ESC European Society of Cardiology

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

A meeting of the ESC Cardiovascular Round Table (CRT),
with contribution from the European Medicines Agency (EMA)

"Cardiovascular Safety at the Heart of Cancer Care"

20-21 January 2026
Amsterdam

GOBIERNO DE ESPAÑA MINISTERIO DE SANIDAD

agencia española de medicamentos y productos sanitarios

Regulatory Perspective:

How the EMA Addresses CV Safety in Innovation

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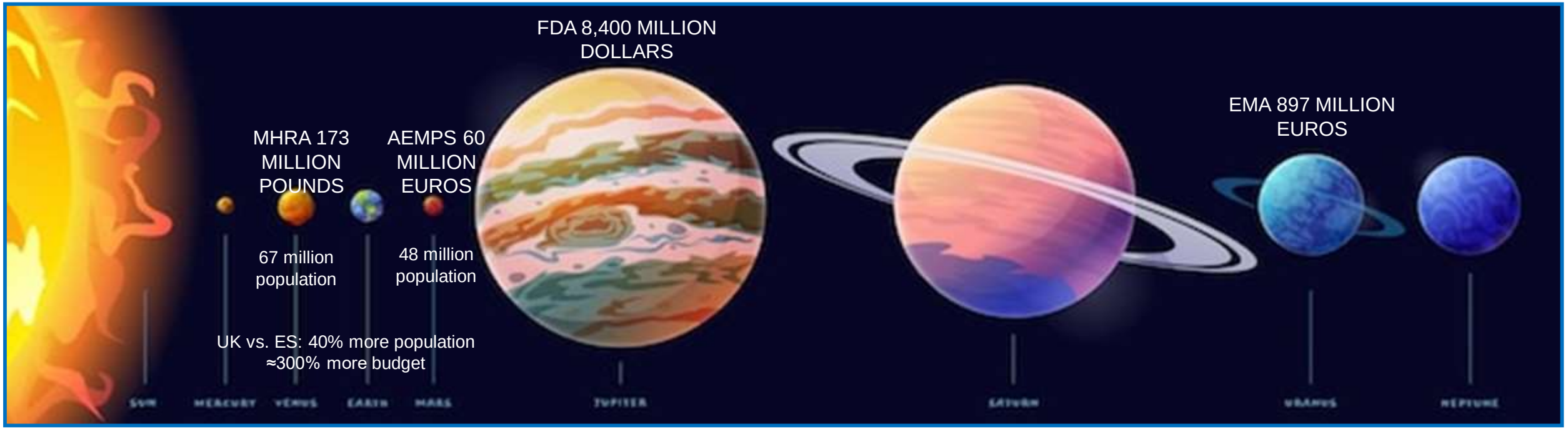
DISCLAIMER

- This presentation might not be the view of the EMA-CVSWP or AEMPS.
- The ideas expressed here represent my personal view and do not bind the organisations mentioned above or any other party.
- I have no conflict of interests (CoI) to declare.
- My declarations of CoI and the CV are publicly available at the EMA website

https://www.ema.europa.eu/sites/default/files/ContactsandExperts/experts_files/agomezoutes_CV_en.pdf

Regulatory agencies



VARIABLE	AEMPS	EMA	FDA
Staff, n	600	879	18.000 (9.351 CBER, CDER, CDRH, CVM),
Annual Budget, millon euros/dollars	60 mill. € (20 mill. € Profit)	897 mill. €	8,400 mill. $
Population covered, million people	47	448	330
Budget per inhabitant	1.3 (€0 cost)	2.0	25.5

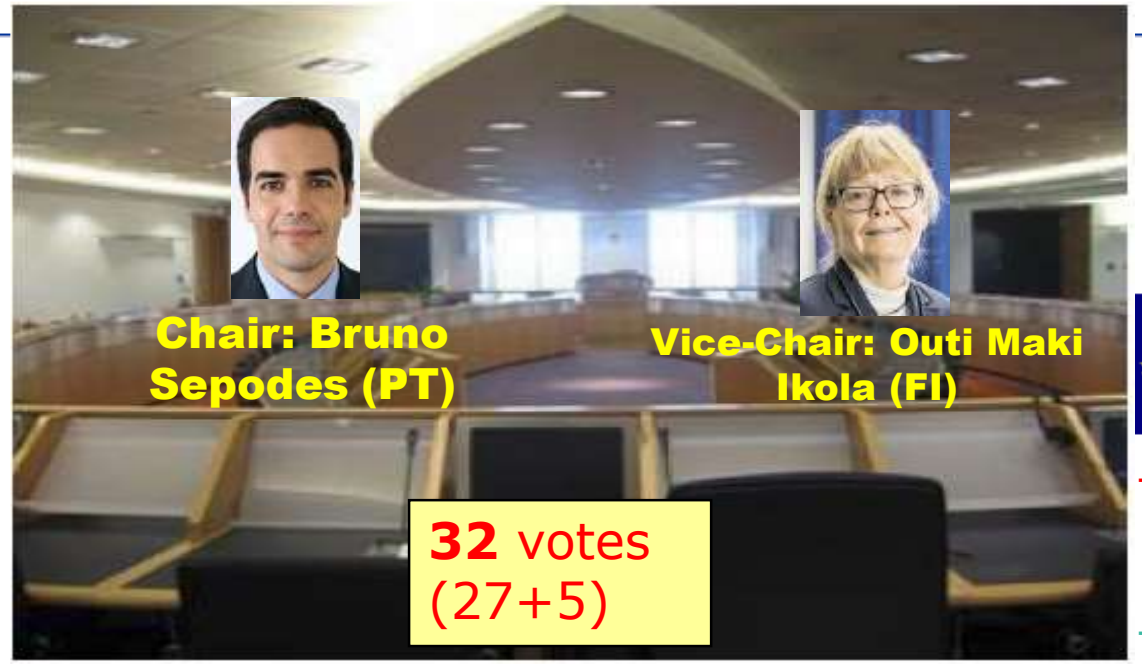
AEMPS = Spanish Medicines Agency; CBER = Center for Biologics Evaluation and Research; CDER = Center for Drug Evaluation and Research; CDRH = Center for Devices and Radiological Health; CVM = Center for Veterinary Medicine; EMA = European Medicines Agency; FDA = Food and Drug Administration

Activities of different regulatory agencies

ACTIVITIES	AEMPS	MHRA	EMA	FDA
Assessment of medicinal products (including GTs, ATMPs)	Yes	Yes (UK)	Yes (Coordination of Centralized procedures, CHMP)	Yes (US) CBER
Team of assessors (quality, non-clinical, clinical)	Yes	Yes (UK)	No (National Agencies)	Yes (US)
Autorisation of medicinal products	Yes (Nat., DC, MRP)	Yes (UK)	No (European Commission)	Yes (US)
Scientific advice	Yes (Nat., SNSA)	Yes (UK)	Yes (SAWP)	Yes (US)
Information to healthcare professionals, patients and users	Yes	Yes (UK)	Yes	Yes (US)
Pharmacovigilance	Yes (Nat., DC, MRP, Centralized)	Yes (UK)	Yes (coordination, PRAC)	Yes (US)
Assessment of medical devices	Yes	Yes (UK)	No	Yes (US)
CE marking (for medical devices)	Yes (AEMPS is also a notified body, NB)	Yes (UK. MHRA works with NB)	No	Yes (US)
Autorization of clinical trials	Yes	Yes (UK)	No (but coordination in COVID)	Yes (US)
Control of ilegal and falsified medicines	Yes	Yes (UK)	Yes (coordination)	Yes (US)
Control of food	No (AESAN)	No	No	Yes (US)
Control of poisons and biologic weapons	No (Ministries of Defense, Interior, Dpt. Public Health)	No	No	Yes (US)

AEMPS = Agencia Española de Medicamentos y Productos Sanitarios; AESAN = Agencia Española de seguridad alimentaria; DCP = decentralised procedures; EMA = European Medicines Agency; FDA = US Food and Drug Administration; MRP = mutual recognition procedure; PRAC = Pharmacovigilance Committee of the EMA; SAWP = Scientific Advice Working Party of the EMA-CHMP; UK = United Kingdom; US = United States of America.

CHMP 2026



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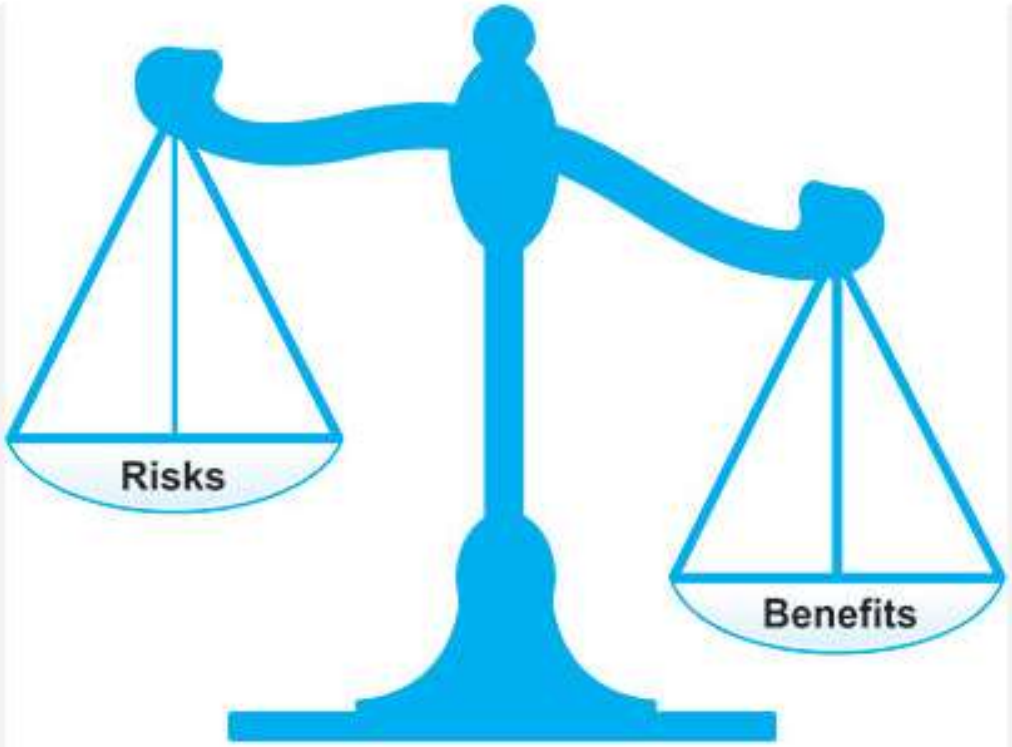
France
-Sol Ruiz
Iceland
Latvia
Cyprus
Italy
Ireland
Romania
Bulgaria
Norway

- Chairman & Vice-Chairman.
- 2 scientific expert members (CHMP member + alternate) nominated by each of the **27** Member States (54 potential co/rapporteurs; **27 votes**).
- 2 scientific expert members (CHMP member + alternate) from NO and IS (observers)
- **5** co-opted members as appointed by Management Board (2 biologic and advanced therapies, 1 statistician, 1 quality, 1 pharmacovigilance) (**5 votes**).
- https://www.ema.europa.eu/en/committees/committee-medicinal-products-human-use-chmp/chmp-members

BENEFIT-RISK ASSESSMENT



Regulatory authority evaluates the balance for population and individuals

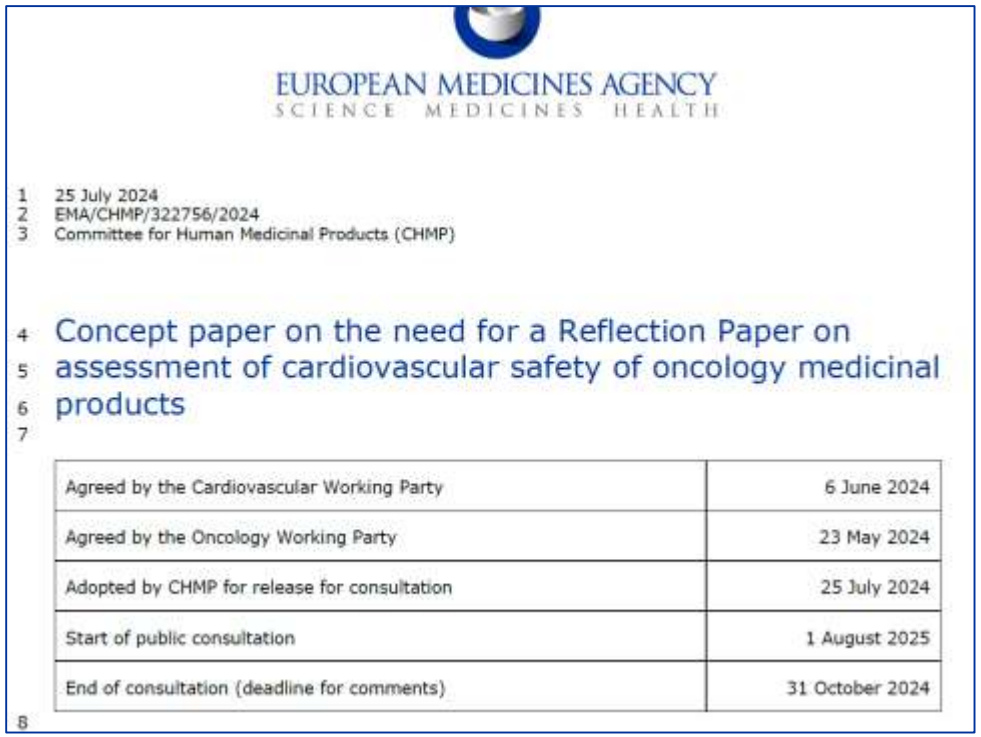
Prescriber evaluates the balance for patient

Patients evaluates the balance for himself

DRAFT Reflection Paper on investigation and assessment of cardiovascular safety of anticancer medicinal products

CVSWP Coordinators: Antonio Gómez Outes & Gabriella Passacqualle

Developed by the CVSWP in collaboration with the ONCWP



EUROPEAN MEDICINES AGENCY
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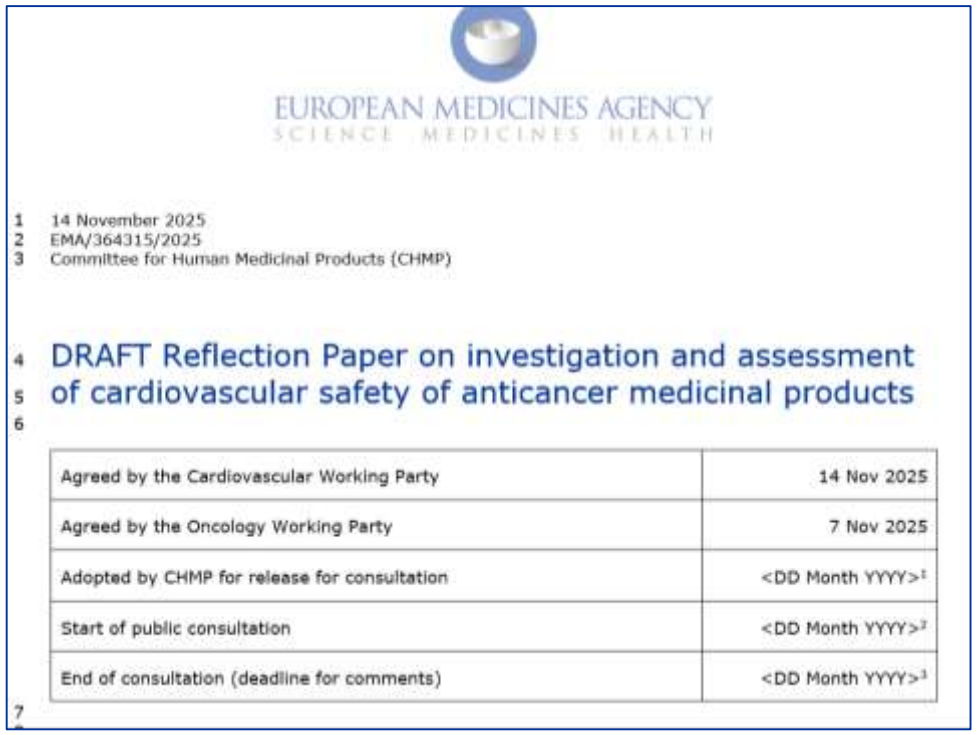
25 July 2024
EMA/CHMP/322756/2024
Committee for Human Medicinal Products (CHMP)

Concept paper on the need for a Reflection Paper on assessment of cardiovascular safety of oncology medicinal products

Agreed by the Cardiovascular Working Party	6 June 2024
Agreed by the Oncology Working Party	23 May 2024
Adopted by CHMP for release for consultation	25 July 2024
Start of public consultation	1 August 2025
End of consultation (deadline for comments)	31 October 2024



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 November 2025
EMA/364315/2025
Committee for Human Medicinal Products (CHMP)

DRAFT Reflection Paper on investigation and assessment of cardiovascular safety of anticancer medicinal products

Agreed by the Cardiovascular Working Party	14 Nov 2025
Agreed by the Oncology Working Party	7 Nov 2025
Adopted by CHMP for release for consultation	<DD Month YYYY>[1]
Start of public consultation	<DD Month YYYY>[2]
End of consultation (deadline for comments)	<DD Month YYYY>[3]

Adopted by the CHMP in 2024

Proposed for adoption for release for 6-month public consultation in Jan 2026.

FORWARDED TO YOU FOR COMMENTS

Final RP to be elaborated by 2027 in line with the CVS WP Work Plan

EMA

1. Introduction I

Cardiovascular (CV) toxicity is increasingly relevant in oncology drug development:

- Up to **one third of cancer patients** experience CV toxicity during treatment
- Risk is driven by older patient **age**, **comorbidities**, and **novel anticancer mechanisms**
- Existing EMA and ICH guidance does not specifically address CV safety of medical products for the treatment of people living with cancer
- This RP provides recommendations for the **planning, data collection, and evaluation of CV safety** of anticancer medicinal products

1. Introduction II

1. **Cardiac dysfunction/heart failure** [e.g., induced by anthracyclines, human epidermal growth factor receptor 2 (HER2) targeted agents];
2. **Myocarditis** [e.g., induced by anthracyclines (e.g.:doxorubicin), antimetabolites (e.g.: fluorouracil), alkylating agents (e.g.: cyclophosphamide), and immune checkpoint inhibitors (ICIs)];
3. **Arrhythmias/QT prolongation** [e.g., associated with arsenic trioxide, some tyrosine kinase inhibitors (TKIs) targeting the breakpoint cluster region-Abelson (BCR-Abl) oncogene locus, and cyclin-dependent kinase (CDK) 4/6 inhibitors like ribociclib];
4. **Hypertension** [e.g., induced by targeted agents such as vascular endothelial growth factor TKIs (VEGF-TKIs), the proteasome inhibitor carfilzomib, mTOR (mammalian Target of Rapamycin) inhibitors, TKIs targeting the B-raf (rapidly accelerated fibrosarcoma) protein kinase (BRAF), the mitogen-activated protein/extracellular signal-regulated kinase (MEK), and Bruton's tyrosine kinase (BTK)];
5. **Vascular toxicity**, including myocardial infarction, stroke, transient ischemic attack, venous thromboembolic event, arterial thromboembolism, peripheral ischemia, vasculitis, vascular disorder, and venous injury (e.g., some of them associated with targeted therapies like CAR-T, VEGF-TKIs, TKIs targeting the BCR-Abl fusion protein, such as nilotinib and ponatinib, and the epidermal growth factor receptor inhibitor erlotinib);
6. **Valvular heart diseases** (e.g., anthracyclines like doxorubicin, anti-HER2 agents like trastuzumab, and some chemotherapy drugs like cyclophosphamide and ifosfamide have been associated with heart valve problems);
7. **Pulmonary hypertension** (e.g., chemotherapeutic agents like bleomycin, mitomycin, and cyclophosphamide, as well as TKIs such as dasatinib, immunomodulatory agents like interferons, and some proteasome inhibitors such as carfilzomib, have been linked to this side effect); and
8. **Pericardial diseases** [anthracyclines, alkylating agents (e.g.: cyclophosphamide), antimetabolytes (e.g.: cytarabine), and the antitumor antibiotic bleomycin are known to cause pericarditis, while TKIs like dasatinib, as well as the trans retinoic acid differentiation agent and the alkylating agent busulfan, have been associated with pericardial effusions).

1. Introduction III

- A tailored, **risk-based approach** is recommended, characterized by two extremes:
  - at **lower end**, risk is considered low (well-established pharmacological class with no known CV safety concerns),
  - at **high end** risk is substantial (novel pharmacological class/MoA, NC data indicating CV toxicity, CV safety signals during development)

For the **low-cardiac risk** category of anticancer products, **safety monitoring** during clinical experimentation supported by a **clinical and nonclinical evaluation of the QT/QTc interval prolongation** and pro-arrhythmic potential **may suffice**, unless CV safety signals do emerge that would require further characterization

For products **with a substantial risk** and for those products where the **risk category could not be easily assigned** (novelty of the class, very limited early clinical exposure), **a more detailed assessment of CV safety is warranted** that should be considered **at the planning stage** of the registration trial

2. Scope

- Addresses lack of uniformity in CV toxicity endpoints in oncology trials
  - Focuses on baseline CV risk characterization, and monitoring, assessment and follow-up of CV safety in oncology trials

- Applicable to all new anticancer medicinal products where there is a potential risk of CV toxicity
  - Covers aspects of CV safety in selection of population, trial design, prospective definition of CV endpoints, CV safety monitoring, baseline data collection, management of CV toxicities, reporting of CV outcomes
  - Includes implications for RMP and product labelling

3. Legal and Regulatory Framework

- To be read alongside existing EMA and ICH safety guidelines
  - Includes ICH S7, E14/S7B, E2A, E2F and E9(R1)

4. Selection of Populations

- Appropriate population selection is critical for CV risk assessment
  - Inclusion criteria should consider **baseline CV risk**, **previous exposure to cardiotoxic therapies**, presence of **underlying CV disease** and **comorbidities**
  - Avoid **unjustified exclusion** of patients with pre-existing CV disease (but avoid including **patients at excessively high risk**)

- Baseline CV assessment should include clinical history, physical examination, laboratory tests (biomarkers), genetic markers, ECG and imaging (echo, MRI, CTA)
  - Identification of **high-risk subgroups** supports tailored monitoring
  - Standardized data collection **improves comparability** across studies

5. Study Design and Duration

- **Randomized controlled trials** are **optimal** for CV safety assessment
- **Follow-up** duration should capture **late-onset CV toxicities**
- There is a need to balance the assessment of both **oncologic (PFS and OS)** and **CV outcomes** (i.e. competing OS and CV death)
- **Real-world data** may complement clinical trials evidence to inform further about the long-term CV safety if the methodology used is pre-defined and scientifically sound
- Treatment doses may be reduced to protect patient's subgroups that have experienced CV events

6. CV Endpoints

- CV endpoints should be prospectively defined and standardized
  - Use consensus definitions from cardio-oncology societies *

  ** Herrmann J, Lenihan D, Armenian S, Barac A, Blaes A, Cardinale D, et al. Defining cardiovascular toxicities of cancer therapies: an International Cardio-Oncology Society (IC-OS) consensus statement. Eur Heart J. 2022; 43: 280-99.*

- Both clinical and subclinical events should be captured
  - Endpoints should be mapped to Common Terminology Criteria for Adverse Events (CTCAE terminology)
  - Pre-specified analyses are recommended, acknowledging limited power

** IC-OS consensus statement includes:*

A. Cardiac dysfunction/heart failure

B. Myocarditis

C. Arrhythmias/QT prolongation

D. Hypertension

E. Vascular toxicity

F. Valvular heart disease

G. Pulmonary hypertension

H. Pericardial diseases

7. CV Safety Monitoring

- Continuous **CV monitoring** during registration trials is essential
  - Includes ECGs, CV biomarkers and imaging assessments
  - Monitoring intensity should reflect the product's CV risk profile

- **Clear protocols** for intervention, dose modification or discontinuation of cancer therapy, use of cardioprotective agents and management of CV toxicities
  - Multidisciplinary collaboration between **oncologists** and **cardiologists**
  - Post-treatment **follow-up** should be **standardized** across arms

8. Risk Management Plan (RMP)

- Some CV risks may only emerge post-authorization
  - RMPs should address identified and potential CV risks
  - Additional risk minimization measures may be required

- Product labelling should clearly describe CV risks
  - Guidance on monitoring and management must be included
  - Post-marketing surveillance and RWD support ongoing safety evaluation

9. Conclusions (I)

- Cardiovascular safety is an increasingly important aspect of anticancer drug development
  - Risk is influenced by patient characteristics, treatment duration and novel mechanisms of action
  - A tailored, risk-based approach considering the totality of evidence is essential
  - Early and comprehensive baseline CV risk assessment improves safety characterization

10. Conclusions (II)

- Prospective and standardized CV endpoints enhance consistency and reliability
  - Continuous monitoring and multidisciplinary cardio-oncology collaboration improve patient protection
  - CV risks should be integrated into Risk Management Plans and product labelling
  - The approach will allow for **balancing the risk of cancer treatment-related CV toxicity (CTR-CVT) against the absolute benefit of the cancer treatment** and will facilitate easier comparison between different treatment approaches in the intended indication

Many thanks for your kind attention

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