EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 January 2026
EMA/4366/2026
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the revision of the Guideline on Clinical Evaluation of Diagnostic agents and its appendix 1 on imaging agents

Agreed by Methodology Working Party (MWP)	September 2025
Adopted by CHMP for release for consultation	19 January 2026
Start of public consultation	30 January 2026
End of consultation (deadline for comments)	30 April 2026

The proposed guideline will replace the 'GUIDELINE ON CLINICAL EVALUATION OF DIAGNOSTIC30 April 2026 AGENTS' (CPMP/EWP/1119/98/Rev. 1) and the 'APPENDIX 1 TO THE GUIDELINE ON CLINICAL EVALUATION OF DIAGNOSTIC AGENTS (CPMP/EWP/1119/98 REV. 1) ON IMAGING AGENTS' (EMEA/CHMP/EWP/321180/2008).

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	Diagnostic agents, imaging agents, theranostics, marketing authorisation

1. Introduction

Diagnostic agents are medicinal products used for diagnosis and/or monitoring of a disease. These diagnostic medicinal products include contrast agents (for computer tomography – CT, magnetic resonance tomography – MRI, ultrasound), radiopharmaceuticals (radionuclide generators, ready for use radiopharmaceuticals, radionuclide precursors, kits for radiopharmaceutical preparations), dyes/colouring agents/fluorophores, and non-imaging agents. The licensing of diagnostic agents is subject to the same stringent regulatory requirements as other medicinal products, ensuring a uniform standard of safety, efficacy, and quality. The principles used for the evaluation of medicinal products with respect to quality, pharmacology, toxicology, pharmacokinetics and safety also apply to diagnostic agents; however, as diagnostic agents are used to diagnose and/or monitor diseases/conditions and

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not for treatment, clinical development programmes should be adapted for these purposes. As for other medicinal products, benefits and risks related to the use of diagnostic agents are taken into account when granting a marketing authorisation.

2. Problem statement

The current guideline on Clinical evaluation of Diagnostic Agents (CPMP/EWP/1119/98/Rev. 1) was adopted in 2009. The same applies to its APPENDIX 1 (CHMP/EWP/321180/2008) on imaging agents. Since then, the scientific landscape and the regulatory thinking have evolved, and the guideline needs to reflect such evolution.

3. Discussion (on the problem statement)

In the proposed update of the guidance documents, a range of essential issues will be systematically addressed to ensure the guidance reflects current scientific and regulatory standards and provides clear and practical advice to stakeholders.

The following issues will be addressed:

General improvements

- Restructuring of the guideline is necessary to better accommodate the specific characteristics of different types of diagnostic medicinal products. This differentiation is necessary to ensure that each type of diagnostic agent is addressed with the level of detail and specificity it requires**:**
    - Radiopharmaceuticals (radionuclide generators, radionuclide precursors, and kits for radiopharmaceutical preparation, ready for use radiopharmaceuticals);
    - Contrast agents (for MRI, CT, Ultrasound, fluorophores/optical imaging);
    - Non-imaging agents, including dyes/colourants.
- Readability and nomenclature will be improved to remove ambiguity, facilitate implementation, and promote regulatory consistency. This will include:
    - Streamlining of the text, update and standardisation of (the list of) definitions, inclusion of cross-references, restructuring/rewording of the text to improve readability, etc.

Guidance on the required clinical packages to substantiate specific indications and clinical situations will be elaborated to provide applicants with a clearer understanding of the expectations for different indications and clinical contexts. This is relevant to reduce uncertainty, align study planning with regulatory needs, and improve the efficiency of dossier assessment. The following clinical situations/indications will be addressed:

- Theranostics/patient selection for targeted treatment/prediction: Given the growing evidence of the use of radiopharmaceuticals for patient selection and therapy prediction in clinical practice, detailed regulatory guidance is required;
- Monitoring of the course of a disease and/or treatment effects: Increasing clinical use of molecular imaging for longitudinal disease monitoring highlights the need for guidance on acceptable study designs, endpoints, and validation of imaging medicinal products;
- Prognostic indication: Although diagnostic imaging is applied in the experimental settings, formal regulatory standards for demonstrating prognostic value are not yet established;

- Claims: "detection of distribution and density" of specific molecules/structures: Based on accumulated regulatory experience, specific guidance will be provided;
- Diagnosis of vascular pathology/angiography: Based on accumulated regulatory experience, specific and harmonised guidance will be provided;
- Lymphography and lymph node detection: Based on accumulated regulatory experience, specific and harmonised guidance will be provided;
- Intraoperative detection of a pathology: Given the established role of radiopharmaceuticals in intraoperative diagnostics, guidance is needed to define the level of clinical evidence required, appropriate study endpoints, and methodological aspects to serve regulatory purpose;
- Further indications, as relevant.

Guidance on various overarching topics in clinical development will be improved and extended. These refinements are essential to ensure that development programmes for diagnostic agents generate robust, interpretable, and clinically relevant data:

- Relevance of proper **dose-finding**, and posology (weight-based vs. Fixed dose range, calculation of effective dose, etc.);
- Relevance of selection of the optimal **time-to-scan**;
- Development of **image read methodology**: relevance of early and proper evaluation and subsequent validation in phase 3; recommendations regarding the methods (e.g. ROC curves), etc.;
- Ability of diagnostic imaging to **differentiate from concomitant conditions** – relevance and how the data shall be gained;
- Relevance of **quantitative/semiquantitative reading methods** and requirements for the clinical package;
- Considerations for **AI-assisted diagnostic methods**.

Guidance on Technical performance will be improved and extended, emphasizing its pivotal role in ensuring the reproducibility and reliability of diagnostic tools:

- Requirements for **intra- and inter-reader variability** testing: confirmatory vs. non-confirmatory testing, definition of benchmarks for the acceptable variability, guidance for interpretation.
- Requirements for **test-re-test reliability** of diagnostic methods (variability of repeated scans): particularly relevant in the context of longitudinal assessments, e.g. for the indication "monitoring of disease progression/treatment effects".

The guideline will be modified to incorporate information on the attributes of the estimands (EMA/CHMP/ICH/436221/2017); and additional guidance on methodology of assessment of efficacy will be provided to better support in designing scientifically sound clinical studies:

- **Study design**: **Examples of clinical study designs** will be included for various indications and specific clinical situations: e.g. Alzheimer's Disease (or other dementias), cancer staging, lymph node detection, detection of vascular pathology, monitoring of response to treatment, etc.);

- Precise definition of and additional guidance will be provided on
    - **(surrogate) standard of truth**.
    - **choice of comparators**;
- Guidance will be given on how to accurately define the **scientific question of interest**;
- **Outcomes**: detailed guidance will be provided on
    - **parameters relevant for the assessment of clinical benefit**, (e.g., **diagnostic thinking, impact on patient management)**, including the assessment methodology thereof (e.g., validation needed, separate questionnaire on diagnostic thinking/definition);
    - the use of "**clinical outcomes**" as an endpoint (e.g., when "clinical outcomes" can be used as proof of efficacy);
    - the use and acceptability of **subject-, region-, and lesion-based outcomes, including** the requirement of location-matched analysis;
    - **assessment of concordance/agreement**
    - **detection rates** as primary endpoints (e.g., when to use).
- Choice of **summary measure**: guidance will be provided on the role of different summary measures, including the merits of likelihoods versus measures that are dependent on prevalence such as positive/negative predictive value;
- **Intercurrent events** will be discussed.

Additional guidance on assessment of safety to ensure adequate risk characterisation, especially in situations involving repeated exposure and radioactive substances will be provided:

- Need of more extended safety assessment in case of **repeated use** and depending on the administered dose and the substance characteristics;
- Detailed guidance on evaluation of **radiation safety** (e.g. especially in the case if repeated scans are targeted, need of evaluation of external radiation/exposure to radiation of health care professionals and family members).

Other

- Basic rules and criteria for the use of **published evidence** will be defined, specifying acceptable sources and criteria for acceptance of published studies, to ensure that literature-based evidence meets quality standards.

4. Recommendation

The MWP and CHMP recommend revising the existing Guideline on Clinical Evaluation of Diagnostics Agents and its Appendix 1 on Imaging Agents taking into account the issues identified above.

5. Proposed timetable

The Concept paper will be published for a three-month public consultation period. MWP will take into account all comments received during the public consultation on the concept paper when preparing the draft guideline.

It is planned to release for consultation a draft CHMP guidance document not later than Q3 2027.

6. Resource requirements for preparation

The preparation of the concept paper and the further revision of the guideline will involve the EMA-MWP and the temporary Drafting Group appointed by the MWP. Other Working Parties of the CHMP will be consulted.

7. Impact assessment (anticipated)

This proposed revised guideline on the clinical evaluation of diagnostic agents including imaging agents will address specific regulatory and methodological aspects not covered, or requiring update and clarification in the current version of the guideline and its appendix 1. These aspects will improve the development and marketing authorisation process of this class of medicinal products for the benefit of all stakeholders.

8. Interested parties

Pharmaceutical Industry, Healthcare Professionals associations (e.g., European Association of Nuclear Medicine (EANM), European Society of Urogenital Radiology (ESUR), European Association of Cardiovascular Imaging (EACVI), Society of Nuclear Medicine and Molecular Imaging (SNMMI), European Society of Radiology (ESR), European Society of Cardiovascular Radiology (ESCR), European Society of Gastrointestinal and Abdominal Radiology (ESGAR), European Society for Head and Neck Radiology (eshnr), European Society of Oncologic Imaging (ESOI), European Society of Paediatric Radiology (ESPR)), Patients' organisations, EU Competent Authorities.

9. References to literature, guidelines, etc.

Directives of the European Atomic Energy Community (EURATOM) (Directive 2013/59/Euratom).

Directive 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use as amended

GUIDELINE ON CLINICAL EVALUATION OF DIAGNOSTIC AGENTS (CPMP/EWP/1119/98/Rev. 1)

APPENDIX 1 TO THE GUIDELINE ON CLINICAL EVALUATION OF DIAGNOSTIC AGENTS (CPMP/EWP/1119/98 REV. 1) ON IMAGING AGENTS (EMEA/CHMP/EWP/321180/2008)