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June 18, 2003

Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 98D-0785 – Revised Draft Guidance for Industry: Medical Imaging Drugs and Biological Products (May 2003)

Dear Sir/Madam:

PETNET Pharmaceuticals, Inc. (PETNET) is a nationwide health product company dedicated to positron emission tomography (PET). We operate 39 cyclotron-based PET nuclear pharmacies nationally and internationally, and we are the leading producer of radiopharmaceuticals for PET. We estimate that our MetaTrace® brand of F 18 Fludeoxyglucose (FDG) accounts for almost 60% of the commercially-supplied FDG in use today.

PETNET is committed to the research, development and commercialization of new PET imaging probes and, therefore has great interest in the subject of this guidance. Although this guidance does not specifically address the PET approval procedures mandated by Section 121 of the Modernization Act, we understand that the general principles contained in this document will be reflected in the FDA proposed rules for PET products.

Regarding the safety assessment of PET imaging probes, PETNET is aligned with the Academy of Molecular Imaging (AMI) and the Society of Nuclear Medicine (SNM) in the desire for a safety assessment framework that expedites the development and commercialization of new agents as intended by Sections 121 and 122 of the Modernization Act. Your acknowledgement of the contribution of dose or mass in the design of a focused safety evaluation is welcomed. Consideration of micro-doses (defined as less than 1/100th the dose calculated to yield a pharmacological effect) is particularly relevant in the field of PET, where virtually all imaging probes are administered at sub-pharmacological doses. The unique relationship of microdoses to safety has been acknowledged by the European Agency for the Evaluation of Medicinal Products. The construct of a safety assessment program needed to support human clinical trials using microdosing is discussed in a Position Paper accepted in January, 2003 for implementation in July, 2003.[1] We believe a similar acknowledgement from FDA is warranted for PET, due to the predominance of low mass PET imaging probes.

[1] The European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, "Position Paper on Non-clinical Safety Studies to Support Clinical Trials with a Single Microdose." CPMP/SWP/2599/02, January 23, 2003.

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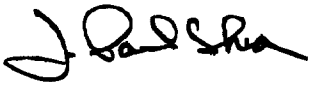
Regarding Clinical Indications for PET imaging probes, we suggest consideration of an additional indication. PET imaging probes have a uniquely powerful contribution to make in therapeutic drug development. PET imaging probes can be designed to monitor a large diversity of physiological processes, with the potential of serving as biomarkers for the validation of drug targets and to predict or monitor drug response. As with genetic testing, such biomarkers can facilitate the efficient development of new therapeutics and bring the right drugs to the right patients. With clinical trial experience, biomarkers can evolve into surrogate markers and their contribution to clinical practice secured. The incorporation of surrogate markers in clinical trials benefits the developer as well as the regulator in assessing the performance of the drug. However, before they can enter clinical trials, where their clinical utility can be tested and verified, they must receive regulatory approval. An FDA approval of an imaging probe as a biomarker would greatly facilitate and encourage the use of such agents to contribute to the discovery of new and effective therapeutics.

As acknowledged by Congress in Section 121 of the Modernization Act, PET imaging probes are a unique category of imaging agents. As approval procedures for PET imaging probes are developed, the proper assessment of safety to facilitate human testing, and the assignment of proper indications to acknowledge PET's unique potential to impact clinical practice and therapeutics will insure that unwarranted regulatory burdens do not preclude physician and patient access to this important technology.

We thank you for the opportunity to present our views.

Sincerely,



J. Paul Shea, Ph.D.
Vice President
Regulatory Affairs

The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 23 January 2003
CPMP/SWP/2599/02

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

POSITION PAPER ON NON-CLINICAL SAFETY STUDIES TO SUPPORT CLINICAL TRIALS WITH A SINGLE MICRODOSE

DISCUSSION IN THE SAFETY WORKING PARTY	June 2002
TRANSMISSION TO CPMP	June 2002
RELEASE FOR CONSULTATION	June 2002
DEADLINE FOR COMMENTS	September 2002
DISCUSSION OF COMMENTS BY THE SAFETY WORKING PARTY	October 2002
ADOPTION BY CPMP	January 2003
DATE OF COMING INTO OPERATION	July 2003

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POSITION PAPER ON NON-CLINICAL SAFETY STUDIES TO SUPPORT CLINICAL TRIALS WITH A SINGLE MICRODOSE

1 INTRODUCTION

Non-clinical safety studies to support the conduct of human clinical trials for pharmaceuticals has been internationally harmonised by the International Conference on Harmonisation as outlined in International Conference on Harmonisation (ICH) Topic M3: Note for Guidance on Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals, Topic S7A: Note for Guidance on Safety Pharmacology Studies for Human Pharmaceuticals and Topic S7B: Note for Guidance on Safety Pharmacology Studies for assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals. However, different regional requirements still exist with regard to non-clinical studies to support the first dose to humans.

2 SCOPE

This Position Paper defines common standards of the non-clinical safety studies needed to support human clinical trials of a single dose of a pharmacologically active compound using microdose techniques.

In the current context, the term "microdose" is defined as less than 1/100th of the dose calculated to yield a pharmacological effect of the test substance based on primary pharmacodynamic data obtained *in vitro* and *in vivo* (typically doses in, or below, the low microgram range) and at a maximum dose of ≤ 100 microgram. An example of such a clinical trial is the early characterisation of a substance's pharmacokinetic- / distribution properties or receptor selectivity profile using positron emission tomography (PET) imaging, accelerator mass spectrometry (AMS) or other very sensitive analytical techniques.

The clinical trials covered by this Position Paper will be exploratory in nature (pre - phase I) and may be conducted with a single test substance or with a number of closely related pharmaceutical candidates to choose the preferred candidate or formulation for further development. In any case the total amount of test compound(s) administered should not exceed 100 micrograms.

The non-clinical safety testing should be sufficient to assess the safety of clinical trial participants and patients in line with the requirements outlined in the Helsinki Declaration. However, the extent of required studies should be proportionate to the nature and scope of the clinical trial. Therefore the CPMP proposes that certain deviations from the existing CPMP/ICH notes for guidance to support pre-phase I clinical trials may be scientifically justified.

3 OVERVIEW OF EXISTING GUIDANCE FOR NON-CLINICAL SAFETY STUDIES TO SUPPORT SAFETY IN FIRST HUMAN CLINICAL TRIALS OF NEW PHARMACEUTICAL CANDIDATES

Non-clinical studies to support human clinical trials have been harmonised (see Introduction); regional differences still exist regarding non-clinical testing to support the first dose to humans. In the European Union, repeated dose toxicity studies in two species (one non-rodent) for a minimum duration of 2 weeks are required to support a single, first human dose. However, in the United States of America, single dose acute toxicity studies are in some cases considered sufficient to support a single dose human clinical trial.

In 1996, the FDA published a notice on single dose acute toxicity studies for pharmaceuticals that would allow for the use of single-dose toxicity studies to support single dose studies in humans.

ICH M3 includes a requirement for safety pharmacology studies, which is detailed further in the ICH S7A guideline and guidance on the assessment of QT interval prolongation by non-cardiovascular medicinal products is given in the ICH S7B guideline.

For biotechnology-derived medicinal products, the safety assessment should be considered on a case-by-case basis, which would also apply to single microdose human clinical trials. Guidance is given in ICH Topic S6.

For anticancer medicinal products, guidance for non-clinical evaluation before first human dose is given in the CPMP Note for Guidance on the Pre-clinical Evaluation of Anticancer Medicinal Products.

4 RECOMMENDATIONS

4.1 EXTENDED SINGLE-DOSE TOXICITY STUDY AND OTHER EFFECTS ON VITAL ORGAN FUNCTION

The ICH M3 recommendation is for safety pharmacology, single dose toxicity studies and repeated dose toxicity studies. This set of studies may be replaced by an extended single-dose toxicity study in only one mammalian species if the choice of species could be justified based on comparative in vitro metabolism data and by comparative data on in vitro primary pharmacodynamics / biological activity.

The extended single-dose toxicity study should include a control group, and a sufficient number of treatment groups to allow the establishment of the dose inducing a minimal toxic effect. For compounds with low toxicity a limit dose approach could be used. Allometric scaling from animal species to man[1] and using a safety factor of 1000 should be used to set the limit dose. If a toxic effect is observed at the limit dose, the non-toxic dose level should be established.

The number of animals should be sufficient to ensure reliable interpretation of the study results. The use of both genders should be considered. The extended single-dose toxicity study should be designed to obtain the maximum amount of information from the smallest number of animals. Two routes of administration should generally be used, the intravenous as well as the intended clinical route, which would also allow assessment of local tolerance. When intravenous dosing is the route of administration in humans, this route alone in animal testing would generally be sufficient.

The study period should be 14 days and include an interim sacrifice on Day 2 (day of dosing defined as Day 1). All mortalities should be recorded. Time of onset, duration, and reversibility of toxicity and clinical observations should be recorded. Gross necropsy should be performed on all animals, including those sacrificed moribund, found dead, or terminated at Days 2 and 14. .

The extended single-dose toxicity study should be designed to obtain information on haematology and clinical chemistry at a minimum of two time points (Days 2 and 14) and histopathology.

Information should also be obtained on any other organ system where the test substance localises and e.g., those organ systems intended to be visualised by imaging agents.

In addition, all available background information on the test substance and/or close pharmaceuticals as well as on the therapeutic class with respect to vital organ function and other safety parameters obtained in drug screening should be provided. Examples of such data are receptor screening profiles, activity at HERG and other ion channels, effect on action potentials, behavioural screens etc.

4.2 GENOTOXICITY STUDIES

In vitro genotoxicity studies should be performed as recommended in relevant ICH guidance.

[1] See CPMP/ICH/283/95 for factors in allometric scaling

However, if a test substance belongs to a well-known chemical class for which genotoxicity data are available on other class representatives, performance of abridged/reduced versions of mutation test in bacteria (Ames test) and chromosome aberration, mouse lymphoma or in vitro micronucleus tests may be sufficient. If abridged/reduced versions of genotoxicity tests are used, data demonstrating that the modification is scientifically justified and provides valid data should be provided. If an equivocal or positive finding is obtained, additional testing should be performed.

4.3 LOCAL TOLERANCE STUDIES

Local tolerance studies may not be needed when the clinical route of administration is used in the extended single-dose toxicity study.

5 FINAL REMARKS

With respect to radiopharmaceuticals, the corresponding stable isotope test substance should be used for both the extended single-dose toxicity study and the genotoxicity studies.

Before entry into man, adequate information should be available on the primary pharmacodynamics of each test substance in the screening programme, e.g., when a number of structural analogues are included in the screening programme.

A sponsor should always ensure that an appropriate safety assessment is performed before entry into humans. If toxicity is observed, this may need to be clarified by additional investigations before entry into humans. Margins of safety and type of toxicity observed should be assessed.

All non-clinical safety studies should be conducted in accordance with the principles of Good Laboratory Practice (GLP).

The reduced/abbreviated testing (as compared to the ICH guidance M3, S7Aand S7B) outlined above is not sufficient to support clinical trial situations with escalating dose regimes or higher doses / exposures than indicated above. Guidance for such trials is found in the ICH M3, S7A and S7B.
The non-clinical safety assessment of biotechnology-derived products should be considered on a case-by-case basis as outlined in ICH Topic S6. Guidance for non-clinical testing of anti-cancer medicinal products is given in the CPMP Note for Guidance on the Pre-clinical Evaluation of Anti-cancer Medicinal Products. The extended single-dose toxicity study approach and the recommendation for genotoxicity studies given in this Position Paper may not be relevant for these product categories.

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