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The Use of Published Clinical Study Reports to Support the United States Food and Drug Administration Approval of Imaging Agents

Short-running title: Published Reports and FDA Approval of Imaging Agents or Reporting Imaging Agent Studies (shortened to meet format expectations of 5/26/16)

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Abstract

Pharmaceutical companies typically perform prospective, multicenter phase 3 clinical studies to support approval of a new imaging agent by the US Food and Drug Administration (FDA). In uncommon situations, FDA has approved imaging agents based solely, or in large part, on the clinical study experience described in published reports, including reports of exploratory (i.e., phase 1 or 2) studies performed at a single clinical site. We performed a survey of published reports to assess the potential for the information to support FDA approval of a commonly cited investigational imaging agent. Our survey revealed critical data limitations in most publications, all of which reported exploratory clinical studies. Here we summarize the precedent for FDA approval of imaging agents using effectiveness data from publications, FDA guidance, and our experience in reviewing publications. We also present a key data checklist for investigators to consider in the design, conduct and reporting of exploratory clinical studies for publication. We encourage editors and peer-reviewers to consider requiring these key data items when reviewing these reports for publication.

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INTRODUCTION

The US Food and Drug Administration (FDA) regulates imaging agents as drugs. Before approving a new drug, FDA law and regulations require manufacturers to verify the drug's effectiveness in adequate and well-controlled clinical studies. Typically, prospectively designed, multicenter phase 3 clinical studies are performed to obtain the definitive effectiveness data. While these types of studies are widely recognized as the most robust source of efficacy data, FDA has been flexible in interpreting the nature of "adequate and well-controlled clinical studies" by describing situations in which a single adequate and well-controlled clinical study may verify a drug's effectiveness and also the unique situation in which published reports alone may establish a new drug's effectiveness. Indeed, FDA has long noted that the effectiveness of a small number of new drugs was established primarily or exclusively with published reports, including secretin for evaluation of pancreatic function, bleomycin and talc for malignant pleural effusion and doxycycline for malaria. (*1*)

To date, five FDA-approved imaging drugs have had definitive effectiveness data derived from published reports, including one drug where site images and source data were re-evaluated (Table 1). The effectiveness data for Fludeoxyglucose F 18 (FDG) and Ammonia N 13 Injection were generated from reviews FDA performed following implementation of the 1997 Food and Drug Administration Modernization Act, which contained directives specifically applicable to positron emission tomography (PET) drugs. (*2-4*) In 2012, FDA approved Choline C 11 Injection using publication-based effectiveness data that pertained solely to patients with suspected prostate cancer recurrence and non-informative conventional imaging results. (*5*) The 2016 FDA approval of Fluciclovine F18 Injection relied upon a reinterpretation and reanalysis of source data and images from two clinical sites in which the original data were initially

summarized in publications. (*6*) Also in 2016, two published reports provided important supportive effectiveness information for the approval of Gallium Ga 68 Dotatate Injection. (*7*) Most of these publications described single center, exploratory (i.e., phase 1 or 2) clinical studies. Building upon this precedent, we performed a pilot review of published literature to assess its potential to support FDA approval of Choline F 18 for use in the suspected prostate cancer recurrence setting. In evaluating the published reports, we relied upon FDA guidance and precedent to assess the quality of the published data, as summarized below.

FDA GUIDANCE ON THE USE OF PUBLISHED LITERATURE TO ESTABLISH DRUG EFFECTIVENESS

FDA guidance and public presentations by FDA staff emphasize the importance of independent substantiation of experimental clinical study results. (*1,8,9,10*) Consequently, definitive effectiveness data from more than one adequate and well-controlled clinical study is usually submitted in a new drug marketing application to the Agency. The need for independent substantiation of clinical data is due to multiple factors: the recognition that results obtained in a single clinical center may be dependent on site or investigator-specific factors, the presence of undetected systematic biases within a single study as well as the potential for chance alone being responsible for a single study's results. Additionally, publication bias (e.g., the tendency to publish desirable study results versus undesirable results) may make published data unrepresentative of the true clinical experience with a drug. These factors are reflected within FDA's advice on the use of published reports to establish the effectiveness of a drug, as summarized below.

"The following factors increase the possibility of reliance on published reports alone to support approval of a new product or new use:

a. Multiple studies conducted by different investigators where each of the studies clearly has an adequate design and where the findings across studies are consistent.
b. A high level of detail in the published reports, including clear and adequate descriptions of statistical plans, analytical methods (prospectively determined), and study endpoints, and a full accounting of all enrolled patients.
c. Clearly appropriate endpoints that can be objectively assessed and are not dependent on investigator judgment (e.g., overall mortality, blood pressure, or microbial eradication). Such endpoints are more readily interpreted than more subjective endpoints such as cause-specific mortality or relief of symptoms.
d. Robust results achieved by protocol-specified analyses that yield a consistent conclusion of efficacy and do not require selected post hoc analyses such as covariate adjustment, subsetting, or reduced data sets (e.g., analysis of only responders or compliant patients, or of an "eligible" or "evaluable" subset).
e. Conduct of studies by groups with properly documented operating procedures and a history of implementing such procedures effectively." (1)

The items cited above underscore the legal requirement for a manufacturer to supply *substantial* evidence of a new drug's effectiveness. FDA has further emphasized that the interpretation of this clinical evidence, whether derived from publications and/or manufacturer-sponsored clinical studies, must be considered in the context of the drug's proposed labeling. For example, the published literature might robustly support an imaging drug's effectiveness only within a specific group of patients, as exemplified by the approval of Choline C 11. (*5*)

PRECEDENT FOR IMAGING DRUG APPROVAL BASED ON PUBLISHED REPORTS

The FDA approvals for FDG (two clinical settings), Ammonia N 13 and Choline C 11 were based, in large part, upon effectiveness data described in publications that met certain report selection criteria, as outlined in Table 1. Similar criteria were used to assess information

within the published reports supporting the effectiveness of Gallium Ga 68 Dotatate. Published reports were important to understanding the effectiveness of Fluciclovine F18, although the definitive data were derived from re-interpretation of clinical site images.

The FDA reviews of published data, which are available on the Internet, describe the factors reviewers considered in the selection of the most useful published reports. (*2-7*) In general, these factors focused upon the ability to assess the performance of the imaging agent relative to a truth standard, such as histology (i.e., sensitivity/specificity), the applicability of the studied subjects to a clinically-relevant patient population and the details within image interpretation process, especially the measures used to minimize interpretation bias.

As summarized in FDA reviews for the three imaging agents with effectiveness data based predominantly on published reports (FDG, Ammonia N 13, Choline C11), most selected publications described single center clinical studies, particularly academician-sponsored clinical studies. Across all selected publications, the total sample size of the effectiveness database for these agents ranged from over one-thousand subjects (FDG) to 98 subjects (Choline C 11). The number of subjects within any single key study report ranged from 193 (Ammonia N 13) to only 13 (Choline C 11). The FDA reviewers cited many limitations of the published data, including numerous deficiencies in study detail as well as the observation that some publications appeared to represent repetitive reports of the same patients. In these apparent repetitive reporting situations, the reviewers selected only the publication that contained the largest number of patients.

Published reports definitively supported the use of FDG in both a cardiac and oncologic setting. The separate reviews, performed in 1999, included extensive reports of performance data for the cardiac indication and more limited performance data for the oncologic indication. The

extent of sensitivity/specificity results in the cardiac setting appeared to parallel the straightforwardness of establishing a truth standard in this setting (e.g., coronary arteriography or an independent measure of myocardial perfusion), compared to the more challenging truth standards in the oncologic setting (histopathology and/or other imaging modalities and/or clinical follow-up). Among the publication deficiencies, the FDG reviewers were especially concerned about the paucity of image interpretation information. For example, in the cardiac setting, the FDA reviewer noted, "…blinding of the readers to critical information was sufficient, though not optimal, in this set of articles." Similarly, in the oncologic setting, the reviewer noted, "Many details about image evaluation were absent from the studies, inter- and intra-reader variations in interpretation were, on the whole, either not mentioned, or discussed in limited fashion." Nevertheless, the reviewers concluded that the totality of the selected publications, all of which described prospective clinical studies, demonstrated substantial evidence of FDG efficacy.

The review of Ammonia N 13 publications, also performed in 1999, focused heavily upon a key study that the FDA reviewer assessed as meeting the expectations for a prospective, adequate and well-controlled clinical study, including the use of a sample size (n = 193) that allowed an estimate of imaging outcomes in patient subsets. The meaningfulness of this study's results was bolstered by the findings in three published reports of retrospective studies. The reviewer concluded that Ammonia N 13 effectiveness was demonstrated based upon the consistency of the results among the studies, emphasizing how the studies were performed by different investigators and included patients with an appropriate range of clinical characteristics.

The FDA's Choline C 11 review was notable in that the data supporting the agent's effectiveness were largely derived from subsets of patients described within the publications. As summarized by FDA, the sponsor of the marketing application performed a review of

publications but selected only reports that described at least 30 patients. FDA further examined the published literature, including reports of studies that included at least 10 patients. At the conclusion of these reviews, the nature and limited extent of the published data were reflected in the drug's labeling, in that the drug was indicated only for use among patients with suspected prostate cancer recurrence *and* who had non-informative bone scintigraphy, computerized tomography or magnetic resonance imaging. The effectiveness conclusion appeared to focus upon the clinical importance of the imaging result in the setting of an otherwise anatomically unlocalized cancer.

Published clinical reports provided differing roles within the FDA reviews for Gallium Ga 68 Dotatate and Fluciclovine F18. The key effectiveness data for Gallium Ga 68 Dotatate in the neuroendocrine tumor setting were derived from a prospective single site study in which source data were made available to FDA for inspection and analysis. Independent substantiation of these data was provided by FDA's assessment of a meta-analysis and systematic review performed by the drug's marketing application sponsor. FDA reviewers did not regard the meta-analysis as analytically sound to verify effectiveness; however, FDA review of individual publications culminated in a finding of sufficient support from two published reports of single site, retrospective studies, which were summarized in the drug's labeling. Fluciclovine F18 effectiveness among patients with recurrent prostate cancer was initially summarized by two single site clinical investigators in publications. The drug's marketing application sponsor subsequently accessed each clinical site's original data and images and performed data re-analyses and image reinterpretation. The key Fluciclovine F 18 clinical study compared imaging results to a histopathology truth standard; supportive effectiveness was provided by a single site study that compared Fluciclovine F18 images to Choline C11 images.

Following completion of the reviews, the FDA-approved drug labeling for each imaging agent reflected the extent and nature of the clinical effectiveness data, particularly with respect to the label's *Indication* statement, as shown below.

Fludeoxyglucose F 18 Injection:

- For the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging.

- For assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer.

Ammonia N 13 Injection indication:

- For diagnostic PET imaging of the myocardium under rest or pharmacologic stress conditions to evaluate myocardial perfusion in patients with suspected or existing coronary artery disease.

Choline C 11 Injection:

- For positron emission tomography (PET) imaging of patients with suspected prostate cancer recurrence and non-informative bone scintigraphy, computerized tomography (CT) or magnetic resonance imaging. In these patients, ^{11}C-choline PET imaging may help identify potential sites of prostate cancer recurrence for subsequent histologic confirmation. Suspected prostate recurrence is based upon elevated blood prostate specific antigen (PSA) levels following initial therapy. In clinical studies, images were produced with PET/CT coregistration.

  Limitation of Use: ^{11}C-choline PET imaging is not a replacement for histologic verification of recurrent prostate cancer.

Fluciclovine F 18 Injection:

- For positron emission tomography (PET) imaging in men with suspected prostate cancer recurrence based on elevated blood prostate specific antigen (PSA) levels following prior treatment.

Kit for the Preparation of Gallium Ga 68 Dotatate Injection:

- For use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult and pediatric patients.

AN EXPLORATION OF PUBLISHED REPORTS TO POTENTIALLY SUPPORT APPROVAL OF A NEW IMAGING AGENT

Following the precedent for Choline C 11, in April 2014 we surveyed published literature to estimate its potential to support FDA approval of the investigational agent Choline F 18 (F-18 fluoromethylcholine). Our goal was to focus upon a clinical setting that directly aligned with the labeling indication for Choline C 11, i.e., to assist in the evaluation of patients with suspected prostate cancer recurrence and non-informative conventional imaging.

In a search of the National Library of Medicine's Medline® database, we identified 171 publications signaled by the key search terms (fluorocholine or F-choline or 18F-choline or fluoromethylcholine or fluoroethylcholine and prostate or prostatic or prostate cancer). A review of all the abstracts identified 33 publications (21 prospective studies and 12 retrospective studies) describing the use of Choline F 18 and a reference test in the recurrent prostate cancer setting. All 33 publications were from academic institutions and cited exploratory clinical studies. Detailed review of the publications revealed a single study describing Choline F 18 imaging among patients with suspected prostate cancer recurrence and non-informative conventional imaging. (*11*) This single-center study reported choline F18 consensus read imaging results for 30 patients relative to a pathology truth standard. The study focused upon the variability of imaging results over a range of imaging techniques and acquisition-initiation times. With only a single indication-applicable study identified, our survey of published reports suggested that the information was insufficient to verify the effectiveness of Choline F 18 imaging among patients with suspected prostate cancer recurrence *and* non-informative conventional imaging.

We subsequently examined the published reports to identify studies that estimated the effectiveness of Choline F 18 imaging among *any* patients with suspected recurrent prostate cancer. We screened the publications to select for studies that provided *any* mention of the following items: the Choline F 18 dose; whether image interpretation was masked to clinical information; image interpretation method (independent and/or consensus); and start time for image acquisition. In alignment with FDA expectations for minimizing bias, we assigned greatest value to studies that described independent reader results (not consensus) and interpretation of images masked to clinical information. Only one publication met all the selection criteria. (*12*) This single-center experience in 50 patients suggested excellent Choline F 18 imaging performance, yet we could identify no other similarly detailed reports. The predominant deficiencies within the publications were: minimal or no mention of image interpretation methods; no or incomplete description of a truth standard/reference test; and limited or no description of whether the truth standard/reference test was applied to all or only some of the studied patients.

CONCLUSIONS AND RECOMMENDATIONS

Translation of investigational imaging agent research into clinical practice necessitates FDA-approval of the agent, clear delineation of the imaging agent's role in medical care and sufficient reimbursement to assure a ready supply of the agent. The first step in this process, FDA approval, usually follows a commercial manufacturer-sponsored phase 1 through 3 clinical study drug development paradigm. In this process, manufacturers are typically assured of patent protection and often a period of marketing exclusivity for their agents. These financial market

incentives provide the resources that allow manufacturers to provide extensive source data and regulatory-formatted clinical study documents to support FDA approval of a new drug; in these situations, published reports typically supply supportive and/or ancillary information, such as increasing the number of drug-exposed patients for safety evaluation.

A number of investigational agents lack patent protection and have little or no potential for clinical development by commercial manufacturers, despite extensive publication of promising imaging results by academic investigators. In these situations, the published literature may form the only logistically feasible method of verifying the investigational imaging agent's effectiveness. We believe greater attention to methodological details within published study reports of these agents could markedly enhance the public health value of the research by facilitating the agent's potential for FDA approval. Even for imaging agents with commercial development potential, the addition of key details within exploratory study reports may importantly impact phase 3 study designs and limit patients risks during development of the imaging agent.

Based upon the FDA precedent for imaging agent approval using published study reports, we have developed a checklist for investigators to consider when developing an exploratory study report for publication so that the data have the potential to contribute to an application for FDA approval. Report expectations for more advanced studies that definitively assess drug effectiveness and diagnostic accuracy are standardized within the CONSORT and STARD statements. (*13,14*)

Within the appendix, we outline the items that we believe represent the minimal information an investigator-author should particularly consider in the design, conduct and reporting of an investigational imaging agent exploratory clinical study. We encourage attention

to these items even in situations where diagnostic accuracy may only relate peripherally to the focus of the manuscript. We also encourage professional societies to consider refining our checklist and/or developing additional standards for the design, conduct and reporting of exploratory clinical studies.

The appendix checklist emphasizes items that intuitively seem obvious, yet our experience suggests few published reports of investigational imaging agents actually contain these data elements. Conceivably, the imaging information was not described in the studies because it was regarded as not pertinent to the key points of the publication and/or the study was thought to be too exploratory in nature for further use in imaging agent development. For example, some publications focused upon variations in imaging acquisition or co-registration methods in anticipation of future clinical studies. Our observations of very limited detail within published reports of exploratory clinical imaging agent studies aligns with the experience observed in other medical fields. (*15,16*)

We encourage authors, editors and peer-reviewers to consider the potential of all clinical studies to add to the body of data assessing an investigational imaging agent's effectiveness and safety, including exploratory clinical studies. These considerations are especially important for low mass dose imaging agents that appear unlikely to necessitate large population safety studies for further development. While a single-site study may explore imaging outcomes among a small number of patients and the experience appear to provide only exploratory information, multiple similar reports may culminate in a substantial body of safety and effectiveness data.

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To help support further imaging agent development, identify and/or summarize:

1. Imaging agent and its dose (mass and radiation dose)
2. Study design

   Prospective or retrospective?
   Single center?
3. Patient disposition:

   How many enrolled?
   How many completed all evaluations?
   How many had missing images and/or truth standard results?
4. Main patient characteristics

   Age
   Gender
   Disease status (e.g., newly diagnosed, suspected disease, recurrent disease)
5. Main patient preparation features

   Fasting?
   Drug avoidance prior to imaging?
6. Main image acquisition features:

   Time of acquisition onset post drug injection.
   Anatomical imaging acquisition field, e.g., "thorax through pelvis."
7. Image read methods, especially methods to minimize bias:

   Independent or consensus? Independent is typically preferred, with results reported by reader.
   Number of readers? Radiologists? Nuclear medicine physicians?
   Randomization in image presentation?
   Masked to clinical data and/or truth standard result? Masking is typically preferred.
8. Truth standard or reference test:

   Was the truth standard or reference test applied to all patients?
   If not, how many patients had an alternative to the truth standard/reference test?
9. Primary endpoint result

   Hypothesis-testing primary endpoint or was the study solely exploratory?
   Did the study use a pre-specified statistical analytical plan?
   Which results derived from post-hoc data explorations?
10. Safety results

    How were patients monitored for safety?

Appendix. A checklist of the minimum expectations to consider in design, conduct and reporting of investigational imaging agent exploratory clinical trials.

Table 1. FDA-approved Imaging Drugs with Effectiveness Data from Published Reports

Drug	F 18 FDG	F 18 FDG	N 18 Ammonia	C 11 Choline	F 18 Fluciclovine	Ga 68 Dotatate
Clinical setting	Cardiac	Oncologic	Cardiac	Recurrent prostate cancer	Recurrent prostate cancer	Somatostatin receptor positive NET
Published report selection criteria	• Truth standard & imaging outcome established for each patient • Prospective • Patient characteristics described • Image interpretation methods described • Truth standard detailed for each patient • Methods for minimizing bias (e.g., masking, description of any patient/image selection bias)	• Comparison between images and a pathology truth standard • Prospective • Eligibility criteria define a clinically-applicable patient population • Clearly defined endpoints • Detailed data on study findings • Methods for minimizing bias (e.g., masking, randomization, multiple independent readers) • Sample size > 50	• Comparison between images and a truth standard of an accepted myocardial perfusion method or coronary arteriography • Prospective • Clearly defined endpoints • Eligibility criteria define a clinically-applicable patient population • Detailed study results • Methods for minimizing bias (e.g., masking, randomization)	• Prospective or retrospective • Adequate patient disposition description • Comparison of images to a pathology truth standard • Measures to control bias in image interpretation • Study drug dose • Analytical procedure description • Non-informative conventional imaging • Sample size ≥ 10	• Site images available for reinterpretation • Site data available for reanalysis	• Prospective or retrospective • Adequate patient disposition description • Comparison of images to a truth standard of histopathology and/or clinical follow-up • Description of image interpretation
Number of studies in publications	10 studies met all report selection criteria	2 key studies met all report selection criteria; 16 studies variably met selection criteria	1 key study met all report selection criteria; 3 studies met all selection criteria except for using a retrospective design	2 prospective studies and 2 retrospective studies	2 prospective studies	2 retrospective studies
Patients in publications	298	1,311, including 155 patients in the 2 key studies	293, including 193 patients in the key study	98	201	167
Main observations	Sensitivity/specificity	Sensitivity/specificity	Sensitivity/specificity	Sensitivity/specificity	T/F positive and negatives; agreement with comparator	T/F positive and negatives

NET = neuroendocrine tumors; T/F = true and false