

# EU Regulation of in vivo Diagnostics Regulatory Assessment of Diagnostic Agents

2<sup>nd</sup> Regulatory Workshop

University of Pretoria

9<sup>th</sup> October, 2014



## Research

# Googling for a diagnosis—use of Google as a diagnostic aid: internet based study

*BMJ* 2006 ; 333 doi: <http://dx.doi.org/10.1136/bmj.39003.640567.AE> (Published 30 November 2006)

Cite this as: *BMJ* 2006;333:1143

Article

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Peer review

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## Diagnostic Agents

- Any pharmaceutical product used as part of a diagnostic test (i.e. together with the equipment and procedures that are needed to assess the test result).
- Medicinal products used for diagnosis or monitoring of a disease
- *Diagnostic test: any procedure performed to increase the probability of a correct diagnosis.*

# Summary Product Characteristics

Target disease or condition  
(diagnosis)

Active substance X 0.25 mmol/ml, solution for injection

This medicinal product is for diagnostic use only.

Contrast enhancement in magnetic resonance angiography (CE-MRA).

Active substance X is indicated for contrast-enhanced magnetic resonance angiography for visualisation of abdominal or limb vessels in patients with suspected or known vascular disease.

- **4.1 Therapeutic indications**

The indication(s) should be stated clearly and concisely and should define the target disease or condition distinguishing between treatment (symptomatic, curative or modifying the evolution or progression of the disease), prevention (primary or secondary) and **diagnostic indication**. When appropriate it should define the target population especially when restrictions to the patient populations apply.



## Initial Guidance

### POINTS TO CONSIDER ON THE EVALUATION OF DIAGNOSTIC AGENTS

DISCUSSION IN THE EFFICACY WORKING PARTY	May 1998 / January 2000
TRANSMISSION TO CPMP	November 2000
RELEASE FOR CONSULTATION	November 2000
DEADLINE FOR COMMENTS	February 2001
DISCUSSION IN THE EFFICACY WORKING PARTY	June 2001
TRANSMISSION TO CPMP	November 2001
ADOPTION BY CPMP	November 2001

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# Updated Guidance

<b>GUIDELINE ON CLINICAL EVALUATION OF DIAGNOSTIC AGENTS</b>
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<b>DISCUSSION IN THE EFFICACY WORKING PARTY (EWP)</b>	May 1998/ January 2000
<b>TRANSMISSION TO CPMP</b>	November 2000
<b>RELEASE FOR CONSULTATION</b>	November 2000
<b>DEADLINE FOR COMMENTS</b>	February 2001
<b>DISCUSSION IN THE EFFICACY WORKING PARTY</b>	June 2001
<b>TRANSMISSION TO CPMP</b>	November 2001
<b>ADOPTION BY CPMP</b>	November 2001
<b>DRAFT REV. 1 AGREED BY EFFICACY WORKING PARTY</b>	April 2008
<b>ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION</b>	26 June 2008
<b>END OF CONSULTATION (DEADLINE FOR COMMENTS)</b>	31 December 2008
<b>AGREED BY EFFICACY WORKING PARTY</b>	June 2009
<b>ADOPTION BY CHMP</b>	23 July 2009
<b>DATE FOR COMING INTO EFFECT</b>	1 February 2010



## Updated Guidance

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

<b>DRAFT AGREED BY EFFICACY WORKING PARTY</b>	April 2008
<b>ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION</b>	26 June 2008
<b>END OF CONSULTATION (DEADLINE FOR COMMENTS)</b>	31 December 2008
<b>AGREED BY EFFICACY WORKING PARTY</b>	June 2009
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<b>DATE FOR COMING INTO EFFECT</b>	1 February 2010

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## The Role of Diagnostics in Health Care

- **Diagnosing** disease or ruling out the presence of a disease;
  - **Predicting** the potential risk of eventually developing a disease or disorder;
  - **Determining** the likely course or outcomes of a disease;
  - **Choosing** the most effective and appropriate treatment;
  - **Guiding** disease management; and
  - **Monitoring** response to treatment throughout care.
-





## Medicinal Products as Diagnostic

Includes

- Radiopharmaceuticals as defined in Directive 89/343/EC, for diagnostic use
  - Contrast agents for use in imaging techniques
  - Compounds used in diagnostic tests that do not involve radioisotopes
  - Various stains/markers
-



## Indications: diagnostic claims

- Structure delineation for imaging agents or some stains/markers;
- Functional, biological and physiological evaluation; provide clinically useful information on functional, physiological or biological evaluations of a tissue, organ or body region when compared to the reference product or the standard of truth
- Detection and/or assessment of disease, as well as prognostic and/or therapeutic management guidance.



## Imaging Agents Classification

- According to physical properties
  - Route of administration
  - Pharmacokinetics
  - Imaging modality
- 
- Specific or targeted agents
  - Non specific , non targeted agents



## Indications

- For the detection of lesions of the liver suspected to be due to metastatic disease or hepatocellular carcinomas.
- As an adjunct to MRI to aid in the investigation of focal pancreatic lesions.
- In patients with suspected or established coronary artery disease, to provide opacification of cardiac chambers and improvement of left ventricular endocardial border delineation at both rest and stress.

# Diagnostic Agents are

Similar to other agents

- Require quality safety and efficacy
- Positive benefit risk

But also different

In order to establish an indication for a diagnostic agent, it is necessary to demonstrate its benefit by assessing its

- technical performance (including procedural convenience),
- diagnostic performance,
- impact on diagnostic thinking, patient management, and clinical outcome,
- as well as its safety.



## Diagnostic Agents

- Part of a diagnostic workup, assist in making correct diagnosis
  - Should increase the likelihood of knowing disease status
  - Correct diagnosis is beneficial
  - Incorrect may be hazardous
- 
- Is risk the same for diagnostic and therapeutic?
-



# The Efficacy of Diagnostic Imaging



Dennis G. Fryback, PhD

John R. Thornbury, MD

## Abstract

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The authors discuss the assessment of the contribution of diagnostic imaging to the patient management process. A hierarchical model of efficacy is presented as an organizing structure for appraisal of the literature on efficacy of imaging. Demonstration of efficacy at each lower level in this hierarchy is logically necessary, but not sufficient, to assure efficacy at higher levels. Level 1 concerns technical quality of the images; Level 2 addresses diagnostic accuracy, sensitivity, and specificity associated with interpretation of the images. Next, Level 3 focuses on whether the information produces change in the referring physician's diagnostic thinking. Such a change is a logical prerequisite for Level 4 efficacy, which concerns effect on the patient management plan. Level 5 efficacy studies measure (or compute) effect of the information on patient outcomes. Finally, at Level 6, analyses examine societal costs and benefits of a diagnostic imaging technology. The pioneering contributions of Dr. Lee B. Lusted in the study of diagnostic imaging efficacy are highlighted.

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Key words: diagnostic imaging

efficacy studies

cost-effectiveness

ROC analysis. (Med Decis Making 1991;11:88- 94)

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Review Article

**The evaluation of diagnostic tests: evidence on technical and diagnostic accuracy, impact on patient outcome and cost-effectiveness is needed**

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## Results

First, the test's technical accuracy refers to the ability to produce usable information under standardized conditions. In a second step, the place of the new test in the clinical pathway is determined. Thirdly, the test's diagnostic accuracy is assessed, depending on its intended goal. The fourth step assesses the test's impact on the patient outcome. Depending on the place of the test in the clinical pathway, existing evidence can be used, or new evidence will be needed. At the final step, a cost-effectiveness analysis assesses the test's financial and societal consequences.

## Conclusion

Diagnostic tests evaluation should consider the technical accuracy, the test's place in the clinical pathway, its diagnostic accuracy, and its impact on patient outcome.





## In Clinical Trials

- The demonstration of clinical benefit should be tailored to the diagnostic agent being used and its potential claims. In most cases, clinical benefit of a diagnostic agent may be demonstrated by assessing its technical performance, diagnostic performance and by an appropriate discussion on the impact on diagnostic thinking.
- Depending on the type of claim, and in some particular situations (e.g. where no standard of truth is available), impact on patient management, and clinical outcome, may also need to be assessed.
- In addition, the measurement of clinical outcome might also be required if a diagnostic agent has e.g. better diagnostic performance but is less safe than other diagnostic procedures.



## Clinical Trials

- Usual requirements: trial objectives, products and methods investigated, testing procedures, trial population.....
- Available data on diagnostic performance to date
- Performance in terms of sensitivity, specificity, positive and negative predictive value
- Post test probability of a correct diagnosis in a study population reflecting clinical practice.



## What do we need to know?

- How reliable is it?
- Is it valid? Does it measure what it's supposed to measure?
- What's the added value as compared to not performing the new test?



## Standard of Truth

Standard of truth is believed to give the **true state of a patient or the true value of a measurement**. It provides an independent way of assessing the same variable being assessed by the investigational diagnostic agent.

Used to demonstrate that the **results obtained with the investigational diagnostic agent are valid** and to define diagnostic performance.

After the standard of truth has been selected (e.g. histopathology after surgery), the hypothesis for the expected diagnostic performance of the investigational agent in reference to the standard of truth should be determined to reflect the intended population and clinical setting for use of the diagnostic agent.



## Standard of Truth

- Compare the results with the investigational diagnostic agent with the results of the standard of truth. Clear description of the testing procedures is required and the choice of standard of truth needs to be justified.
- In the absence of standard of truth, a surrogate standard of truth, such as an appropriate combination of tests, clinical data, repeat diagnostic work-up and clinical follow-up, may be used to provide a good approximation to the true disease state.
- The choice of the surrogate standard of truth is of major importance for the interpretation of study data and needs to be fully described and justified.



## No standard of truth

- If well documented comparator available, “concordance” in a cross-over study can be used as outcome measure. Study population should be representative for the variability of the condition under investigation. In the case of discordant findings in the individual patient, further investigations such as biopsies or long term follow-up without intervention should be undertaken to establish the true state of the findings.
  - If this is not feasible, it might be necessary to conduct a randomised parallel group study comparing the new test as add-on to the standard procedure versus the standard procedure. Impact of patient management and clinical outcome would in these rare cases provide the necessary information of the benefit of the new diagnostic procedure.
  - In cases where a standard of truth cannot be used, regulatory acceptance through scientific advice procedures is recommended prior to the initiation of confirmatory trials.
-



## Comparator

- In the event that an investigational agent is being developed as an alternative or improvement over existing diagnostic agents, comparative studies are requested where both investigational agent and selected comparator are compared to the standard of truth. It is essential to **ensure that the selected comparator is appropriate, widely accepted in the EU for the claimed indication and reflects current medical practice.**
- The choice of a comparator must be **justified** and the corresponding procedures clearly described. The comparison should include an evaluation of both efficacy and safety data.



## Endpoints

- Often related the disease and how it is assessed
- Examples include diagnostic performance (sensitivity and specificity), predictive values, likelihood ratios, evaluation prognosis, impact on diagnostic thinking or on clinical outcome
- Mostly, appropriate co-primary endpoints are sensitivity and specificity; improvement in specificity, sensitivity and in certainty of diagnosis is reflected in improvement of a diagnostic thinking
- Endpoints should be clinically relevant and measurable in all patients





## Technical Performance

- Procedural aspect: potential advantages and disadvantages in relation to convenience and material safety for product preparation, handling, mode of administration, timing of procedure.
- Convenience and safety from both the patient and technologists perspective
- Reproducibility of the results obtained with the diagnostic test (all quantitative information)



## Impact on diagnostic thinking

- Refers to the impact of a test result on post-test versus pre-test probability of a correct diagnosis
- The impact on diagnostic thinking may be presented numerically; the rate of cases where diagnostic uncertainty with a new agent has decreased as compared to pre-test diagnosis should be reported (percentage, and confidence intervals). Positive and negative predictive values may help clinicians modify diagnostic thinking if reasonable thresholds have been reached.
- The impact on diagnostic thinking may influence patient management (e.g. change in a stage of a disease may induce a change in treatment) or not.



## **Impact on therapeutic decisions and clinical outcome**

Refers to a description and quantification of impact of diagnostic information gained with the diagnostic agents on patient management

Where appropriate, impact on patient management is assessed prospectively by using appropriate questionnaires and quantified by the rate of change in patient management pre- and post-test. All elements to be taken into account to establish the scheduled management of a given patient should be clearly defined in the study protocol.

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## Image Evaluation: Blinding

Blinded image evaluation by independent readers is recommended for phase III efficacy trials

- Readers have little or no knowledge of the patient's characteristics or prior history.
  - Assess reliability of a test result
  - Demanding artificial setting
  - Fully blinded
  - Image evaluation blinded for outcome
  - Sequential unblinding
-



## Blinded reading

- ‘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, to minimise observer bias in the assessment of efficacy of imaging agents and is recommended for the phase III studies.
- 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

The ‘on-site’ (unblinded) evaluation is performed by 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.

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## Test reliability

- Inter reader variability and other sources of unreliability are sources of error
  - Inter-reader: a reasonable number of readers engaged, trained and allocated to evaluate the test results
  - Within reader: same test results assessed repeatedly by the same reader
  - Readers and training
  - “Aggressive” readers
-



## Reader training

- “.....blinded readers had read images in what was considered by the applicant to be an overly conservative manner (i.e., reading with high specificity). As a result, the decision was made to re-train the readers to read with increased sensitivity while maintaining high accuracy”



## **MA should address**

- Technical performance
  - Diagnostic performance
  - Impact on diagnostic thinking
  - Impact on patient management (therapeutic decisions and clinical outcome)
  - Safety
  - Patient acceptability and test simplicity ( vs comparators)
-





## Requirements for Authorisation

- Adequate technical and diagnostic performance of a new diagnostic agent in relation to a standard of truth and, when appropriate, to an established comparator in the clinical context in which the diagnostic agent is to be used in well-designed superiority or non-inferiority trials.
- **When it is already known that intervention following the use of diagnostic agent/comparator leads to a clinical benefit, it will not be required to re-demonstrate the impact on diagnostic thinking** for each subsequent use of a diagnostic agent in the same setting.
- However, relevant impact on diagnostic thinking and/or patient management in the appropriate clinical context should be demonstrated, if therapeutic consequences of the diagnosis obtained with a new agent are not obvious, or the benefit/risk balance is unclear, and if the diagnostic agent itself may have immediate therapeutic implications. It may be useful to refer to published literature.



**CHMP**

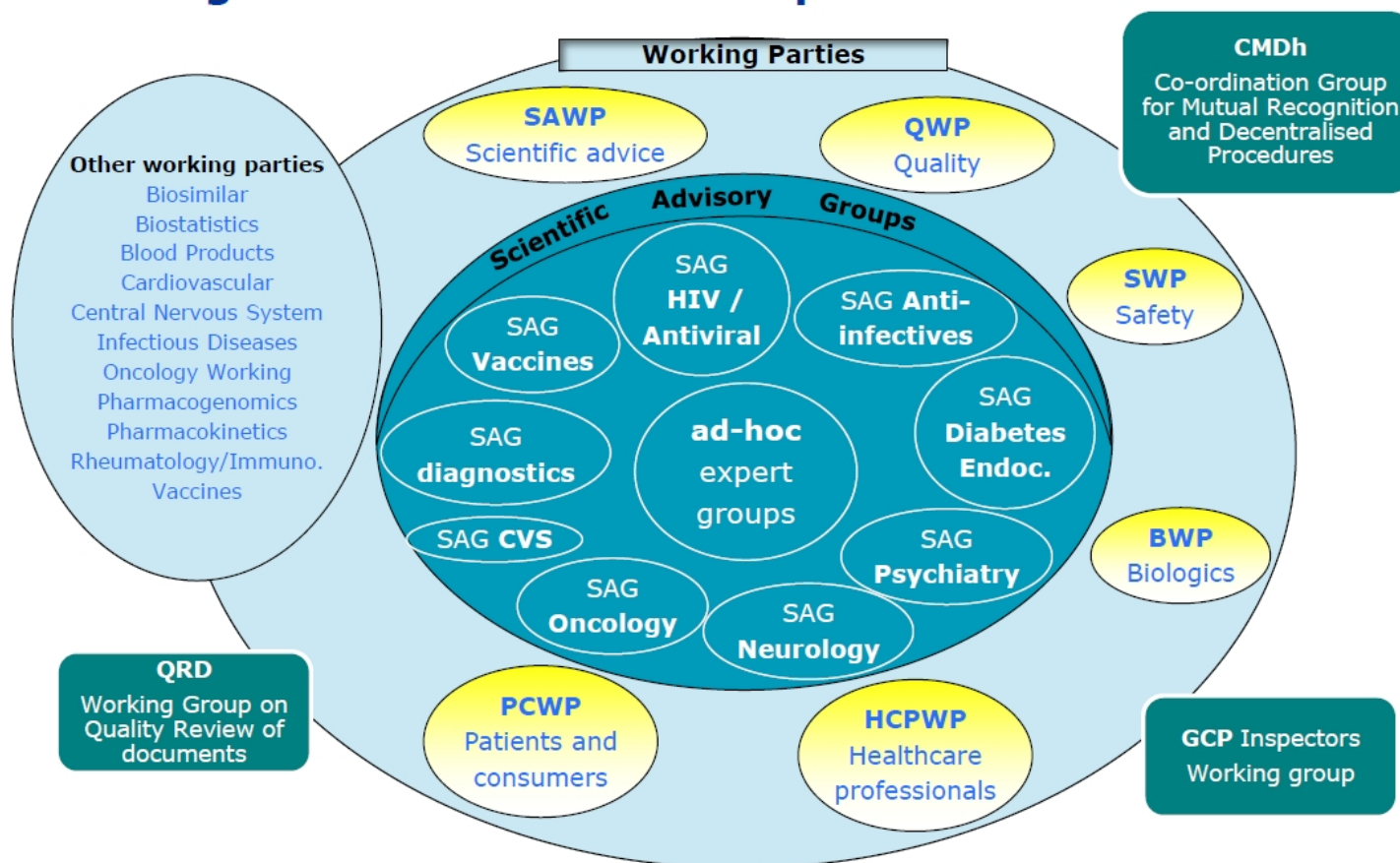


Chairperson: Tomas Salmonson



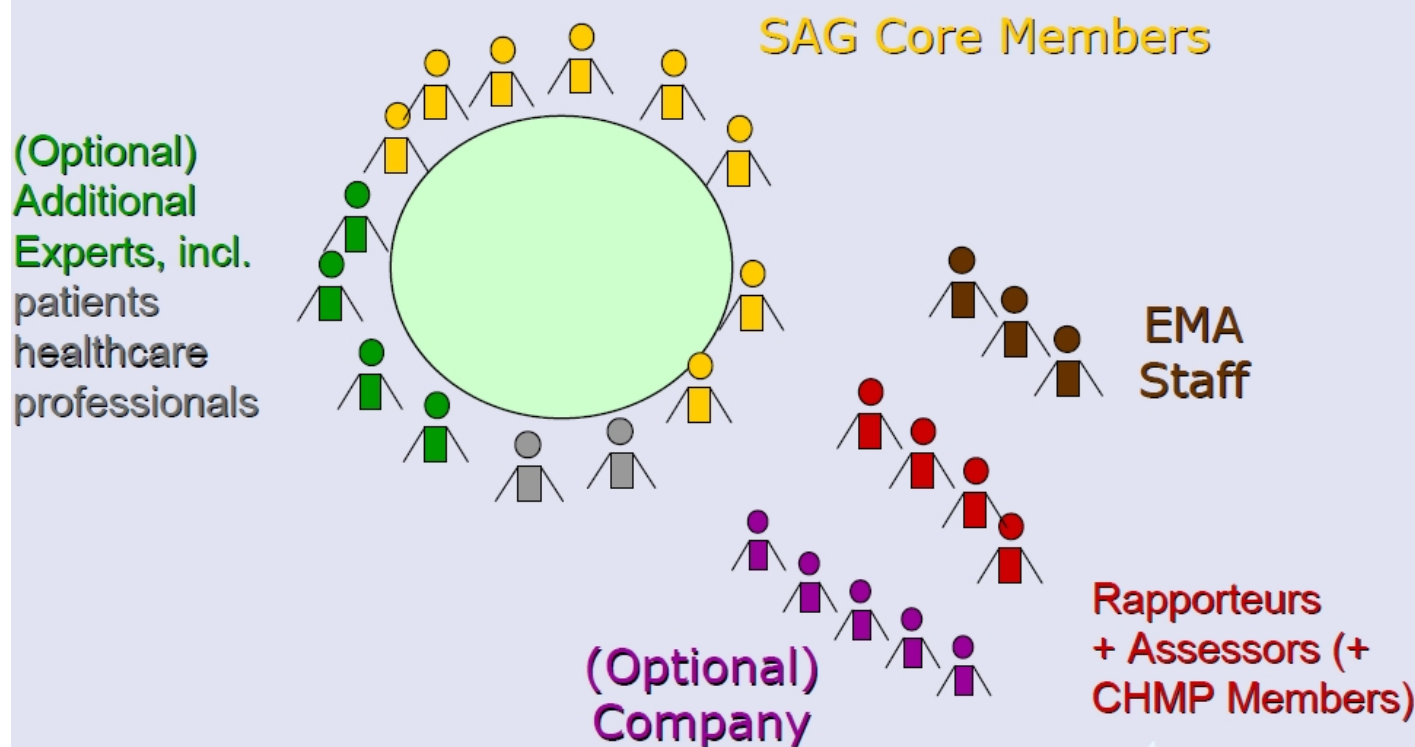
# SAG Diagnostics

## Working Parties and other Groups





## Who participates in a SAG meeting?





## Company – CHMP – SAG Communication



Company  
presents  
(open part of  
SAG meeting)



## Scientific Advisory Groups

- CHMP Request for SAG Meeting
  - Rapporteurs indicate need for SAG
    - CHMP adopts Questions to SAG
    - List of additional experts
    - Date for the meeting
    - Company to attend or not
  - SAG meeting: Written answers to CHMP questions
  - SAG chair briefs CHMP during plenary
-



## SAG Outcome

- Ideally clear and definite answers
- Require clear and definite questions
- Careful consideration of issues
- Ask the right questions!





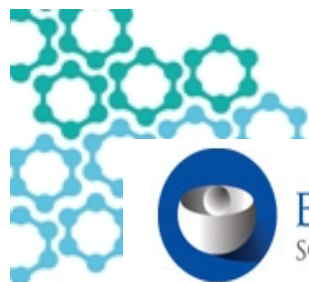
## Working Parties vs. SAGs

<b>WPs</b>	<b>SAGs</b>
Members normally <b>regulators</b> from national agencies	Members normally <b>academic clinical experts, patients</b>
CHMP delegates <b>drafting guidelines</b> (rarely product related issues with exceptions)	CHMP asks questions mainly in the context of <b>evaluation of products</b>
Meet <b>regularly</b> , publish work programme	Meet <b>when needed</b>

In both cases, the CHMP remains responsible for its final opinion

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Pre-authorisation

Post-opinion

Post-authorisation

Product information

Scientific advice and  
protocol assistance

▼ Scientific guidelines

Search guidelines

Quality

Q&A on quality

Biologicals

Non-clinical

▼ Clinical efficacy and  
safety

Clinical pharmacology  
and  
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## Clinical efficacy and safety: Radiopharmaceuticals and Diagnostic Agents



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**This page lists the European Medicines Agency's scientific guidelines on radiopharmaceuticals and diagnostic agents.**

If you have comments on a document which is open for consultation, please use the [form for submission of comments on scientific guidelines](#).

*Please note that the EWP Secretariat email address ([ewpsecretariat@ema.europa.eu](mailto:ewpsecretariat@ema.europa.eu)) no longer exists. Therefore, please submit your comments from now on to the following email address: [radiopharmaceuticalsdg@ema.europa.eu](mailto:radiopharmaceuticalsdg@ema.europa.eu).*

More information is available on the activities of the CHMP's [Radiopharmaceuticals Drafting Group](#).

Topic	Documents	Reference number	Publication date	Effective date	Remarks
Guideline on core SmPC and package leaflet for sodium fluoride ( <sup>18</sup> F)	 <a href="#">Draft guideline</a>	EMA/CHMP/465616/2014	Release for consultation July 2014		Deadline for comments 31 October 2014
Core SmPC and Package Leaflet for 4 ( <sup>99</sup> Mo/ <sup>99</sup> mTc) generator	 <a href="#">Draft guideline</a>	EMA/773757/2013	Release for consultation January 2014		Deadline for comments 15 April 2014



# CONCEPT PAPER ON HARMONISATION CLINICAL ASPECTS RADIOPHARMACEUTICALS



Harmonisation and update of the clinical aspects in the authorised conditions of use for radiopharmaceuticals and other diagnostic medicinal products in the European market, by the formulation of a **core SmPC** for their active substance, would provide a useful document to assure **consistency of their authorisation and use**. This procedure would be necessary **for widely used radiopharmaceuticals and certain other relevant diagnostic medicinal products** registered in Europe and registered PET radiopharmaceuticals.

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## Core SmPC

- Basic information that has been agreed on the basis of previous assessment and which is considered as basic/minimal information for that product.
- The purpose of this core SmPC is to provide applicants and regulators with harmonised guidance on the information to be included in the Summary of product characteristics (SmPC)



## Concept Paper: core SmPC

- Update is mandatory for existing core SmPCs from a scientific point of view as well as for ensuring compliance with the Points to Consider on the Evaluation of the diagnostic agents (CPMP/EWP/1119/98), the guideline of the SmPC (October 2005) and the QRD templates for the documents of information of medicinal products. Indeed, **indications** for these medicinal products should be reviewed for their use with state-of-the-art techniques and to describe the population and the clinical context in which they have been studied and have actually **proven to be effective and safe**, as CPMP/EWP/1119/98 states, and not just the type of scintigraphic procedure. **Posology, precautions of use, interaction with other medicines, adverse reactions and dosimetry** should also be reviewed.



## Core SmPC

Harmonisation procedure for radiopharmaceuticals and diagnostic medicinal products in order to achieve:

An update of the relevant existing core SmPCs for:

- Those radiopharmaceuticals involved in the Coordinated Procedure taking place at the early 90's at EMEA.
- Fludeoxyglucose (18F).

A formulation of a core SmPC for:

- Widely used radiopharmaceuticals authorised when the Coordinated Procedure conclude and in the European market (such as sestamibi, tetrofosmine, etc.).
  - Relevant registered PET radiopharmaceuticals.
  - Other relevant well-established diagnostic medicinal products commonly used in clinical practice in Europe.
-



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## Radiopharmaceuticals Drafting Group

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The **Radiopharmaceuticals Drafting Group** was set up by the Committee for Medicinal Products for Human Use (CHMP) in order to draft guidelines relating to radiopharmaceuticals and to provide occasional support to scientific advice.

### Mandate, rules of procedure and work programme

More information on the Drafting Group's responsibilities and composition is available in these documents:

- ▶ [Mandate, objectives and rules of procedure for the temporary working parties and drafting groups](#)
- ▶ [Work plan](#)

### Composition

The Drafting Group is composed of [European experts](#) selected from or associated with the national agencies with specific expertise in radiopharmaceuticals. Nominations for members are adopted by the CHMP.





## **Review class-related core safety information: iodinated contrast agents**

Action: Draft annex for harmonisation of wording on safety information in the core SmPC/PL of iodinated contrast agents.

Comments: With the SmPC advisory group, the RadDG will prepare an annex to harmonise class-related safety information aspects for core SmPCs of iodinated contrast agents.

## **Review class-related core safety information: Gadolinium-based contrast agents**

Action: Draft annex for harmonisation of wording on safety information in the core SmPC/PL of Gadolinium-based contrast agents.

Comments: With the SmPC advisory group, the RadDG will prepare an annex to the SmPC for Gadolinium-based contrast agents to harmonise class-related safety information aspects for core SmPCs of Gadolinium-based contrast agents.



## Diagnostics and the SmPC

- Indications 4.1
- Information on pivotal studies in 5.1
- Dosimetry: section 11
- Instructions for preparation of radiopharmaceuticals : section 12





# Some examples



## Optimark

- ....use with magnetic resonance imaging (MRI) of the central nervous system (CNS) and liver. It provides contrast enhancement and facilitates visualization and helps with the characterization of focal lesions and abnormal structures in the CNS and liver....



## Optimark

- 4 pivotal studies shared the same design, being multi-centre, randomised, double-blind, non-inferiority studies to evaluate the safety, tolerance, and efficacy of OptiMARK compared to Magnevist in CNS or liver lesion.
- In the two pivotal CNS studies the Primary Efficacy Endpoint, the mean difference in change in contrast score as assessed from pre to post-contrast images between OptiMARK and Magnevist was  $0.018 \pm 0.061$ . The lower bound of the two-sided 95% CI (-0.14) for this difference was superior to the pre-defined non-inferiority margin ( $\Delta = -0.5$ ) demonstrating that OptiMARK is not inferior to Magnevist with respect to the change in contrast score
- In the two pivotal liver studies the mean difference in change in contrast score as assessed from pre to post-contrast images between OptiMARK and Magnevist was  $0.013 \pm 0.049$ . The lower bound of the two-sided 95% CI (-0.08) for this difference was superior to the pre-defined non-inferiority margin ( $\Delta = -0.5$ ), demonstrating that OptiMARK is not inferior to Magnevist with respect to the change in contrast score as assessed from pre to post-contrast images.
- Analysis of multiple secondary endpoints like sensitivity, specificity and accuracy showed a comparable performance between OptiMARK and Magnevist.



## Vasovist ( now Ablavar)

- Indicated for contrast-enhanced magnetic resonance angiography (CE-MRA) for visualisation of abdominal or limb vessels in adults only, with suspected or known vascular disease



- The efficacy of Gadofosveset was shown in two phase II dose-finding studies and four main phase III studies. In patients with known or suspected abdominal or limb vascular disease Gadofosveset enhanced MRA was more accurate than unenhanced MRA for detection of stenosis greater than 50%.
- Gadofosveset enhanced MRA showed a statistically significant improvement in diagnostic efficacy (sensitivity, specificity, and overall accuracy) compared to unenhanced MRA.
- It was clear that a higher number of patients would undergo XRA procedure based on unenhanced MRA alone compared to MS-325 enhanced MRA. Thus, use of Gadofosveset enhanced MRA will result in substantial reduction in number of patients who would be exposed to the known risks of XRA.



## Luminality

- Luminality is an **ultrasound** contrast-enhancing agent for use in adult patients in whom non-contrast echocardiography was suboptimal (suboptimal is considered to indicate that at least two of six segments in the 4- or 2-chamber view of the ventricular border were not evaluable) and who have suspected or established coronary artery disease, to **provide opacification** of cardiac chambers and improvement of left ventricular endocardial border delineation at both rest and stress.



# Luminity Clinical Studies



## Key Features of the Clinical Studies Supporting the Claims for Efficacy in the Echocardiography Indication

Study	No. Subjects Treated with Luminity (Placebo)	Mode of Luminity Administration	Main Type of Ultrasound Imaging	Parallel Placebo Group	Type of Control Standard Diagnostic Technique	Unenhanced vs Enhanced Images	Blinded Read
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### PIVOTAL ECHOCARDIOGRAPHY STUDIES

DMP 115-004	69 (18)	Bolus	Fundamental	Yes	–	Yes	Yes
DMP 115-005	100 (24)	Bolus	Fundamental	Yes	–	Yes	Yes
DMP 115-006	67 (–)	Bolus	Fundamental	No	MRI	Yes	Yes
DMP 115-007	59 (–)	Bolus	Fundamental	No	MRI	Yes	Yes
DMP 115-017	64 (–)	Bolus + infusion	Fundamental	No	–	Yes	Yes

### SUPPORTIVE ECHOCARDIOGRAPHY STUDIES

DMP 115-018	78 (40)	Infusion	Non-linear	Yes	Nuclear imaging	No	Yes
DMP 115-022	87 (43)	Infusion	Non-linear	Yes	Nuclear imaging	No	Yes
DMP 115-209	69 (–)	Infusion	Non-linear	No	Coronary angiography	No	Yes
DMP 115-211	26 (–)	Bolus + infusion	Non-linear	–*	–*	–*	No
DMP 115-902	42 (14)	Bolus	Fundamental	Yes	–	Yes	Yes

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## DaTSCAN ioflupane ( $^{123}\text{I}$ ) 74 MBq

DaTSCAN is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum:

- In adult patients with clinically uncertain Parkinsonian Syndromes, for example those with early symptoms, in order to help differentiate Essential Tremor from Parkinsonian Syndromes related to idiopathic Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy.

DaTSCAN is unable to discriminate between Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy.

- In adult patients, to help differentiate probable dementia with Lewy bodies from Alzheimer's disease.

DaTSCAN is unable to discriminate between dementia with Lewy bodies and Parkinson's disease dementia.





## DaTSCAN

- The primary efficacy criteria were visual assessment of ioflupane ( $^{123}\text{I}$ ) striatal uptake determined by institutional read (clinical diagnosis of the patient by the study site). The secondary variable was visual assessment of striatal uptake determined by blinded read (consensus diagnosis of a panel composed of 5 readers, blinded to the clinical diagnosis).
- In addition, a semi-quantitative assessment of regional interest was also determined.
- In general, the objective was to compare the accuracy of diagnosis by DaTSCAN to the best possible clinical diagnosis, according to movement disorder specialists.



## Amyvid florbetapir ( $^{18}\text{F}$ )

- Amyvid is a radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of  $\beta$ -amyloid neuritic plaque density in the brains of adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive impairment. Amyvid should be used in conjunction with a clinical evaluation.
- A negative scan indicates sparse or no plaques, which is not consistent with a diagnosis of AD. For the limitations in the interpretation of a positive scan, see sections 4.4 and 5.1.



## Interpretation of Amyvid images

- Amyvid images should only be interpreted by readers **trained** in the interpretation of PET images with florbetapir (18F). A negative scan indicates sparse or no density of cortical  $\beta$ -amyloid plaques. A positive scan indicates moderate to frequent density. Image interpretation errors in the estimation of brain  $\beta$ -amyloid neuritic plaque density, including false negatives, have been observed.

## Limitations of use

- A positive scan does not independently establish a diagnosis of AD or other cognitive disorder since neuritic plaque deposition in grey matter may be present in asymptomatic elderly and some neurodegenerative dementias (Alzheimer's disease, Lewy body dementia, Parkinson's disease dementia).
- For the limitations of use in patients with mild cognitive impairment (MCI), see section 5.1.
- The efficacy of Amyvid for predicting development of AD or monitoring response to therapy has not been established (see section 5.1).



## Amyvid

- PET images (binary read method (positive or negative) conducted by 5 independent academic nuclear medicine physicians.
  - Autopsy data as standard of truth for detection of pathologically significant density of A $\beta$  neuritic plaques (i.e. moderate to frequent neuritic plaque density).
  - Review clinical usefulness
  - Impact on diagnostic thinking
-



## Amyvid

- The company should continue to develop and validate a quantitative PET reading methodology based on their product.
- The company is encouraged to perform a study to assess the impact on diagnostic thinking and patient management since the therapeutic consequences of the diagnosis of labelling brain  $\beta$ -amyloid are not obvious. For the design, parallel HTA/scientific advice is recommended.



## Neuraceq florbetaben (18F)

- Neuraceq is a radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of  $\beta$ -amyloid neuritic plaque density in the brains of adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive impairment. Neuraceq should be used in conjunction with a clinical evaluation.
- A negative scan indicates sparse or no plaques, which is not consistent with a diagnosis of AD. For the limitations in the interpretation of a positive scan, see sections 4.4 and 5.1.
- A PET scan with florbetaben (18F) should be requested by clinicians experienced in the clinical management of neurodegenerative disorders.
- Neuraceq images should only be interpreted by readers trained in the interpretation of PET images with florbetaben (18F). A recent co-registered computed tomography (CT) scan or magnetic resonance (MR) imaging of the patient to get a fused PET-CT or PET-MR image is recommended in cases of uncertainty about the location of grey matter and of the grey/white matter border in the PET scan (see section 4.4. Interpretation of Neuraceq images).



## Neuraceq

### Limitations of use

- A positive scan does not independently establish a diagnosis of AD or other cognitive disorder since neuritic plaque deposition in grey matter may be present in asymptomatic elderly and some neurodegenerative dementias (Alzheimer's disease, Lewy body dementia, Parkinson's disease dementia).
- For the limitations of use in patients with mild cognitive impairment (MCI), see section 5.1.
- The efficacy of florbetaben (18F) for predicting development of AD or monitoring response to therapy has not been established (see section 5.1).



## Neuraceq

- sensitivity and specificity of the visual assessment of regional tracer uptake in the florbetaben (18F) PET images compared to histological verification of the presence or absence of cerebral beta-amyloid in the respective post mortem specimens.
- sensitivity and specificity of the composite “whole brain” regional visual assessment (collapsed from the regional PET visual assessment results) in detecting/excluding cerebral  $\beta$ -amyloid plaques based on the “whole brain” histopathological verification of the presence/absence of  $\beta$ -amyloid deposition (collapsed from the results of the regional histological findings from the Pathology Consensus Panel). To determine the sensitivity and specificity of the quantitative assessment of regional tracer uptake in florbetaben (18F) PET images compared to histological verification of the presence or absence of cerebral  $\beta$ -amyloid in the respective postmortem specimens.





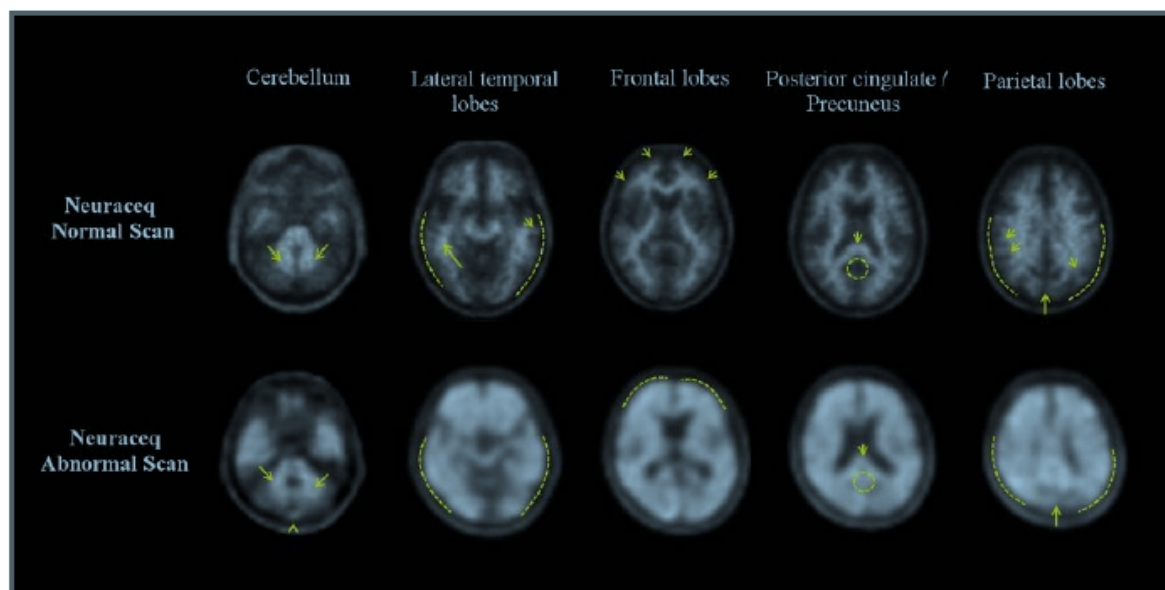
## Other agents:

- Optison (perflutren).. Echocardiography
- Sonovue (sulphur hexafluoride)... Echo
- Echogen.. Echo
- Sinerem (withdrawn)
- Leukoscan (sulesomab).. Osteomyelitis imaging



## Diagnostics and the SmPC

**Figure 1: Neuraceq PET cases showing examples of negative florbetaben ( $^{18}\text{F}$ ) PET scan (top row) and positive scan (bottom row).**



The overall decision of the visual PET scan assessment is subject-based and based on a binary outcome as 'positive' or 'negative'. A subject is classified as "positive" or "negative" based on the brain amyloid plaque load (BAPL) score (Table 2) which is derived from RCTU scores in the four brain regions (Table 1).



## In Summary

- Wide range of possible agents
- Scientific advice likely to be helpful ( if not essential)
- Issues are standard of truth/ comparator
- Consistency of performance



Thank you for your attention

