What Does It Take to Develop a New PET Drug?

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The simplest answer is deceptively straightforward: a good candidate drug, technical expertise, focused research work, financial resources, time and luck. The challenges to meet these criteria are widely recognized as less cumbersome for diagnostic PET drugs than for therapeutic drugs. Still, clinical trials study many new PET drugs, yet few are approved by the FDA—averaging about one every two years in the recent past.

Why such a disconnect between the research PET drug pipeline and approved drugs? The answer applies to all new drugs: the development process is cumbersome, and during this process new drugs often do not live up to their expectations, including commercial viability. Here, I provide a brief overview of the PET drug development process, which has evolved over many years, largely in response to the public’s questions and concerns about the safety and efficacy of new drugs.

When a new drug is approved by the FDA, it is approved for a “sponsor” to manufacture that drug at one or more facilities and to market it to patients and clinicians, consistent with the drug’s prescribing information (i.e., label). An FDA New Drug Application (NDA) approval changes an investigational PET drug into a commercial commodity—a product that patients buy, albeit typically via third-party payers. Accordingly, patients and their clinicians expect the drug to do what the label says it will do.

Ensuring that the newly approved PET drug performs as it should is the responsibility of the drug sponsor. In parallel with this responsibility, the FDA is charged with verifying that the drug sponsor has met the legal standards for the drug’s manufacture and commercial marketing. These legal standards largely parallel the answers to readily apparent safety and efficacy questions (Table 1).

Over the past two decades, FDA has developed regulations and advisory documents that address the unique features of a new PET drug. In 1997, an amendment to the U.S. Food Drug and Cosmetic Act clarified how PET drug efficacy was to be demonstrated. The law prompted FDA to state explicitly that the effectiveness of a diagnostic radiopharmaceutical (including a PET drug) is assessed by evaluating the drug/scan’s ability to provide useful clinical information related to its purported use. That is, the ability to provide useful clinical information may be the benefit of a new PET drug.

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This clarification highlights how the development of a new PET drug may importantly differ from that of a therapeutic drug. Whereas clinical trials of therapeutic drugs typically must show how a new drug helps patients live longer or better, the FDA may recognize clinically useful information from the PET scan as the new PET drug’s benefit. For this reason, phase III clinical trials of PET drugs have typically examined how well the scan performs (e.g., sensitivity and specificity) in providing clinically useful information. These types of clinical trials are typically far less burdensome than clinical trials that must evaluate patient survival or improved health.

Results of the tests cited in Table 1 illustrate why no more than one in 10 new drugs tested in clinical trials will ultimately be approved by the FDA—an experience probably true for PET drugs, as well. Indeed, a new PET drug may complete all initial animal and human testing, yet phase III studies fail to demonstrate acceptable scan performance—perhaps due to inappropriate dose, biological variability, scan interpretation procedures or, in part, bad luck.

The luck factor is probably less a risk for new PET drugs, compared to therapeutic drugs, because PET clinical trials typically compare the scan results from a patient to a truth standard obtained from the same patient, while therapeutic drug trials often compare one patient group to another group. Hence, one would expect early PET clinical trials to produce results readily reproduced in phase III clinical trials.

Why that expectation hasn’t panned out can be analyzed in terms of the time-proven steps of new PET drug development, as shown in Table 2. In general, the first three steps are the greatest challenge.

### Table 2. Major Steps in New PET Drug Development

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### Step 1: New Drug Identification and Proof-of-Concept Testing

The discovery and/or design of a new PET drug often follows background research on cellular processes or receptors. For example, 18F-fludeoxyglucose (18F-FDG) PET scanning evolved from research that showed glucose metabolism was often accelerated in cancer cells. A similar cancer cell metabolism paradigm prompted the development of 11C-choline for prostate cancer imaging. The amyloid imaging agents generally derived from experience with dyes used to identify amyloid in tissue sections.

Once the target drug is identified, proof-of-concept research is performed—typically in tissue slices, cell lines, and/or animals—to help determine whether the PET drug actually images what it is supposed to image. This very early research is often performed by academic investigators using a PET drug manufactured in the academic laboratory and studied in local animal facilities.

After concluding this proof-of-concept research, the investigator will generally contact the FDA to discuss the information needed to submit an Investigational New Drug Application (IND), which is essential prior to any human testing of the new PET drug. Alternatively, the investigator may work with a drug company, which will assume responsibility for the next steps in drug development.

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Step 2: Drug Manufacture and Key Animal Studies

A new PET drug usually consists of two major parts: the isotope and a ligand molecule. The radiation safety risks for the isotope are generally known, so the ligand molecule is often the major consideration for the new drug’s safety and activity. This ligand usually determines where the drug localizes in the body and whether it might be metabolized, activate cellular receptors or escort excessive radiation to a tissue. Consequently, key animal studies of new PET drugs often use the non-radiolabeled ligand (or “cold-labeled” ligand) to identify toxic effects in animals. These studies also need to adhere to the principles of Good Laboratory Practice (GLP) or justify deviation from GLP.

These key GLP studies use the ligand molecule that is manufactured in the same or nearly the same manner as will be used to produce the PET drugs for first-in-human testing (i.e., pharmaceutical-grade drug). Pharmaceutical-grade drug is important because research-grade drugs may contain molecular alterations, unacceptable impurities or contaminants. At times, an academic investigator laboratory may not be designed to control sufficiently for purity and contamination, requiring the use of a more advanced facility such as an experienced research radiopharmacy or contract manufacturing facility that has experience with current PET drug-specific Good Manufacturing Practices (cGMP).

The main point is that the PET drug (especially the ligand molecule) tested in key animal safety studies needs to be the same or nearly the same as the drug that will be administered to humans. The results from these animal studies must be submitted with the IND to the FDA. Hence, the time and resource challenge in this step is weighted by the manufacturing process and conduct of high quality animal studies.

Step 3: Human Data Generation: Phase I-III Clinical Trials

Clinical data generation is often the most laborious step in new PET drug development. After submission of an IND to the FDA, the agency staff will determine whether the supplied manufacturing information, animal study data and planned phase I trial provide reasonable assurance of safety to allow the new (investigational) PET drug to be tested in humans. Fortunately, many new PET drugs commonly have very low (microgram range or less) mass doses, which allow them to be developed under the FDA’s Exploratory IND paradigm, a process that dramatically limits the extent of animal testing necessary to support a phase I clinical trial.

For example, often the results from a relatively simple dose-ranging study in rodents combined with justifying information from proof-of-concept animal studies and published literature may support the initial clinical trial. Based upon the nature of the PET drug and the available information, FDA reviewers commonly waive the need for the many animal tests that are usually required for therapeutic drugs. Indeed, sponsors conducted no new animal safety studies to support the marketing approval of \(^{18}\)F-FDG and \(^{11}C\)-choline, drugs with ligands that were normal components of body metabolism. In terms of investigational studies, the FDA allowed clinical studies to proceed under an IND (held by the National Cancer Institute) for \(^{89}\)Zr-panitumumab with no animal toxicology studies at all.

Clinical testing of PET drugs generally parallels that for other drugs, with phase I clinical trials commonly enrolling a small number of patients or volunteers (usually <30), followed by more patients being studied in phase II and III clinical trials. This process may take years and considerable expense.

For some PET drugs, however, existing published reports of investigator-initiated clinical trials may minimize this challenge. The sponsor of \(^{68}\)Ga-dotatate, for instance, performed no new clinical trials to support the FDA approval; instead, published reports and existing academic-site clinical experience allowed the FDA to verify the drug’s efficacy. A description of the very streamlined development process supporting the FDA approval of \(^{68}\)Ga-dotatate and \(^{18}\)F-FDG is available online at Drugs@FDA and illustrates the extent to which published reports can be leveraged to facilitate new PET drug development. For IND examples, the NCT’s Cancer Imaging Program has posted many documents online that describe how existing animal and human experience information can be used to support investigational clinical studies for multiple investigational imaging drugs.

Conclusion

Assuring a new PET drug’s safety and efficacy is not easy. I cited only three of the major steps above but want to emphasize that the other steps also require considerable effort. For example, simply compiling documents that sum-marize all the major aspects of manufacturing, animal and human testing may consume substantial time and resources. Further, the actual formatting of an NDA and electronic submission of the information to the FDA can prove so daunting that sponsors may need to hire contractors to help with the submission process. Of utmost importance in the new PET drug development is communication with the FDA review staff to help ensure a timely and efficient drug development process.

The recently approved 21\textsuperscript{st} Century Cures Act contained many directives for FDA to implement in hopes of expediting the development of important new drugs, particularly drug-device products and medical countermeasure drugs. The new law did not change the FDA standards for approval of a new drug and did not directly address new PET drug development. Still, the law’s provisions pertaining to the use of summary (as opposed to detailed) information to support the safety and efficacy of a new indication for drug...
PET in the News

The international literature on PET, PET/CT and PET/MR continues to grow at a pace that challenges both researchers and clinicians. The media has recognized the value of these modalities and regularly features advances in research and technology in the news. In each issue, the PET CoE Newsletter presents a tomographic slice of the breadth of PET media coverage that appears in publications around the world. Additional news articles can be found online at www.snmmi.org under “MI: Making a Difference.”

Radiotargeted therapy with SST2 antagonists could combat multiple human cancers
MedicalXpress

First U.S. Multi-center Investigational Clinical Trial of 177 Lu PSMA-617 Targeted Radioligand Therapy in Metastatic Castration Resistant Prostate Cancer Receives FDA Clearance
Yahoo

Research shows PET scans can help improve esophageal cancer outcomes
DOTmed

Here’s How Stress Might Cause Heart Attacks, Strokes
NBC News

PET/CT remains best option for head, neck cancer
Aunt Minnie

New drug added to Alzheimer’s study using novel PET tracer to track tau protein
DOTmed

Experts suggest expansion of molecular imaging to treat cancer
UPI

Watch for PET/CT to grow as an aid to image-guided biopsies of children
Health Imaging

PET/MRI can advance uterine cervix cancer detection
Aunt Minnie Europe

PiB-PET could open window on common meningiomas
Aunt Minnie

(previously approved drug should simplify the process for expanding the approved uses of PET drugs. In light of the FDA’s progressive streamlining of the data submission expectations and research advances, the future for new PET drug development appears more promising than ever.

References

SNMMI and ISMRM also sponsored a joint PET/MRI webinar last November.

The first project of the Treatment Response Using PET Taskforce was a two-part CE article on lymphoma published in The Journal of Nuclear Medicine. Response Assessment Criteria and Their Applications in Lymphoma: Part 1 was in the June 2016 issue; Part 2 was in the January 2017 issue. Future topics under consideration include novel FDG uptake metrics, response metrics for head/neck cancer and pediatric cancer response criteria.

Finally, I would like to draw your attention to a fantastic resource for daily use in your practice: the PET Tracer Encyclopedia, which is available on the PET CoE website. It currently has 12 tracer guides, and another four tracer guides (^{82}Ru, ^{18}F-floorbetaben, ^{68}Ga-DOTATATE, and ^{18}F-FAZA) are in progress. The PET Tracer Encyclopedia Taskforce plans to collaborate with CTN and the Radiopharmaceutical Sciences Council on the new tracer guides and a WIKI site.

I want to thank all the PET CoE members who have contributed to these and other center projects for sharing their time and expertise to promote the quality, value, and safety of molecular imaging and nuclear medicine; to advance new imaging technologies; and to support professionals in the field.

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(President’s Report. Continued from page 1.)
In the featured article from the February 2017 issue of The Journal of Nuclear Medicine, researchers document the first-in-human application of a new imaging agent to help find prostate cancer in both early and advanced stages and plan treatment. The study indicates that the new agent—a PET radiotracer—is both safe and effective.

The new agent is a gallium-68 (Ga-68)-labeled peptide BBN-RGD agent that targets both gastrin-releasing peptide receptor (GRPR) and integrin αvβ3. Dual receptor-targeting provides advantages over single targeting by allowing tumor contrast when either or both receptor types are expressed, improving binding affinity and increasing the number of effective receptors.

Approximately one in seven men will be diagnosed with prostate cancer in his lifetime. In 2017, the American Cancer Society estimates that there will be more than 161,000 new prostate cancer cases in the United States and around 27,000 deaths from the disease. “Although treatable at the early stage, prostate cancer is prone to metastasis,” explains Xiaoyuan Chen, PhD, senior investigator, Laboratory of Molecular Imaging and Nanomedicine at the U.S. National Institute of Biomedical Imaging and Bioengineering. “An effective and specific imaging method of detecting both primary and metastatic lesions is thus of critical importance to manage patients with prostate cancer.”

This study included 13 patients with prostate cancer (four newly diagnosed and nine post-therapy) and five healthy volunteers. Ga-68-BBN-RGD PET/CT detected 20 bone lesions in seven patients either with primary prostate cancer or after radical prostatectomy. The patients with bone metastases did not necessarily have an elevated prostate specific antigen level. “This result is better than MDP bone scan,” Chen notes. “MDP bone scan is sensitive but lacks specificity because localized skeletal accumulation Tc-99m-MDP can also be observed in the case of trauma and infection.” No adverse side effects were found during the whole procedure and two-week follow-up, demonstrating the safety of Ga-68-BBN-RGD.

“Compounds capable of targeting more than one biomarker have the ability of binding to both early and metastatic stages of prostate cancer, creating the possibility for a more prompt and accurate diagnostic profile for both the primary and the metastatic tumors,” explains Chen.

Looking ahead, Chen says, “Ga-68-BBN-RGD could play an additive role in staging and detecting prostate cancer and provide guidance for internal radiation therapy using the same peptide labeled with therapeutic radionuclides. He points out that larger scale clinical investigations are warranted.

Authors of the article “Clinical translation of a dual integrin αvβ3 and GRPR targeting PET radiotracer 68Ga-BBN-RGD” include Jingjing Zhang, Fang Li, Shaobo Yan, Li Huo, Libo Chen, Xinrong Fan, Weigang Yan, Zhiyuan Li and Zhaohui Zhu, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; Gang Niu, Lixin Lang, Xuefeng Yan, and Xiaoyuan Chen, National Institute of Biomedical Imaging and Bioengineering (NIBIB), National Institutes of Health, Bethesda, Maryland.

This work was supported by the Intramural Research Program of the National Institute of Biomedical Imaging and Bioengineering, National Institutes of Health, the National Natural Science Foundation of China projects (81171369, 81171370, and 81271614), and a Special Scientific Research Fund for Public Welfare of Healthcare in China (201402001).
The PET Center of Excellence Newsletter is a quarterly member information service published under the direction of the PET CoE leadership and SNMMI.

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