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Endocrinology and Cardiovascular Office
Human Medicines Division

Consolidated 3-year rolling work plan for the Cardiovascular Working Party(CVSWP) – Priorities 2025

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Work plan period: January 2025 – December 2027 (with a first review point after one year)

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1. Strategic goals

1.1. Main strategic goals

Cardiovascular diseases (CVD) remain a leading cause of death globally and the number one cause of death in the EU. They account for 45% and 39% of fatalities in females and males, respectively according to 2021 report from the ESC Atlas Project[1]. Most recent data from the Global Burden of Disease database estimate that, in the EU, more than 60 million people live with CVD, and that close to 13 million new cases of CVD occur every year[2].

The Cardiovascular Working Party (CVS WP) aims at playing a role in the reduction of CVD, diabetes and obesity through supporting the development of new medicinal products for prevention and treatment of diseases in these fields.

The following are the main strategic goals:

- Provide the requested and **state-of-the-art support** to the EMA Committees regarding the CVD, diabetes and obesity fields.
- Deliver appropriate **guidance** documents to support and improve the development and authorisation of medicines regarding the CVD, diabetes and obesity fields based on the most recent scientific insights and where patient-reported outcomes are considered alongside clinical endpoints.
- Review **the need** for development of new guidelines/position papers in CVS, diabetes and obesity fields as well as revision of the existing guidelines on a case-by-case basis based on EMA scientific advice (SA)/protocol assistance (PA), qualification procedures and also based on pipeline forecasts in this field.
- Raise the understanding of all aspects of CVD, diabetes and obesity fields and ensure transfer of experience to EU NTC network through developing appropriate **training**.
- Develop systematic and structured Stakeholder engagement (Industry, Academia, Healthcare Professionals, Patients and International (including national) Regulators at domain level.
- Maintain and expand the collaboration with learned societies and patients organisations in CVD, diabetes and obesity fields.
- Build knowledge regarding new methodologies to measure and define clinical endpoints in the field and ensure that the innovative methods of outcome measurement are adequately described in guidelines in the field of CVS, diabetes and obesity (including gene-therapy, artificial intelligence (AI)-based methods and novel methods to measure outcome in rare diseases, use of real world data/registries) to increase patient-centricity.
- Ensure that the development and implementation of new methodologies, such as AI and gene therapy in CVS/obesity and diabetes fields, are aligned with patient-centered outcomes, emphasizing the real-world impact on patients' quality of life.
- Develop and expand connections and links to assessors from national agencies, academic and clinical experts specialising in the CVD, diabetes and obesity fields via the European Specialised Expert Community Cardiovascular Diseases (ESEC CVD) and to provide oversite for the activities of the ESEC CVD including communication and training.

[1] European Heart Journal, Volume 43, Issue 8, 21 February 2022, Pages 716–799, https://doi.org/10.1093/eurheartj/ehab892
[2] https://www.escardio.org/static-file/Escardio/Advocacy/Documents/2020%20ESC-EHN-blueprint_digital%20edition.pdf

- Maintain and expand the collaboration with international regulators.

The following are the short and long term strategic goals in terms of guidelines development:

1.2. Short-term strategic goals

(1) To release a *Draft Guideline updating the Note on clinical investigation of medicinal products for the treatment of peripheral arterial occlusive disease (CPMP/EWP/714/98 rev.2)* for public consultation.

In the field of peripheral arterial disease (PAD) the CVS WP will aim to ensure that the EMA updated Guideline tackles the following areas: new clinical classifications to describe the symptomatic severity of the disease; endpoints to establish efficacy in different settings to add clarity, to reflect the value of preventing major adverse limb events when pharmacological therapy in conjunction with other treatment modalities, to discuss the acceptable ways of establishing symptomatic benefit or to base the efficacy demonstration on complete ulcer healing or other local endpoints. The concept of estimands will be briefly contextualised in the field of PAD trials. Issues specific to ATMP development for PAD will be covered (vasculogenesis, angiogenesis, arteriogenesis and immunomodulation and limb salvage in addition to symptomatic benefit).

(2) To release the *Draft revised Paediatric addendum to CHMP Guidelines on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension (CHMP/EWP/213972/10 Rev. 1)* for public consultation.

An EMA/FDA workshop was organised on 12 June 2017 to discuss the requirements for the development of medicines for pulmonary arterial hypertension (PAH) that address the high unmet medical needs in children. The objectives were to analyse the problems related to the conduct of clinical trials in children with PAH, to refine endpoints and study design, to address the challenges identified, to set priorities for future research, to provide medicine developers with more guidance specific to global product development taking into account current limitations in the development, to investigate potential compatible agreements between regulators and to identify remaining points to be addressed in the next steps. In this context the revision of the Paediatric Addendum for PAH is proposed.

(3) To release the *Draft revised Paediatric addendum on weight control in children (EMEA/CHMP/EWP/517497/2007 Rev. 1)* for public consultation.

In view of the fact that significant time passed since the PA was developed and that there are numerous developments in this field the revision of the PA is proposed. It is planned that the discussion in the updated PA will cover a run-in period and its adequate length, the inclusion criteria to match the end users population, the type of control needed for trials, the recommended primary and secondary endpoints. Safety section and the characteristics of the follow up period will be revised as well.

(4) To release the *Draft Reflection Paper for evaluation of cardiovascular safety of oncology medicinal products* for public consultation.

In view of growing interest and awareness regarding cardio-oncology field as well as increased number of patients surviving cancer, there is a need for use of harmonized definitions in collection of cardiovascular (CV) toxicity endpoints. Many studies have assessed CV toxicities in patients undergoing various types of cancer therapies; however, direct comparisons have proven difficult due to lack of uniformity in CV toxicity endpoints that are collected. CV toxicity sometimes only becomes evident after a large cumulative dose of a drug/metabolite has accumulated in the heart, or it is so rare that a safety signal requires thousands of patients exposed. In such cases, it will be difficult to delineate the CV safety profile of the new compound for rare events before authorization, and these

uncertainties should be managed under the RMP. However, some CV events may be apparent in the short term and/or manifest with common frequency shortly after specific treatments. Therefore, there is a room for improvement in reporting and assessing CV safety outcomes in oncology trials.

1.3. Long-term strategic goals

- To release the *Final Guideline updating the Note on clinical investigation of medicinal products for the treatment of peripheral arterial occlusive disease (CPMP/EWP/714/98 Rev.2)*.
- To release the *Final revised Paediatric addendum to CHMP Guidelines on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension (CHMP/EWP/213972/10 Rev.1).*
- To release the *Final revised Paediatric addendum on weight control in children (EMEA/CHMP/EWP/517497/2007 Rev. 1)*.
- To release the *Final Reflection Paper for evaluation of cardiovascular safety of oncology medicinal products.*
- To develop the Reflection Paper on overlapping aspects of patients health including CV, Kidney, Metabolic diseases

2. Tactical goals

2.1. Guidance activities

Guideline activities will be performed by one or two Rapporteurs supported by the Drafting Groups that report back to the CVS WP on a regular basis.

(A) Activities ongoing/to be finalised in 2025

New EU Guidelines:

Action: Lead

Reflection paper for evaluation of cardiovascular safety of oncology medicinal products.

Target date	• Concept paper released for public consultation in 3Q2024 • Draft Reflection Paper to be released for 6 months public consultation 4Q2025
Comments	To be developed in collaboration with Oncology WP.

Revision of existing EU Guidelines:

Action: Lead

Paediatric addendum to CHMP Guidelines on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension (CHMP/EWP/213972/10)

Target date	• Concept paper was released for public consultation until 30 September 2023; • Draft Addendum to be released for 6 months public consultation in 4Q2024
Comments	Developed in collaboration with Paediatric Committee (PDCO) and Methodology Working Party (MWP). Stakeholder consultation planned to enhance knowledge regarding PD endpoints that could support extrapolation plan and modelling and simulation approaches in this field.

Action: Lead

Note on clinical investigation of medicinal products for the treatment of peripheral arterial occlusive disease (CPMP/EWP/714/98 rev.1)

Target date	• Concept paper released for public consultation until 30 June 2019; • Draft Guideline to be released for 6 months public consultation 3Q2024;

Action: Lead

Paediatric addendum on weight control in children (EMEA/CHMP/EWP/517497/2007)

Target date	• Concept paper to be released for public consultation in 3Q2024; • Draft Guideline to be released for 6 months public consultation 3Q2025
Comments	To be developed in collaboration with Paediatric Committee (PDCO).

(B) Activities to be started in 2025

New EU Guidelines:

Action: Lead

Reflection paper for evaluation of cardiovascular safety of oncology medicinal products.

Target date	• Draft Reflection Paper to be elaborated in 2025 • Final Reflection Paper to be released in 2026
Comments	To be developed in collaboration with Oncology WP.

Revision of existing EU Guidelines:

Action: Lead

Paediatric addendum to CHMP Guidelines on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension (CHMP/EWP/213972/10)

Target date	• Draft Addendum to be elaborated in 2025 • Final Addendum to be released in 2026;
Comments	Developed in collaboration with Paediatric Committee (PDCO).

Action: Lead

Note on clinical investigation of medicinal products for the treatment of peripheral arterial occlusive disease (CPMP/EWP/714/98 rev.1)

Target date	• Final Guideline to be drafted in 2025 after the completion of the public consultation; • Final Guideline to be released in 2026

Action: Lead

Paediatric addendum on weight control in children (EMEA/CHMP/EWP/517497/2007)

Target date	• Draft Guideline to be released for 6 months public consultation in 2025 • Final Guideline to be released in 2026
Comments	To be developed in collaboration with PDCO.

Input to work developed by other Groups

Provide specialised input from CV, diabetes and obesity fields perspective on the Draft Reflection Paper on Patient Experience Data.

(B) Activities to be started in 2026-27

To be determined based on progress of work in 2025.

The CVS WP will consider in 2026 – 2027:

- the development of the Reflection Paper on overlapping aspects of patients health including CV, Kidney, Metabolic diseases
- the revision of the Guideline on clinical investigation of medicinal products in the treatment of hypertension EMA/CHMP/29947/2013/Rev. 4 (Previous ref. number EMA/238/1995/Rev. 3)

2.2. Training and workshop activities

- Contribute to assessors trainings organised by the EU Network Training Centre (EU NTC). In this context to provide *Training on Guideline on clinical investigation of medicinal products in the*

treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 2). The following three modules are to be developed: (1) Developing and licensing medicinal products for the treatment of type 2 diabetes (except insulin medicinal products); (2) Developing and licensing insulin preparations for the treatment of type 1 and type 2 diabetes; (3) Developing and licensing medicinal products for delaying the start/prevention of type 1 diabetes.

- Maintain awareness of issues arising in the field CVD, diabetes, obesity (via for example discussion with stakeholders and/or review of scientific advices provided by the EMA) in order to identify the need for review and update of guidelines and development of additional guidance documents.
- Contribution to the establishment and leadership for activities of European Specialised Expert Community (ESEC) - Cardiovascular Diseases in line with the mandate adopted by the CHMP.

2.3. Communication and Stakeholder activities

2.3.1. European level

- Introduce and maintain systematic and structured Stakeholder Consultation via public consultation with regards to CVS WP Work Plan and Guidelines under development (including with healthcare providers organisations, patients and pharmaceutical industry/other commercial sponsors).
- Continue to meet with interested parties to discuss general matters (e.g. emerging trends, horizon scanning, framework revisions) or specific scientific issues as foreseen in the 3-year rolling strategic plan and/or with the agreement of the relevant Committee(s)/Domains for emerging issues.
- Engagement and interactions with learned societies (e.g. European Society of Cardiology (ESC), Association for European Paediatric and Congenital Cardiology (AEPC), European Association for the Study of Diabetes [EASD], European Association for the Study of Obesity [EASO], The European Federation of Internal Medicine (EFIM), European Respiratory Society (ERS), European Association for Clinical Pharmacology and Therapeutic (EACPT), European Union Geriatric Medicine Society and other expert communities in the field of CVS, diabetes and obesity.
- Engagement and interactions with patient organisations in the field (i.e. European Heart Network [EHN], European Pulmonary Hypertension Association (PHA Europe)).
- Co-organise a workshop with the Cardiovascular Round Table (CRT) of the ESC related to understanding of patient benefit and benefit/risk in cardiovascular field including patient representatives.
- Participate in selected workshops and conferences organised by learned societies in the field (e.g. European Society of Cardiology (ESC) CVS Round Table (CRT) Workshops) on the topics relevant for the work of the WP.
- Update Patients' and Consumers' Working Party (PCWP)/Healthcare Professionals' Working Party (HCPWP) on the ongoing activities of the CVS WP at least once over the 3-year period. This will support further awareness and understanding of the WPs activities amongst patients, consumers and HCPs and how their work contributes to scientific, methodological and regulatory guidance. It will also provide an opportunity for PCWP/HCPWP to raise any points of interest/concern.

2.3.2. International level

- Identify and maintain significant bilateral/multilateral interactions: regular teleconferences with regulators FDA, HC, Swiss Medic, PMDA to exchange experience in CVD, diabetes and obesity fields.

- Contribution to the development of the ICH Guidelines on request from the CHMP.

2.4. Multidisciplinary collaboration

- Provide input in the field of CVD, diabetes or obesity on request of other EMA working party or Committee under supervision of the CHMP.

3. Operational goals

3.1. Pre-submission activities

- The CVSWP will provide product-related support in the field of CVD, diabetes or obesity upon request from the SAWP during pre-submission phase.

3.2. Evaluation and supervision activities

- The CVSWP will provide product-related support in the field of CVD, diabetes or obesity upon request from Committees during initial evaluation of medicinal products or in the post-authorisation phase.

4. List of Abbreviations

AEPC - Association for European Paediatric and Congenital Cardiology

CP – Concept Paper

CVD – Cardiovascular diseases

EASD - European Association for the Study of Diabetes

EASO - European Association for the Study of Obesity

ESEC CVD – European Specialized Expert Community - Cardiovascular Diseases

ESC – European Society of Cardiology

EU NTC - EU Network Training Centre

IMI – Innovative Medicines Initiative

SAWP – Scientific Advice Working Party

PA – Paediatric Addendum