

Paper 2

PET Imaging: Scenarios to illustrate regulatory issues

Purpose: for use in discussion of how different regulatory routes may apply in different circumstances

The MHRA web pages have recently been updated to provide guidance to sponsors of clinical trials using PET ligands and include earlier versions of these scenarios, which have now been revised and expanded in preparation for this workshop. The pages - which contain further useful illustrative guidance - may be found through the following links:

<http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/SpecialInterestGroups/PET/PETGeneralinformation/index.htm>

<http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/SpecialInterestGroups/PET/PETAdditionalinformation/index.htm>

Contents:

Studies on healthy volunteers:

Example A
Example B
Example C (b)
Example D (a)

Studies in patients:

Example C (a)
Example D (b) (c)
Example E (a) (b)
Example F (a) (b)
Examples G, H, I, J, K

Examples A through E are primarily from the neurosciences; F through K relate to cancer.

A Investigating an established radiotracer in healthy volunteers

In this example a drug company is using a commonly used PET tool to assess receptor occupancy of a new product X.

Trial Design:	Open label study, in healthy volunteers, to investigate the receptor occupancy of product X
Purpose of Trial:	Receptor occupancy of product X in the human brain
Products:	Product X 11C- labelled DASB (a high-selectivity radioligand for labelling the CNS serotonin neurotransmitter transporter)
Key Parameters:	Receptor occupancy of Product X
Product Classification:	Product X - IMP 11C- labelled DASB - NIMP
Rationale:	DASB is a commonly used PET tool for end point assessment. The study requires a CTA, product X requires an IMPD and IMPMA, however, there is no requirement for DASB to hold either.

Manufacture of DASB should be to the good manufacturing practice standard for pharmaceutical processing (GMP), with the burden of proof of its Safety and Quality documented in the Investigator Brochure.

Note: Historically, the PET community has followed the "Specials" licence (SL) application process for such compounds. The SL would allow the company to demonstrate manufacture of DASB to GMP and allow the physician in charge of the trial to request its use. However, patient benefit cannot be clearly demonstrated in this application which means that use of the SL is not appropriate. In such a case, the site instead needs to ensure that it is able to demonstrate that it can meet GMP standards using another mechanism.

This scenario reflects current MHRA approaches, which are intended to be more risk-based and to minimise unnecessary restrictions.

B Comparison of two neurotransmitter receptor radiotracers, one of which could become a diagnostic tool, while the other acts as best current “gold standard”

Trial Design:	Open label study, in healthy volunteers to assess the anatomical selectivity of microdoses of novel PET ligand Y.
Purpose of Trial:	To investigate the receptor selectivity of novel PET ligand Y in comparison to the “gold standard” PET ligand currently in use (Raclopride).
Products	Raclopride (a pharmacological antagonist that binds dopamine D2 receptors, used primarily in studies of Parkinson’s Disease) Ligand Y
Key Parameters:	Selectivity of Product Y for a particular receptor and its binding affinity.
Product Classification:	Raclopride – NIMP Ligand Y – NIMP
Rationale:	Raclopride is a commonly used PET product acting as a challenge agent to provide a baseline of effect. Ligand Y is the object of the study; however it is not a medicine or “active substance in pharmaceutical form”, not one of the designated products in the CTA flow diagram on the MHRA website and has no clinical/pharmacological effect. The study is not looking at product safety or efficacy in a clinical context: it is a study of distribution to inform about its potential utility as an endpoint assessment tool. Therefore no CTA is required.

Manufacture of Raclopride and Ligand Y should be to GMP, with the burden of proof of their Safety and Quality documented in the Investigator Brochure.

In summary, no CTA is required under the current algorithm because Raclopride is already well established as a NIMP and Ligand Y is being investigated only as an alternative potential endpoint assessment tool. If Ligand Y proves to have a high specific binding activity as a result of receptor occupancy/affinity studies, it has potential to replace Raclopride in future receptor characterisation studies.

This is a useful example for discussion at the meeting because the conclusion is very finely balanced. Some investigators would view Ligand Y as an IMP because the team are investigating the properties of a novel radiotracer and one that might be able to be developed as a diagnostic tool at some later stage.

- C Set of studies using a new amyloid radiotracer, AV-45, in study participants who may or may not have asymptomatic Alzheimer's Disease (AD). Each sub-study addresses a distinct question and anticipates a distinct regulatory framework:**
- a) Investigation of whether established ligand AV45 binds to amyloid protein in patients diagnosed with AD to confirm the potential to select subjects with pre-clinical pathology**
 - b) Investigation of how a potential therapeutic molecule, X, might reduce brain amyloid plaque burden**
 - c) Investigation of whether binding or changes in binding after treatment with X predict the outcome of presentation with clinical AD in patients**

Trial Design: Open label study, in "healthy" volunteers, to investigate the effect of drug company product X in an asymptomatic pre-Alzheimer's population, as determined by amyloid plaque build-up.

Purpose of Trial: Effect of product X on amyloid plaques

Products: Product X
11C- labelled AV45 (a ligand that binds amyloid, a protein that is present in Alzheimer's disease)

Key Parameters: Identification of asymptomatic population with plaque build-up. Quantitation of change in volume of plaques under the influence of product X

Product Classification: Product X - IMP
11C- labelled AV45 - NIMP

Rationale: The study requires a CTA and product X requires an IMPD and IMPMA. However, there is no requirement for AV45 to hold either (because it will be used as a screening tool to identify asymptomatic subjects with higher amyloid plaque burden, and then for end point assessment) for applications in (a) and (b). A "Specials" licence would allow the study investigators to demonstrate manufacture of AV45 to GMP and the physician in charge of the trial could request its use under such a licence.

Although with AD patients the "Specials" licence should be applicable, the use of a "Specials" licence in relation to the studies on healthy participants (b) would appear to be inappropriate.

In application (c) binding of AV-45 is related to clinical outcome. If this is in the context of assessing whether AV-45 could become a diagnostic imaging agent for AD, then it would be considered as an IMP. However, it is possible that the study could also be framed in terms of assessing whether the load of amyloid determines the rate of neurodegeneration in AD, in which case it might not be considered an IMP, but rather an endpoint assessment tool, but this data then should not be used in direct support of a licensing application for AV-45 for AD diagnosis at a future date.

This example demonstrates how the framing of a question can determine whether a PET radiotracer is regarded as an IMP or not, e.g., sub-study (a) could arguably be defined as IJMP for AV-45 since the research question is about whether AV-45 binds to amyloid protein.

D Studies of antibody-tagged biological agents that either do or do not have a biological effect at very low (tracer) doses for:
a) An extension of first in man studies
b) Application of an antibody with approved clinical use

Trial Design:	<p>a) Open label study in healthy volunteers, to use PET to investigate the distribution of an antibody A, already licensed for use in cancer patients, after labelling it with a positron-emitting isotope for the first time. No biological effect of the parent antibody is known at the microdoses to be used for PET.</p> <p>b) Open label study in patients with the autoimmune condition Systemic Lupus Erythematosus (SLE). This SLE study will use PET to assess the magnitude of increases in focal expression of the epitope recognised by antibody A in kidneys during a flare of SLE, on the basis that the epitope is shared by immune cells.</p> <p>c) Open label study in cancer patients, to evaluate the potential of radiolabelled antibody A to identify residual tumour after a full therapeutic course of the antibody.</p>
Purpose of Trial:	<p>a) To define the kinetics and distribution of the antibody in order to understand properties of such molecules and guide future biopharmaceutical design.</p> <p>b) To evaluate increases in binding potential indicating increased inflammatory cell infiltration into the kidneys during an SLE flare to increase disease understanding.</p> <p>c) To evaluate PET as a method for improving patient outcome by optimising the length of treatment needed for tumour reduction.</p>
Products:	<p>Antibody product Isotope-labelled antibody</p>
Key Parameters:	<p>Kinetics and distribution of antibody</p>
Product Classification:	<p>Antibody product – NIMP in (c) as it is licensed for this use Labelled antibody- IMP for (a) and for (c) but NIMP for (b)</p>
Rationale:	<p>Study (a) requires a CTA, antibody-tagged product Z requires an IMPD and IMPMA, as properties of the radiotracer are being defined.</p> <p>Study (b) may not require a CTA because antibody A is an established compound and the labelled form is simply being used as an endpoint assessment tool.</p> <p>Study c) requires a CTA and the antibody-tagged product requires an IMPD and IMPMA.</p> <p>In all cases, a toxicity study will be required in a single species. Although the acceptable (or lack of) toxicity of the licensed antibody is well described at low doses, the chemical modification of the antibody for its use as a radiotracer has the potential to change the pharmacology. Demonstration of acceptable toxicity for the labelled antibody is needed. Additionally (all cases), the imaging centre will require an MHRA IMP manufacturing licence.</p>

E Studies on the neuropharmacology in the context of a specific condition (eg depression) in patients:

- a) Use of compound intended eventually to treat depression ie that will affect the clinical outcome, to understand its interactions with receptors in ways that could allow it to be used in a more effective way
- b) Use of compound to develop and approach for studying, e.g. receptor occupancy, along the drug development pathway

Trial Design:	<p>a) Open label, pilot study to assess the potential for stratification of patients with major depression for treatment with either X or Y, both drugs licensed for use in depression, based on binding potential for the 5HT1A receptor.</p> <p>b) A study to test whether there are differences in 5HT1A receptor in healthy subjects at risk of major depressive disorder using PET measures of binding potential.</p>
Purpose of Trial:	<p>a) to investigate a possible approach to treatment stratification for high risk patients; b) to better define the neurobiology of depression</p>
Products:	<p>Licensed drugs X and Y 5HT1A radiotracer</p>
Key Parameters:	<p>In (a), the clinical outcomes after treatment Both, 5HT1A binding potential</p>
Product Classification:	<p>5HT1A radiotracer- IMP for (a); NIMP for (b)</p>
Rationale:	<p>The licensed drugs are being used appropriately within their indication and are therefore NIMPs. The radiotracer is being used as an endpoint assessment tool for (b), but is being evaluated as a potential stratifier for diagnosis sub-types of depression distinguished by responsiveness to drugs X and Y.</p> <p>Use of a "Specials" licence is appropriate for (a), but, as healthy volunteers are being studied, it does not seem appropriate for (b).</p> <p>The centre will require an IMP manufacturing licence.</p> <p><i>This example demonstrates another 'grey area' where interpretation comes down to the precise objective of the study (or the way that the objective is presented). It could be argued that the radiotracer for a) is an NIMP, e.g., if it was intended as an experimental medicine study for proof of mechanism of the licensed drugs and not as a way of adding to potential clinical efficacy in application.</i></p>

- F Different scenarios with PET imaging involving three centres:**
- a) First centre carries out the PET imaging and patients from all three sites travel to this centre for the experimental study**
 - b) First centre generates the PET agents for use in patients at all three sites**

Trial Design: Open label study to investigate the binding potential of a novel marker of apoptosis, (which is non-toxic in the microdose range) in cancers after conventional treatment

Purpose of Trial: To assess the extent to which apoptosis is increased after conventional treatments

Products: Product C

Key Parameters: Binding potential of Product C

Product Classification: Product C – IMP

Rationale: The radiotracer is for end point assessment with pre-clinical data used to verify dosimetry. However, the study would require a CTA and product C will require an IMPD and IMPMA if the intention would be to establish the use of product C as a stratifier for clinical treatment response in patients.

In scenario a) it is not necessary for all three sites to make an application to register the products since patients will travel to the lead site. The patient will effectively become a patient of the site carrying out the administration of the radioactive product and therefore there is no need for any other site to provide documentation. The centre will need an MHRA IMP manufacturing licence to produce the radiotracer. In scenario b) all three sites will require registration. However, the lead site manufacturing the ligand may apply on behalf of all three sites, with the other two sites supplying subsidiary information (site specific information – related to the handling of the radiopharmaceutical and the methods of administration).

G Investigating a radiotracer used in other countries in patients but unlicensed

In this example an NHS Trust department wishes to use a tracer that in other countries has been used in patients with the same cancer. This is registered as an audit, intended to improve the methodology.

Audit Design:	to assess whether product X identifies sites of altered cell physiology characteristic of malignancy
Purpose of use of the radioactive product:	Can product C-11 X be used as a methodological tool to detect sites of altered of the radioactive cell physiology characteristic of malignancy?
Products:	C-11 X
Key Parameters:	Uptake of C-11 X in malignant sites
Product Classification:	C-11 X - NIMP
Rationale:	<p>C-11 X is a PET tool used in other countries to identify malignancy. In this trial, the biological endpoint properties are being further investigated. The study is not a clinical trial. Audit that includes follow-up of tumour biological characteristics in order to confirm understanding of the endpoint assessment still does not suggest that this is a clinical trial, as the intent is to improve the methodology. Product C-11 X can be made under a Specials Licence with no CTA or IMP required. However, if the results were used to assess the potential of the tracer to predict clinical outcome, then there is potential that the "audit" is a clinical trial that could need a CTA.</p> <p>Manufacture of C-11 X should be to GMP.</p> <p><i>Note: Historically, the PET community has followed the "Specials" licence (SL) application process for such compounds. The SL would allow the NHS Trust to demonstrate manufacture of C-11 X to GMP and allow the physician in charge of the trial to request its use. Possible patient benefit is expected from the use of the product elsewhere and therefore the SL is appropriate. All other regulatory requirements would need to be fulfilled.</i></p>

H Investigating an established radiotracer in patients

In this example an NHS Trust is using a PET tool that is commonly used outside the UK, to assess the extent of a particular malignancy in patients with the disease.

Trial Design: Open label clinical study, in patients with a known malignancy, to investigate the uptake of Product C-11 X

Purpose of Trial: To assess the sensitivity and specificity of C-11 X in the assessment of metastatic malignancy

Products: Product C-11 X

Key Parameters: Uptake of Product C-11 X at sites of malignancy

Product Classification: Product C-11X - IMP

Rationale: C-11 X is a commonly used PET tool for assessment of this malignancy in other countries but this product has not held an IMP equivalent elsewhere. The study requires a CTA, product C-11 X requires an IMPD and IMPMA since this is a defined clinical trial using the product. An IMP manufacturing licence is needed for the site.

Note: Contrast with the use in G above where a clinical trial is not being carried out. Note difference in intent of use.

I Investigating an established radiotracer in patients

In this example an NHS Trust is evaluating a PET tool to assess how it is handled biologically in relationship to a cancer pathway.

Trial Design: Product C-11 X is being given to assess the relationship of uptake in a cancer with a specific cancer pathway in the tumour cell.

Purpose of Trial: To assess whether Product C-11 X has a direct relationship with a cancer pathway within a cell

Products: Product C-11 X

Key Parameters: Uptake of Product C-11 X at sites of malignancy and relationship to biopsy measurements that will allow the measurement of an intracellular pathway

Product Classification: Product C-11X - NIMP

Rationale: C-11 X is a PET tool that may be useful to assess a particular cancer pathway expressed in a number of cancers that have a poor outcome. The relationship of uptake to this pathway is a proof of principle to show the relationship. If positive, it could be used as a diagnostic agent (as a number of these types of studies may). However, the study described here does not require a CTA or an IMP. This agent is an endpoint assessment tool, use of which does not indicate need for a license. The situation would be different if the purpose of the work was to understand the mechanism of action of the radiotracer.

J Investigating an established radiotracer in patients

In this example an NHS Trust is using a commonly used PET tool (in other countries) to assess the response of a malignancy in patients to an established drug.

Trial Design:	Open label study, in patients with a known malignancy, to investigate the response of the tumour to an established drug using Product C-11 X
Purpose of Trial:	To assess whether the PET profile of Product C-11 X changes after treatment of a cancer with a chemotherapy drug in ways that could be used to assess treatment response and allow this agent to be used as a new clinical biomarker
Products:	Product C-11 X
Key Parameters:	Uptake of Product C-11 X before and after treatment of cancer with a specific chemotherapy drug
Product Classification:	Product C-11X - IMP
Rationale:	C-11 X is a commonly used PET tool for assessment of this malignancy in other countries but this product has not held an IMP equivalent elsewhere. For use in the UK, the study requires a CTA, and product C-11 X requires an IMPD and IMPMA since this is a defined clinical trial with the product. However, if the intent of the study is simply to assess the pharmacological response to established drug in order to define the biology of the drug action, use of the radiotracer could be considered as endpoint assessment and the study might not need a CTA or the tracer an IMPD or IMPMA.

K Investigating an established radiotracer in patients

In this example an NHS Trust is using a commonly used PET tracer (FDG) and comparing it to another PET product (used in other European countries but not licensed) to assess whether the new agent is better than the routinely used PET tracer FDG agent in a particular malignancy in patients with the disease.

Trial Design: Open label study, in patients with a known malignancy, to investigate the uptake of Product C-11 X compared to product FDG

Purpose of Trial: To assess whether C-11 X is better than FDG in the assessment of metastatic malignancy

Products: Product C-11 X and FDG

Key Parameters: Uptake of Product C-11 X at sites of malignancy

Product Classification: Product C-11X – IMP
FDG - SL

Rationale: C-11 X is a commonly used PET tool for assessment of this malignancy in other countries but this product has not held an IMP equivalent elsewhere. If “better than” implies “greater sensitivity or specificity for clinical diagnosis”, then the study requires a CTA and product C-11 X requires an IMPD and IMPMA. However, if “better than” implies “greater sensitivity or specificity for the biochemical changes associated with known tumours”, then this could be considered as a comparison between outcomes from two (conventional and novel) endpoint assessment tools, which may not require filing for a CTA (see example B above). In such a situation, it may need to be made clear that malignancy is being used as an “in vivo” model for evaluation of biological properties of alternative imaging agents.

Note: This is a further example of how the regulatory pathway selected will depend on how the research question is expressed.

Glossary of Terms¹

CTA	Clinical Trial Authorisation.
GMP	Good Manufacturing Practice. This is a recognised standard for pharmaceutical processing and manufacture ensuring medicinal products are consistently produced and controlled.
IMP	Investigational Medical Product. These are unlicensed medicines undergoing clinical trial.
IMPD	Investigational Medicinal Product Dossier.
IMPMA	Investigational Medicinal Product Marketing Authorisation.
IRAS	Integrated Research Application System. This is a single system for applying for the permissions and approvals for health and social care/community research in the UK. It streamlines the process for seeking relevant approvals as you are not required to enter the details for a single project in separate application forms.
NIMP	Non Investigational Medicinal Product. A compound which is classified as not an IMP in the study in which it is used.
Orange Guide	Alternative title for the "Rules and Guidance for Pharmaceutical Manufacturers and Distributors" because of its traditional orange cover.
Orphan Drug	A drug for a rare disease. The indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence.
QPs	Qualified Person. A QP must certify every batch of a medicine before release to the EU market. Article 51 of Directive 2001/83/EC defines the duties of the Qualified Person and more information can be found in the Orange Guide.
'Specials Licence'	'Specials' are unlicensed medicines which are manufactured under a manufacturer's specials licence (MS) for a special clinical need and are under the responsibility of the prescribing doctor. There is no requirement for QP certification. IMPs are governed by different legislation (The Medicines for Human Use (Clinical Trials) Regulation 2004 as amended [SI 2004 1031]). IMPs are not 'Specials'. A CTA application including a description of the IMPs has to have been submitted to the MHRA.

¹ Definitions are taken from the glossary on the MHRA website:
<http://www.mhra.gov.uk/SearchHelp/Glossary/index.htm>