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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

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

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SPECIFIC CONSIDERATIONS FOR IMAGING AGENTS

This appendix should be read in conjunction with the general part. Imaging agents refer to both radiopharmaceuticals and contrast agents in this document.

An analysis of the following issues is required in an application for imaging agents:

- Classification of imaging agents.
- Efficacy criteria.
- Methodological issues.
- Safety assessment.

1 CLASSIFICATION OF IMAGING AGENTS

Imaging agents can be classified according to various principles, *e.g.*:

- Physical properties (*e.g.*, density, viscosity, osmolality).
- Route of administration (*e.g.*, oral, intravenous, intra arterial, intrathecal, intra-rectal, intra-articular, intra-cavitary).
- Pharmacokinetics.
- Imaging modality, *e.g.* X-ray, MRI, scintigraphy, etc.

A more clinically relevant classification of imaging agents relies upon their targeted or non-targeted nature:

(i) Targeted agents can enhance one or more anatomical sites as determined by factors such as functions or biological processes, *e.g.* imaging agents specific for the lymphatic system. Their affinity for an anatomical site, a system of function or a biological process makes the diagnostic claim straightforward. The indication will be limited to the target site (*e.g.*, gastrointestinal tract for an oral agent), system of function (*e.g.*, lymph node MRI for superparamagnetic nanoparticles) or biological function (*e.g.*, receptor imaging scintigraphy).

(ii) Non-targeted agents are widely distributed in the body before being eliminated through the lungs (*e.g.*, gas-filled microbubbles), kidneys (*e.g.*, iodinated contrast agents), or digestive tract. This category includes iodinated contrast agents, non-specific gadolinium chelates, and some PET agents *e.g.* H₂O-(¹⁵O). The non-targeted contrast agents can have different indications for different parts of the body. A claim for application of a non-targeted agent to different anatomical sites would be acceptable provided that the experimental agent has been shown to be clinically useful and, when appropriate, non-inferior to an active comparator belonging to the same group and for which the relevant anatomical territories have been studied.

Major systems that should be systematically included in trials for a whole body indication are those in which the imaging agent would be expected to exhibit different pharmacokinetic behaviours. These systems include the brain (because of the blood-brain-barrier), liver, kidneys and blood vessels.

The anatomical targets of an imaging agent depend on both the route of administration and the pharmacokinetics. Local administration induces an anatomical delineation at the site of the injection. Different phases of drug pharmacokinetics can result in varying anatomical targets over time, and thus different enhancement properties. For example, a non-targeted iodinated contrast agent administered as an intravenous bolus enhances the blood vessels (angiographic phase) initially, then the parenchyma (*e.g.*, liver, spleen, kidneys) and finally the urinary tract. Similarly, a liver targeted nanoparticulate agent distributes in the vasculature (non angiographic phase) before being taken up by the liver or the lymph nodes.

An imaging agent can therefore be used for different imaging purposes. With the rapid development of imaging techniques (scintigraphy, PET, CT, MRI and US), new uses of an already approved drug can emerge with new developments in instruments or techniques.

2 EVALUATION OF EFFICACY

Requirements for development and assessment of diagnostic agents have been described in the general part of the document. Additional considerations for imaging agents are detailed below.

2.1 Assessment of efficacy

2.1.1 Technical performance and practicality

The evaluation of the technical performance of a diagnostic agent intended for imaging should comprise the procedural aspect, the quality and readability of diagnostic images, and the reproducibility of their readings.

Procedural aspect:

As stated in 5.1 of the general part of this note, the potential advantages or disadvantages of the diagnostic agent should be evaluated from both the patient and technologists sides. For imaging agent, a special emphasis should be put on the administration route, on the timing of the imaging procedure (number of imaging sequences, delay of waiting in particular for radiopharmaceuticals, total duration of a typical procedure, need for repeated administration within one single procedure etc.) and on potential irradiation of the patient, the technologist and others in the vicinity, in comparison with already approved agents for similar diagnostic test.

Diagnostic images:

The evaluation of the use of a new agent on image quality and readability can be qualitative or quantitative.

Qualitative assessment includes:

1) Subjective criteria:

- + degree/quality of contrast enhancement;
- + conspicuity of normal and/or abnormal structures;
- + degree of distinction between normal and abnormal structures;
- + confidence in the interpretation of images using graded scales.

2) Objective criteria:

- + Description of pattern of enhancement;
- + Description of normal / abnormal findings;
- + Localisation and counting of lesions.

Quantitative assessment consists on measuring the ability of the new agent to alter the image density/signal intensity of target structures (normal structures, abnormal structures, etc.).

This can be done by measuring signal intensities during time course after administration of the imaging agents, to calculate parameters like target to noise ratio, percent enhancement.

Reproducibility of image reading.

The images should be blind read with the use of appropriate reading grids, frequently using scale for the level of certainty of the findings. This procedure permits to check the level of accordance of the interpretation between several readers of the same images. An overall evaluation of this accordance should be proposed *e.g.* using the kappa coefficient. Discrepant interpretations and their potential consequences in term of patient management should be highlighted and discussed.

When quantitative measurements are made with a specific imaging modality, special care should be taken in the methodological description of machine or scanner calibrations with appropriate phantoms. The requirements concerning the reproducibility of the quantitative results described in 5.1 of the general part of this note should be followed even when the quantitative measurements are associated with qualitative information.

2.1.2 Diagnostic performance

See general part of this note.

2.1.3 Technological dependence

An imaging agent is only useful in combination with an appropriate device designed for the detection of the physical effect of the agent. There is a strong dependence between the efficacy of the medicinal product and the technical equipment used to create the image. The fast evolving technological progresses can be such that an imaging drug developed over several years could become obsolete by the time of marketing application.

The efficacy of the imaging agent can sometimes depend on or be enhanced by an interaction between the physical process and the agent. For example, new acoustic emission sequences produced by state of the art US machines are designed to destroy the microbubbles of the ultrasound contrast agent, hence multiplying the signal enhancement properties of the contrast agent.

In summary, the imaging device is a key consideration in the design of clinical trials, and the applicant should pay special attention to:

- Technological choices in the development plan.
- Considerations on whether these technological choices are still valid at the time of the marketing authorisation.
- Any other concerns regarding interaction between the agent and the relevant technology.

3 METHODOLOGICAL ISSUES

3.1 Placebo and comparator

3.1.1 Need for placebo

For most imaging agents, the effect of the agent is so obvious on the post contrast images that the value of use of a placebo is very limited. In certain cases where the vehicle might have a contrast effect (*e.g.*, saline in US), a vehicle controlled study may be appropriate to demonstrate that the imaging agent has an effect beyond that of the vehicle. For the assessment of tolerability, administration of placebo followed by a dummy imaging procedure can be useful.

3.1.2 Comparator

For all imaging contrast agents developed as alternative or improvement over registered diagnostic agents, comparative studies are required. It is only when no active comparator is registered that the unenhanced imaging procedure may serve as an appropriate comparator, providing unenhanced procedure is considered state of the art for the claimed indication, which must be discussed and demonstrated in the protocol.

3.2 Bias

It is important to minimise the extent of possible observer bias by determining the true disease-state of subjects using the standard of truth independent of the experimental agent and of comparator. Refer to section 3.7.in the general part of this note. Possible bias in trial design, conduct and interpretation of results must be critically appraised in the Clinical Overview.

3.3 Image evaluation and blinding

Training of readers may be based on images obtained from phase I or II trials. Consistency between readers should be measured quantitatively.

There are several possibilities of blinding the readers in clinical trials on imaging agents.

- **Fully blinded image evaluation:** readers do not have any knowledge of the following: patient specific information (history, physical examination, results of other imaging studies), results of evaluation with the standard of truth, final diagnosis, patient outcome, inclusion and exclusion criteria, treatments, the agent used to obtain a given image.

- **Image evaluation blinded for outcome:** no knowledge of the results of evaluation with the standard of truth, treatments, final diagnosis or patient outcome. The readers might have knowledge on patient's history, physical examination, laboratory results, or results of other (ancillary) imaging studies, as well as of general inclusion and exclusion criteria.
- **Sequential unblinding:** readers evaluate images with progressively more clinical information on each read. Sequential unblinding is useful to mimic routine clinical practice. It is usually done in three steps: fully blinded image evaluation, then image evaluation blinded for outcome, then, to determine diagnostic performance of the imaging investigational agent, the results of the previous two evaluations are compared to the results of the standard of truth.

Blinded image evaluations (either fully blinded image evaluation or image evaluation blinded to outcome) by independent readers are recommended for the phase III efficacy trials.

In principle, full blinding off-site reading is recommended. In some cases, where the aim is to reflect the added diagnostic value of an investigational test to available diagnostic tools, a sequential unblinding may be used. However, extreme care is needed in the design of these studies so that the pre-test diagnostic accuracy of the baseline assessment is not deflated, thereby facilitating the demonstration of the added diagnostic value of the investigational product. In addition, a conventional blinded reader assessment designed to provide supportive evidence of efficacy is recommended.

3.3.1 Independent image evaluations

'Off-site' or external evaluation is the evaluation performed at sites not involved in the conduct of the study and by the readers who have no contact with patients or investigators. Off-site evaluation is considered to be the best way to minimise observer bias in the assessment of the efficacy of imaging agents and is recommended for the phase III studies.

These off-site assessment readings should be done by:

- Independent readers (unaware of findings of other readers, who do not participate in the study at the site of origin of the readings).
- Blinded readers (means that the reader is unaware of the clinical context and the imaging agent used). Readers external to participating centres might also be blinded for inclusion/exclusion criteria for the study, as well as which agent was administered first.
- A representative sample (2 or more) of readers. The reader is an intrinsic part of the diagnostic process in the same way as, *e.g.*, the imaging equipment.

The sequence of external evaluation of the imaging data should be randomised and the evaluation of images should be done in pairs (non-enhanced and enhanced) as well as separately to provide maximal information.

For the assessment of impact on diagnostic thinking, appropriate clinical information including the results of previously performed diagnostic tests needs to be provided. Depending on the agent, and the proposed indication, sequential unblinding may in certain circumstances be appropriate allowing the readers to form a judgement first without and then with prior relevant clinical information.

The 'on-site' (unblinded) evaluation of images is performed by the investigators involved in the conduct of the study and/or in the care of the patient. The on-site evaluation may be biased by lack of blinding to comparator test or other results and should not be presented as sole proof of efficacy even though this approach mirrors routine clinical practice.

Consensus reads: may be performed after individual readings have been completed. As readers are not independent any more, consensus read should not serve as primary image evaluation; however, they are useful to determine diagnostic performance of the investigational test.

3.3.2 Test reliability

Inter-reader variability and other sources of unreliability are often important sources of error in the interpretation of imaging modalities. It is recognised that frequently acquisition of medical images cannot be repeated on individuals, but inter- and within-reader variability should be investigated. In order to assess inter-reader variability, a reasonable number of readers should be engaged, trained and allocated to evaluate the same set of images as part of the development plan. Similarly to evaluate

within-reader variability, the same quantitative results, when an imaging modality yields quantitative measurements *e.g.* left ventricular ejection fraction, should be assessed repeatedly by the same reader. Test reliability may be investigated with and/or without masking of clinical data.

3.3.3 Dependency on study specific conditions

The competence of readers charged with interpreting diagnostic data can influence the evaluation of the accuracy of a test whenever assessment of test results involves some subjective element. The trial protocol should therefore explain how readers are trained to interpret the experimental test results.

The conduct of multicentre trials designed to provide on-site test results may also help to assess the diagnostic performance in settings closer to clinical practice.

3.4 Anatomical sites

3.4.1 Non-targeted agents

In the case of non-targeted agents that can enhance different anatomical sites after intravenous injection, confirmatory trials with an already approved comparator using similar conditions of administration are recommended.

3.4.2 Targeted agents

In the case of an agent targeting a system with multiple anatomical sites (*e.g.*, lymph node imaging, arthrography), the choice of the representative anatomical site(s) for the clinical trials should be discussed and justified by the applicant. The extension from one anatomical site to another (*e.g.*, shoulder to knee arthrography) should be discussed based on physiological, anatomical and imaging technique similarities, and might need justification (*e.g.*, lymph node scintigraphy in the thorax versus the abdomen).

4 SAFETY ASSESSMENT

Refer to safety assessment in the general part of this note. In addition, the safety of the imaging procedure itself has to be addressed.

Radiation exposure when radiopharmaceuticals are used

Information about absorbed radiation doses in various body tissues should be presented by the applicant and the estimation should preferably be based on studies in patients. The calculations should take into account factors like pathophysiology and age and must include the contribution of radionuclidic impurities to the radiation dose, the long-term elimination of the radiopharmaceutical and the radioactive degradation products.

Calculations of absorbed dose to organs should preferably be performed in accordance with the MIRD schedules. If other methods of calculation are used, details must be given with references to the original reports.

4.1 Posology and method of administration

The route of administration and the recommended administered activity (MBq or MBq/kg of body mass) for patients based on the dosage findings studies and clinical trials should be presented.

The diagnostic quality of nuclear medicine images (scintigraphy, tomoscintigraphy SPECT or positron emission tomography PET) is influenced by many factors that have to be adjusted: the performance of the detector, the waiting time between administration and image acquisition, image acquisition duration, target/non target activity ratios.

Administered activity is the most important parameter because it is one of the few which are determined by the specialist physician and is in direct relation with the total number of counts in scintigraphy or of coincident events in PET which reflects the information contained within the image. Administered activity is also the major determinant of radiation exposure of the patient, the attending people and the environment.

Radiopharmaceuticals contain only small amounts of the active substance and do not show any measurable pharmacodynamic effect. However, radiation is a general property of all radiopharmaceuticals, and patients will inevitably receive radiation dose. Irradiation related to the

administration of radiopharmaceuticals is devoid of short-term side effects, but long-term safety is a concern. Therefore, optimisation of the irradiation and thus of the administered activity is requested by Euratom directive 97-43 and must be performed during phase I and II clinical studies using various clinical protocols, based for example on the minimum number of counts required for image acquisition for a particular radiopharmaceutical in a particular clinical context.

4.2 Absorbed dose to organs and whole body

The absorbed dose to the organ receiving the highest radiation exposure must be stated as well as absorbed doses to all organs included in the calculation of the effective dose. The unit must be milligrays per unit activity administered (mGy/MBq) and milligrays to each of the targets organs for the average recommended administered activity.

4.3 Effective dose

The estimation of the radiation dose must be summarised in terms of the effective dose, using the weighing factors given by ICRP. The units should be millisieverts per unit of activity (mSv/MBq) and millisieverts for the average recommended administered activity in MBq. In very young children a minimum activity, necessary to obtain images of sufficient quality, should be given when appropriate, leading to an effective dose that should be specified.