATMPs are new medical products based on genes, cells and tissues, which offer new treatment opportunities for many diseases and injuries. There are four main groups:

- **Gene-therapy medicines**
  They are medicines that contain genes leading to a therapeutic effect. They work by inserting 'recombinant' genes into cells, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases. A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources.
- **Somatic-cell therapy medicines**
  These contain cells or tissues that have been manipulated to change their biological characteristics. They can be used to cure, diagnose or prevent diseases;
- **Tissue-engineered medicines**
  These contain cells or tissues that have been modified so they can be used to repair, regenerate or replace tissue.
- **Combined advanced-therapy medicines**
  These are medicines that contain one or more medical devices as an integral part of the medicine. An example of this is cells embedded in a biodegradable matrix or scaffold.

Authorisation under exceptional circumstances
It allows patients access to medicines that cannot be approved under a standard authorisation as comprehensive data cannot be obtained, either because there are only very few patients with the disease, the collection of complete information on the efficacy and safety of the medicine would be unethical, or there are gaps in the scientific knowledge. These medicines are subject to specific post-authorisation obligations and monitoring.

Compliance check
It is performed to verify that all the measures agreed in a *Paediatric Investigation Plan* (PIP) and reflected in the Agency's decision have been conducted in accordance with the decision, including the agreed timelines. Full compliance with all studies/measured contained in the PIP is one of several prerequisites for obtaining the rewards and incentives provided for in Articles 36 to 38 of the Paediatric Regulation.

Conditional marketing authorisation
It is granted to a medicine that addresses unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

Designation, orphan medicinal product
A status assigned to a medicine intended for use against 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.

European Public Assessment Report (EPAR)
It is a lay-language document, which provides a summary of the grounds on which the EMA/CHMP based its recommendation for the medicine to receive a marketing authorisation. This happens when a manufacturer develops a generic medicine based on a reference medicine, but with a different strength or given by a different route.

Hybrid application for marketing authorisation
Hybrid applications rely partly on the results of tests on the reference medicine and partly on new data from clinical trials.

Informed consent application for marketing authorisation
An informed consent application makes use of data from the dossier of a previously authorised medicine, with the marketing authorisation holder of that medicine giving consent for the use of their data in the application.

Orphan Legislation
Regulation (EC) No 141/2000 on orphan medicinal products

Paediatric Investigation Plan (PIP)
It sets out a programme for the development of a medicine in the paediatric population. It aims to generate the necessary quality, safety and efficacy data through studies to support the authorisation of the medicine for use in children of all ages. These data have to be submitted to the EMA, or national competent authorities, as part of an application for a marketing authorisation for a new medicine, or for one covered by a patent.

Paediatric Use Marketing Authorisation (PUMA)
It is a dedicated marketing authorisation for medicinal products indicated exclusively for use in the paediatric population, or subsets thereof, with, if necessary, an age-appropriate formulation. It has been designed to promote paediatric development of already authorised products which are no longer covered by a patent. Benefits are 8 years of data protection and 10 years market protection

Patient-reported outcomes (PROs)
Measurements based on data provided directly by patients regarding their health condition without interpretation of the patient's response by a clinician or anyone else.

Patient-reported outcome measures (PROMs)
They are instruments, scales, or single-item measures that have been developed to measure PROs, for example a self-completed questionnaire to assess pain.

Periodic Safety Update Reports (PSURs)
Periodic reports that the evaluate the benefit-risk balance of a medicine as evidence is gathered in clinical use. They are submitted by marketing authorisation holders at defined time points after the authorisation.

Co-funded by the Health Programme of the European Union

Acknowledgements: This publication (or activity) has been funded with support from the European Union's Health Programme. This material only reflects the views of the author, and funders cannot be held responsible for any use which may be made of the information contained herein. Icons in this issue made by Freepik from www.flaticon.com

Post-authorisation efficacy studies (PAES)
PAES are studies relating to authorised medicinal products conducted within the therapeutic indication with the aim of addressing well-reasoned scientific uncertainties on aspects of the evidence of benefits of a medicine that could not be resolved before authorisation or were identified afterwards.

Post-authorisation safety studies (PASS)
A PASS is carried out after a medicine has been authorised to obtain further information on its safety, or to measure the effectiveness of risk-management measures. The PRAC is responsible for assessing the protocols of imposed PASSs and for assessing their results.

Prevalence
In the context of the Orphan Legislation, the prevalence refers to the number of persons with the condition at the time the application is made, divided by the population of the European Union (EU) at that time. It requires demonstration through authoritative references that the disease or condition for which the medicinal product is intended affects not more than 5 in 10,000 persons in the EU, when the application is made.

Public summaries of PDCO evaluations of PIPs
They describe the applicant's proposal for the development of their medicine in children, the PDCO's conclusion on the potential use of the medicine in the paediatric population, the plan agreed between the committee and the applicant at the completion of the procedure (including any partial waivers or deferrals) and the next steps.

Referral procedures for safety reasons
A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a particular medicine or a class of medicines on behalf of the European Commission or a Member State.

Risk Management Plans (RMPs)
RMPs are regulatory documents submitted by medicine developers when they apply for marketing authorisation and include information on the medicine's safety profile; how its risks will be prevented or minimised in patients; plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine; risk factors for developing adverse reactions; measuring the effectiveness of risk-minimisation measures.

Scientific advice/protocol assistance
Through scientific advice, companies can ask the EMA for advice on whether they are conducting the appropriate tests and studies during the clinical development of a given product. In the case of orphan medicines for the treatment of rare diseases, it also includes advice on1) the demonstration of significant benefit for the designated orphan indication and on 2) similarity or clinical superiority over other medicines; which are criteria for the authorisation of an orphan medicine.

Significant benefit
Demonstrating a significant benefit, this is demonstrating a "clinically relevant advantage or a major contribution to patients" is one of the criteria that medicines for the treatment of rare diseases must fulfil to benefit from 10 years of market exclusivity once they have been authorised. For further information, read the *workshop report: Demonstrating significant benefit of orphan medicines*, held at the EMA in December 2015.

Safety signal
A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature, but their presence does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of a safety signal is required to establish whether or not there is a causal relationship between the medicine and the adverse event.

Similar active substance
It means an identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of them) and which acts via the same mechanism.

Scientific Advisory Group (SAG)
SAGs have been established to provide an independent recommendation on scientific/technical matters related to products under evaluation through centralised regulatory procedures and referrals by the CHMP or any other scientific issue relevant to the work of the Committee.

Waiver
A waiver can be issued if there is evidence that the medicine concerned is likely to be ineffective or unsafe in the paediatric population, or that the disease or condition targeted occurs only in adult populations, or that the medicine, or the performance of trials, does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

Co-funded by the Health Programme of the European Union

Acknowledgements: This publication (or activity) has been funded with support from the European Union's Health Programme. This material only reflects the views of the author, and funders cannot be held responsible for any use which may be made of the information contained herein. Icons in this issue made by Freepik from www.flaticon.com