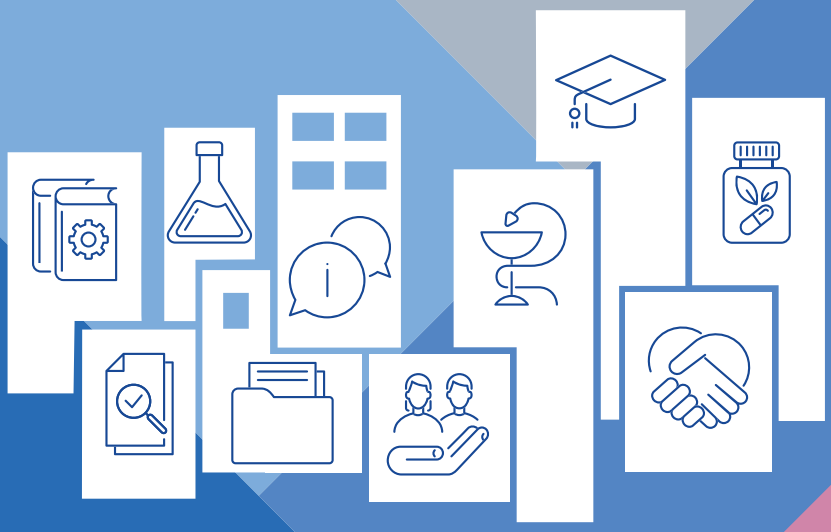
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

User guide for micro, small and medium-sized enterprises



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User guide for micro, small and medium-sized enterprises

On the administrative and procedural aspects of the provisions laid down in Regulation (EC) No 726/2004 and Regulation (EU) 2019/6, that are of particular relevance to SMEs

EMA SME Office

Addressing the needs of small
and medium-sized enterprises

Latest revised version – November 2023

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Introduction

1. Introduction

This guide has been prepared for micro, small and medium sized enterprises ('SMEs') operating in the pharmaceutical sector. Its aim is to facilitate understanding of the main aspects of medicinal product legislation.

The guide is structured to follow the chronological stages of developing a medicinal product. An overview of the scientific data requirements for obtaining a marketing authorisation in the European Union ('EU') is provided. The regulatory procedures in place to optimise development and obtain an EU marketing authorisation are also summarised.

The guide focuses primarily on the requirements for authorising medicinal products for human or veterinary use. It also includes a section on activities related to medical devices. The guide is not intended to be an exhaustive document but rather to raise SMEs' awareness of the various sources of information available, with links throughout the text to additional information.

In December 2005, Commission Regulation (EC) No 2049/2005 ('SME Regulation') introduced provisions aimed at promoting innovation and the development of new medicinal products for human and veterinary use by SMEs. This guide is intended to fulfil the obligation laid down in Article 12 of the SME Regulation, which calls on the European Medicines Agency ('EMA' or 'Agency') to publish a 'User Guide' on the administrative and procedural aspects of medicines legislation which are of particular relevance to SMEs.

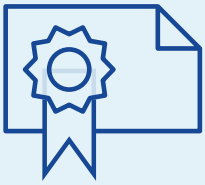
Pursuant to the SME Regulation, companies can access financial assistance (in the form of fee reductions and deferrals) and administrative assistance from the Agency, details of which are outlined in section 2 of this guide. To facilitate contact with the Agency, a 'SME Office' was launched in December 2005 and is dedicated to addressing the particular needs of smaller companies.

Any feedback on the content or format of this guide should be forwarded to the SME office: sme@ema.europa.eu.

1.1. Obtaining a marketing authorisation within the European Union

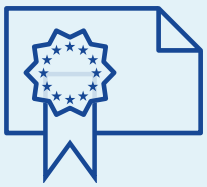
Prior to marketing a medicinal product[1] in the EU, a marketing authorisation must be obtained. The company who holds the authorisation to place the medicinal product on the market and who is legally responsible for marketing the medicinal product (so-called 'marketing authorisation holder'), must be "established"[2] within the European Economic Area (EEA) (Iceland, Liechtenstein, Norway and the member states of the EU).

In the EU, there are two types of marketing authorisation:



National marketing authorisations (national, decentralised and mutual recognition procedures (MRP)): issued by competent authorities of individual member states. The medicinal product may be put on the market in all member states that have granted an authorisation for it.

OR



Union marketing authorisation (centralised procedure): granted by the European Commission, following a positive opinion from EMA. This is a single authorisation that allows the medicinal product to be put on the market in all member states.

Approved conditions of use are laid down in the summary of product characteristics[3] (prescribing information for health professionals), the labelling and the package leaflet for users[4].

This user guide will focus on the use of the centralised procedure for obtaining a Union marketing authorisation. Further details are published in the respective 'human regulatory' and 'veterinary regulatory' sections of the EMA website. Further information on the regulatory routes for obtaining national marketing authorisations, including the mutual recognition and decentralised procedure, are highlighted in section 1.1.2. below. Applicants for human medicines are advised to refer to Volume 2A of the Notice to Applicants for more detailed information.

1.1.1. Union marketing authorisation – the centralised procedure

The EMA coordinates the existing scientific resources of the member states to evaluate and supervise medicinal products for both human and veterinary use throughout the EU. EMA is primarily involved in the centralised procedure for obtaining a union marketing authorisation.

The Agency also gives scientific advice to research-based companies on the development of new medicinal products (see section 3.4.) and develops guidelines on quality, safety and efficacy testing requirements (see section 3.5.).

[1]) A medicinal product for human use is defined in Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001, a veterinary medicinal product is defined by Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018

[2]) Being established shall be understood as having a permanent legal structure (formed in accordance with the law of an EU Member State or other EEA country). That allows the concerned person to assume the duties and responsibilities as well as to perform the tasks laid down by Union law. For reference on establishing see point 2 of Chapter I, Vol. 2A (human medicines) of the Notice to Applicants

[3]) In accordance with Article 11 of Directive 2001/83/EC for human medicines and Article 35 of Regulation (EU) 2019/6 for veterinary medicines.

[4]) In accordance with Articles 54, 55, 59 and 63 of Directive 2001/83/EC for human medicines and Articles 10-16 of Regulation (EU) 2019/6 for veterinary medicines.

For queries relating to: orphan designation, paediatric investigation plans, scientific advice, filing an application for marketing authorisation through the centralised procedure, and EudraVigilance, the Agency is the primary point of contact.

If an SME has any doubt about the appropriate point of contact for a particular issue, the SME office can provide assistance: sme@ema.europa.eu

The centralised procedure is mandatory for certain types of medicinal products and optional for others. Medicinal products for human and veterinary use developed by means of one of specified biotechnological processes[5], and advanced therapy medicinal products (ATMPs) for human use, human medicinal products containing a new active substance for treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorders, diabetes, viral diseases, auto-immune diseases/other immune dysfunctions, and designated orphan medicinal products fall within the mandatory scope and must be filed centrally at EMA. The centralised procedure is also mandatory for veterinary medicinal products (VMPs) intended primarily for use as performance enhancers, those containing an active substance which has not yet been authorised as a VMP within the Union, biological VMPs which contain or consist of engineered allogeneic tissues or cells, and novel therapy veterinary medicinal products.

The centralised procedure is optional for medicinal products for human use containing a new active substance approved in the Union after May 2004 for indications other than those stated above, and for products which constitute a significant therapeutic, scientific or technical innovation, or products for which the granting of the Union authorisation would be in the interest of patients at Union level. It is also an option for certain medicinal products intended for paediatric use, or for generics of reference medicinal products authorised through the centralised procedure.

For VMPs, the centralised procedure is also optional for medicinal products which no other marketing authorisation has been granted within the Union.

Companies, which intend to apply for the Union authorisation, should confirm eligibility for evaluation through the centralised procedure with EMA at least 7 months prior to submitting the centralised marketing application (see section 6.1.).

In order to obtain the Union authorisation, an application must be submitted to EMA. The scientific evaluation of the application is carried out by the Committee for Medicinal Products for Human Use (CHMP) or the Committee for Veterinary Medicinal Products (CVMP) of EMA, and a scientific opinion is prepared also in co-operation with other EMA committees, as applicable. The opinion is sent to the European Commission, which drafts a decision and, having consulted the member states through the relevant Standing Committee, adopts the decision and grants a marketing authorisation.

Such a marketing authorisation is valid throughout the Union and confers the same rights and obligations in each of the member states as a marketing authorisation granted by that member state.

The centralised procedure is described in section 6 of this guide.

1.1.2. National marketing authorisations – national, mutual recognition & decentralised procedures

Each Member State of the EU, as well as Iceland, Liechtenstein and Norway, has its own national authority responsible for regulating medicinal products for human and veterinary use. These authorities have a common website called the Heads of Medicines Agencies (HMA) website that serves as a useful connection point to the websites of individual authorities.

[5]) Recombinant DNA technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells or hybridoma and monoclonal antibody methods (see Annex of Regulation no 726/2004)

The authorities of the member states are responsible for granting marketing authorisations for medicinal products placed on their markets, with the exception of medicinal products subject to centralised procedure. If a company seeks a national marketing authorisation, an application must be submitted to the competent authority of the Member State concerned. If a company is seeking a national marketing authorisation in more than one Member State, the mutual recognition or decentralised procedure are available to facilitate the granting of harmonised national authorisations across the member states. Chapter 2 of Volume 2A of the Notice to Applicants should be consulted for further information on medicinal products for human use.

Sponsors with queries relating to: regulatory approval for the conduct of clinical trials, national scientific advice, manufacturing authorisations, filing an application for marketing authorisation nationally (through the mutual recognition or decentralised procedure), reporting of adverse events, or pricing and reimbursement matters, are advised to contact the relevant national competent authority.

1.1.3. Overview of (data) requirements for obtaining marketing authorisation in the EU

An application for marketing authorisation for a new medicinal product for human use must generally be accompanied by the particulars and documents set out in Article 8(3) and Annex I of Directive 2001/83/EC. The requirements include data generated from pharmaceutical (physicochemical, biological or microbiological) tests, non-clinical (toxicological and pharmacological) tests and clinical trials, evaluation of the potential environmental risks posed by the medicinal product, aswell as a risk management plan and a summary of the pharmacovigilance site master file (see section 4.1-4.3 and section 7). For new medicines there is a requirement to agree a paediatric investigation plan and/or deferral and/or waiver with the EMA early in development (see section 4.6.).

An application for marketing authorisation for a new medicinal product for veterinary use must generally be accompanied by the particulars and documents set out in Annex II of Regulation (EU) 2019/6 of the European Parliament and of the Council on veterinary medicinal products. As for medicines intended for human use, the requirements include data generated from pharmaceutical (physicochemical, biological or microbiological) tests, non-clinical (toxicological and pharmacological) tests and clinical trials, and an evaluation of the potential environmental risks posed by the medicinal product.

Foodstuffs such as meat, milk or eggs must not contain residue levels of veterinary medicines or biocidal products that might represent a hazard to the health of the consumer. Regulation (EC) No 470/2009 lays down the rules and procedures for the establishment of maximum residue limits (MRLs).

An overview of the key issues to be addressed in the development of medicinal products for human use and veterinary use are outlined in section 4 and 5 of this guide respectively.

1.2. EU legislative framework for pharmaceuticals

All EU legislative texts are published in the Official Journal of the European Union (OJEU) in all EU official languages.

Directives and regulations are available in the EUR-Lex website of the European Union. Information on human medicines is available in EudraLex section of the European Commission's health website. The texts listed in the following table (and in section 4.7.1. on good manufacturing practice (GMP)) form the legislative backbone of the medicinal product regulation in EU. The Notice to Applicants facilitates the interpretation and application of the Union pharmaceutical legislation and should be consulted by any potential applicant for a Union marketing authorisation for human use. The Notice to Applicants is not legally binding, and companies should always refer to the legal texts for legislative requirements.

Key EU legislation

General legislation

Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004, as amended, on the centralised procedure for the **authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency.**

Regulation (EU) No 2019/5 of the European Parliament and of the Council of 11 December 2018 **amending Regulation (EC) No 726/2004** laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

Regulation No (EU) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a **reinforced role for the European Medicines Agency in crisis preparedness** and **management for medicinal products and medical devices.**

Commission Regulation (EC) No 2049/2005 of 15 December 2005 setting out **provisions for SMEs.**

Human medicines

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001, as amended, laying down the **Community code** relating to medicinal products for human use.

Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the performance of **pharmacovigilance activities** provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council.

Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 laying down provisions for **orphan medicinal products**.

Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the **criteria for designation of a medicinal product as an orphan medicinal product** and definitions of the concepts 'similar medicinal product' and 'clinical superiority'.

Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006, as amended on **medicinal products for paediatric use**.

Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on **advanced therapy medicinal products**.

Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on **clinical trials** on medicinal products for human use.

Commission Implementing Regulation (EU) 2017/556 of 24 March 2017 laying down detailed arrangements for the **good clinical practice inspection** procedures pursuant to Regulation (EU) No 536/2014 of the European Parliament and of the Council.

Veterinary medicines

Regulation (EU) No 2019/6 of the European Parliament and of the Council of 11 December 2018 on **veterinary medicinal products**, as amended.

Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the **establishment of residue limits** of pharmacologically active substances in foodstuffs of animal origin.

Medical devices

Regulation (EU) No 2017/745 of the European Parliament and of the Council of 5 April 2017 on **medical devices.**

Regulation (EU) No 2017/746 of the European Parliament and of the Council of 5 April 2017 on ***in vitro*** **diagnostic** medical devices.

1.2.1. Upcoming legislative changes

Revision of the legislation on medicinal products for human use

The European Commission is currently undertaking a review of the legislation on medicinal products for human use. The purpose of this revision aims at creating a future proof regulatory framework and at supporting industry in promoting research and technologies that actually reach patients in order to fulfil their therapeutic needs while addressing market failure. Further information is available on the European Commission's website: A pharmaceutical strategy for Europe.

Revision of the legislation on EMA fees

On 13 December 2022, the Commission adopted a proposal for a Regulation of the European Parliament and of the Council to update and simplify the fees charged by EMA. Further information is available on the European Commission's website.

1.3. IT systems

EMA provides different platforms, systems and databases for the submission of applications, data management and to ensure secure communication between applicants and EMA/EU network. The most commonly used systems by SMEs are summarised below. For technical support and assistance, see Assistance with EMA information technology (IT) systems.

1.3.1. IRIS platform

Applicants applying for procedures to support medicines' development (see chapter 3 and 4) (e.g. orphan designation, scientific advice, PRIME) need to use the EMA's secure online IRIS platform. The IRIS platform can be used to support other procedures such as the reporting of changes on marketing status or the submission of notifications of parallel distribution. For information on the procedures supported by IRIS and guidance on using it, refer to IRIS homepage.

SMEs are advised to register in advance of submitting a procedure to EMA as there are preliminary requirements and steps to be completed.

Before submitting an application in IRIS, applicants have to:

- Have an active EMA account (see EMA Account Management — EMA's secure online platform for requesting and managing access to EMA applications);
- Register their organisation in EMA's Organisation Management Service (OMS, see also section 1.3.2. below);
- Have an appropriate user access role and affiliation to an organisation (see EMA Account Management);
- Have a valid Research Product Identifier (RPI) and active substance registration for scientific applications such as orphan designation, scientific advice or ITF meeting;
- Have a customer account number if the application requires a fee (see the EMA webpage)

For details, please refer to 'Access and submission' and 'IRIS guide to registration'.

1.3.2. SPOR platform

SPOR is an acronym used for Substance, Product, Organisational and Referential Master Data. Master data are structured data which have a standard format and a single source which helps with systems' interoperability, efficiency, quality and reliability. Commission Implementing Regulation (EU) No 520/2012 requires regulatory authorities and marketing authorisation holders to use ISO IDMP standards which specify the use of standardised definitions for the identification and description of medicinal products for human use. Applicants will need to comply with SPOR requirements for master data registration.For further details, see EMA website on SPOR and SPOR data management services.

SPOR supplies master data to the electronic application forms (eAF) for submitting applications to EMA and national competent authorities for initial marketing authorisations, variations and renewals for human and veterinary medicines (see 1.3.3) or to the IRIS platform (1.3.1). Users can select information supplied directly by these master data services when preparing their regulatory submission.

1.3.3. Electronic submissions for marketing authorisation applications (eSubmissions)

To submit a marketing authorisation application (MAA) for a human or veterinary medicinal product (see chapter 6), applicants need to use the interactive pdf based electronic Application Forms (eAFs).

The forms are available at the eSubmission website and do not require registration.

EMA is working on a replacement of the interactive pdf forms with a new web-based application form hosted on a dedicated secure online portal — the Product Lifecycle Management Portal (PLM Portal).

eCTD is the only acceptable electronic format for all applications for human medicines and all submission types in the context of the centralised procedure (e.g. new applications, variations, renewals). Guidance on regulatory information in electronic format for human medicinal products is provided in The EU Harmonised technical eCTD guidance version 5.0.

For veterinary medicines applications, the VNeeS structure is the required format, with CTD format for the quality section also accepted. Detailed guidance is available on the EMA website and the veterinary eSubmission page.

The eSubmission Gateway Syncplicity Web Client is an electronic submission channel that allows applicants to submit documents supporting all types of applications to EMA securely over the internet in any electronic format. It is mandatory for all human and veterinary submissions. SMEs are advised to register well in advance of a submission to use the electronic submission channel (see details in Web Client User Guidance).

1.3.4. Clinical Trials Information System (CTIS)

CTIS is the system for the submission, supervision and authorisation of clinical trial applications for human medicines in the EU/EEA. CTIS consists of dedicated secure workspaces for sponsors and authorities and a public website enabling the search of information on clinical trials (see section 4.4).

To submit clinical trials applications, applicants need to register with CTIS.

For further details see EMA webpage on CTIS training and support.

1.3.5. EudraVigilance

EudraVigilance is the system for reporting, managing and analysing information on suspected adverse reactions to human medicines, which have been authorised or being studied in clinical trials in the EU/EEA.

EMA operates the system on behalf of the EU medicines regulatory network (see section 7.4 and 7.5).

SMEs holding or applying for a marketing authorisation in the EU/EEA and sponsors of clinical trials need to register with EudraVigilance for the electronic data interchange of pharmacovigilance information.

For details on registration see the EMA webpage on EudraVigilance.

1.3.6. Union Product Database (UPD)

The UPD serves as a single source of information on all authorised veterinary medicines and their availability in the EU/EEA. EMA maintains the Union Product Database and its public interface — the veterinary medicines information website — in collaboration with Member States and the European Commission (see section 6.13).

For further details, please refer to the EMA webpage on UPD.

SME initiative

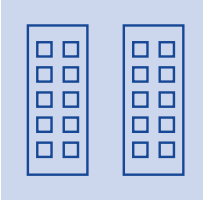
2. SME initiative

2.1 Objectives

The primary aim of the SME initiative is to promote innovation and the development of new medicinal products by smaller companies. To achieve this, incentives are provided to help SMEs overcome the main financial and administrative hurdles associated with pre-marketing procedures, particularly scientific advice, marketing authorisation application and inspection procedures. The initiative also introduced incentives for post-authorisation procedures.

2.2. Definition of an SME

In determining which companies are eligible for SME incentives, EMA applies the EU definition of micro, small and medium-sized enterprises provided in Commission recommendation 2003/361/EC. This means that companies are classified according to their category (autonomous, partner or linked) and size (micro, small or medium), as defined below:



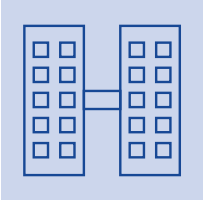
AUTONOMOUS ENTERPRISE*

My enterprise holds less than 25% (capital or voting rights) in another and/or another holds less than 25% in mine.

* Note: there are exceptions for certain types of investors. See article 3(2) in the Annex of Commission recommendation 2003/361/EC.

PARTNER ENTERPRISE

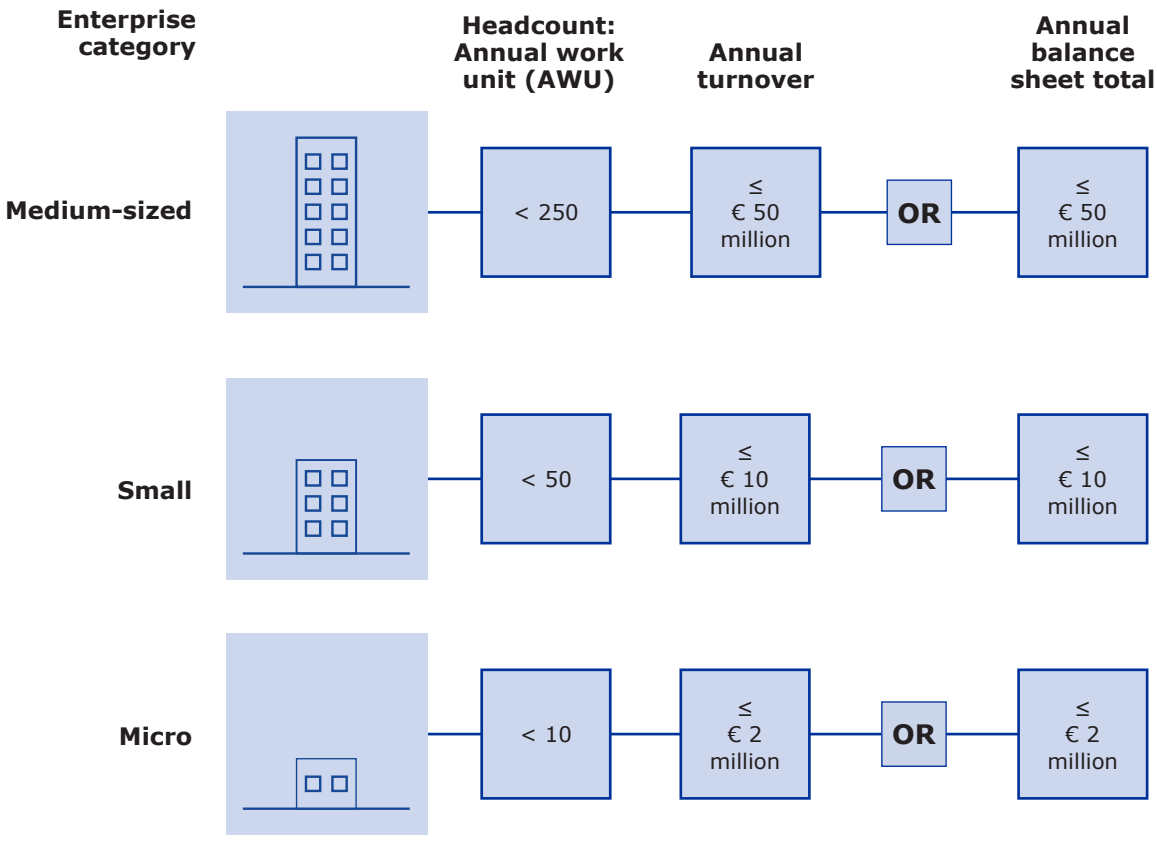
My enterprise holds at least 25% (capital or voting rights), but no more than 50% in another and/or another holds at least 25%, but no more than 50% in mine.



LINKED ENTERPRISE

My enterprise holds more than 50% of the shareholders' or members' voting rights in another and/or another holds more than 50% in mine.

SME THRESHOLDS (COMMISSION RECOMMENDATION 2003/361/EC)



Depending on the category in which the enterprise fits, some or all of the headcount and financial data from other partner or linked enterprises may need to be counted when calculating whether the SME criteria are met.

'User guide to the SME Definition', published by the European Commission, provides further information on the definition of an SME. The user guide is available in all official EU languages.

2.3. Role of the SME office

The SME office was established at EMA to offer assistance to SMEs who, due to lack of experience with the centralised authorisation procedure or lack of familiarity with the Agency and its procedures, may otherwise experience difficulties with the development and marketing of their new medicinal products. The SME office facilitates contacts with the relevant scientific and regulatory staff within the Agency to address any questions that may arise during the development of a medicinal product, particularly in the run up to submitting a marketing authorisation application.

2.4. Incentives for SMEs (EU provisions and national provisions)

2.4.1. Incentives offered by EMA

The EU incentives offered by the Agency apply to both the human and veterinary sectors, and include:

- Regulatory, administrative and procedural assistance from the Agency's SME office including SME briefing meetings;
- Fee incentives
  - Fee reductions for scientific advice, scientific services, inspections and (for veterinary medicines) establishment of maximum residue limits;
  - Fee exemptions for certain administrative services of EMA;
  - Deferral of the fee payable for an application for marketing authorisation or related inspection;
  - Conditional fee exemption where scientific advice is actually taken into account and a marketing authorisation application is not successful;
  - Fee reductions and exemptions for post-authorisation procedures;
  - Fee reductions and exemptions for pharmacovigilance activities.
- Certification of quality/non-clinical data for advanced therapy medicinal products (ATMPs) intended for human use;
- Translations of the product information documents submitted in the application for marketing authorisation;
- Waiver of the medical dictionary for regulatory activities (MedDRA) licensing fee when registering with EudraVigilance. This is only available for micro- or small enterprises, not for medium-sized enterprises;
- Inclusion in the SME public register.

Fee reductions/deferrals

SMEs operating in the pharmaceutical sector are often innovative companies that can notably benefit from the access to scientific expertise at EU level. The SME initiative has been designed, with a substantial 90% fee reduction for scientific advice, to encourage SMEs to seek advice from EMA on all issues relating to the development of new medicinal products, with a view to maximise the chances of a successful marketing authorisation (see section 3.4). For products of human use, in the specific case of designated orphan products (see section 4.5) or products eligible to the PRIME scheme (see section 3.2), the fee for scientific advice is fully waived.

Other financial incentives include a 90% fee reduction for any good manufacturing practice (GMP), good clinical practice (GCP), good laboratory practice (GLP), or pharmacovigilance inspections requested by EMA, and the possibility to request deferred payment of any pre-authorisation inspection fee. For veterinary medicines, there is also the possibility to receive a 90% fee reduction for applications for the establishment of maximum residue limits. Fee incentives are also offered for administrative services from EMA (e.g. EMA certificates of medicinal products, 'Article 58' scientific opinions for human products intended exclusively for markets outside the EU and consultation on medical devices).

In the run up to filing an application for marketing authorisation, the fee payable to EMA for review of the application may place financial constraints on smaller companies. For SMEs, fee payment may be deferred by up to 45 days after the date of notification of the centralised marketing authorisation, or, in the event of withdrawal of the application, within 45 days from the date of notification of withdrawal. In the event of a negative outcome, where scientific advice has previously been sought from EMA and taken into account in the development of the medicinal product, the fee for the application for marketing authorisation will be fully waived by the Agency ('conditional fee exemption').

Fee incentives also apply for post-authorisation procedures for centrally authorised products and pharmacovigilance activities for all products for human use irrespective of the authorisation route, and for centrally authorised products for veterinary use. For post-authorisation incentives, full fee

exemptions apply (for micro-sized enterprises) or a 40% fee reduction (for small or medium-sized enterprises).

Fee incentives also apply for consultation on medical devices.

Further information on fee incentives is available to SME applicants at the EMA website and in the document 'Explanatory note on fees payable to the European Medicines Agency' as well as in the 'Explanatory note on pharmacovigilance fees payable to the European Medicines Agency'.

Access to incentives

Access to the fee reductions and deferrals outlined above will be subject to the applicant company's SME status being assigned by EMA and remaining valid on the date that the fee falls due for the relevant application or procedure (see section 2.5). The financial incentives will not be applied retrospectively.

If a product is out-licensed to another company during a procedure, the EMA SME office should be informed immediately. If the new company licensing in the product does not meet the SME criteria, there will be no further access to the provisions of the SME Regulation with effect from the date of the signature of the licensing agreement. Any fees shall no longer be subject to fee deferral pursuant to the SME Regulation (see also section 2.5.3 for access to incentives in case of a merger or acquisition).

For pharmacovigilance activities, access to the fee incentives will be subject to the applicant company's SME status being assigned by EMA or will be based on the submitted SME declaration.

Certification of advanced therapy medicinal products

Advanced therapy medicinal products (ATMPs) are often developed by SMEs. As an incentive to develop such products, an SME can submit to EMA, the results of studies carried out to demonstrate the quality and non-clinical safety of ATMPs and request evaluation and certification of the data, independently of any MAA. Although not legally binding, the certification procedure should facilitate the evaluation of any future application for clinical trials and marketing authorisation based on the same data (see section 3.3.2 for information on certification).

Translation of product information

Translating the product information into all EU official languages represents a considerable financial and administrative burden to SMEs entering the EU market. Thus, EMA provides the translations of the product information and relevant opinion annexes required to grant an initial EU marketing authorisation. Translations into EU official languages are provided free of charge by the Agency.

Due to the timelines required to translate the product information, the Agency initiates translations through the Centre de Traduction (CdT) in Luxembourg at the time of CHMP/CVMP opinion. These translations are then checked by the national competent authorities in the member states. To be eligible for translation assistance, the company's SME status must be valid at the time that the translations are initiated. It is the responsibility of the applicant SME to provide Norwegian and Icelandic translations.

Practical details are sent to the applicant in advance of the opinion. The translations timetable is sent to the applicant together with the opinion.

SME briefing meetings

Small enterprises with limited resources often lack experience or are unfamiliar with the regulatory approval process.

Opening up early dialogue with EMA during development, such as scientific advice, and during the pre-submission phase of marketing authorisation application, can be challenging for SMEs, which may have limited capacity or experience to navigate the regulatory landscape for pharmaceuticals.

The SME office offers SME briefing meetings, which provide a platform for a company to discuss its planned regulatory strategy, for a human or veterinary product development. These meetings help SMEs to find out about available procedures, guidance and incentives and allow SMEs to engage in an early dialogue with an EMA multidisciplinary team (e.g. scientific advice, PRIME, regulatory affairs, orphan medicines or quality offices) depending on the questions raised. SMEs are encouraged to approach the SME office to request

a briefing meeting at any stage of their product development. An applicant should send an email to SME@ema.europa.eu around one to two months in advance of the meeting, and include background information on the product, mechanism of action, stage of development, previous interactions with authorities or EU funding scheme (when applicable) and questions to be addressed. The SME office will review the request to see the best way to address it, will request additional information if needed and will set up an SME briefing meeting as appropriate.

SME briefing meetings are provided free of charge by EMA.

2.4.2. Other EU incentives for SMEs

Further information on the whole spectrum of EU policies, legislation, programmes and initiatives relevant to Europe's SMEs is available from the European Commission through its European portal for SMEs.

The EU's key funding programme for research and innovation is Horizon Europe. Further information on open calls on funding opportunities can be found at the Horizon Europe website.

Detailed information on the EU financial support available to SMEs can also be accessed via a single access point on EU Finance.

2.4.3. National provisions for SMEs

Commission Regulation (EC) No 2049/2005 requires the SME user guide to reference existing national provisions for SMEs, applicable to the pharmaceutical sector. These are provided in Annex 1 published as a separate document on the EMA website.

If companies have a query relating to any existing national provision and would like to contact the national competent authority in question, contact points are also provided in Annex 1.

2.5. How to request SME status

2.5.1. Assignment of SME status

Companies wishing to benefit from SME incentives should visit the SME office section of EMA website first. Before requesting financial or administrative assistance from the Agency, companies should complete the form 'Declaration on the qualification of an enterprise as a micro, small or medium-sized enterprise (SME)'. This should be submitted to the SME office, together with the most recent annual accounts (audited, if possible) for the applicant enterprise and any linked or partner enterprise, the proof of establishment of the organisation in the EEA (i.e. an EU Member State, Iceland, Liechtenstein or Norway), and details of upstream (i.e. owners of your enterprise's shares or voting rights) and downstream ownership structure (i.e. your enterprise's participation in other companies in terms of shares or voting rights) in the form of, e.g. an overview chart of the company structure. Companies are strongly recommended to read 'The User guide to the SME Definition', published by the European Commission, before completing the form. It is particularly useful in helping to determine whether the applicant company is an autonomous, partner or linked enterprise, and whether it is necessary to complete the annexes to the declaration form (see section 2.2 on the definition of an SME).

If the application meets the SME criteria, EMA will issue the enterprise with an EMA-SME number. At that point the company may benefit from the incentives offered by the SME Regulation. The Agency reserves the right to request further information from the company to establish that the SME criteria are met and may, at any time, perform audits as part of its SME programme. The applicant enterprise will be liable to consequences in case of a false declaration.

2.5.2. Newly established or non-EEA enterprises

If your enterprise is newly established and does not have finalised financial reports, estimates should be provided for the reference period declared together with an indication of when the first annual accounts will be available.

For non-EEA companies, there are essentially two options to access SME incentives:

- To apply once the company has established a subsidiary in the EEA. For proof of establishment the SME office requires a copy of the certificate of incorporation in the company's commercial register. In such cases, the SME declaration can be submitted in the name of the newly established subsidiary with details of the parent company as a 'linked' enterprise, or

- To indirectly benefit from the SME incentives through an EU established SME regulatory consultancy.

SME regulatory consultancies may seek to benefit from the provisions of the SME Regulation on behalf of non-EEA based clients only if both they and the client meet the SME criteria (i.e. fall below headcount and financial thresholds). In this case, both the regulatory consultant and the non-EEA based company should submit SME declarations. If successful, the regulatory consultant would receive an SME notification and the non-EEA based company would be listed in annex to that notification as an SME client company. It is not possible for an SME regulatory consultant to be considered eligible if they are acting on behalf of non-SME clients, as this would be contrary to the objectives of the SME Regulation.

2.5.3. Maintenance of SME status

A company's SME status expires two years after the date of closure of the accounts on which the declaration has been based. In order to extend SME status, companies are advised to submit via e-mail an updated SME declaration form for the company based on the latest approved accounts.

It is only necessary to submit supporting accounts and ownership data where one of the following applies:

- Change in the type of the enterprise (autonomous, partner, linked) or significant changes in the upstream or downstream ownership structure (e.g. acquisition, takeover, merger of the applicant or its partner/linked entities);

- SME thresholds exceeded over one accounting period[6];

- The company's previous submission was based on a bona fide estimate of the headcount and financial data;

- The company's SME status has expired and there are one or more years of accounting data missing since the last submission.

EMA will send out individual reminders for renewal prior to SME status expiry.

In the event that a registered SME is acquired by or merges with another company, the SME office at EMA should be informed immediately. If the SME criteria are no longer met, then with effect from the date of the change in ownership, the company will have no further access to the provisions of the SME Regulation (see also section 2.4.1 for access to incentives in case of out-licensing).

[6]) According to Article 4.2 in the Annex to Commission Recommendation 2003/361/EC

Support to medicinal product development

3

3. Support to medicinal product development

3.1. Innovation task force (ITF)

For sponsors developing innovative medicines, new technologies (e.g. nanotechnologies and artificial intelligence-based technologies) and new scientific approaches (e.g. new approach methodologies to reduce animal use and complex clinical trial methodology), the ITF provides a platform for informal dialogue with the Agency for both human and veterinary products.

SMEs can approach ITF and proactively identify scientific, legal and regulatory issues arising from their developments. The scientific discussions are led by experts from the EU network, the Agency's working parties and committees, where the best available scientific expertise is represented.

EMA's ITF also provides advice to medicine developers on eligibility to EMA procedures relating to the research and development of borderline products (see section 3.6).

The meetings are free of charge and aim to facilitate the informal exchange of information and guidance in the development process, complementing and reinforcing existing formal procedures (e.g. scientific advice, ATMP certification).

Further information on how to contact the ITF, including form for requesting ITF briefing meeting, is available on the EMA website.

General queries can be sent to ITFsecretariat@ema.europa.eu.

For innovative veterinary medicinal products, queries can be sent to itfvet@ema.europa.eu.

3.2. PRIority MEdicines (PRIME) scheme for human medicines

PRIME (PRIority MEdicines) is a voluntary scheme to support the development of new medicines for human use that have the potential to address an unmet medical need and facilitate their timely access to patients. The scheme focuses on medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients with no treatment options. The scheme is limited to products under development and yet to be placed on the EU market.

The scheme provides enhanced scientific and regulatory support through key features:

- Early appointment of a rapporteur from the scientific committees (see section 6.2);
- Assignment of a dedicated EMA contact point;
- Dedicated meeting with the rapporteur and experts to provide guidance on the development plan and regulatory strategy ('kick off meeting');
- Scientific advice involving stakeholders such as health-technology-assessment bodies and patients as applicable (see section 3.4), including parallel EMA-FDA advice for products developed for both the EU and the US market;
- Submission readiness meeting approximately 1 year before the MAA submission date to discuss development status and maturity of the dossier in view of the planned type of MAA;
- Eligibility to additional SME fee reductions for scientific advice.

PRIME products are also expected to benefit from the available early access tools such as accelerated assessment, which will be confirmed at the time of marketing authorisation application (see also section 6.14.1).

PRIME is open to sponsors on the basis of preliminary clinical evidence. SMEs and applicants from the academic sector can apply earlier on the basis of compelling non-clinical data and tolerability data from initial clinical trials.

EMA provides pre-submission support to applicants planning a PRIME application, including the possibility of a virtual pre-submission meeting to discuss the eligibility of their development to PRIME.

Further information on PRIME scheme, including detailed information on how to apply is available on the EMA website. General queries can be sent to prime@ema.europa.eu.

3.3. Advanced therapy medicinal products (ATMPs) for human medicines

3.3.1. ATMP classification procedure

Advanced therapy medicinal products (ATMPs) are defined in Regulation (EC) No 1394/2007 as gene therapy, somatic cell therapy and human tissue engineering.

Sponsors requiring clarification as to whether their product is classified as an ATMP can receive confirmation from the Committee for Advanced Therapies (CAT) prior to submitting any application to the Agency. This advice is provided free of charge within 60 days of receipt of a valid request from an applicant. The Agency publishes summaries of these recommendations after deletion of all commercially confidential information.

For more information SMEs are advised to refer to the 'Procedural advice on classification as an ATMP'. Requests for ATMP classification can be submitted to atmpclassification@ema.europa.eu.

3.3.2. Certification for ATMPs

The certification procedure for ATMPs is open exclusively to SMEs. It provides a mechanism for companies to receive scientific feedback on quality and non-clinical data generated during the course of development. The certification procedure aims to provide support for companies seeking to attract investors for the development of their product or to license it out.

Through certification, companies can receive an evaluation of their data according to the current review standards for marketing authorisation. Certification is complementary to the scientific advice process (see section 3.4). Whereas scientific advice provides feedback on future development proposals and protocols, certification provides a scientific evaluation of experimental data already generated. Companies can then seek scientific advice on how to resolve any deficiencies that may have been highlighted during the certification assessment.

An SME can submit an application for certification containing either quality data alone or both quality and non-clinical data at any time during the development of an ATMP. The process can be repeated as development proceeds. The procedure for certification consists of a 90-day review by the CAT with the possibility to request clarifications.

For more information SMEs are advised to refer to the procedural advice and guidance on the EMA website. Any procedural questions and general queries can be sent to AdvancedTherapies@ema.europa.eu.

Detailed information on ATMPs is provided at EMA webpage.

3.4. Scientific advice/ protocol assistance

At any stage of development, and irrespective of the eligibility to use the centralised procedure for marketing authorisation, sponsors can request scientific advice from EMA for both human and veterinary medicinal products. SMEs are particularly encouraged to initiate an early dialogue with the Agency, in the form of scientific advice. This helps the sponsor to ensure that the appropriate tests and studies are performed, so that no major objections regarding the design of the tests are raised during evaluation of the marketing authorisation application. Such major objections can significantly delay the marketing of a product, and in certain cases may result in the

refusal of the marketing authorisation. Following the Agency's advice therefore increases the probability of a positive outcome.

For human medicinal products, scientific advice is given by the EMA's Committee for Medicinal Products for Human Use (CHMP) on the recommendation of the Scientific Advice Working Party (SAWP-H). For veterinary products, it is given by the Committee for Veterinary Medicinal Products (CVMP) on the recommendation of the veterinary equivalent working party, the SAWP-V. Both scientific advice working parties have monthly meetings.

Guidance on how to put together a request for scientific advice for human medicinal products and veterinary medicinal products, including detailed information on how to apply, templates for notifying intent of submission and submission deadlines, is available on the Agency's website.

3.4.1. Scope of scientific advice

Scientific advice may be sought on the tests and studies required to support an application for marketing authorisation for a medicinal product for human or veterinary use (see sections 4.1-4.3 and sections 5.1-5.5, respectively) in the areas of:

- Quality (chemical, pharmaceutical and biological testing);
- Non-clinical/safety (toxicological and pharmacological tests);
- Clinical aspects (clinical safety and efficacy; conditional marketing authorisation; post-authorisation efficacy/safety studies);
- Data requirements for limited markets for veterinary medicinal products in line with published guidelines;
- The establishment of new Maximum Residue Limits (MRLs) or extrapolation of existing MRLs for veterinary medicinal products.

Scientific advice for designated orphan medicinal products (applies to medicinal products for human use only; section 4.5) is called 'protocol assistance' and, in addition to the above, may include questions relating to:

- Demonstration of significant benefit within the scope of the designated orphan indication;
- Issues addressing similarity/clinical superiority in case other potentially similar orphan medicinal products have market exclusivity in the concerned therapeutic indication.

Guidance on how to seek protocol assistance for designated orphan medicinal products is available on the EMA website.

It is also now possible for sponsors to make use of Joint Scientific Consultations of EMA and Health Technology Assessment (HTA) bodies and receive advice in parallel (see EMA webpage). HTAs provide information to decision makers about the clinical and cost effectiveness of medicines, medical technologies and health systems. Many EU member states have established HTA systems to support decision makers in pricing and reimbursement decisions. Sponsors considering such parallel requests are advised to contact the scientific advice secretariat (scientificadvice@ema.europa.eu).

For veterinary medicinal products, scientific advice requests may include questions relating to products classified as limited markets. Sponsors may request scientific advice on the data requirements and the limited market guidelines (see section 5.7).

Sponsors that are intending to seek scientific advice for either human or veterinary products in the EU and the US may consider asking for parallel EMA-FDA scientific advice. In this case, the application is evaluated by both agencies at the same time and the EU and US experts discuss together with a view to reaching the same conclusions.

Novel methodologies

Sponsors can also request advice from EMA on innovative methods or drug development tools for medicinal products for human use through a voluntary qualification process:

- Qualification advice on future protocols and methods for further method development towards qualification, based on the evaluation of the scientific rationale and on preliminary data submitted;

- Qualification opinion on the acceptability of a specific use of the proposed method (e.g. use of a biomarker) in a research and development (R&D) context (non-clinical or clinical studies), based on the assessment of submitted data.

3.4.2. Fee reductions for scientific advice

The scientific advice procedure attracts a fee, which varies depending on the scope of the advice. This may deter some companies from seeking advice early on in development, or from making several successive requests. Therefore, access to the Agency's scientific advice has been facilitated for SMEs by a substantial 90% fee reduction. Furthermore, as the scientific evaluation of a marketing authorisation application is more likely to be favourable where scientific advice has been sought from the Agency, in the event of a negative outcome, a conditional exemption of the fee for the application for marketing authorisation will be given to applicants who have requested such advice and who have actually taken it into account in the development of their medicinal product.

Scientific advice is free of charge for paediatric developments of medicinal products, for products eligible to the PRIME scheme and for SMEs developing designated orphan medicinal products (protocol assistance).

Further information on the level of fee reductions/ deferrals available to SME applicants is available in the document 'Explanatory note on fees payable to the European Medicines Agency'.

3.5. Scientific guidelines and position papers

Scientific guidelines for human and veterinary medicinal products are available on the EMA website.

In addition, other useful documents, such as position papers, question-and-answer documents, or general regulatory guidelines can be found on the:

EMA website:

under 'marketing authorisation' on the'human medicines' page or on the 'veterinary medicines' page.

AND

European Commission website:

in the notice to applicants, vol. 2C – regulatory guidelines for human medicines..

The search tool available on EMA website can be consulted to find information on authorised medicines at EMA and documents such as the summary basis for approval and European Public Assessment Reports (EPAR). See further information on medicinal products in section 8.1.

3.6. Borderline products

Borderline products are healthcare products for which there is uncertainty over which regulatory framework applies. Borderlines can be between medicinal products, medical devices, cosmetics, biocidal products, herbal medicines and food supplements.

National competent authorities classify borderline products either as medicinal products or, for example, as medical devices on a case-by-case basis. This determines the applicable regulatory framework.

Applicants who are unclear on the correct classification of their product should consult a national competent authority and provide information on the product's composition and constituents, a scientific explanation of the mode of action and its intended purpose.

In case of scientific questions arising for the classification of the product, the EMA's ITF (see section 3.1) can guide medicine developers with scientific views to support development of the borderline products or as applicable further interactions with EMA procedures relating to the research and development of borderline products.

4

Medicinal product development for human medicines

4. Medicinal product development for human medicines

(including joint HUMAN and VETERINARY aspects for GMP/GDP/GCP/GLP)

The data requirements for an application for marketing authorisation for a human medicinal product are laid down in EU legislation, in particular Annex I of Directive 2001/83/EC (see section 1.2). Guidance is available in the scientific guidelines adopted at ICH and EU levels, and in the Notice to applicants (NTA) which includes guidance on the common technical document (CTD) (see section 6.6).

An overview of the pharmaceutical, non-clinical and clinical development of a medicinal product for human use is provided in sections 4.1-4.3 below. For detailed information, SME companies should consult the EMA website where scientific guidelines are published (see section 3.5).

The SME office monitors applications for marketing authorisation (MAA) submitted to the Agency by SMEs and reports annually on the outcomes. The success rate of SMEs has improved over the years, but still lags behind the average for all applicants. The need for additional clinical data (module 5) to support the applications is one of the main reasons for refusal or withdrawal of the MAAs. The quality documentation (module 3) has also been found to be a particular problem area for many SMEs.

To ensure that the appropriate studies are performed and that there are no major objections regarding the study design at the time of the evaluation of the marketing authorisation application, SMEs are particularly encouraged to seek scientific advice from EMA (see section 3.4). The importance of opening up an early dialogue with the Agency on all aspects of development, including quality, is underlined.

Figure 1 provides an overview of the various opportunities for dialogue offered to SMEs throughout the development of a medicinal product.

4.1. Quality

The pharmaceutical quality of a medicinal product (human or veterinary) consists of two main pillars: active substance and finished product. The purpose of the pharmaceutical development is to develop a formulation that will be fit for its intended use, that is to consistently deliver the active substance at the site of action at the required dose, and that will be stable throughout its shelf-life.

4.1.1. Active substance (drug substance)

An active substance means a substance with physiological or pharmacological activity, which is responsible for the claimed clinical effect of the product, be it therapeutic, prophylactic or diagnostic.

Depending on their source, active substances can be classified as inorganic substances, herbal substances and herbal preparations, 'chemical' (synthetic or semi-synthetic, or isolated and purified from herbal sources or microorganisms) and biological active substances.

The amount of information to be generated during development depends on whether the active substance is a new substance, being used for the first time in a medicinal product in the EU, or an existing active substance (either described in a pharmacopoeia, or not). However, in all cases the active substance should be well characterised and manufactured by well described and adequately controlled manufacturing methods (see section 4.7.1).

For new active substances, applicants are encouraged to apply for an international non-proprietary name (INN) as early as possible in the clinical development. INNs are assigned by the World Health Organisation (WHO), to whom requests should be submitted.

When developing a medicinal product, the following key issues should be addressed with regards to active substances:

General information: Structural formula, including relative and absolute stereochemistry, molecular formula, and relative molecular mass. Examples of physicochemical and biological properties that might need to be examined include solubility, water content, particle size, crystal properties, biological activity, and permeability. The solid-state properties that might affect the in vivo performance are of particular importance. Additionally for proteinaceous biological active substances the schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and biological activity should be available.

Manufacture: The manufacturing process should be well described and understood. All critical parameters should be identified and appropriately controlled. It should also be demonstrated that the process can reproducibly produce a substance with the desired quality characteristics. In addition, the starting materials, that is all the materials from which the active substance is manufactured, should be evaluated and documented.

Biological active substances are often generated by cell substrates (microbial cells or cell lines derived from human or animal sources that possess the full potential for generation of the active substance). For cell substrates having a cell banking system, all procedures to generate the master cell bank and the working cell bank(s) should be documented. Characterisation and testing of banked cell substrates should be carried out to confirm their identity, purity, stability and suitability for manufacturing use. Particular attention should be given to potential contamination from adventitious agents (see section 4.1.3).

When there is a change in the manufacturing process of a chemical or biological active substance, it should be ensured that it will not affect the product. For biological active substances in particular, consideration should be given to performing a comparability exercise. If the analytical data are not sufficiently reassuring, additional evidence from bridging non-clinical and clinical studies will be required.

Characterisation: Extensive characterisation is performed in the development phase and, where necessary, following significant process changes. Characterisation is necessary to allow relevant specifications to be established.

The potential for isomerism, identification of stereochemistry, and polymorphism should be evaluated. The purity of a substance is often judged by examining the impurities it contains. Therefore, special emphasis should be given to characterising the impurities which arise from the method of manufacture and also those produced on storage, by degradation. Similarly, how impurities are generated should be described. If the level of impurities exceeds certain thresholds specified in the ICH and VICH guidelines on impurities, their toxicological significance becomes important from a safety point of view. Therefore, these impurities have to be 'qualified' (usually with reference to formal toxicology studies) to demonstrate they are safe.

Control of active substance: Specifications are critical quality standards that are based on thorough characterisation and on the mechanistic understanding of how formulation and process factors can impact product performance. Specifications should reflect the characteristics an active substance should have to meet its intended purpose. Conformity with specifications should provide assurance that quality is maintained from the time of release to the end of the shelf-life/re-test period. The acceptance criteria should be established and justified based on data obtained during development, including manufacturing consistency studies, stability studies and lots used in non-clinical and/or clinical studies. The analytical procedures that will be used to test the critical-to-quality attributes should be adequately validated in accordance with (V)ICH guidelines.

Stability: The applicant should study how the quality of the active substance varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. This will allow the definition of practical storage conditions and a 'window of use' called the shelf-life/re-test period (during which the substance may be used without further testing).

Submission of information for active substances: There are three ways to present the information relating to the active substance in a marketing authorisation application:

- Full data is presented in the dossier.
- Active Substance Master File (ASMF): An ASMF contains all the necessary information on the active substance and is composed of two separate sections. The "applicant's part"

contains the majority of the information (non-confidential) and is available to the applicant. However, in the "restricted part" the active substance manufacturer can submit detailed information relating to the manufacturing process, controls and validation and this is submitted directly to the competent authorities in order to protect the manufacturer's intellectual property. The concept of the ASMF applies only to "well-defined active substances". It therefore cannot be used for e.g. biological active substances, excipients, finished products, container materials.

- Certificate of suitability (CEP): The manufacturer of the active substance may apply to the Certification of Substances Division (DCEP) of the EDQM with documentation requesting evaluation of the suitability of the relevant European Pharmacopoeia (Ph. Eur.) monograph for the control of the chemical purity and microbiological quality of their active substance. If a CEP is available from the active substance manufacturer, reference to this is made in the application and no additional information needs to be submitted for those parts of the dossier covered by the CEP. However, additional information might be necessary depending on how the attributes of the active substance affect the finished product performance, for example, particle size or sterility. Manufacturers or suppliers of excipients, herbal substances and preparations used in the production or preparation of pharmaceutical products or any product with transmissible spongiform encephalopathy (TSE) risk, may also choose to apply for a CEP.

4.1.2. Finished product (drug product)

The key issues that applicants should address during the development of the finished product are summarised below:

Formulation development: When developing a formulation, it is important to identify attributes that are critical to the quality of the finished product, taking into consideration its intended usage, route of administration and the specific needs of the intended patient population (for example, paediatrics or the elderly).

The choice of all the excipients should be justified. Although excipients are usually inactive substances, their safety for the target population (for example, paediatric population or the target animal species) should be considered.

The potential effect of the physicochemical properties of the active substance (for example, water content, solubility, particle size distribution, polymorphic or solid-state form) on the performance of the finished product should be evaluated. Other key issues to be investigated are the compatibility of the active substance with the excipients, containers and closures. For combination products, the compatibility of active substances with each other should also be evaluated.

It is highly likely that during the product's development there will be changes in the formulation and manufacturing process. In all cases the differences between the clinical formulations used and the formulation intended to be marketed should be discussed and their equivalence demonstrated (using either *in vitro* or comparative *in vivo* studies, as appropriate).

If the formulation contains a novel excipient, that is, an excipient used forthe first time in an EU-authorised medicinal product, or by a new route of administration, then full details of its manufacture, characterisation and control, with cross references to supporting safety data (non-clinical/safety and/or clinical) should be provided. As there can be no confidential master file for excipients, applicants should provide all such information in the application for marketing authorisation.

Microbiological attributes: All parameters relevant to the microbiological attributes of the dosage form should be evaluated. Examples include the selection and effectiveness of preservative systems in products containing anti-microbial preservatives, and, for sterile products, selection and description of the sterilisation process and the integrity of the container/closure system for prevention of microbial contamination. The compatibility of the drug product with reconstitution diluent(s) or dosage devices (e.g. precipitation of drug

substance in solution, sorption on injection vessels, stability) should also be demonstrated.

Process development: It is important to consider the critical formulation attributes, together with the manufacturing process options, in order to address the selection of the manufacturing process and confirm theappropriateness of its components.
The manufacturer must have adequate knowledge of the manufacturing process in order to ensure that material and process variability is adequately understood and managed. In general, process development studies should provide the basis for process improvement, process validation and continuous process verification. In some cases, e.g. for complex products, theapplicant may decide to perform enhanced development studies over a wider range of material attributes, manufacturing process options and process parameters. These studies coupled with the use of statistical experimental design techniques, risk management principles and on-line, in-line or at-line analytical methods may lead to a better understanding of the process and the product. Such studies may be used to support real time release testing and more flexible regulatory approaches in setting the operational limits of the process as well as potential process changes during the lifecycle of the product. For manufacturing process changes for biological/ biotechnological products, the same recommendations as mentioned above (for active substances) apply.

Manufacture, control of excipients and the finished product, and stability: As with active substances, the manufacturing process used for the finished product should be carefully designed so that it consistently produces a product of the intended quality. All critical steps should be identified and controlled with appropriate in-process controls. Batch-to-batch consistency must be demonstrated using appropriate process validation studies. The usual process validation approach is to manufacture a number of production scale batches to confirm that the process is under control. For non-standard processes (e.g. manufacture of specialised dosage forms, or use of new/highly specialised technologies, as well as non-standard sterilisation methods), the validation data usually need to be provided with the submission. For all other processes these data may be generated in accordance with approved protocols once production starts. It is also possible to follow other validation approaches, e.g. a continuous process verification scheme, provided that this is appropriately justified and supported by adequate development studies.

Appropriate specifications should be set for the excipients and the finished product and validated methods should be used for their testing.

The stability of the finished product should be demonstrated throughout its proposed shelf-life under the proposed storage conditions. The stability studies should be performed in accordance with the (V)ICH recommendations (e.g. storage conditions, duration) unless otherwise justified. For multiple dose containers, the proposed in-use shelf-life should be similarly demonstrated. In all cases, the analytical methods that are used to test the product should be stability indicating.

4.1.3. Other specific issues

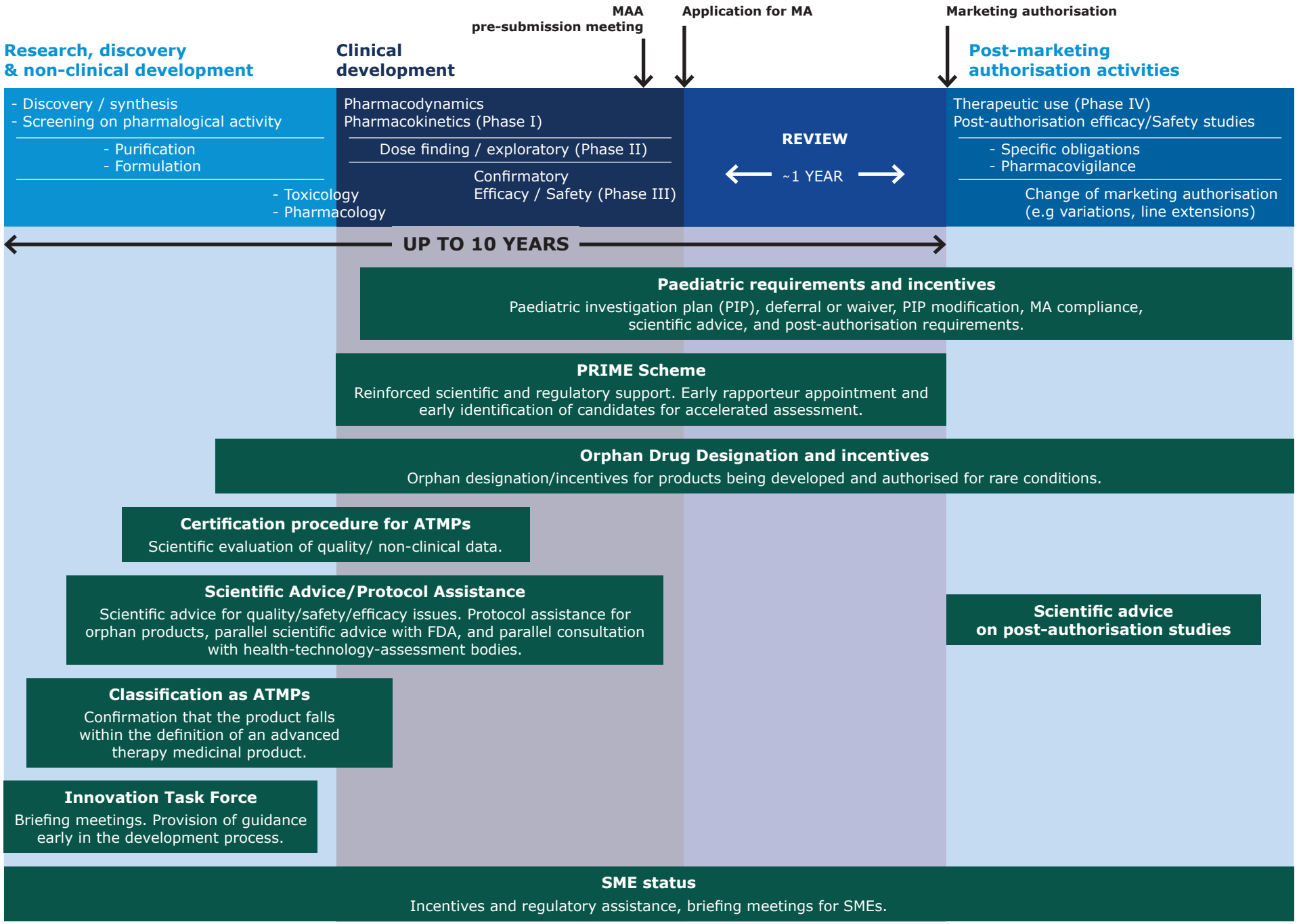
Adventitious agents: All materials of human or animal origin used in the manufacturing processes of either the active substance or the finished product or coming into contact with the active substance or finished product during the manufacturing process, should be identified. The risk with respect to potential contamination with adventitious agents of human or animal origin should be assessed.

Transmissible Spongiform Encephalopathy (TSE) agents: The latest Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products should be applied. Suppliers of any substances with a TSE risk used in production or preparation of medicinal products can apply to the Ph. Eur. for a TSE certificate. Such certificates can then be used by marketing authorisation applicants (for more information, see the EDQM website).

Viral safety: The risk of introducing viruses into the product and the capacity of the manufacturing process to remove or inactivate viruses should also be evaluated.

Other adventitious agents: Detailed information regarding other adventitious agents, such as bacteria, mycoplasma and fungi should be provided.

Figure 1. Overview of medicinal products development, incentives and opportunities for dialogue with EMA



Nitrosamine impurities: Applicants are required to have appropriate control strategies to prevent or limit the presence of nitrosamine impurities and, where necessary, improve their manufacturing processes. For more information, see the EMA website.

4.2. Non-clinical development

The non-clinical development consists of four main parts:

- **Pharmacology**
- **Pharmacokinetics & Metabolism**
- **Toxicology**
- **Environmental Risk Assessment**

The purpose of non-clinical development is to evaluate the pharmacodynamic and toxicity profiles by the clinical route of administration prior to initiating clinical studies, to predict potential safety problems at a given exposure and to investigate particular safety aspects as detailed below.

Some of the non-clinical studies need to be performed before administration of first dose to human while others can run in parallel to clinical trials (see figure 1). Pivotal studies should be performed according to GLP standards. Non-clinical safety studies should be planned and designed to represent an approach that is scientifically and ethically appropriate. The 3Rs principles – the replacement, refinement and reduction of animal use in research – should be considered in the design of the preclinical program.

The summary below outlines the important tests generally required. The non-clinical programme required to support clinical trials or marketing authorisation will depend on several factors including the modality of the active substance (e.g. chemical, biological or advanced therapy medicinal product), the intended clinical trial population, target indication and the maximum duration of dosing. For comprehensive details please refer to the relevant scientific guidelines (section 3.5). ICH M3(R2) guideline on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals and CHMP guidance on first-in-human clinical trials provide guidance on the non-clinical safety studies required for the conduct of clinical trials. For ATMPs, a risk-based approach should be applied to identify the necessary non-clinical data on a case-by-case basis. For further guidance, see the guideline on the risk-based approach.

4.2.1. Pharmacology

This part of the development addresses the pharmacodynamics of a new product in the non-clinical setting.

Pharmacodynamics includes the investigation of "primary" pharmacodynamics, which comprises *in vitro*, and *in vivo* effects related to the proposed therapeutic indication. There are many established animal models for various conditions. If there are no models available, sponsors should investigate the added value of developing a relevant model. Moreover, several novel products react only with human epitopes which may be different in experimental animals. In this case sponsors may consider developing a homologous product which would react with the animal epitope or develop transgene animal models. In addition, investigation of "secondary" pharmacodynamics (effects other than those related to the proposed therapeutic indications) is required. Safety pharmacology addresses undesired pharmacodynamic effects on specific physiological systems. The minimum safety pharmacology requirements are the core battery exploring the vital functions of the central nervous, cardiovascular and respiratory systems in relation to exposure in the therapeutic range and above, generally after a single dose administration. See 'ICH S7A: Safety pharmacology studies for human pharmaceuticals' and 'ICH S7B: ICH S7B Non-clinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals for detailed guidance. It may be possible to investigate some safety pharmacology endpoints in pivotal toxicology studies.

Finally, it may be necessary to investigate pharmacodynamic drug interactions with medicinal products that are likely to be administered for the same condition.

4.2.2. Pharmacokinetics & metabolism

This part of the development comprises studies investigating the absorption, excretion, tissue distribution, metabolism and pharmacokinetic drug interactions. The area under the matrix level concentration-time curve (AUC), Cmax at the expected peak concentration and C (time) at certain time points after administration are the most commonly used parameters in assessing exposure in pharmacokinetics studies. Other parameters include urinary and faecal excretion, bioavailability, elimination half-life, fraction of unbound drug, volume of distribution and tissue distribution. Metabolism is important to consider in the evaluation of the relevance of toxicity for humans. Many of these investigations, particularly those on distribution and excretion, are preferably conducted using radiolabelled compound. Where appropriate, placental transfer and transfer into milk can be studied. *In vitro* models (e.g. liver microsomes or hepatocytes in culture) comparing the metabolic profile between animal species and humans contribute to the choice of the most relevant animal species to support clinical trials and marketing authorisation.

4.2.3. Toxicology & toxicokinetics

The following studies should generally be performed during the development:

Single and repeated dose toxicity: The primary goal is to characterise the toxicological profile of the medicinal product following repeated daily administrations. This includes identification of target organs of toxicity, determination of a No Adverse Effect Level (NOAEL), exposure response relationship and potential reversibility of toxic effects. Unless justified, experiments in two species are required, one of which should be non-rodent, and the duration depends upon the planned human use. Single dose toxicity studies are not required unless this is the intended clinical use. Preliminary dose range finding studies may be necessary to aid in selection of doses in the GLP-compliant pivotal non-clinical studies.
The duration of administration required in pivotal toxicology studies will depend on the duration of clinical trials or, for marketing authorisation, the intended treatment duration. For products for chronic use in humans, repeated dose toxicity studies of at least six months duration are requested (ICH M3). In addition to investigating toxicity, kinetic parameters, in particular exposure (AUC) should be investigated in the pivotal repeated-dose toxicity studies (toxicokinetics). Toxicokinetics provide means of obtaining multiple dose pharmacokinetic data in the test species in the range of doses used in toxicology; the ratio of AUCs in humans and at the NOAEL in animals allows the calculation of a safety margin (see ICH S3A Toxicokinetics: the assessment of systemic exposure in toxicity studies' and 'ICH S3B Pharmacokinetics: repeated dose tissue distribution studies for further guidance).

Reproductive toxicity: The primary goal is to investigate the effects of the medicinal product on the following steps of reproduction:

- Male and female fertility and early embryonic development (to implantation) in one species, usually rats;
- Embryo foetal development (development of organs during pregnancy) and toxicity in two species, one of which should be a non-rodent (usually rabbit);
- Prenatal and postnatal development in one species, usually rats.

The need for reproductive toxicity studies will depend on the chemical modality (e.g. expanding beyond traditional small molecules), on the clinical trial population and on the anticipated use in the target population.

Juvenile toxicity: For medicinal products intended for paediatric use, possible effects of the product on the ongoing developmental processes in the age group(s) to be treated are taken into consideration. In some instances, studies in juvenile animals are required to allow benefit/risk assessment in these patient populations. Juvenile animal studies should be considered to investigate findings that cannot be adequately, ethically, and safely assessed in paediatric clinical trials. Serious adverse reactions that may be irreversible are of particular concern. The design of non-clinical studies in juvenile animals will vary depending on the findings observed in adult human studies and previous animal studies. Even if adverse reactions on developing organ(s) can be predicted from adult human or animal data, studies in juvenile animals might be warranted if there is a need to

further address a specific concern for the paediatric population or to establish safety factors. The CHMP guideline on non-clinical testing in juvenile animals and the ICH guideline S11 on non-clinical safety testing in support of development of paediatric pharmaceuticals provide recommendations on such studies.

Genotoxicity: Genotoxicity tests are *in vitro* and *in vivo* tests designed to detect compounds which induce genetic damage in the DNA directly or indirectly by various mechanisms. The standard battery comprises tests for mutagenicity in bacteria (Ames test), as well as *in vitro* tests for genotoxicity in mammalian cells and in vivo test for chromosomal damage (micronucleus test usually in the mouse). Compounds which are genotoxic have the potential to induce cancer and/or heritable defects. Genotoxicity tests are required for all products, with the exception of most biological products (see ICH S2(R1) on genotoxicity testing and data interpretation for pharmaceuticals intended for human use for further guidance).

Carcinogenicity: The objectives of carcinogenicity studies are to identify tumorigenic potential in animals and to assess the relevant risk in humans. They are required for pharmaceuticals expected to be administered regularly over a period of at least 6 months and for pharmaceuticals used frequently in an intermittent manner in the treatment of chronic or recurrent conditions. For pharmaceuticals administered infrequently or for a short duration of exposure (e.g. anaesthetics and radiolabelled imaging agents) carcinogenicity studies are not needed unless there is cause for concern. For anticancer medicinal products carcinogenicity studies are normally also not required (see ICH guideline S9 on nonclinical evaluation for anticancer pharmaceuticals).

The carcinogenicity battery consists of two long-term (2-year) studies in the rat and mouse or one long-term study in the rat and one short-term study (6-months) in a transgenic model (see safety guidelines ICH S1A, S1B and S1C). The ICH S1B(R1) addendum provides the opportunity to follow a weight of evidence approach allowing applicants to forego the conduct of a 2-year rat study on a data-driven basis.

Immunotoxicity: In the context of medicinal product development, it is defined as unintended immunosuppression or enhancement. All new human pharmaceuticals should be evaluated for the potential to produce immunotoxicity. Methods include evaluating parameters of the immune system in the standard repeated dose toxicity studies mentioned above and additional immunotoxicity studies conducted, as appropriate, if there is cause for concern. In case additional specific immunotoxicity studies are required, a generally accepted study design in rodents is a 28-day study with consecutive daily dosing. Endpoints can include functional tests, such as T-cell dependent antibody response, as well as immunophenotyping of leucocyte populations.

Local tolerance: The purpose of these studies is to investigate whether pharmaceuticals are tolerated at sites of the body that may come into contact with the product as a result of its administration in clinical use. Usually, one species is required for each type of test (e.g. ocular tolerance and skin toxicity in the rabbit) and the route of administration is guided by the envisaged clinical use. The local tolerance can be specifically evaluated as part of the repeated dose toxicity study or as a specific study (usually single or repeated administration over a number of days).

Phototoxicity: If a significant potential human phototoxicity risk is identified based on all available data, non-clinical (and clinical) experimental evaluation should be undertaken (see ICH M3(R2) and ICH guideline S10 on photosafety evaluation of pharmaceuticals).

4.2.4. Environmental Risk Assessment (ERA)

The purpose of ERA is to investigate the potential environmental risk of the medicinal product following its use in patients. The ERA is mandatory for all marketing authorisation applications although in some cases it can consist of a justification for not submitting data. This evaluation is a stepwise approach. The first part of the investigation estimates the exposure of the environment to the active substance and the potential for bioaccumulation and persistence in the environment. Based on an action limit, the assessment of environmental risk may be terminated at this stage. Above this limit, the fate of the substance in and the effects on the environment should be investigated in a second phase of investigation. Some product classes (e.g. endocrine active agents) require this

second part irrespective of predicted environmental exposure. The required tests for fate and effects in the environment include a chronic toxicity study in fish, and tests in daphnia and algae to determine a predicted no-effect concentration. If there are concerns further tests may be required. Guidance on testing requirements is given in the 'Guideline on the environmental risk assessment of medicinal products for human use' and related Q&A document. For genetically modified organisms (GMOs), a specific ERA is required (see Guideline on environmental risk assessments for medicinal products containing, or consisting of, GMOs).

4.3. Clinical development

The purpose of clinical development is to establish the absorption, distribution, metabolism and excretion (ADME) of a product and the pharmacokinetic and pharmacodynamic characteristics, (including a dose-response relationship and behaviour in special populations). Subsequent development is aimed at demonstrating the efficacy and establishing the safety profile of a medicinal product in a therapeutic indication in order to provide an adequate basis for assessing the benefit/risk relationship to support licensing.

Traditionally clinical development has been often described as consisting of four temporal phases: I – IV. Although these terms tend to be used less rigidly than before and are often combined, they are useful to separate the goals of the different stages of the clinical development. The phase concept is a description of the objectives which are summarised below, not a set of requirements. It is also important to realise that the temporal phases do not imply a fixed order of studies since for some medicinal products in a development plan the typical sequence will not be appropriate or necessary. Detailed information is available in the ICH E8 Note for guidance on general considerations for clinical trials. For comprehensive details please refer to the relevant scientific guidelines (section 3.5).

4.3.1. Human pharmacology studies (phase I)

This includes the initial administration of a new product into humans i.e. the first in human (FIH) study. The purpose of FIH trials is to evaluate an investigational medicinal product (IMP) in humans for the first time, to study the human pharmacology, tolerability and safety of the IMP and to compare how effects seen in non-clinical studies translate into humans. Detailed guidance is available in the Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products.

More generally, studies in this early phase of development do not aim to formally assess efficacy and may be conducted in healthy volunteer subjects or patients. Due to ethical reasons medicinal products with significant potential toxicity, e.g. cytotoxic compounds used in cancer treatment, are usually studied in patients already in this phase.

The objectives of these studies typically involve one or a combination of the following:

Using both single and multiple administration of increasing doses, initial safety and tolerability is assessed, which helps guide the dose for future therapeutic trials. Preliminary characterisation of absorption, distribution, metabolism, and excretion (ADME) and human pharmacokinetics is another goal of these early studies. For orally administered medicinal products, the study of food effects on bioavailability is important. Moreover, depending on the product and the endpoint studied, pharmacodynamic studies and studies relating blood levels of the administered dose of a product (exposure) to a specific response (PK/PD studies) may be conducted in healthy volunteer subjects or in patients. Pharmacodynamic endpoints may include for example, biochemical or physiological parameters, receptor occupancy. Although clinical activity is normally not the primary objective of this first phase, in some cases data may be collected as a secondary objective; for example, when assessing the pharmacokinetics of a sleeping pill it is possible to obtain some results on potential activity (sleep-inducing effect).

4.3.2. Therapeutic exploratory studies (phase II)

The goal of this phase is to explore therapeutic activity in patients. These studies are typically conducted in a group of patients who are selected by relatively narrow criteria, leading to a relatively homogeneous population. An important goal for this phase is to determine the dose(s) and regimen for the clinical efficacy and safety trials. Early studies in this phase often utilise dose escalation designs (see Note for guidance ICH E4 on dose response information to support drug registration) to give an early estimate of dose response, whereby an initial low dose is increased until optimal response or until occurrence of adverse events. The dose response relationship for the indication in question can be confirmed in later parallel dose-response design studies. In this phase, therapeutic activity can be explored using endpoints, which can be evaluated in a shorter time period than the actual therapeutic goal. For example, shrinking of the tumour mass in a particular cancer could be a suitable endpoint to assess activity in phase II, but would normally not be sufficient to demonstrate efficacy in phase III, where "hard" clinical endpoints like survival of the patient would be more relevant. When the results of this phase become available, it is decided if it is justified to proceed to the extensive phase III development.

4.3.3. Clinical efficacy and safety (phase III)

The goal is to confirm the preliminary evidence accumulated in the exploratory stage and to establish efficacy and safety. These studies are intended to provide an adequate basis for establishing the benefit/risk ratio and marketing approval. Therefore, a sufficiently high number of patients must be enrolled (usually several hundreds to several thousands) and exposed to the investigational medicinal product for a duration which will provide adequate efficacy and safety data for the envisaged clinical use. Generally, for medicines being developed for chronic use, studies of at least 6 months duration are required. The studies must generally be controlled, i.e. compare the product under development to placebo (a pharmaceutical preparation containing no active agent, made to look just like the test compound) and/or to active treatment depending on the condition and the product under investigation. In addition, the studies must generally be double-blind, i.e. neither the treating physician nor the patient know the treatment administered (test drug, placebo, active comparator). Usually, two phase III trials would be required for approval but under specific circumstances one well-conducted large trial may be sufficient. In addition to clinical efficacy, demonstration of safety is the second important goal of this phase. The requirements for investigating the adverse events profile are described in the ICH E 1: Note for guidance on population exposure: the extent of population exposure to assess clinical safety. Generally, 300-600 patients treated for six months, and 100 patients exposed for a minimum of one-year are considered to constitute an acceptable safety database. However, clinical trials before marketing authorisation have limitations to detect rare adverse events. An event occurring in less than 1/1,000 patients will normally not be detected in the pre-marketing phase.

4.3.4. Therapeutic use/ clinical utility (traditionally phase IV)

These are studies related to the approved therapeutic indication which are conducted post marketing. Their goal is to gather additional information about the medicinal products benefits, risks and optimal use in the broad population. Commonly conducted studies include additional drug-drug interaction, safety studies and studies designed to support use under the approved indication, e.g. mortality/morbidity studies, epidemiological studies. Please refer to sections 6.11 and 7.2 for further information on Post-Authorisation Efficacy and Safety (PASS/PAES) studies.

4.3.5. Adaptive designs

Traditionally the protocol of a clinical trial is finalised prior to study start and no changes are allowed during the conduct of the study. In some instances, however, studies can be planned with a so-called adaptive design involving design modifications based on the results of an interim analysis during the study. Such a design has the potential to speed up the process of drug development or can be used to allocate resources more efficiently without lowering scientific and regulatory standards. For further information, refer to the reflection paper on the EMA website.

4.3.6. Use of big data to support decision-making

In the context of medicines regulation, big data includes real world data such as electronic health records, registry data and health insurance data, pooled clinical trials data, datasets from spontaneously reported suspected adverse drug reaction reports, and genomics, proteomics and metabolomics datasets.

In line with the European Medicines Regulatory Network (EMRN) strategy to 2025 and the Agency's Regulatory Science Strategy to 2025, EMA and the EMRN are working towards establishing a framework to enable better integration of real-world data (RWD)/real-world evidence (RWE) alongside the gold standard of controlled trials into regulatory decisions on the development, authorisation and supervision of medicines.

Projects are being piloted to enable the use and establish value of RWE and individual patient data from clinical trials. For further information see EMA website on big data.

4.4. Clinical trial applications and their management

The Clinical Trials Regulation

The way clinical trials for human medicines are conducted in the European Union (EU) and the European Economic Area (EEA) has undergone a major change with the coming into force of the Clinical Trials Regulation (Regulation (EU) No 536/2014).

The Clinical Trials Regulation harmonises the assessment and supervision of clinical trial applications throughout the EU/EEA. When the Regulation became applicable on 31 January 2022, it repealed the existing Clinical Trials Directive (EC) No 2001/20/EC.

Under the Clinical Trials Directive, sponsors submitted applications for clinical trials separately in each EU/EEA country. Under the Clinical Trials Regulation, sponsors use the Clinical Trials Information System (CTIS) as the single EU/EEA entry point for the authorisation of clinical trials and their subsequent substantial modifications.

The Clinical Trials Regulation foresees a three-year transition period from the Directive to the Regulation.

- Since 31 January 2023, submission of initial clinical trial applications according to the Regulation is mandatory.
- From 31 January 2025, all ongoing trials approved under the Clinical Trials Directive before 31 January 2023 will need to transition to the regime of the Regulation and to CTIS.

Under the Clinical Trial Regulation, the authorisation and oversight of clinical trials remains the responsibility of the EU/EEA member states. EMA is responsible for the maintenance of CTIS and the European Commission ensures oversight and control of the implementation of the Clinical Trials Regulation.

A compilation of legislative and guidance documents for clinical trials, referred to as the 'EudraLex volume 10 – clinical trials guidelines' has been published by the European Commission and includes guidance on:

- Application and application documents for starting a clinical trial, to be submitted to the competent authorities of the member states and the ethics committees;
- Safety monitoring and reporting of adverse reactions, and serious breaches arising during clinical trials;
- Requirements for manufacturing and import authorisation of investigational medicinal products (IMP) including biological IMP and auxiliary medicinal products in clinical trials;
- Qualification of inspectors and inspection procedures.

It also includes additional documents and clinical trials legislation.

The Clinical Trials Information System (CTIS)

CTIS has become the single-entry point for the submission, supervision and authorisation of clinical trial applications for human medicines in the EU/EEA.

CTIS consists of dedicated secure workspaces for sponsors and authorities and a public website enabling the search of information on clinical trials.

In the sponsor secure workspace, clinical trial sponsors and other organisations working on clinical trials can:

- Manage users and users' roles;
- Compile and submit clinical trial applications for initial trials and substantial modifications;
- Cross-refer to product documents in other clinical trials;
- Record clinical trials results.

Other activities such as notifications, searches and responses to requests are also possible.

In the authority secure workspace, member states can perform several tasks such as:

- Manage users and users' roles;
- View clinical trial application dossiers;
- Manage tasks related to the assessment of clinical trials;
- Collaborate between member states;
- Record inspections of sites and clinical trials;
- Conduct union controls.

EMA performs the system administration and amends the publication of trial information and documents upon request.

The public website allows members of the public to access information on all clinical trials conducted in the EU/EEA as outlined by the Clinical Trial regulation. The website provides the following features:

- Search of clinical trial information;
- Download information and reports.

CTIS together with other EMA IT tools, also supports the coordinated assessment of safety reporting in clinical trials.

To help organisations involved in clinical trials for human medicines, EMA has created an online modular training programme on how to use CTIS. In this online training program, a dedicated module (Module 19) is created for SMEs and academia.

EudraCT

EudraCT is a database for clinical trials initiated in the EU between 1 May 2004 and 30 January 2023 which was established pursuant to Clinical Trial Directive 2001/20/EC.

CTIS replaces EudraCT as the EU/EEA entry point for information on clinical trials. EudraCT remains available as a historical archive of clinical trials.

Sponsors are encouraged to submit a summary of clinical trials results to EudraCT for closed trials that have been reported in EudraCT.

Since 31 January 2023, EudraCT is not available for submission of initial clinical trial applications. Clinical trials cannot continue running utilising EudraCT beyond 30 January 2025. Therefore, if sponsors are running trials that they expect to continue beyond 30 January 2025, sponsors will need to move (transition) them to CTIS before the transition period expires (30 January 2025).

EudraCT will remain active after the end of the transition period for submission of summary results of trials completed under the Directive.

Clinical trial application and the investigational medicinal product (IMP)

A clinical trial application consists of administrative information and the scientific data necessary for demonstration of the quality, safety and efficacy of the investigational medicinal product (IMP). With regards to the quality of the IMP, it is anticipated that in the early development stages information on the analytical methods, their validation, the setting of specifications and the stability might be incomplete. For his reason, for human medicinal products, different requirements are set for IMPs to be used in phase I, II and III trials. For further information the CHMP Guideline on the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials should be consulted.

SMEs should be aware that if the final formulation differs from that of the IMP used in earlier clinical trials, the relevance of the earlier material compared to the product tested in later phases should be described. Special consideration should be given to changes in quality parameters with potential clinical relevance e.g. *in vitro* dissolution rate.

Public information on clinical trials

Information on clinical trials is made publicly available through the CTIS public website and the EU clinical trials register (based on the data available in EudraCT).

The CTIS public website provides information on all clinical trials in CTIS, since 31 January 2022. Transparency is a key objective of the Clinical Trials Regulation, and clinical trials information held in CTIS is publicly disclosed unless one or more of the following exceptions apply:

- To protect personal data;
- To protect commercially confidential information (CCI), in particular taking into account the marketing authorisation status of the medicinal product, unless there is an overriding public interest in disclosure;
- To protect confidential communication between member states in preparing their assessment;
- To protect the supervision of clinical trials by EU member states.

The information that will be made public for all clinical trials registered in CTIS includes:

- The main characteristics of the trial comprising design, scientific and, where applicable, therapeutic intent, title, identification of the investigational medicinal products (IMPs), treatment arms, treatment population and number of subjects, inclusion and exclusion criteria and main objectives and endpoints;
- Conclusion of the assessment and decision on the trial;
- Information updated during the trial to indicate the start and end dates of recruitment;
- Substantial modifications to the trial;
- The end date of the trial, with reasons for which trials are ended prematurely where applicable, and, 12 months later, the summary of results and a summary in lay language;
- Clinical study reports for clinical trials on medicines for which a marketing authorisation has been granted, the procedure completed, or the marketing authorisation application withdrawn.

Deferral procedures apply under which sponsors can request a deferral of certain information related to the clinical trial. More information on the publication and deferral procedures can be found in the Appendix, on disclosure rules, to the functional specifications for the EU portal and EU database to be audited.

The EU clinical trials register contains information extracted from EudraCT on trials authorised under the Clinical Trials Directive. The register allows to search for protocol-related information and summary of clinical trials results on interventional clinical trials for medicines which were authorised in the EU/EEA and reported in EudraCT, and also in clinical trials authorised to be carried out outside of the EU where these trials are part of a paediatric investigation plan.

The list of fields that are made publicly available on the CTIS public website is referenced in the CTIS sponsor handbook and also on the EMA website under CTIS training. A Questions and Answers document on the Clinical Trials Regulation is published in chapter V of 'EudraLex volume 10 – clinical trials guidelines'.

An interim guidance and annex for sponsors on how to approach the protection of personal data and CCI when using CTIS is published at EMA website.

In addition, the Clinical Trials Search Portal provides access to a central database containing trial registration data sets provided by several different international registries including countries outside of EU/EEA. This portal provides also links to the full original records.

The clinical trial facilitation group (CTFG) and the voluntary harmonisation procedure (VHP)

The Clinical Trial Facilitation Group (CTFG) was established during the implementation of clinical trials Directive 2001/20/EC and continues to operate with the implementation of the Clinical Trials Regulation. The CTFG provides a forum to discuss and agree on common principles and processes to be applied throughout the European medicines regulatory network. It also promotes harmonisation of clinical trial assessment decisions and administrative processes across the national competent authorities (NCAs).

Prior to the entry into force of the Clinical Trials Regulation and CTIS, the CTFG provided a voluntary harmonization procedure (VHP) for the assessment of multinational clinical trial applications.

CTIS has now replaced the VHP as the tool for the harmonised submission and assessment of clinical trial applications in the EU/EEA. Trials that benefitted from the VHP should in principle qualify to transition into CTIS and early transition is recommended. Sponsors should ensure that the clinical trial protocol is harmonised with the relevant member states and that the harmonisation procedures are completed prior to submission in CTIS. Rules applicable to trials initiated under the Directive and additional considerations have been included in the Questions and Answers document in chapter V of 'EudraLex volume 10 – clinical trials guidelines' for the Clinical Trials Regulation.

4.5. Measures for orphan medicines

Orphan designation

'Orphan' medicinal products are those intended to diagnose, prevent or treat life-threatening or serious and debilitating conditions that are rare and affect not more than 5 in 10,000 persons in the European Union.

Incentives

EU incentives available from EMA for sponsors[7] and pharmaceutical companies developing orphan medicinal products include:

- A 10-year period of market exclusivity after the grant of a marketing authorisation;
- Protocol assistance (scientific advice, see section 3.4);
- Fee reduction for certain centralised activities;
- Direct access to the EMA centralised procedure for the application for marketing authorisation.

To be eligible for orphan incentives, medicinal products should be designated through the Community procedure for orphan designation. Orphan designation may be obtained at any stage of development provided a proper scientific justification and data supporting the intended use is submitted. EMA, through its Committee for Orphan Medicinal Products (COMP) is responsible for reviewing designation applications and issuing an opinion, which is transformed into a decision by the European Commission.

The designated medicinal products are published on the Community register of orphan medicinal products as well as on the EMA webpage.

Guidance on the format and content of applications for designation as orphan medicinal products is available at the EU Commission website. Applications for orphan drug designation are free of charge. Full details on how to apply (including guidance on calculation and reporting of the prevalence and the elements to support medical plausibility and the assumption of significant benefit) are available on the EMA website.

EMA offers assistance to sponsors on the preparation of orphan designation applications through free pre-submission meetings. Requests for pre-submission meetings as well as the submission for an orphan designation are all done via the IRIS portal https://iris.ema.europa.eu/.

Contrary to the US legislation on paediatric obligations (PREA), orphan-designated medicinal products are not exempted from the obligations of the paediatric regulation in the EU (see below). Sponsors are therefore encouraged to consider these requirements and discuss them during the pre-submission meeting.

[7]) 'Sponsor' means any legal or natural person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product.

Orphan marketing authorisation

Prior to the grant of a marketing authorisation, the COMP will review the criteria on which the orphan designation has been based to confirm the assumptions made at the time of designation. Accordingly, at the time of submission of the application for marketing authorisation, the applicant is asked to submit a report to EMA via IRIS demonstrating that the orphan criteria are still met.

In accordance with Article 8 of Regulation (EC) No 141/2000 once a designated orphan medicinal product is authorised, it is granted a ten year period of market exclusivity. This market exclusivity protects the originator's medicinal product in the authorised 'orphan' therapeutic indication. As such, 'similar' medicinal products will not be granted a marketing authorisation for the same therapeutic indication unless the originator gives consent, is unable to supply sufficient quantities of the medicinal product, or the second applicant demonstrates that although similar, the medicinal product is clinically superior to the originator.

The definitions of 'similar' medicinal product and 'clinically superior', in this context, are laid down in Article 3 of Commission Regulation (EC) No 847/2000.

It is important for SMEs to note, when preparing an application for marketing authorisation, that where a designated orphan medicinal product has been authorised for the condition which covers the proposed therapeutic indication being applied for, and a period of market exclusivity is in force, the possible 'similarity' with the authorised orphan medicinal product must be addressed in the application for marketing authorisation. If applicable, the applicant must then argue clinical superiority or justify that one of the derogations noted above applies.

The overall judgment of similarity includes an evaluation of the indication, the mechanism of action and the molecular structure.

4.6. Paediatric development

Requirements for the development and authorisation of medicines for use in children in the EU are set out in Regulation (EC) No 1901/2006.

The overall aim is to improve the health of the children in the EU by increasing the research, development, and authorisation of medicines for use in children. To this end, a system of obligations, incentives and rewards has been put in place. It is imperative that SMEs familiarise themselves with these requirements very early on in development, to benefit from support offered and to avoid delays in the regulatory approval process.

System of obligations, incentives and rewards

The obligations and rewards listed below apply irrespective of the route of authorisation of the medicinal product (centralised vs. non-centralised).

For unauthorised medicinal products: There is an obligation to submit the results of studies conducted in compliance with an agreed paediatric investigation plan (PIP)[8], to have an application for a new marketing authorisation being validated, and its assessment initiated. An exemption (waiver) from this obligation may be issued by EMA when such paediatric development is not needed or not appropriate. Deferrals may also be granted which means that the initiation or completion of some or all of the studies in the agreed PIP can occur after the company has applied for marketing authorisation in adults, in the same condition(s). However, for deferred measures a binding date of initiation (where appropriate) and completion needs to be identified. It is therefore important to apply for the PIP (with or without deferral) or the waiver as early as possible.

Applications under certain types of legal bases (for example generic, biosimilar, homoeopathic and traditional herbal products, or those applied for as "well-established use") are exempt from these requirements.

[8]) The PIP is a research and development programme, aimed at ensuring that the necessary data are generated to determine the conditions in which a medicinal product may be authorised for the paediatric population.

For non-orphan medicinal products, the reward for conducting the paediatric development in compliance with a paediatric investigation plan is a six-month extension of the Supplementary Protection Certificate, provided that the results of the studies are included in the product information and that authorisation is obtained in all EU member states. This reward can be obtained even if the results of these studies fail to support a new paediatric indication.

For unauthorised orphan medicinal products: the obligations for unauthorised medicinal products outlined above also apply. The reward for orphan medicinal products is two years of market exclusivity in addition to the existing 10-year exclusivity awarded under the EU orphan regulation if the results are included in the product information.

For authorised patented medicinal products: The requirements and rewards described above also apply when seeking a variation or extension of an existing marketing authorisation for a new indication (including paediatric), new route of administration or new pharmaceutical form, when the product is covered by a supplementary protection certificate or a qualifying patent. As with new medicines, waivers or deferrals may also be granted, and the rewards are the same as above. The PIP and/or waiver must cover all existing and planned new indications, pharmaceutical forms and routes of administration.

For "off-patent" medicinal products: Medicines not covered by a supplementary protection certificate or a qualifying patent, and developed by the Marketing Authorisation Holder solely for paediatric use and with an appropriate formulation can benefit from a specific type of marketing authorisation — the paediatric-use marketing authorisation (PUMA) — which grants 10 years of data protection. To apply for a PUMA, a PIP must be agreed with EMA beforehand, and will be subject to compliance check.

It is important for SMEs to be aware that there is a requirement to agree the paediatric investigation plan (PIP) early on, in the development of the medicinal product, i.e. not later than at the time human pharmacokinetic studies are completed in adults. The Agency, through its paediatric committee (PDCO) is responsible for assessing the applications for paediatric investigation plans, waivers and deferrals and formulating an opinion, which is subsequently transformed into a binding decision.

The PIP covers the timing and measures required to study the safety and efficacy of the product, with an age-appropriate formulation if relevant, in all paediatric subsets affected by the condition.

A guideline providing details on the format and content of applications for agreement or modification of a paediatric investigation plan, requests for waivers or deferrals, the operation of the compliance check and the criteria for assessing significant studies is available. Further details on how to apply, including a questions & answers document, are available on the Agency's website. There is no fee associated with these applications.

The Agency offers the possibility of a pre-submission meeting (via teleconference) for SMEs in advance of the submission of their application for a PIP, deferral and/or waiver. This is aimed at improving the quality of applications and facilitating their validation rather than performing a scientific pre assessment. It is particularly recommended for (potential) orphan medicinal products. To discuss these meetings, contact the Paediatric Office via AskEMA.

The Agency also provides free scientific advice on the development of medicinal products for paediatric indications (see section 3.4).

Once the PDCO has agreed the PIP, the applicant will need to comply with the plan, as the agreed PIP is binding for the company. As the development of the medicinal product progresses, there may be a need for companies to apply for a modification of the agreed PIP if it is no longer appropriate or unworkable. If the medicinal product is approved in the EU, annual reports on the deferred measures in the PIP must be submitted to the Agency.

A compliance check will be necessary before any application for marketing authorisation (even for an adult indication) can be considered valid, unless all measures in the PIP are deferred and there is no due date for initiation or completion of a study/measure. The same applies to some subsequent regulatory applications for authorised products, as described above. To prevent delays in the validation process, applicants are advised to submit compliance check requests to the PDCO as

soon as possible and at least 3 months in advance of the submission of the regulatory application; multiple compliance check requests are also possible, for example after completion of separate studies/measures.

Other key measures in the paediatric regulation

These include:

- An increased transparency of paediatric information. The marketing authorisation holder should submit results of any paediatric study (whether part of a PIP or not) to the concerned competent authority within 6 months of their completion. Protocols and results of paediatric clinical trials performed both inside the EU and anywhere else in the world, if the trial is part of a paediatric investigation plan, will be publicly available in the EU clinical trials register (EU CTR, see section 4.4);

- EU funding for research on off-patent medicines for paediatric use may be delivered through EU research programmes;

- Measures to increase the robustness of pharmacovigilance (safety monitoring) for medicines;

- An EU inventory of the therapeutic needs of children to focus research, development and authorisation of paediatric medicines;

- An Agency-based EU network of networks, investigators and trial centres with recognised expertise in performing clinical studies in children (Enpr-EMA). Enpr-EMA acts as a contact point for a number of specialty and multi-specialty networks facilitating patient recruitment. It also offers expert advice when preparing a PIP application and provides access to academic partners through established collaboration with the SME office at EMA.

4.7 GMP/GDP/GCP/ GLP for human and veterinary medicines

4.7.1. Good manufacturing practice (GMP)

Good manufacturing practice (GMP) is defined as that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use. Principles and guidelines for GMP are stated in Commission Delegated Regulation (EU) 2017/1569 for investigational medicinal products and Commission Directives (EU) 2017/1572 and Directive 91/412/EEC for respectively medicinal products for human use and veterinary medicinal products. Compliance with these principles and guidelines is mandatory within the European economic area. Interpretation of these requirements is provided in the EU guidelines to good manufacturing practice - medicinal products for human and veterinary use published by the European Commission. This guide to GMP consists of detailed guidelines (part I, II and III) which are supplemented by a series of annexes and related documents specific for certain types of products or topics.

A public site, EudraGMDP, is also available for information on manufacturing authorisations and GMP certificates.

The manufacture of medicinal products in the EEA is undertaken subject to the holding of a manufacturing and importation authorisation. Such authorisation is also required for imports from third countries into a Member State. The national competent authorities of the member states enter the manufacturing and importation authorisations that they issue into EudraGMDP.

Following a site inspection, a certificate of good manufacturing practice is issued to the manufacturer if the outcome of the inspection demonstrates that the manufacturer complies with the principles of GMP, as provided by the EU legislation. The national competent authority which performs the inspection shall enter the GMP certificates information into EudraGMDP. If the outcome of the inspection is that the manufacturer does not comply with the principles of GMP, the

information is also entered into EudraGMDP, as a GMP non-compliance statement.

Manufacturing authorisation holders are obliged to comply with GMP requirements for medicinal products and to use as starting materials only active substances manufactured in accordance with the guidelines on GMP for starting materials.

The active pharmaceutical ingredient (API) registration certificates are publicly accessible through the EudraGMDP database. Finished product manufacturers are required to verify that the active substances used in their products are manufactured according to GMP through audits of the manufacturer.

The falsified medicines Directive 2011/62/EU introduced, for human medicines, strengthened provisions for the supervision of active substance manufacture, which includes an obligation for national competent authorities to register active substance manufacturers, importers and distributors established on their territories. Information on the legal framework on the falsified medicines directive can be found on the European Commission website.

Marketing and manufacturing authorisation holders are obliged to report to EMA any product quality defects, including suspected ones, of centrally authorised medicine products which could result in a recall or impact supply.

Shortages of medicines are increasingly challenging to healthcare systems and can impact on patient care. These shortages can occur for many reasons, such as manufacturing difficulties, problems affecting the quality of medicines or increased demand. To report potential or actual shortages of medicines caused by GMP-non-compliance or quality problems, SMEs should e-mail qdefect@ema.europa.eu and AvailablitySPOC@ema.europa.eu in parallel, and clearly indicate if the problem identified is likely to lead to a shortage. For further information, a reflection paper has been published on the EMA website. Potential or actual shortages caused by other non-GMP-related issues such as unexpected increase in demand may be notified to EMA by completing Annex 1 of Guidance for MAHs on the detection and notification of shortages and sending this by email to AvailabilitySPOC@ema.europa.eu.

4.7.2. Good distribution practice (GDP)

The wholesale distribution of medicinal products is an important activity in the integrated supply chain management. Good distribution practice (GDP) should be implemented through a quality system operated by the distributor or wholesaler. The aim of GDP is to ensure that the level of quality of authorised medicines, determined by GMP, is maintained throughout the distribution network to retail pharmacists and other entities selling medicines to the general public. The quality system should also ensure the right products are delivered to the right addressee within a satisfactory time period. A tracing system should enable any faulty products to be found and there should be an effective recall procedure. The principles of GDP are stated in Directive 2001/83/EC and guidance on good distribution practice of medicinal products for human use published in a Commission guideline 2015/C 95/01.

For veterinary medicinal products, GDP principles are set in Commission Regulation (EU) 2021/1248 and in Commission Regulation (EU) 2021/1280 for active substances used as starting materials. For veterinary medicinal products, the Agency maintains a Union database on manufacturing, import and wholesale distribution.

In order to strengthen the supervision by regulatory agencies of the supply chain for medicinal products for human use, the falsified medicines Directive 2011/62/EU introduced stricter obligations for wholesale distributors and brokers. An extension of the publicly accessible EudraGMDP database includes wholesale distribution authorisations issued by member states, GDP certificates and non-compliance reports.

4.7.3. Good clinical practice (GCP)

Clinical trials included in any marketing authorisation application in the EU are legally required to be conducted in accordance with Good clinical practice (GCP).

GCP is an international ethical and scientific quality standard for designing, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and wellbeing of

trial subjects are protected; consistent with the principles that have their origin in the declaration of Helsinki, and that the clinical trial data are credible. Requirements for the conduct of clinical trials in Europe, including GCP, GMP and inspections, are set out in the Clinical Trials Regulation 536/2014, Commission Implementing Regulation 2017/556 and Commission Delegated Regulation (EU) 2017/1569. Guidelines on clinical trials are available under 'EudraLex – Volume 10'.

GCP concerning veterinary medicinal products is an international ethical and scientific quality standard for designing, conducting, monitoring, recording, auditing, analysing and reporting of clinical studies evaluating veterinary medicines; and developed under the principles of the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) - CVMP/VICH/595/98. The Annex to Regulation (EU) 2019/6, as amended, sets out conditions for the conduct of field trials included in applications for veterinary marketing authorisation.

4.7.4. Good laboratory practice (GLP)

Good laboratory practice (GLP) defines a set of rules and criteria for a quality system concerned with the organisational process and the conditions under which non-clinical studies are planned, performed, monitored, recorded, reported and archived. Detailed information about GLP can be found on the linked websites of the Organisation for Economic Co-operation and Development (OECD) and the European Commission (see Directive 2004/9/EC and Directive 2004/10/EC). For human products, Annex I to Directive 2001/83/EC, as amended, indicates that safety tests reported in marketing authorisation applications should be performed in compliance with the principles of GLP. For veterinary products, in accordance with Annex II to Regulation (EU) 2019/6, as amended, pharmacological, toxicological, residue and safety tests shall be carried out in conformity with GLP provisions. The same principles apply for tests carried out for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin.

4.7.5. Inspections

GMP, GLP, GCP and PhV inspections may be requested in connection with an application for a marketing authorisation at national or at EU level. The sites to be inspected (manufacturing and quality control sites, non-clinical study sites, clinical trials sites or sites where pharmacovigilance activities are conducted) should be "inspection ready" at the time of submission of the application and throughout the assessment.

EMA is responsible for the co-ordination of pre-authorisation GMP, GLP, GCP and pharmacovigilance inspections in connection with the granting of a marketing authorisation by the Union.
All information concerning centralised inspections activities can be found on the inspection section of the EMA webpage.

In case of an accelerated assessment procedure (see section 6.14.1) the applicant is encouraged to contact EMA prior to submission of the request in order to determine the need for any pre-authorisation inspection. Further information is available in the pre-authorisation guidance.

4.8. Medical devices

Medical devices are products or equipment (e.g. instruments, software, implants or materials) intended for a medical purpose, which primary mode of action is not achieved via pharmacological, immunological or metabolic means (see definition in Article 2(1) of Regulation (EU) 2017/745)[9].

In vitro diagnostic medical devices are devices used *in vitro* to provide information on a physiological or pathological state, a disease or an impairment or to predict treatment response or influence therapeutic measures (see definition in Article 2(2) of Regulation (EU) 2017/746).

In the EU, medical devices and *in vitro* diagnostic devices can only be placed on the market if they meet the requirements set out in these regulations.

Medical devices are divided into classes[10] according to their risk (from class I to IIa, IIb and III, the highest risk class for medical devices and from class A to B, C, D for *in vitro* diagnostic devices), which impacts the regulatory requirements the device must comply with during the entire product lifecycle.

Manufacturers can place a CE mark on a medical device once it has passed a conformity assessment. The conformity assessment can be conducted by the device manufacturer itself for class I devices, if they are not sterile, measuring devices or reusable surgical instruments. For all other devices, the involvement of a third part assessment body - the notified body – is needed.

For certain **high-risk medical devices**, notified bodies must consult specific expert panels for:

- An opinion on the notified body's clinical assessment for every class III implantable devices or every class IIb active device intended to administer or remove medicinal products from the body. This is called **the clinical evaluation consultation procedure (CECP).**
- A view on the manufacturer's performance evaluation report for every class D *in vitro* diagnostic medical device. This is called the **performance evaluation consultation procedure (PECP).**

EMA provides technical secretariat for the experts panels activities.

EMA is also involved in regulatory procedures for medical devices as follows:

- *Medicines approved under the centralised procedure used in combination with a medical device:*
  - Medical devices may be an integral part of a medicinal product (e.g. to administer a medicinal product like pre-filled syringes or inhalers). In this case, EMA assesses the overall benefit-risk of the combination. The device part of the combination must comply with the relevant safety and performance requirements (see Art 117 and Annex I of Regulation (EU) 2017/745).
  - Medical devices may be indicated to be used with a medicinal product whether they are co-packaged with the medicinal product or obtained separately but referenced in its product information (e.g. reusable pen to be used with cartridges). In this case, the device(s) must comply with all the requirements of the medical device regulations and EMA will assess the safe and effective use of the medicine in combination with the medical device.
- *Medical devices with an ancillary medicinal substance*[11] — In the context of their conformity assessment, the notified body must seek a scientific opinion from the EMA or a national competent authority on the quality and safety of the ancillary medicinal substance including the benefit-risk of incorporating the substance in the device. If the ancillary substance falls under the list of substances to be assessed under the centralised procedure, the notified body must consult the EMA.

[9]) A guidance on borderline products provides general principles and examples on the classification as medical device or medicinal product. Also, national competent authorities for medicinal products and medical devices can be consulted for questions on classification.
[10]) See classification rules in Annex VIII of Regulation (EU) 2017/745
[11]) An ancillary medicinal substance is a medicine that is incorporated within a medical device where the main mode of action is due to the device.

- *Companion diagnostics*[12] — as part of the conformity assessment of these *in vitro* diagnostic medical devices, a notified body must seek a scientific opinion from EMA or a national competent authority on the suitability of a companion diagnostic in relation to the medicinal product. If the medicinal product falls within the scope of the centralised procedure, the notified body must consult EMA.

- *Medical devices made of substances or of combinations of substances that are systemically absorbed by the human body* — as part of the conformity assessment of such medical devices, a notified body must seek a scientific opinion from EMA or a national competent authority on the compliance of the substance with the requirements laid down in Annex I to Directive 2001/83/EC (including an assessment of absorption, distribution, metabolism, excretion, interactions, local tolerance, toxicity of the substance(s)).

Detailed information on medical devices is available on the European Commission and EMA webpages.

[12]) A companion diagnostic is an *in vitro* diagnostic test that supports the safe and effective use of a specific medicinal product, by identifying patients that are suitable or unsuitable for treatment.

Medicinal product development for veterinary medicines

5. Medicinal product development for veterinary medicines

The data requirements for an application for marketing authorisation for a veterinary medicinal product are laid down in EU legislation, in particular Annex II of Regulation (EU) 2019/6 as amended by Commission Delegated Regulation (EU) 2021/805 of 8 March 2021.

Dossier requirements are detailed for specific types of veterinary medicinal products (e.g. biologicals and immunologicals, products other than biologicals, novel therapies such as gene and cell therapies), applications (e.g. generic, hybrid, combination, limited markets, and exceptional circumstances applications) or particular dossiers (e.g. vaccine antigen master files, multi-strain dossier, vaccine platform technology).

If an application concerns an antimicrobial veterinary medicinal product, the following will also need to be submitted:

- Documentation on the direct or indirect risks to public or animal health or to the environment of use of the antimicrobial veterinary medicinal product in animals;
- Information about risk mitigation measures to limit antimicrobial resistance development related to the use of the veterinary medicinal product.

Further guidance is available in scientific guidelines and other guidance documents, adopted at VICH and EU level, and published on the EMA website.

Foodstuffs obtained from animals treated with veterinary medicinal products must not contain residues which might constitute a health hazard to the consumer. Therefore, no marketing authorisation for any veterinary medicinal product intended for food-producing animals can be granted in the European Union unless maximum residue limits (MRL) have been established or their need excluded, for any pharmacologically active substance contained in the product.

The establishment of MRLs is a Community procedure regulated by Regulation (EC) No 470/2009, Commission implementing Regulation (EU) 2017/12, Commission Regulation (EU) 2017/880 and Commission Regulation (EU) 2018/782. The requirement for MRLs applies to the active principle(s) but also excipients or adjuvant, if they are pharmacologically active (see section 5.1).

An overview of the studies required to establish the safety and efficacy of a medicinal product for veterinary use as well as MRLs is provided in the sections below. For detailed information, SMEs should consult the EMA website where all current scientific guidelines are published (see section 3.5).

To ensure that the appropriate studies are performed and that there are no major objections regarding the study design at the time of the evaluation of the marketing authorisation application, SMEs are strongly encouraged to seek scientific advice from EMA (see section 3.4) and request as early as feasible a pre-submission meeting with the EMA, for a planned application for marketing authorisation.

5.1. Maximum residue limits (MRL)

If there is no MRL established for a pharmacologically active substance in the relevant food-producing target species and food commodity, an application to establish, extend or modify an MRL for residues of veterinary medicinal products in foodstuffs of animal origin should be submitted to the Agency for evaluation by the CVMP.

Safety and residue studies have to be conducted and submitted with an MRL application. These studies are intended to demonstrate that no harmful residues result in foodstuffs of animal origin from the normal conditions of use of the substance under consideration. Details on the studies to be conducted can be found on the EMA website.

Safety studies should include pharmacological, toxicological and other relevant studies such as studies on potential microbiological activity. The

toxicological studies include repeat-dose toxicity, reproduction and developmental toxicity, genotoxicity and carcinogenicity testing, and testing of other effects, e.g. delayed neurotoxicity, where appropriate due to the type of substance.

The safety studies are required to establish the acceptable daily intake (ADI). The ADI is an estimate of the substance and/or its residues, expressed in terms of µg or mg per kg body weight that can be ingested by a person daily over a lifetime without any appreciable health risk.

Residue studies, including pharmacokinetics tests, are required to determine the nature and actual level of residues and their elimination in the target animal and in particular edible tissues (muscle, fat or fat and skin, liver and kidney) and other food products of animal origin (milk, eggs or honey). Therefore, investigations of the elimination of residues from edible tissues and other food products of animal origin should be conducted. To validate the residue depletion studies, validated analytical methods for identifying and measuring the residues in the tissues and food products should be developed.

On the basis of the safety and residue studies, MRLs are established for the animal species for which the veterinary medicinal product is intended to be used (e.g. cattle). Where an extension of existing MRLs to other animal species (e.g. extension to pigs) or specific food commodities (e.g. milk, eggs) is considered, only residue studies with regards to the relevant target species should be performed as the ADI is the same regardless of the indications.

Modifications of existing MRLs can be requested, if new safety studies allow the modification of the ADI, or if new residue studies allow amendment of the MRLs.

At the end of the evaluation process, the CVMP adopts an opinion, which is then submitted to the European Commission for adoption by the Standing Committee. Depending on the conclusions, a pharmacologically active substance may be included in table 1 (allowed substances) or table 2 (forbidden substances) of Commission Regulation (EU) No 37/2010. Table 1 (allowed substances) of the regulation includes substances for which MRLs, including provisional MRLs, have been established, and substances for which it was concluded that consumer safety could be ensured without the need to establish MRL values. Table 2 (forbidden substances) includes substances for which no safe limit could be established or for which there were insufficient data to allow a recommendation for inclusion of the substance in table 1. Specific questions on MRLs can be addressed to MRL@ema.europa.eu.

5.2. Quality

As similar quality requirements generally apply for human and veterinary medicines, a common quality section covering both medicinal products for human use and veterinary use is provided in this guide for ease of reference (see section 4.1). Guidelines and other guidance documents published on the EMA website also generally apply to both medicinal product for human and veterinary use with specific requirements to veterinary medicines detailed in the joint guidelines or set out in specific guidance published for veterinary medicines.

In addition, many veterinary products are subject to the requirements of individual European pharmacopoeia monographs.

5.3. Safety

The safety of a product has to be demonstrated through "safety" studies, and for products intended for food-producing species also with "residue" studies. This part of the development should address the target animal safety (companion animals or food producing species), consumer safety, user safety and the environmental impact of the product.

Safety studies investigate the active substance(s) and excipients, if relevant. The research should focus both on the pharmacology (pharmacodynamics and pharmacokinetics) and toxicology.

The pharmacodynamic studies should take into account tests in experimental and target animals. The pharmacokinetic studies should investigate the absorption of the active substance, its distribution, metabolism and excretion in animals.

Toxicology studies should assess single and repeated dose toxicity, tolerance in the target species, reproduction and developmental toxicity,

genotoxicity and carcinogenicity. Tests on other effects such as immunotoxicity, dermal or eye irritation, neurotoxicity and antimicrobial properties might also be needed depending on the veterinary medicinal product. For products for food-producing animals, many of the safety studies required for marketing authorisation might have been provided in the preceding MRL application.

For antimicrobials, data on the potential emergence of resistant bacteria or resistance determinants of relevance for human health which are associated with the use of veterinary medicinal products are required.

An assessment of the user safety should be conducted, evaluating the risks for the persons that may be exposed to the product (e.g. pet owners, veterinarians, and farmers) based on the safety studies conducted and considering the potential exposure.

An environmental risk assessment is also required for all applications. The environmental risk assessment is conducted in two phases. In phase I, an exposure driven screening is conducted to determine if the product leads to an extensive exposure of the environment. In most cases, only data already available in the dossier are required. If, based on the conclusions of the phase I assessment, an in-depth environmental risk assessment becomes necessary, specific investigations on the potential effects on representative organisms and fate of medicinal products in the environment (e.g. studies on effects on aquatic organisms and biodegradation) will be required (phase II assessment).

Residue studies to establish a withdrawal period should be carried out if the product is intended for use in food producing animals. These studies should be carried out in the target species by the intended route and investigate the depletion of residues from the edible tissues (muscle, fat or fat and skin, liver and kidney), as well as from milk, eggs or honey, as appropriate.

5.4. Efficacy

The efficacy of a product should be demonstrated with "pre-clinical studies" and "clinical trials".

Preclinical studies should investigate the pharmacology, dose selection, tolerance in the target animal species and resistance development, if relevant. Usually, these studies are undertaken in healthy animals of the target animal species, although some studies may also involve diseased animals.

Pharmacology studies should investigate the pharmacodynamics and pharmacokinetics (absorption, distribution, metabolism, excretion) relevant for the application i.e. for the proposed indication, dosage, route of administration and target species.

For medicinal products such as antimicrobials and antiparasitics, information on current resistance if applicable, and the potential emergence of resistance of clinical relevance for the claimed indication in the target animal species is required.

Data should also be provided to justify the proposed dose, including the dosing interval, the treatment duration and any re-treatment interval to support the proposed dose. This is usually done with dose determination (titration) studies, investigating different dose levels, and dose confirmation studies using the proposed dose. Depending on the type of product, the justification for the proposed dose based on data such as PK-PD calculations supported by clinical data might be accepted.

Tolerance in the target species should usually be demonstrated by target animal tolerance studies using multiples of the recommended daily dose over an extended time period. In addition, observations from other studies conducted (such as field or dose determination studies) or relevant published literature should be provided.

Clinical trials are performed mostly in diseased animals, under field conditions. These studies should provide a clear picture of the therapeutic efficacy and safety of the product, in comparison with other product(s) authorised in the EU for the same indication (positive control) or untreated animals (negative control). Field trials should include sufficient animal numbers and should usually be conducted in Europe with the final product formulation using the proposed dose, route and duration of administration. They should take into account different climatic/animal husbandry systems, especially for products such as antimicrobials and antiparasitics.

5.5. Biologicals

Due to the widespread use of bovine serum and other animal-derived components in many immunological veterinary medicinal products (IVMPs), specific measures concerning the prevention of the transmission of animal spongiform encephalopathies may be required (see section 4.1.3).

The testing for extraneous agents is particularly relevant for IVMPs and the relevant guidelines concerning this issue should be taken into account. Annex II to Regulation (EU) 2019/6 and the Ph. Eur. monographs on vaccines and immunosera for veterinary use (0062 and 0030 respectively) require the testing of immunological veterinary medicinal products for potential contaminants. Further guidance is available on the EMA website.

If the IVMP contains or consists of genetically modified organisms (GMOs), as defined by Directive 2001/18/EC, the requirements of Article 8(5) of Regulation (EU) 2019/6 on veterinary medicinal products which contain or consist of GMOs should be fulfilled.

Various tests and/or field studies should be conducted to show the potential risks from the product under the proposed conditions of use including target animal safety. For live vaccines, the assessment should focus on the potential shedding by vaccinated animals, the risk to unvaccinated animals or any other species and the potential of the strain used to revert to virulence.

Active substances of IVMPs are exempted from MRL requirements.

Various tests and/or field trials should be conducted to confirm efficacy of the product in relation to all claims made for the product with regards to the properties, effects and use.

5.6. GMP/GDP/GLP/GCP

A common GMP/GDP/GLP/GCP section, covering both medicinal products for human use and veterinary use, is provided in this guide for ease of reference (see section 4.7).

5.7. Limited market products

Data requirements for products classified as intended for a limited market by CVMP may be more flexible and are decided on a case-by-case basis in accordance with the published CVMP Limited Market guidelines and conditions for the authorisation set out in Article 23 of Regulation (EU) 2019/6 as amended. Data requirements can be discussed with regulatory authorities in advance of the regulatory submission and scientific advice on dossier requirements can be requested. Guidance is published on the EMA website along with information on how to request a classification by CVMP. Specific questions may be sent to VetLimitedMarkets@ema.europa.eu.

Application for centralised marketing authorisation

6. Application for centralised marketing authorisation

6.1. Access to the centralised procedure

The centralised procedure is mandatory for certain types of human medicinal products such as those developed by certain biotechnological processes, advanced therapy medicinal products, designated orphans, and those containing new active substances for the treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorders, diabetes, auto-immune diseases, other immune dysfunctions and viral diseases.

The centralised procedure may also be used on a voluntary basis for other medicinal products containing a new active substance, or medicinal products which constitute a significant therapeutic, scientific or technical innovation or that the granting of a Union marketing authorisation would be in the interests of patients at EU level. It is also an option for certain medicinal products intended for paediatric use, or for generics of reference medicinal products authorised through the centralised procedure. Further guidance on the mandatory, and optional scope of the centralised procedure is given in the pre-authorisation guidance on the EMA website.

The centralised procedure is mandatory for certain types of veterinary medicinal products (VMPs) such as those developed by certain biotechnological processes, products intended primarily for use as performance enhancers, products containing an active substance which has not been authorised as a VMP within the Union at the date of the submission of the application, biological VMPs products which contain or consist of engineered allogeneic tissues or cells, and novel therapies such as gene therapy, regenerative medicine, tissue engineering, blood product therapy, phase therapy or nanotechnology-based.

The centralised procedure may also be used on a voluntary basis for products other than those mentioned previously. For those, a centralised marketing authorisation may be granted if no other marketing authorisation has been granted for the veterinary medicinal product within the Union. This includes, for example, generics of veterinary medicinal products authorised nationally.

Regardless of whether the product falls into the mandatory or optional scope, an 'eligibility request' should always be submitted using the 'pre-submission request form' template together with relevant additional justification in Annex (e.g. draft summary of product characteristics, and for optional scope a justification for eligibility).

EMA recommends applicants for human medicines to submit an eligibility request, preferably, at the earliest 18 months before submission of the marketing authorisation application (MAA), and at the latest 7 months before the MAA is filed with EMA, at which point it may be submitted together with the "letter of intent to submit" (i.e. official notification that an applicant will submit an eligible application).

For veterinary medicinal product applications, a pre-submission request form should be completed and sent together with appropriate attachments via EMA ServiceNow. The eligibility request for the centralised procedure should be sent at least 7 months in advance of any submission date.

Following discussion at CHMP or CVMP, EMA will inform the applicant of the outcome of the eligibility procedure. Further guidance on how to request access to the centralised procedure, is given in the EMA pre-submission guidance (human and veterinary).

6.2. Selection of rapporteur/ co-rapporteur

For any scientific evaluation in the centralised procedure a 'rapporteur', and if relevant a 'co-rapporteur' will be appointed from the members or alternate members of the CHMP/CVMP. A rapporteur and a co-rapporteur from the pharmacovigilance risk assessment committee

(PRAC) will also be appointed for all new medicinal products for human use. For advanced therapy medicinal products, a rapporteur and a co-rapporteur will be appointed by the committee for advanced therapies (CAT). The role of the (co-)rapporteur is to perform the scientific evaluation and to prepare an assessment report for the relevant committee according to an agreed timetable.

The appointment of the rapporteur/co-rapporteur is made on the basis of objective criteria, which will ensure the provision of objective scientific opinions and will allow the use of the best available expertise in the EEA in the relevant scientific area.

The appointment process for rapporteur/co-rapporteur is usually initiated at the CHMP/CVMP meeting following the receipt of the 'pre-submission request form' (intent to submit MA). Such appointment can be, but is not always, connected to a possible earlier request for eligibility for assessment via the centralised procedure (see section 6.1) and for human medicinal products initiated at the earliest 7 months before the intended submission date. For products which are eligible to the PRIME scheme, rapporteurs' appointment takes place earlier (see section 3.2). Further guidance on the appointment of rapporteurs for human medicinal products and veterinary medicinal products, is given on the EMA website.

6.3. (Invented) Name of products evaluated via the centralised procedure

The centralised procedure requires one single name for the medicinal product to be authorised. This may be an invented name not liable to confusion with the common name, or it may be a common name or scientific name that is accompanied either by a trademark or the name of the Marketing Authorisation Holder. A common name is the international non-proprietary name (INN) recommended by the World Health Organisation, or, if one does not exist, the usual common name.

Although it is not mandatory under EU legislation, many companies submitting marketing authorisation applications under the centralised procedure use invented names for their medicinal products. EMA assesses whether the invented name proposed for a medicinal product could create a public-health concern or potential safety risks. For human medicinal products, details about the criteria used for checking the proposed invented names are detailed in the guideline on the acceptability of names for human medicinal products processed through the centralised procedure. For veterinary medicinal products there is a separate guideline on the acceptability of names for veterinary medicinal products processed through the centralised procedure.

Further information on how to submit (invented) name(s) for review, including the request form for completion and submission timelines, can be found in the pre-submission guidance on the EMA website for both human and veterinary medicinal products.

6.4. EMA contact point in the centralised procedure

For an initial marketing authorisation application (MAA), a Procedure Lead (PL) for medicinal products for human use, or Procedure Coordinator (PC) for VMPs, is allocated at time of confirmation of eligibility to the centralised procedure and is the primary contact point for the applicant prior to submission and throughout the procedure until the decision is granted by the European Commission.

The PL/PC will serve as the main liaison person between the EMA product team[13], the rapporteurs and the applicant. The PL/PC, in close co-operation with the EMA product team and the rapporteurs, will ensure that the applicant is kept informed of all aspects related to the MAA evaluation.

The applicant should contact the PL/PC for all questions regarding the evaluation procedure such as pre-submission guidance, procedural questions during evaluation and timetables for review.

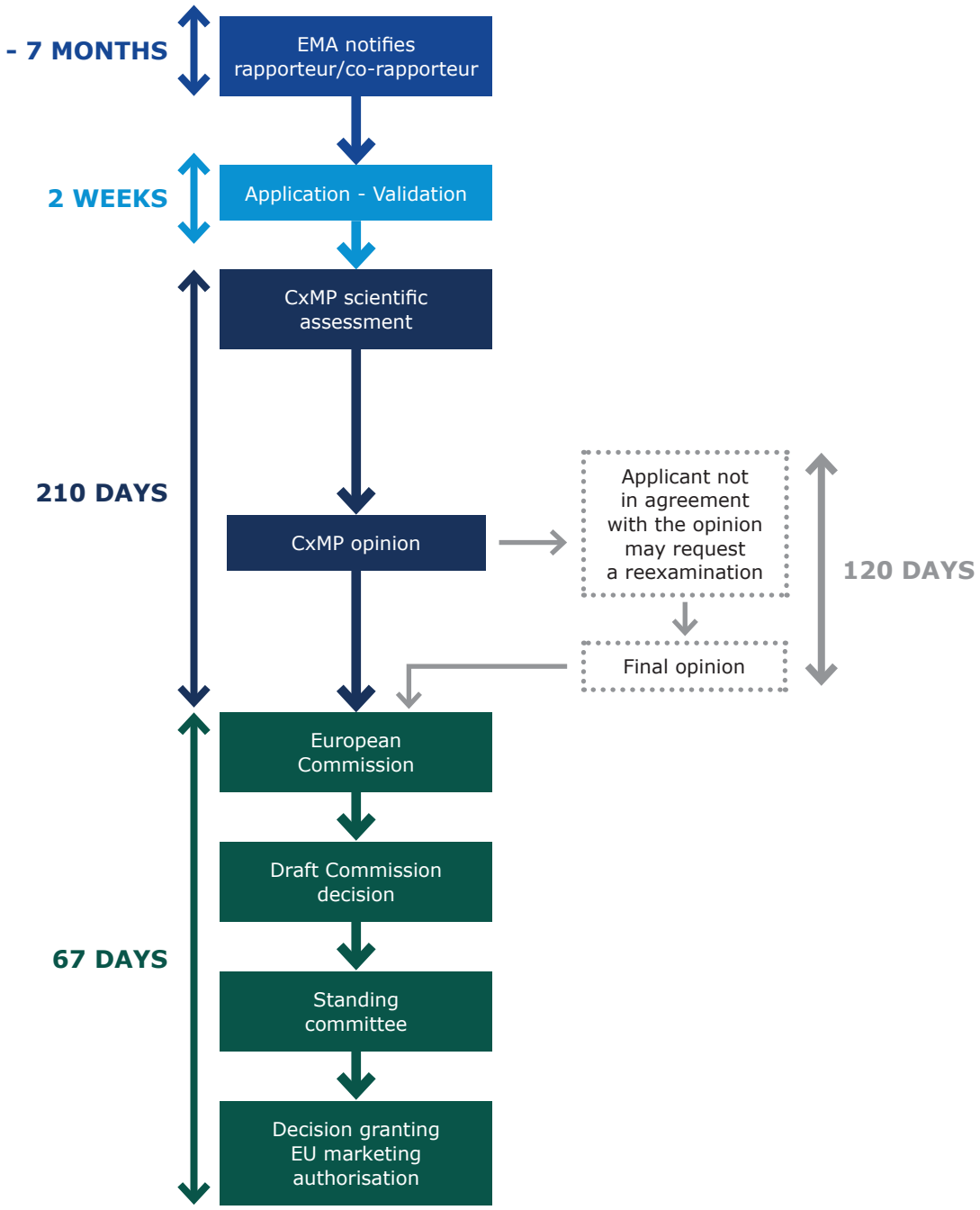
[13]) The EMA product team is composed of EMA staff allocated from different offices to support the pre- and post-authorisation activities of a specific product.

Questions concerning the validation of the MAA, once submitted, will be dealt by an assigned Validation Officer.

At certain milestones during the evaluation procedure, the PL/PC will contact the applicant to facilitate the discussion on the scientific evaluation of the dossier. These include clarification and oral explanation meetings, feedback from committee discussions, discussion on post-authorisation measures and product information. These interactions occur in close co-operation with the rapporteurs.

Occasionally other members from the EMA Product team may contact the applicant directly to facilitate the discussion on specific aspects (e.g. quality mock-up review).

Figure 2. Overview of the centralised procedure



6.5. EMA pre-submission interactions

When preparing the submission of a marketing authorisation application, applicants have the opportunity to interact with EMA to discuss procedural or regulatory issues in relation to the upcoming submission, and to establish contacts with EMA staff that will be involved with the application. Not all pre-submission interactions will require a dedicated meeting. If the need for a meeting is identified, it will be held remotely. For further details see section on 'How are MAA pre-submission interactions structured' in the EMA pre-submission guidance for human and veterinary medicines.

For human medicines, following the receipt of the pre-submission interactions form with the complete set of relevant annexes, the EMA PL will review and discuss the questions and background documents received with the EMA Product team members. A set of consolidated written responses to the questions raised by the applicant will be sent by EMA to the applicant within 3 weeks from receipt of these documents. The applicant may request a teleconference meeting with EMA in case further clarifications are needed on the written responses already received. It is anticipated that in some complex cases, a tailored pre-submission meeting with relevant members of the EMA product team may be required. Within the written responses, EMA will inform the applicant if such meeting is considered needed.

6.6. Compilation of the application dossier

Data generated from pharmaceutical tests, non-clinical and clinical tests and trials with the medicinal product concerned, as well as other information required by the EU legislation, need to be provided to EMA and all CHMP/CVMP members for evaluation. All applications have to be submitted in English.

The application dossier for medicinal products for human use must be presented in accordance with the EU-CTD (Common Technical Document) presentation outlined in Volume 2B of the notice to applicants published on the Commission website.

The CTD is an internationally agreed format for the preparation of a well-structured application to be submitted to regulatory authorities in the ICH (International Council for Harmonisation) countries. The CTD provides a harmonised format of presentation of the necessary data to support the application in accordance with the legal/scientific requirements of each region. The EU-CTD is organised in five modules: module 1 contains the specific EU administrative and prescribing information. The structure of modules 2, 3, 4, and 5 is common for all regions and will contain the high-level summaries and quality, non-clinical and clinical documentation respectively.

For veterinary medicinal products, the application dossier should be presented in accordance with Annex II of Regulation (EU) 2019/6, as amended by Commission Delegated Regulation (EU) 2021/805 and guidance published on the VET eSubmission webpage.

EMA implements an electronic-only submission for all applications for marketing authorisation.

For human medicines applications, the electronic Common Technical Document (eCTD) is the required format. eCTD is the only acceptable electronic format for all applications and all submission types. Non-eCTD electronic applications are no longer a valid format for submission. The latest version of the ICH M2 eCTD specification can be found on the ICH website, and the current version of the eCTD EU module 1 specification can be found on the eSubmission website. Further guidance on eCTD submissions is also available in the harmonised guidance for eCTD submissions in the EU.

For veterinary medicines applications, the VNeeS structure is the required format, however, CTD format for part 2 (quality) is also accepted. The guideline on eSubmissions for veterinary products outlines the requirements for electronic veterinary dossiers, and guidance is available on the EMA website and the veterinary eSubmission page.

The use of the eSubmission Gateway or eSubmission Syncplicity Web client is mandatory for all electronic submissions through the centralised procedure. More information is available on the eSubmission Gateway page.

Detailed information on submission requirements for EMA, (co-)rapporteur, and CHMP/CVMP members is given in the EMA pre-submission guidance (human and veterinary) on the EMA website. All submissions for Centrally and non-Centrally Authorised Products (MRP/DCP/NP/SRP) for human and veterinary procedures sent to EMA via the eSubmission Gateway or eSubmission Web Client are available via the Common Repository and are considered delivered to all National Competent Authorities' representatives, alternates and scientific experts. Submission of additional copies directly to the NCAs on CD/DVD or via the Common European Submission Portal (CESP) is no longer accepted, as it might lead to validation issues and cause delays.

Submission requirements for procedures such as referrals, ASMFs, NAP submissions related to EMA coordinated procedures and ancillary medicinal substances in medical device are available on the EMA webpage.

The use of the Electronic Application Form (eAF) is mandatory for all procedures in the EU (Centralised procedure, Mutual Recognition Procedure, De-Centralised Procedure and by default National procedure), for human and veterinary products. The electronic application forms should be used for all initial MAA, variations and renewal applications. The forms and all related guidance documents are available on the eAF website and in the PLM Portal. Information related to the web-based electronic Application Form hosted in the Product Lifecycle Management (PLM) Portal is available on the eSubmission website and in the PLM Portal.

The eAFs should always be submitted as a part of the submission dossier within the eCTD sequence (human medicines) or within the VNeeS folder structure (veterinary medicines).

For the product information, EMA provides the applicant with a template of what must be included in these documents. The latest version of these templates for human and veterinary medicines are available on the EMA website.

6.7. Submission and validation of the application dossier

Recommended submission dates for human and veterinary medicinal products are published on the EMA website. If the original indicated submission date cannot be met, the applicant should immediately inform EMA, the rapporteur and co-rapporteur. A delayed submission can impact the planned activities of the assessment teams of rapporteurs and co-rapporteurs.

EMA will check if the application meets all relevant legal and procedural EU requirements ('validation') before the start of the scientific evaluation. Applicants should be aware that for medicinal products for human use, a compliance check for paediatric requirements may be necessary (see section 4.6). SMEs should indicate in section 2.4.1 of the eAF the SME status and provide in Annex 5.7 of the eAF, a valid SME number.

Further information for human medicines can be found on section 4 of the pre-authorization guidance. Applicants are encouraged to use the administrative checklist to ensure that the dossier complies with requirements and issues are avoided during validation.

EMA will issue an invoice on the date of the notification of the administrative validation to the applicant, and fees will normally be payable within 45 days of the date of the said notification. For SME applicants, the fee payment may be deferred (see section 2.4).

6.8. Evaluation of the application

Once the application is validated, EMA starts the evaluation procedure at the monthly starting date published on the EMA website. EMA will ensure that the **evaluation is finalised within 210 days** (assessment time not including clock-stops for the applicant to provide a response to questions from the CHMP/CVMP). In exceptional or well-justified cases, this timeline may be shortened (accelerated assessment) or extended by 90 days (veterinary applications only).

The procedure can be summarised as follows:

In the first evaluation phase, the rapporteur and co-rapporteur prepare assessment reports on the application within 80 days (85 days for veterinary products). The assessment reports are sent to all other CHMP/CVMP members for comments and to the applicant for information. Following discussion of the assessment reports, the CHMP/CVMP adopts a "list of questions", identifying 'major objections' and/or 'other concerns', which will be sent to the applicant by day 120.

The rapporteur and co-rapporteur then assess the applicant's responses (second evaluation phase), submit their joint assessment for discussion to the CHMP/CVMP and, taking into account the conclusions of this debate, prepare a final assessment report which also includes the draft product information. The CHMP/CVMP will adopt such report together with a list of outstanding issues if necessary. Based on the content of the list of outstanding issues, an oral explanation with the applicant might be planned. Once the evaluation is completed, the CHMP/CVMP adopts a favourable or unfavourable opinion on whether to grant the authorisation.

During the assessment, the CHMP/ CVMP may consult scientific advisory (SAGs) or ad-hoc expert groups in connection with the evaluation of specific types of medicinal products or treatments, to which the committee may ask for expert's views on a number of points. Scientific advisory or ad-hoc expert groups are established by the relevant committee. They consist of European experts selected according to the particular expertise required on the basis of nominations from the CHMP/CVMP or EMA.

A more detailed **standard timetable** for the evaluation of an application in the centralised procedure is provided below:

DAY	ACTION
1	Start of the procedure
80 (85 Vet)	Receipt of the assessment report(s) from rapporteur and co-rapporteur by CHMP/CVMP members and EMA. Sent to applicant for information only.
100	Rapporteur, co-rapporteur, other CHMP/CVMP members and EMA receive comments from members of the CHMP/CVMP.
115	Receipt of draft list of questions (including the CHMP/CVMP recommendation and scientific discussion) from rapporteur and co-rapporteur.
120	CHMP/CVMP adopts the list of questions as well as the overall conclusions and review of the scientific data to be sent to the applicant by EMA. Clock stop.

The applicant is expected to respond within the timeframe agreed by the CHMP/CVMP from the date of receipt of the questions, which is usually 3 months for human medicinal products. Applicants may request an additional 3-month period by writing to the CHMP chairman outlining their reasons. For veterinary procedures the standard timeframe for response is 6 months, which may be extended upon justified request. If the applicant is unable to respond within the timeframe, then careful consideration should be given to withdraw the application and resubmit, if necessary, after obtaining scientific advice, when the full information is available.

Further guidance on the response time for procedures relating to human medicinal products is provided in the EMA guidance on the EMA website.

DAY	ACTION
121	Submission of the applicant's responses, including revised product information in English. Restart of the clock.

After receipt of the responses, the following standard timetable applies:

DAY	ACTION
150 (160 Vet)	Joint response assessment report from rapporteur and co-rapporteur received by CHMP/CVMP members and EMA. Sent to applicant for information only.
170	Deadline for comments from CHMP/CVMP members to be sent to rapporteur and co-rapporteur, EMA and other CHMP/CVMP members.
180	CHMP/CVMP discussion and decision on the need to adopt a list of "outstanding issues" and/or an oral explanation by the applicant. If an oral explanation is needed, the clock is stopped to allow the applicant to prepare the oral explanation. Clock stop.

Applicants should normally respond (or prepare for an oral explanation) within one month. In exceptional circumstances an extension may be granted if scientifically justified.

DAY	ACTION
181	Restart of the clock and oral explanation (if needed).

Information on how oral explanations are conducted is available on the EMA website.

At the conclusion of the oral explanation, representatives of the applicant will be invited to leave and the CHMP/CVMP will discuss and provide a preliminary recommendation on the acceptability of the application. The applicant will be informed of the trend at CHMP/ CVMP level at the end of the scientific discussion ahead of any formal vote to conclude the evaluation process.

DAY	ACTION
By 210	Adoption of CHMP/CVMP opinion + CHMP/CVMP assessment report (and timetable for the provision of product information translations)

EMA will prepare a "summary of opinion" (for favourable as well as unfavourable opinions) in liaison with the applicant. Such summaries will be published on the EMA website after the adoption of the CHMP/CVMP opinion.

If during the assessment procedure an applicant decides to withdraw its application before an opinion is adopted, EMA will make this information public on its website together with the relevant assessment report.

Evaluation of the risk management plan by the PRAC for human medicines

Applicants are required to submit a risk management plan (RMP) at the time of marketing authorisation application and keep it up to date during the lifecycle of the product. The RMP will be subject to review by the pharmacovigilance risk assessment committee (PRAC) in parallel to the CHMP review.

For more information on the RMP, please refer to Good pharmacovigilance practices (GVP) module V and the EMA website (see also section 7.2).

Evaluation of advanced therapy medicinal products by the CAT for human medicines

For advanced therapy medicinal products (ATMPs) the scientific evaluation is carried out primarily by the committee for advanced therapies (CAT), which prepares the draft opinion on the quality, safety and efficacy for final approval by the CHMP. For this reason, a slightly different timetable applies to ATMP applications.

For more information on the ATMPs evaluation procedure, please refer to the EMA website.

6.9. Re-examination of the CHMP/CVMP opinion

The applicant may notify EMA or CHMP/CVMP in writing of their intent to request a re-examination of the CHMP/CVMP opinion within 15 days of its receipt (after which, if such a request is not made, the opinion becomes final). Upon receipt of the notification of intent, the CHMP/CVMP will appoint a new set of (co)rapporteur to re-examine its opinion. The detailed grounds for the re-examination request must be forwarded to EMA **within 60 days** after receipt of the opinion, at which time point the re-examination assessment procedure will start.

Following the receipt of the detailed grounds for the re-examination, the rapporteurs will assess the application within 60 (human) or 90 (veterinary) days. Upon request of the applicant or the CHMP/CVMP, a scientific advisory group (SAG) or ad-hoc expert group may be involved in the re-examination, and an oral explanation can be held.

At the end of the re-examination procedure, the CHMP/CVMP will adopt a final opinion either confirming its previous opinion or changing that opinion on the application. No clock-stops apply to this procedure.

For further guidance on the re-examination procedure for human medicinal products and CHMP timetable for assessment, refer to the EMA website. For veterinary medicinal products please refer to the veterinary procedural advice.

For ATMPs, please refer to the following guidance: Procedural advice on the evaluation of advanced therapy medicinal product.

6.10. Conditions to the marketing authorisation

The marketing authorisation holder (MAH) can be imposed the obligation to conduct post-authorisation measures. These conditions, whilst not precluding the approval of a marketing authorisation or other post-authorisation procedures, are considered to be key to the benefit-risk balance of the product.

These obligations can be imposed at the time of the granting of the marketing authorisation or later. These can consist of post-authorisation safety or efficacy study, or additional pharmacovigilance activity included in the Risk Management Plan (see also 7.2).

Further information on Conditional Marketing Authorisation (CMA) on section 6.14.2.

6.11. Post-authorisation efficacy studies (PAES)

To support a benefit-risk for a medicine, demonstration of benefit is required from trials that are appropriately designed and conducted in accordance with applicable guidance. A PAES may nevertheless be needed to increase the understanding of therapeutic efficacy.

For human medicines, delegated Regulation (EU) No 357/2014 provides details on PAES that may be imposed at time of, or after the marketing authorisation of centrally (CAPs) and nationally authorised medicinal products (NAPs). Guidance on PAES within or outside the scope of Delegated Regulation (EU) No 357/2014 is available. Information on post-authorisation safety studies (PASS) is provided in section 7.2.

For veterinary medicines, the MAH may be required to conduct post-authorisation studies for antimicrobials in order to ensure that the benefit-risk balance remains positive given the potential development of antimicrobial resistance, or in the case of a marketing authorisation under exceptional circumstances (see section 6.14.4).

6.12. Publication of clinical data for human medicines ('policy 0070')

EMA proactively publishes the clinical reports submitted under the centralised procedure for human medicines after consultation with the company on the redaction of commercially confidential information (CCI) and the anonymisation of protected personal data (PPD). The policy applies to clinical reports contained in all initial MAA submitted on or after 1 January 2015, and to applications submitted on or after 1 July 2015 for extension of indication or line extension, irrespective of the dossier outcome (positive or negative opinion or withdrawn). The policy was suspended in 2018 due to the relocation of the EMA and its Business Continuity Plan and has been re-activated as of September 2023, with a limited scope initially, only for new active substances. Invitation letters are sent to all companies, with the list of clinical documents in scope, where the clinical data for a marketing authorisation are expected to be published.

The data published are module 2.5 (clinical overview), module 2.7 (clinical summary), module 5 [clinical study reports (CSRs) and appendices 16.1.1 (protocol and protocol amendments), 16.1.2 (sample case report form) and 16.1.9 (documentation of statistical methods)]. Such data either use the common technical document (CTD) format or another format.

The publication process includes the submission of a "redaction proposal version", a consultation phase and a submission of a "final redacted version". A pre-submission meeting with EMA is offered to discuss preparation of the package.

The timeline for providing a "redaction proposal version" package by the company is determined by CHMP opinion and is expected, from Day 180 to 30 days after opinion, for review.
The final clinical data package is expected to be published four months after CHMP opinion.

The validity of the proposed CCI redactions, the anonymisation report outlining compliance in the treatment of the PPD, including a review of PPD redactions/anonymisation in the documents provided is assessed by EMA in a "redaction proposal version" package. EMA communicates its conclusion and comments for the entire set of the submitted clinical reports after consultation with the company.

The company then carries out the redactions to create a "final redacted version" of each clinical report. The final package is sent as a new eCTD sequence to EMA for publication.

Redacted/anonymised clinical reports are published by EMA on its corporate website. Prior to publication, EMA will watermark each page of the clinical reports in the "final redacted version".

For withdrawn applications, the publication of the redacted/ anonymised clinical reports will take place within 150 days after the receipt of the withdrawal letter.

For more details on policy 0070, including procedural aspects, identification and redaction of CCI, anonymisation of PPD, SMEs are advised to refer to guidance on the EMA website.

6.13. Decision-making process

After adoption of the CHMP/CVMP opinion, EMA has 15 days to forward its (final) opinion to the Commission. This is the start of the "decision-making process", whereby the CHMP/CVMP opinion will be turned into a legally binding Commission decision for all member states and the applicant.

The Commission decision granting a marketing authorisation to the medicinal product concerned includes the agreed product information. The Commission decision is legally binding in all member states and the product information must therefore be provided in all EU official languages. The translations of the product information are normally provided by the applicant five days after adoption of the CHMP/CVMP opinion.

Further details on the handling of translations are available on the EMA website. For SME applicants, EMA will provide translations of product information into the EU official languages. The translations will be reviewed by the member states before transmission to the Commission (see section 2.4.1).

During the decision-making process, the Commission services check that the marketing authorisation complies with Union law, consulting various Commission directorates-general. In addition, the Commission consults the Standing Committee, which consists of representatives of all EU member states. The opinion of the Standing Committee will normally be given by written procedure.

The Commission prepares a draft Commission decision within 15 days. Member states have 22 days (human medicines) or 10 days (veterinary medicines) to forward their written observations on the draft decision to the Commission. Within this time-limit, member states must inform the Commission whether they approve the draft, reject it, or abstain. Any member state failing to respond within the time-limit to express its opposition or intention to abstain from voting is deemed to have approved the draft.

The Commission will take a final decision within 15 calendar days after the end of the Standing Committee phase. The decision will be sent to the applicant and published in the EU "Official Journal".

The Union marketing authorisation for the medicinal product will be granted in **67 days** (human) or **55 days** (veterinary) **after adoption** of the final CHMP/CVMP opinion.

Once the Union marketing authorisation is granted, EMA will publish the CHMP/CVMP assessment report on the medicinal product which includes the reasons for its opinion in favour of granting authorisation, after deletion of any information of commercially confidential nature. This document is called the European public assessment report (EPAR).

The EPAR for human medicines also includes a summary in the official EU languages, written in a manner that is understandable to the public. EPARs and their summaries are published on the EMA website.

For veterinary medicines, the Union Product Database (UPD) is available for all veterinary medicines authorised in the EU (i.e. centrally as well as nationally authorised ones). The public assessment report from CVMP and the product information will be published in the UPD. Upload of the product data in the UPD is a responsibility of the national competent authority or the Agency, though MAHs have the responsibility to check that the information is correct.

A marketing authorisation for a medicinal product for human use is generally valid for five years. There is an exception when a conditional marketing authorisation for human medicinal products has been granted (see section 6.14.2). The marketing authorisation may be renewed after five years on the basis of a re-evaluation by EMA/CHMP of the benefit-risk balance of the product, upon application by the holder at least nine months before expiry. Once renewed, the marketing authorisation shall be valid for an unlimited period, unless the Commission decides on the basis of the CHMP recommendation that due to justified grounds relating usually to pharmacovigilance that there is a need to proceed with one additional five-year renewal.

A marketing authorisation for veterinary medicines authorised under Regulation (EU) 2019/6 is generally valid for an unlimited period with exceptions for marketing authorisations for limited markets (see section 5.7) or under exceptional circumstances (see section 6.14.4).

6.14. Early access to the EU market

An overview of the support available for early access for human medicines is available on the EMA website.

6.14.1. Accelerated assessment

In order to meet the expectations of patients as well as animal owners and to take account of the increasingly rapid progress of science and therapies, it is possible to obtain a marketing authorisation via an 'accelerated assessment procedure' (that is, within up to **150 days instead of 210 days**) for products which are of major public or animal health interest particularly those bringing a therapeutic innovation.

Any request for accelerated assessment should be made as early as possible before the actual submission of the marketing authorisation application. The request should elaborate on the major benefits expected and present the arguments to support the claim that the medicinal product introduces new methods of therapy or improves on existing methods, thereby addressing to a significant extent the greater unmet needs for maintaining and improving public health.

PRIME products are also expected to benefit from an accelerated assessment, which will be confirmed at the time of marketing authorisation application (see 3.2).

For further details refer to the EMA pre-submission guidance for human medicinal products and veterinary medicinal products. Additionally, please refer to corresponding CHMP and CVMP guidelines.

6.14.2. Conditional marketing authorisation for human medicines

In addition to accelerated assessment (see 6.14.1), in order to meet unmet medical needs of patients and in the interests of public health, the CHMP can recommend the granting of marketing authorisations on the basis of less complete data than are normally required. In such cases, the granting of a marketing authorisation is subject to certain specific obligations and has to be renewed annually ('conditional marketing authorisation').

This may apply to medicinal products used in seriously debilitating or life-threatening diseases, emergency situations in response to public health threats, or products designated as orphan medicinal products.

A conditional marketing authorisation (CMA) can be granted where the CHMP finds that, although comprehensive clinical data referring to the safety and efficacy of the medicinal product have not been supplied, all of the following requirements are met:

- The benefit-risk balance of the medicinal product is positive;
- It is likely that the applicant will be in a position to provide comprehensive data;
- Unmet medical needs will be fulfilled;
- The benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

CMAs are **valid for one year**, on a renewable basis. The holder will be required to complete ongoing studies or to conduct new studies to confirm that the risk-benefit balance is positive. In addition, specific obligations may be imposed in relation to the collection of pharmacovigilance data.

The granting of a CMA allows medicines to reach patients with unmet medical needs earlier and ensures that additional data on a product are generated, submitted, assessed and acted upon.

Applicants are encouraged to engage in early scientific dialogue with EMA and other stakeholders to discuss their development plan for a CMA (see 3.4.1).

For further guidance on the criteria for conditional marketing authorisation, justifications to be provided and the procedure to be followed, refer to the Commission Regulation (EC) No 507/2006 on the Commission website and to the respective CHMP guideline published on the EMA website.

6.14.3. Compassionate use for human medicines

Compassionate use is a treatment option that allows the use of an unauthorised medicine. Under strict conditions, products in development can be made available to groups of patients with life-threatening, long-lasting or seriously debilitating illnesses which cannot be treated satisfactorily with any current authorised therapies and who cannot enter clinical trials. The medicine must be undergoing clinical trials or have entered the marketing authorisation application process and, while early studies will generally have been completed, its safety profile and dosage guidelines may not be fully established.

EMA provides recommendations through the CHMP for medicinal products that are eligible to be authorised via the centralised procedure (see section 6.1), but these do not create a legal framework. Compassionate use programmes are coordinated and implemented by member states which set their own rules and procedures.

Further information is available on the EMA dedicated webpage.

6.14.4. Marketing authorisation under exceptional circumstances

In exceptional circumstances, a marketing authorisation can be granted, subject to certain conditions, particularly concerning the efficacy or safety of the product ('marketing authorisation under exceptional circumstances'). Continuation of the authorisation will be linked to an annual reassessment of these conditions (for veterinary medicines on request of the MAH).

For human medicines, this can apply in cases where the applicant can show that it is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:

- The indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or
- In the present state of scientific knowledge, comprehensive information cannot be provided, or
- It would be contrary to generally accepted principles of medical ethics to collect such information.

For further guidance on the conditions and procedures for the granting of a marketing authorisation under exceptional circumstances, refer to the EMA guidance for human medicinal products published on the EMA website.

For veterinary medicines, this can apply in cases where the applicant can demonstrate that it is not possible to provide certain data on the quality, safety or efficacy and that the benefit to animal or public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

Please refer to the EMA guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances published on the EMA website for more information.

6.15. Marketing of a centrally authorised product in the Union

The marketing authorisation holder (MAH) of a centrally authorised product is legally obliged to inform EMA and the member state(s) concerned as applicable of the dates of the actual marketing of the product in the respective member states, taking into account the various presentations authorised. The MAH should notify EMA within 30 days of the initial placing on the market of the product within the Union.

Thereafter, any subsequent placing on the market or change in the marketing status should be reported.

For human medicines, information on marketing status is reported in the IRIS platform (see How to report marketing status updates to the Agency for CAPs on the EMA website).

For veterinary medicines (i.e. centrally and nationally authorised) the dates of first marketing and on the annual sales should be reported by the MAH in the UPD.

Withdrawn products

The MAH of a centrally authorised product must notify EMA of their request to withdraw at least 2 months in advance unless unforeseeable circumstances which may require an immediate notification (e.g. safety reasons). The update in IRIS would not replace the formal request to address to the European Commission.

The MAH should notify the Agency of their intent not to apply for a renewal of their centralised marketing authorisation at time of expected submission (i.e. at least 9 months prior to MA expiry).

For further details, refer to the 'Questions and Answers' on this topic included in the EMA post-authorisation guidance, which also provides details on obligations for notification of withdrawal from the market of nationally authorised products (national procedures, MRP, DCP). For veterinary medicines, refer to the guidance on the EMA website.

Sunset Clause for human medicines

Any authorisation, which is not followed by the actual marketing in at least one Member State in the European Union within three years after authorisation, will cease to be valid (so-called 'sunset clause'). Similarly, when a product previously marketed in the European Union is no longer actually present on the market of any of the member states of the European Union for three consecutive years, the authorisation will cease to be valid. However, the Commission in exceptional circumstances may grant exemptions from these provisions on duly justified public health grounds.

EMA uses the IRIS platform to collect marketing status updates and monitor the sunset clause provision for centrally authorised medicinal products. This is done in view to notify the Commission when a three consecutive year period without marketing has elapsed, and that the sunset clause provision should take effect.

For more details on this provision, refer to the 'list of questions and answers' on this topic included in the EMA post-authorisation guidance on the EMA website.

6.16. 'EU-M4all' procedure for human medicines

'EU-M4all' is a procedure designed to support access to high priority medicines for patients outside the EU. It was previously known as the 'Article 58' procedure, as the legal basis is Article 58 of Regulation (EC) No 726/2004.

EMA's human medicines committee, the CHMP, can carry out scientific assessments and give opinions on medicines for use exclusively outside the EU. When assessing these medicines, the CHMP cooperates with WHO and national regulators in the countries where the products are expected to be used and applies the same standards as for medicines intended for use inside the EU. Medicines eligible for this procedure include vaccines used in the WHO Expanded Programme on Immunization, or for protection against a public health priority disease, as well as medicines for WHO target diseases such as HIV/AIDS, malaria, dengue and tuberculosis.

Cooperation with WHO and regulators from countries where the products are expected to be used, enriches the epidemiology and local disease expertise, facilitates a benefit-risk assessment tailored to the intended non-EU population, streamlines the WHO prequalification programme and facilitates national registration in target countries.

EMA welcomes parallel applications for a centralised EU marketing authorisation and an opinion under the EU-M4all pathway. For a medicine to be eligible for a parallel evaluation, the active substance(s) must be identical in both applications, with comparable indications, although the formulation, pharmaceutical form or route of administration may be different in the two applications.

Further guidance is provided on the EMA website.

6.17. ‘OPEN’ initiative for human medicines

EMA collaborates with medicines regulators outside the EU in the scientific evaluation of certain medicines, within a framework called ‘OPEN’ (opening procedures at EMA to non-EU authorities).

Within this framework, several regulators evaluate a medicine in parallel with EMA, remaining scientifically and procedurally independent from one another while sharing information, expertise and approaches during the evaluation. The WHO is a partner in the initiative, which aims to accelerate registration and availability of certain medicines in low- and middle-income countries.

Further guidance is provided on the EMA website.

Risk management and pharmacovigilance

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7. Risk management and pharmacovigilance

Pharmacovigilance, or the surveillance of the safety of a medicinal product during its life on the market, is extensively regulated by EU directives and regulations. EMA is co-ordinating pharmacovigilance at EU level with regards to medicinal products for human or veterinary use. EU legislation requires member states to establish national pharmacovigilance systems to collect and evaluate information on adverse reactions to medicinal products or their side effects and to take appropriate action where necessary. It also requires marketing authorisation holders to report suspected adverse reactions to the authorities in certain formats and within specified timeframes. Applicants and marketing authorisation holders are also required to provide competent authorities with a description of their pharmacovigilance system and, where appropriate, of product-related risk management systems.

When a medicinal product is first authorised, the information available comes from experience in non-clinical testing and clinical trials. During the marketing authorisation application evaluation, the potential risks of a medicinal products are weighed against its potential benefits, based on what is known about the medicinal product at that time. Once it is placed on the market and used in a wider population, more information on its benefits and risks becomes available. Pharmacovigilance systems are designed to collect and continuously evaluate this information. If a medicinal product's overall risk/benefit balance changes significantly for any reason, it may become necessary to vary, suspend or withdraw its use.

Strengthened pharmacovigilance legislation for medicinal products for human use (Regulation (EU) No 1235/2010 and Directive 2010/84/EU) has been effective since July 2012, and had significant implications for applicants and holders of European Union marketing authorisations (see 7.2).

EMA together with the member states has drawn up Good pharmacovigilance practices (GVP) as a set of guidelines for the conduct of pharmacovigilance for medicines for human use in the EU.

Strengthened pharmacovigilance for veterinary medicinal products has been introduced through Regulation (EU) 2019/6, and Commission Implementing Regulation (EU) 2021/1281 lays down good pharmacovigilance practices. These provide guidance on signal management, the pharmacovigilance system master file, inspections and communication. Further guidance is given in the Veterinary Good Pharmacovigilance Practice (VGVP), which contains five modules and a glossary.

7.1. Good pharmacovigilance practices (GVP) for human medicines

Good pharmacovigilance practices aim to facilitate the performance of pharmacovigilance activities within the EU and apply to marketing-authorisation holders (MAHs), EMA and national competent authorities. They cover medicines authorised centrally via the Agency as well as medicines authorised at national level.

The guidance on GVP contains 12 modules, each of which covers one major process in pharmacovigilance:

Module I:
pharmacovigilance systems and their quality systems

- Establishment and maintenance of quality assured pharmacovigilance systems for MAHs, competent authorities and EMA, according to ISO general principles.

Module II:
pharmacovigilance system master file (PSMF)

- Requirements for the PSMF, including its maintenance, content and associated submissions to competent authorities.

Module III:
pharmacovigilance inspections

- Planning, conduct, reporting and follow-up of pharmacovigilance inspections in the EU and the role of the different parties involved.

Module IV:
pharmacovigilance audits

- Planning and conduct of legally required audits, and the role, context and management of pharmacovigilance audit activity.

Module V:
risk management systems

- Modular approach to risk management plans (RMPs), aimed at identifying, characterising and minimising a medicinal product's risks.

Module VI:
management and reporting of adverse reactions to medicinal products

- Obligations of competent authorities, MAHs and EMA regarding the collection, data management and reporting of suspected adverse reactions associated with medicinal products authorised in the EU.

Module VII:
periodic safety update report (PSUR)

- Preparation, submission and assessment of PSURs and publication of PSUR-related documents.

Module VIII:
post-authorisation safety studies (PASS)

- Transparency, scientific and quality standards of non-interventional PASSs conducted by MAHs.
- Procedures whereby a competent authority may impose an obligation to conduct a clinical or non-interventional study and the impact on the risk management system.
- Procedures that apply to non-interventional PASS pursuant to an obligation imposed by an EU competent authority for protocol oversight, reporting of results and subsequent changes to the marketing authorisation.

Module IX:
signal management

- Structures and processes for signal management and their application in the setting of EU pharmacovigilance.
- Roles, responsibilities and procedural aspects in the setting of the EU signal management process overseen by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC).
- The reporting of emerging safety issues or suspected adverse reactions by marketing authorisation holders occurring in special situations that may require urgent attention by the competent authority.

Module X:
additional monitoring

- Requirements for product information for medicinal products which are new or present a specific safety concern, encouraging patients and healthcare professionals to report suspected adverse reactions and allowing for additional monitoring of the product's safety profile.

Module XV:
safety communication

- Communication and coordination of safety information in the EU.

Module XVI:
risk minimisation measures: selection of tools and effectiveness indicators

- Selection, development, implementation and co-ordination of risk minimisation measures (RMM), in particular of additional RMMs, as well as the principles and concepts of the evaluation and their effectiveness.
- Roles and responsibilities of marketing authorisation holders and competent authorities in the setting of the EU regulatory network and the contribution of healthcare professional and patient representatives.

Each GVP module should be consulted for further information on pharmacovigilance requirements for medicinal products for human use.

In addition to the module chapters, GVP contains chapters covering product or population specific considerations:

- Vaccines for prophylaxis against infectious diseases;
- Biological medicinal products;
- Paediatric population.

All GVP modules, Addendums and Annexes are grouped under the GVP webpage.

7.2. Key aspects of the EU pharmacovigilance system for human medicines

This section highlights some of the most important aspects of the EU pharmacovigilance legislation. A comprehensive overview of this legislation can be found on the EMA website.

Establishment of the PRAC

The Pharmacovigilance Risk Assessment Committee (PRAC) was formally established in line with the pharmacovigilance legislation to strengthen the safety monitoring and regulatory decision making of medicines across Europe.

The PRAC is responsible for providing recommendations to the Committee for Medicinal Products for Human Use (CHMP) and the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) on any question relating to pharmacovigilance activities in respect of medicinal products for human use and on risk management systems including the monitoring of their effectiveness. It includes experts in medicines safety from regulatory authorities in member states, as well as scientific experts and members representing patients and healthcare professionals nominated by the European Commission.

Pharmacovigilance system master file (PSMF)

MAHs are required to maintain a PSMF which includes an overview of the MAH's current pharmacovigilance system related to one or more products. The PSMF should be permanently available for submission or inspection by the national competent authority within seven days of request. It should be located either at the site in the EU where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site in the EU where the qualified person responsible for pharmacovigilance (QPPV) operates. This file may be also stored in electronic form.

At time of marketing authorisation application, the applicant should submit electronically in the extended EudraVigilance medicinal product dictionary (XEVMPD) information on the PSMF location using the agreed format for an extended EudraVigilance product report message (XEVPRM). The XEVMPD will then assign a unique code (EVCODE) to the master file location, which can be noted in the application. After the granting of the marketing authorisation, any change to the PSMF should be communicated to the authorities through the Article 57 database only, without the need to submit a variation. Companies should continue to ensure their entries in the 'Article 57' database for medicinal products for human use are up to date, including the QPPV and PSMF information.

The PSMF is not part of the marketing authorisation dossier and is maintained independently from the marketing authorisation. The MAA contains only a reference to the location and a summary of the applicant's pharmacovigilance system. A list of locations where PSMFs are kept and contact information for pharmacovigilance enquiries is published by EMA.

GVP module II provides guidance on the requirements for the PSMF, including its maintenance, content and associated submissions to the competent authorities.

Risk management plan (RMP)

The RMP is a stand-alone document which summarises what is known about the safety of the product and discusses how the applicant/MAH will monitor and investigate further the safety profile of the product, and manage the risks associated with it. Guidance on RMP is provided in GVP module V. Additional guidance is available on the EMA website.

All applicants submitting an initial MAA are required to submit an RMP in the application dossier. An RMP (or an update, if one already exists) is also required where there is an application involving a significant change to an existing marketing authorisation or at the request of the Agency or national competent authority. Once a product has an RMP it needs to be updated throughout the lifecycle of the product. Summaries of RMPs will be made public by the Agency.

SMEs are advised to contact the competent authorities to discuss the RMP in advance of its submission.

Post-authorisation safety studies (PASS)

The ability to require and enforce PASS has become part of the Agency's toolkit for improving the benefit-risk monitoring of medicines. A PASS is a study of an authorised medicine which aims at identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicine, or measuring the effectiveness of risk management measures during its lifetime. Such studies provide information to support regulators in decision-making on the safety and benefit-risk profile of a medicine. A PASS may be imposed as a legal requirement on the conditions of a marketing authorisation (see 6.10), may be a requirement of an RMP or conducted voluntarily by an MAH. Guidance on PASS is provided in GVP module VIII. Additional guidance is available on the EMA website.

Information on post-authorisation efficacy studies (PAES) is provided in section 6.11.

Electronic submission of information on medicinal products under article 57(2)

MAHs are required to submit electronically to the Agency information on all medicines authorised or registered in the EU pursuant to Article 57(2) of Regulation (EC) 726/2004. The XEVMPD data-entry tool, also known as EVWEB (see section 7.5), should be used to submit the information.

The aim of the submission of these data is to establish a complete inventory of all medicines authorised for use in the EU and EEA, including medicines authorised centrally via EMA and those authorised at national level. The Agency uses this information to support the analysis of data, regulatory activities and communication.

MAHs are required to submit information on new marketing authorisations within 15 calendar days from the date of notification of the granting of the marketing authorisation by the competent authority. This obligation applies to:

- Nationally authorised medicinal products;
- Centrally authorised medicinal products;
- Medicinal products authorised through the mutual recognition procedure;
- Medicinal products authorised through the decentralised procedure.

MAHs are also required to submit information concerning all medicinal products for which they hold a marketing authorisation in EEA countries outside the EU (i.e. Iceland, Liechtenstein and Norway), as the pharmacovigilance legislation is part of the EEA Agreement.

Information on any amendment to the terms of marketing authorisations following a variation, transfer, renewal, suspension, revocation or withdrawal must be notified to EMA no later than 30 calendar days from the date on which the amendments have been authorised.

For full details on the reporting requirements for MAHs, see the legal notice and detailed guidance on the dedicated EMA webpage.

Periodic safety update reports (PSUR)

The PSUR is a document which provides an evaluation of the risk-benefit balance of a medicinal product at defined time points after its authorisation. It includes a comprehensive and critical analysis of the risk-benefit balance of the product taking into account new or emerging safety information in the context of cumulative information on risk and benefits. Guidance on the content and format of a PSUR is published in GVP module VII.

MAHs are legally required to submit all PSURs[14] to the central PSUR repository using the eSubmission Gateway or the eSubmission (Syncplicity) Web Client. Use of the PSUR repository is mandatory for both centrally and nationally authorised medicines, irrespective of whether they follow the EU single assessment or a purely national assessment procedure.

[14]) Regulation (EU) No 1235/2010; Directive 2010/84/EU; Commission Implementing Regulation (EU) No 520/2012

MAHs for active substances and combinations of active substances that are subject to the EU single assessment must submit the relevant PSURs according to requirements set out in the List of EU reference dates (EURD). The EURD list provides the following information for each active substance/combination it contains:

- Frequency of PSUR submission;
- Data lock point;
- Submission date;
- Requirements for the submission of PSURs for generic, well-established use, homeopathic and traditional herbal products.

The EURD list is a legally binding document and MAHs are responsible for complying with its requirements. The list overrules the 'standard' PSUR submission cycle and any condition related to the frequency of PSUR submission included in a marketing authorisation.

EMA updates the EURD list every month, following its adoption by the Committee for Medicinal Products for Human Use (CHMP) and Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), after consultation of the PRAC.

A single PSUR assessment procedure, with a recommendation from the PRAC, is in place for medicinal products authorised in more than one member state (i.e. products authorised through centralised, mutual recognition or decentralised procedures) and for products subject to different national marketing authorisations containing the same active substance or the same combination of active substances for which the PSUR submission dates and frequency have been harmonised in the EU. This aims to strengthen the risk-benefit review of medicines across the EEA.

MAHs for substances not included in the EURD list shall submit PSURs at least every six months during the first two years following the initial placing on the EU market and once a year for the following two years. Thereafter, the reports should be submitted at three-yearly intervals.

Prior to marketing, PSURs have to be submitted at 6 months intervals once the product is authorised.

In special circumstances, competent authorities in member states can request the submission of a PSUR outside the periodicity specified above. In these cases, the submission should follow the timeline specified in the request, or within 90 calendar days, of the data lock point, if not otherwise specified.

Detailed information on PSUR preparation, submission, assessment and outcomes' implementation can be found on the EMA webpage.

Medicinal products subject to additional monitoring

The Agency maintains a public list of medicinal products subject to additional monitoring, including amongst others all medicinal products for human use containing a new active substance and new biological medicinal products.

These products are to be distinguished from others by a black symbol (i.e. the inverted black triangle▼) and an explanatory sentence in the summary of product characteristics and the package leaflet. Further information is published on the EMA website.

Medical literature monitoring

The Agency is required to monitor the scientific and medical literature to collect further reports of suspected adverse reactions, which will be entered into the EudraVigilance system. A defined list of publications for a defined list of active substances used in a large number of medicines is monitored and made public by the Agency on its website. MAHs should not report cases arising from the literature monitored by the Agency, relating to the active substances subject to the monitoring. However, they should continue to report cases they have identified from the literature not covered by that list.

Specific guidance on medical literature monitoring is available on the EMA webpage and in the Detailed guide regarding the monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency.

7.3. Suspected adverse reaction case reporting obligations for human medicines

Reporting obligations for suspected adverse reactions in individuals of various stakeholders are defined in the legislation, in particular Regulation (EU) No 726/2004, Directive 2001/83/EU, Directive 2001/20/EC and Regulation (EU) No 536/2014.

Such reporting falls either under the scope of Directive 2001/20/EC and Regulation (EU) No 536/2014 for any clinical trial, or under provisions set out in Directive 2001/83/EC and Regulation (EC) No 726/2004 for any non-interventional studies and spontaneous reporting by healthcare professionals or patients. Suspected adverse reactions should not be reported under both regimes that are Directive 2001/20/EC and Regulation (EU) No 536/2014, as well as Regulation (EC) No 726/2004 and Directive 2001/83/EC as this creates duplicate reports.
A detailed explanation of the different reporting rules is provided in chapter VI.C.1 of GVP module VI.

EudraVigilance is the system used for, reporting, managing and evaluating suspected adverse reactions during development and following the marketing authorisation of medicinal products in the European Economic Area (EEA) (see section 7.4).

7.3.1. Sponsors of clinical trials – reporting obligations for human medicines

Sponsors of clinical trials are subject to the following reporting obligations, as laid down in the legislation, Directive 2001/20/EC, Regulation (EU) No 536/2014, and described in the 'Detailed guidance on the collection, verification and presentation of adverse event/ reaction reports arising from clinical trials on medicinal products for human use ('CT-3')'.

All suspected unexpected serious adverse reactions[15] (SUSARs) occurring in interventional clinical trials authorised in the EU have to be reported electronically to the competent authority(ies) and to EudraVigilance Clinical Trial Module (EVCTM) by the sponsor of the clinical trial.

This applies to all investigational medicinal products which are studied in interventional clinical trials conducted in the EEA and includes all SUSARs related to these medicinal products which occur either within or outside the EEA.

- **For fatal and life-threatening SUSARs**

The sponsor should report at least the minimum information as soon as possible and in any case no later than seven days after being made aware of the case of fatal and life-threatening SUSAR to EMA, the competent authority(ies) and the relevant ethics committee of the concerned member state(s). If the initial report is incomplete e.g. if the sponsor has not provided all the information/assessment within seven days, the sponsor should submit a completed report based on the initial information within an additional eight days. In this case, the receipt date should not be changed with regards to the initial report.

If significant new information on an already reported case is received by the sponsor, the clock starts again at day zero i.e. the date of receipt of new information. This information should be reported as a follow-up report within 15 days.

- **For non-fatal and non-life-threatening SUSARs**

They must be reported to EMA, the competent authority(ies) and the relevant ethics committee of the concerned member state(s) where the SUSARs occurred, as soon as possible but no later than 15 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be reported within 15 calendar days.

[15]) '***Adverse reaction***': all untoward and unintended responses to an investigational medicinal product related to any dose administered.
'***Serious adverse event or serious adverse reaction***': any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.
'***Unexpected adverse reaction***': an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product).
For other definitions, please refer to Directive 2001/20/EC.

The sponsor must inform all investigators concerned of all relevant information about SUSARs. When feasible, the information on SUSARs should be aggregated in a line listing of SUSARs in periods as warranted by the nature of the research project/clinical development project and the volume of SUSARs generated. This line listing should be accompanied by a concise summary of the evolving safety profile of the investigational medicinal product (IMP).

There may be cases where a SUSAR turns out to be fatal or life-threatening, whereas initially it was considered as non-fatal or not life-threatening. The non-fatal or non-life-threatening SUSAR should be reported as soon as possible, but within 15 days. The fatal or life-threatening SUSAR follow-up report should be made as soon as possible, but within a maximum of seven days after first knowledge of the reaction being fatal or life-threatening. In cases where a SUSAR turns out to be fatal or life-threatening, whereas initially it was considered as non-fatal or not life-threatening, while the initial report has not yet been submitted, a combined report should be created.

- **Annual safety reports – Development Safety Update Report (DSUR)**

The DSUR is a document submitted by the sponsor to regulatory authorities, which provides a periodic analysis of safety information related to the investigational medicinal product and the assessment of risk to trial participants.

It includes a comprehensive review and evaluation of safety information collected during the reporting period related to a medicinal product under investigation, irrespective of its marketing authorisation status.

Detailed guidance on the content and format of a DSUR is available in the ICH guideline E2F.

7.3.2. MAHs of medicinal products authorised in EEA – reporting obligations for human medicines

Electronic reporting through EudraVigilance Post-authorisation Module (EVPM) is mandatory. The Agency receives all relevant information concerning suspected adverse reactions to medicinal products for human use which have been authorised in the EU.

The holder of the marketing authorisation for a medicinal product for human use should ensure that:

- **All suspected serious adverse reactions**[16] **to an authorised medicinal product occurring within the Community**, regardless of the authorisation procedure[17], which a health-care professional or patient brings to the MAH's attention are recorded and reported promptly to EudraVigilance, no later than 15 calendar days following the receipt of the minimum criteria for expedited reporting.

- **Any other suspected serious adverse reactions to an authorised medicinal occurring outside the Community** of which the MAH may reasonably be expected to be aware is recorded and promptly notified to EudraVigilance, no later than 15 days following receipt of the minimum criteria for expedited reporting. This includes but is not limited to reactions reported in the medical literature (see also section 7.2 above).
  For reporting purposes, any suspected transmission of an infectious agent via a medicinal product should be considered as a serious adverse reaction and such cases should be reported within 15 calendar days.

- **All suspected non-serious adverse reactions to an authorised medicinal product within the Community** have to be reported within 90 calendar days.

Marketing authorisation holders shall not refuse to consider reports of suspected adverse reactions received electronically or by any other appropriate means from patients and healthcare professionals.

[16]) For definition, refer to GVP module VI.
[17]) National, centralised, decentralised or mutual recognition procedures.

The Agency may request specific pharmacovigilance data to be collected by the MAH. Any such data collected should be collated, assessed and submitted to the Agency for evaluation.

7.4. EudraVigilance

EudraVigilance is the system for reporting, managing and analysing information on suspected adverse reactions to medicines which have been authorised or being studied in clinical trials in the EEA. EMA operates the system on behalf of the European Union medicines regulatory network.

This system enables data to be exchanged efficiently between EMA, competent authorities, the marketing authorisation holders, and the sponsors of clinical trials in the EEA. EudraVigilance is a powerful tool for EMA and NCAs to monitor the safety of medicinal products and minimise potential risks related to suspected adverse reactions.

Taking into account pharmacovigilance activities in the pre- and post-authorisation phases, EudraVigilance provides two reporting modules:

- **EudraVigilance clinical trial module (EVCTM)** to facilitate electronic reporting of suspected unexpected serious adverse reactions (SUSARs) occurring in interventional clinical trials as required by Directive 2001/20/EC.
- **EudraVigilance post-authorisation module (EVPM)** designed for reporting post-authorisation individual case safety reports (ICSRs), pursuant to Regulation (EU) No 726/2004 and Directive 2001/84/EU.

EMA publishes data from EudraVigilance in the European database for suspected adverse drug reaction reports (www.adrreports.eu). The EudraVigilance access policy governs the level of access that different stakeholder groups have to adverse drug reactions reports.

7.5. EVWEB

In addition to automated message generation and processing, the EudraVigilance system provides a web-based tool to allow for a manual safety and acknowledgement message creation as well as generation of medicinal product reports via a web interface, called EVWEB.

It is specifically designed for SMEs and non-commercial sponsors, which do not have a fully ICH E2B (R3) compliant pharmacovigilance system and/or ESTRI[18] gateway in place. As such, it provides the necessary tools to allow SMEs to perform secure electronic reporting to EMA and all competent authorities in the EEA in accordance with the aforementioned legislation. It allows safety and acknowledgement messages to be sent and received in compliance with the latest ICH M2 standards. EVWEB also enables all messages to be saved locally and permits standardisation of message senders and receivers registered with the Agency as part of the EudraVigilance community. The same principles apply for medicinal product report messages.

Any MAH, applicant or sponsor of a clinical trial in the EEA can use EVWEB. In order to use EVWEB, a computer with Internet Explorer versions 8 or 10 is required as well as internet access. To access the tool, a staff member of the company (or a nominated and registered representative organisation) is required to undertake and pass EudraVigilance training, which is held at EMA every month and at various venues across the EEA. There is a fee reduction available to SMEs participating in these training sessions. Further information on how to register with EudraVigilance and the list of documents to be provided are detailed on the EudraVigilance website.

Alternatively, SMEs may employ a contract research organisation (CRO) to perform the electronic transmission of ICSRs on their behalf. Some industry associations also offer an electronic reporting service to their member companies, and bilateral agreements with partner organisations are also permitted as long as they are captured within the EudraVigilance registration system and in the pharmacovigilance system master file.

[18]) Electronic transfer of regulatory information, see ICH M2 Electronic common technical document (eCTD) – Scientific guideline | European Medicines Agency (europa.eu)

All medical information in EudraVigilance & EVWEB is coded using MedDRA. MedDRA is a clinically validated international medical dictionary used by regulatory authorities and the regulated biopharmaceutical industry within the USA, the EU and Japan. MedDRA should be used for all regulatory activities especially reporting of ADRs, xEVMPD messages in accordance with article 57, PSURs and RMPs. MedDRA is free within EVWEB for small and micro-sized enterprises, but not for SMEs which are medium-sized.

7.6. Pharmacovigilance for veterinary medicines

MAHs of veterinary medicines are required to follow-up on safety and efficacy of their products during their life on the market in order to ensure continuous assessment of the benefit-risk balance.

The main pharmacovigilance activities and obligations for MAHs are:

- Setting up and maintaining a pharmacovigilance system to perform the pharmacovigilance obligations detailed in legislation. The system is described in the pharmacovigilance master file. MAHs may choose to set up more than one pharmacovigilance system for the authorised medicines, but any given product can only be covered by one pharmacovigilance system. A nominated qualified person for pharmacovigilance (QPPV) is responsible for setting up, maintaining and running the pharmacovigilance activities on behalf of the MAH. The MAH may choose to operate its own pharmacovigilance database.

- Continuous collection and submission of adverse event reports, within 30 days of receipt of the suspected adverse event report, to the Union pharmacovigilance database system. The following adverse events shall be reported: unfavourable and unintended reactions in animals to a VMP, noxious reactions in humans exposed to a VMP, any observation of lack of efficacy, possible environmental problems, investigations into the validity of the withdrawal period in case of products for food producing animals, any suspected transmission of an infectious agent via a VMP, and any unfavourable and unintended reaction in an animal to a medicinal product for human use. MAHs are required to record all suspected adverse events reported to them and that occurred in the EU or a third country or that were published in scientific literature without delay and no later than within 30 days of receipt.

Requirements are outlined in the following key documents:

- The Veterinary Medicinal Products Regulation (Regulation (EU) 2019/6), and

- Commission Implementing Regulation (EU) 2021/1281

Under Regulation (EU) 2019/6 veterinary pharmacovigilance relies on signal management carried out by the MAH, supplemented by targeted signal management for individual products or groups of products carried out by competent authorities, which evaluate the reported adverse events.

Such events need to be recorded in the Union pharmacovigilance database system established by the Agency, which is interconnected with the Union Product database. The Union pharmacovigilance database system consists of EudraVigilance Veterinary, the IRIS module for Veterinary Signal Management for competent authorities and MAHs, and the public portal of EudraVigilance Veterinary for the general public.

Competent authorities have full access to the database, MAHs have access to data related to their products and to non-confidential information of other products. As from 28 January 2024, the general public has access to the number and incidence of adverse events and to results and outcomes of signal management carried out by MAHs.

EMA may request MAHs to carry out post-marketing surveillance studies (PMSS) that collect additional pharmacovigilance data, stating the reasons and setting an appropriate time frame.

Based on the assessment of pharmacovigilance data and without undue delay, the MAH shall where necessary submit an application for variation to the terms of the marketing authorisation.

It is important to remember that the MAH shall not make a public announcement on

pharmacovigilance information in relation to its VMPs without giving prior or simultaneous notification to the Agency (or the national competent authority for nationally authorised products).

The signal management process is outlined in article 81 of the VMP Regulation, and further detailed in the Commission Implementing Regulation (EU) 2021/1281 and the VGVP guideline 'Signal management' module.

The MAH shall record, at least annually, all results and outcomes of the signal management process, including a conclusion on the benefit-risk balance, and, if applicable, references to relevant scientific literature in the pharmacovigilance database.

Further guidance on the pharmacovigilance requirements for veterinary medicinal products is available at the EMA website.

Other useful information

8. Other useful information

8.1. Information on medicinal products

The Community Register of medicinal products is published on the European Commission's website and contains a list of all medicinal products for human and veterinary use authorised via the centralised procedure and all designated orphan medicinal products for human use.

The EMA website contains a vast array of additional product information that may interest SMEs, including:

- Decisions on Paediatric Investigation Plans
- CHMP & CVMP summaries of opinion

Note: The summary of opinion is replaced by the European public assessment report (see below) once the European Commission has taken its decision granting or refusing a marketing authorisation.

- European public assessment reports (EPARs)
- European public MRL assessment reports
- Information on marketing authorisation and marketing authorisation application withdrawals
- Product safety announcements
- Product opinions for non-EU use
- List of referrals
- Information on herbal medicines for human use

A guide describing the information published by EMA on centrally and non-centrally authorised medicinal products for human use is also available on the EMA website.

The Union Product Database (UPD) includes information on veterinary medicines authorised within the EU (through the centralised procedure and by national regulatory authorities).
This database holds assessment reports, summaries of product characteristics and package leaflets for authorised veterinary medicines, and additional information provided by MAHs (date of first placing on the market, annual sales data).
The public documents and relevant information are made available to the general public via the veterinary medicines information website, the public portal of the UPD.

8.2. Contact points at EMA

SME office

The SME office has been set up within the Agency to address the particular needs of smaller companies. The office aims to facilitate communication with SMEs through dedicated personnel within the Agency who will respond to practical or procedural enquiries, monitor applications, and organise workshops and training sessions for SMEs. Any comment on the content of this SME user guide should also be forwarded to the SME office.

SME office contact point:

E-mail: sme@ema.europa.eu

Direct telephone: + 31(0)88 781 8787

Innovative medicines and technologies

Queries relating to innovative medicines and technologies can be sent to:

E-mail: ITFsecretariat@ema.europa.eu

Advanced therapy medicinal products

Queries relating to advanced therapies can be sent to:

E-mail:
AdvancedTherapies@ema.europa.eu

Orphan medicinal product designations

Queries on orphan designations (not related to ongoing orphan designations) can be sent via the 'Send a question to the European Medicines Agency'.

Paediatric medicines

Queries, including general information on PIP and waiver applications, modification procedures and compliance checks, can be sent via the 'Send a question to the European Medicines Agency'.

Scientific advice

For procedural and administrative queries relating scientific advice or to request a free pre-submission meeting:

For medicinal products for human use:
E-mail: ScientificAdvice@ema.europa.eu

For medicinal products for veterinary use:
E-mail: vetscientificadvice@ema.europa.eu

PRIME

Queries can be sent to:

E-mail: prime@ema.europa.eu.

Veterinary limited markets

Queries can be sent to:

E-mail: VetLimitedMarkets@ema.europa.eu

Academia

Queries related to academia activities at EMA can be sent to:

E-mail: academia@ema.europa.eu

General inquiries

The Agency publishes a wide range of documents, including press releases, guidance documents, annual reports and work programmes. These and other documents are available on the EMA website.

To send a request for information from EMA or to make a formal request for access to EMA documents that are not already published on the website, see details provided under 'Send a question to the European Medicines Agency'.

Appendix

Appendix

LIST OF ABBREVIATIONS

ADI	Acceptable Daily Intake
ADR	Adverse Drug Reaction
ASMF	Active Substance Master File
API	Active Pharmaceutical Ingredient
ATMPs	Advanced Therapy Medicinal Products
AUC	Area Under The Curve
AWU	Annual Work Unit
BfArM	Bundesinstitut Für Arzneimittel Und Medizinprodukte
CAT	Committee For Advanced Therapies
CCI	Commercially Confidential Information
CD-ROM	Compact Disc – Read Only Memory
CdT	Centre For Translation
CEP	Certificate Of Suitability
CHMP	Committee For Medicinal Products For Human Use
CMA	Conditional Marketing Authorisation
COMP	Committee For Orphan Medicinal Products
CRO	Contract Research Organisation
CTA	Clinical Trial Applications
CTD	Common Technical Document
CTFG	Clinical Trials Facilitation Group
CTR	Clinical Trials Register
CVMP	Committee For Medicinal Products For Veterinary Use
DDPS	Detailed Description Pharmacovigilance System
DSUR	Development Safety Update Report
DVD	Digital Versatile Disc
EC	European Commission
e-CTD	Electronic Common Technical Document
EDQM	European Directorate For Quality Of Medicines And Health Care
EEA	European Economic Area
EEC	European Economic Community
EMA	European Medicines Agency
EnprEMA	European Network Of Paediatric Research At The European Medicines Agency
EPAR	European Public Assessment Report
ERA	Environmental Risk Assessment
ESTRI	Electronic Standards For The Transfer Of Regulatory Information

EU	European Union
EudraCT	European Clinical Trials Database
EudraGMP	European Database On Manufacturing And Import Authorisations And Good Manufacturing Practice
EURDS	European Union Reference Dates And Frequency Of Submission Of Periodic Safety Update Reports
EVCODE	Eudravigilance Code
EVCTM	Eudravigilance Clinical Trial Module
EVPM	Eudravigilance Post-Authorisation Module
EVVET	Eudravigilance Veterinary
EVWEB	Eudravigilance Web-Based Tool
FDA	Food And Drug Administration
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GLP	Good Laboratory Practice
GMOs	Genetically Modified Organisms
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practice
HTA	Health Technology Assessment
ICH	International Council For Harmonisation
ICTRP	International Clinical Trials Registry Platform
IMP	Investigational Medicinal Product
INN	International Non-Proprietary Name
ISO	International Organisation For Standardisation
ISO IDMP	Iso For The Identification Of Medicinal Products
ITF	Innovation Task Force
IVMPs	Immunological Veterinary Medicinal Products
LMs	Limited Markets
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary For Regulatory Activities
MRL	Maximum Residue Limit
NCA	National Competent Authority
No	Number
NOAEL	No Adverse Effect Level
NRG	(Invented) Name Review Group
NTA	Notice To Applicants
OECD	Organisation For Economic Co-Operation And Development
OJEU	Official Journal Of The European Union
OMS	Organization Management Service
PAES	Post-Authorisation Efficacy Studies
PASS	Post-Authorisation Safety Studies

PC	Procedure Coordinator
PD/PK STUDIES	Pharmacodynamics/Pharmacokinetic Studies
PDCO	Paediatric Committee
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PL	Procedure Lead
PPD	Protected Personal Data
PRAC	Pharmacovigilance Risk Assessment Committee
PREA	Paediatric Research Equity Act
PRIME	Priority Medicines
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PUMA	Paediatric Use Marketing Authorisation
Q&A	Questions & Answers
QPPV	Qualified Person For Pharmacovigilance
R&D	Research & Development
RMP	Risk Management Plan
RPI	Research Product Identifier
RWD	Real-World Data
RWE	Real-World Evidence
SAG	Scientific Advisory Group
SAWP	Scientific Advice Working Party
SAWP-V	Scientific Advice Working Party – Veterinary
SME	Micro, Small And Medium Sized Enterprises
SOP	Standard Operating Procedure
SPOR	Substance, Product, Organisatonal And Referential Master Data
SUSARs	Suspected Unexpected Serious Adverse Reactions
TSE	Transmissible Spongiform Encephalopathy
UPD	Union Products Database
US(A)	United States (Of America)
VGVP	Veterinary Good Pharmacovigilance Practice
VHP	Voluntary Harmonisation Procedure
VICH	International Cooperation On Harmonisation Of Technical Requirements For Registration Of Veterinary Medicinal Products
WHO	World Health Organisation
VMP	Veterinary Medicinal Product
XEVMPD	Extended Eudravigilance Medicinal Product Dictionary
XEVPRM	Extended Eudravigilance Product Report Message

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