Journal of Nuclear Medicine, published on February 7, 2020 as doi:10.2967/jnumed.119.238287

# The Academic NDA: Justification, Process, and Lessons Learned

John J. Sunderland

Division of Nuclear Medicine, Department of Radiology, University of Iowa, Iowa City, Iowa

Corresponding Author:

John J. Sunderland

john-sunderland@uiowa.edu

University of Iowa Hospitals and Clinics

200 Hawkins Drive

Iowa City, IA 52242

Phone: 319-356-1092

Fax: 319 356-2220

**ORCID ID:** 0000-0002-0891-1234

**Word Count:** 6594

**Financial support:** Margie & Robert E. Petersen Foundation

**Running Title:** The Academic NDA

**ABSTRACT**

The University of Iowa recently completed a four-year expedition into the uncharted waters of the FDA New Drug Application (NDA) process that ultimately resulted in approval of $^{68}$Ga-DOTATOC in August of 2019. The journey was enlightening, revealing a highly structured, arcane, but rigorous regulatory approval process. FDA proved to be an efficient, reasonable, and communicative regulatory body that achieved balance between support of the initiative, and their mission-bound/process-bound duty to assure the application met the expected safety and efficacy standards of the agency. With a number of clinically valuable PET radiopharmaceuticals without intellectual property residing in regulatory limbo without industry champions to bring them to marketing approval, there may be justification for a more concerted effort from the molecular imaging community into generating better understanding, support, and perhaps even infrastructure for the *academic NDA*. As a first step, the accompanying manuscript briefly describes the start-to-finish story for $^{68}$Ga-DOTATOC, including a description of the clinical trials, a broad overview of the NDA structured document content, and the distilled experiences associated with the $^{68}$Ga-DOTATOC NDA process. It is anticipated that with sustained free sharing of information relating to the FDA drug registration process, it will prove less daunting and more efficient for future academically sponsored NDA filings for PET imaging agents.

**Keywords:** NDA, [Ga-68]DOTATOC, Neuroendocrine Tumor

## INTRODUCTION

On the morning of 21 August 2019, the University of Iowa's PET Imaging Center received official notification from the Food and Drug Administration (FDA) that their New Drug Application (NDA) for $^{68}$Ga-DOTATOC Injection was approved for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NET) in adult and pediatric patients. This ended a four-year effort by a small team at the University of Iowa to navigate the regulatory gauntlet that is the FDA's highly structured and rigorous process for drug approval. It is the second PET radiopharmaceutical submitted and approved by an academic institution. The Mayo Clinic received approval for Choline C 11 Injection in September of 2012. In both cases the academic institutions have waived exclusivity and opened the market to both academia and industry to submit Abbreviated New Drug Applications (ANDAs) to facilitate access of these drugs to patients.

The road to the $^{68}$Ga-DOTATOC NDA application at the University of Iowa was born nearly two decades ago through clinical research for NET disease being performed by M. Sue O'Dorisio, MD, PhD, Thomas O'Dorisio, MD, and David Bushnell, MD who were amongst the first in the US to perform Y-90 Peptide Receptor Radiation Therapy (PRRT). The University's $^{68}$Ga-DOTATOC imaging program began in 2011 with the purchase of its first $^{68}$Ge/$^{68}$Ga-generator, and the commencement of its first imaging clinical trial "Safety of $^{68}$Ga-DOTA-tyr3-Octreotide PET in Diagnosis of Solid Tumors (GA-68)" in 2012. This trial was the first of three registered clinical trials at the University of Iowa that formed the foundation of the clinical section of NDA.

The NDA process is not for the faint of heart. For the University of Iowa, it was a consuming four-year journey. Although NDA submissions are fully electronic, the $^{68}$Ga-

DOTATOC submission was over 1300 pages and included over 200 hyperlinked documents. This is a remarkably short application by NDA standards, with its brevity attributable to the substantial use of literature for non-clinical sections (animal study and toxicity data), and orphan drug specific rules that allowed for fewer subjects in the pivotal trials that supported the application. For perspective, this is 10-100X shorter than a typical therapeutic drug application for a non-orphan indication. For an academic institution, the planning, drafting, assembly, and electronic submission of the NDA to meet formatting requirements requires contracting with consulting firms. The cost of the drafting and submission process will likely run into the hundreds of thousands of dollars.

For the University of Iowa, total out-of-pocket expenses approached $400,000, with most associated with consultant fees. Included in this total were cash expenses for team travel to FDA. Not included is time/effort spent by the University of Iowa team. A $300,000 grant from the Margie & Robert E. Petersen Foundation helped subsidize some personnel effort and approximately $200,000 of the consultant fees. The core team included the author, a regulatory specialist, a statistician, a PET clinical manager (CNMT), a radiochemist, three nuclear medicine physicians, and a radiologist. Additional important contributions came from technologists and Holden Comprehensive Cancer Center staff. Authoring of NDA text was primarily performed by the author, the radiochemist, the statistician, and our consultants. It is unclear whether these costs are typical for an academic NDA. Each situation is different and a careful pro forma should be created to assure the venture makes financial sense.

The other active participant in the NDA process is FDA itself, and more specifically, CDER and the Division of Medical Imaging Products. Our experience with FDA throughout the entirety of the process was nothing but positive from our face-to-face pre-IND meeting in 2015,

on through pre-approval inspection and label negotiations. It is clear from our interactions that FDA personnel and leadership recognize the value of radiopharmaceuticals and that there appears to be an ingrained culture targeting education, facilitation, and advising in the process of NDA strategy and design. However, their role is necessarily formal and FDA remained appropriately uncompromising in their standards, throughout.

**JUSTIFICATION FOR NDA**

Coincidently, just one week prior to the $^{68}$Ga-DOTATOC approval, the New England Journal of Medicine published a Perspective article entitled "*Sustainable Discovery and Development of Antibiotics — Is a Nonprofit Approach the Future?*" (*1*). The concept for the article was driven by the recent NDA approval of Pretomanid, an antibiotic used to combat a drug-resistant form of tuberculosis, by TB Alliance, a not-for-profit organization whose mission includes development of affordable tuberculosis drugs. In this article the authors propose a non-profit discovery and development model for antibiotics because industry development is at a standstill due to lack of profitability.

Although not identical (there appears to currently be a healthy pipeline of new PET radiopharmaceuticals), there is a similar situation in PET where potentially clinically valuable radiopharmaceuticals with a history of successful utilization in scientific studies and early phase trials languish in regulatory limbo because they have no champion to carry them across the finish line to marketing approval. Industry champions are unlikely to surface due to limited profitability associated with drugs with no clear intellectual property/patent to be claimed. Academic champions are unlikely because academia generally lacks the necessary domain knowledge,

professional motivation, and funds necessary to navigate the NDA process, which is neither easy nor inexpensive.

That said, there are compelling reasons for academic institutions to rise to the challenge of the FDA drug registration process that include benefits to the patient population, expansion of molecular imaging, and institutional economic benefit. To the academician, the economic benefit may sound shallow, but a sound business model is the most compelling component in the institutional discussion to invest in the process.

**Sustainability**

For $^{68}$Ga-DOTATOC and the University of Iowa, the rationale to move forward with the NDA was several-fold, but long-term financial sustainability of our neuroendocrine imaging program was paramount. The price of newly approved radiopharmaceuticals is understandably high. Companies must recoup investment from expenses from the clinical trials, the drug application process, setting up production and distribution systems and building administrative infrastructure to support the enterprise. However, for imaging establishments, reimbursement is uncertain. Even with CMS pass-through reimbursement, the University of Iowa runs only at close to break-even status imaging newer PET radiopharmaceuticals. With the recent pass-through expiration for NETSpot™ and its associated reimbursement decrease, sizeable net losses were anticipated that will be exacerbated by nearby private hospitals ceasing to provide NETSpot™ imaging for this now under-reimbursed procedure. The University of Iowa can produce $^{68}$Ga-DOTATOC at a fraction of the NETSpot™ price, and will likely be able to maintain service to the NET patient population without financial loss indefinitely.

**Financial Opportunity**

If an academic institution's primary motivation includes entrepreneurial pursuits, capitalizing an approved PET radiopharmaceutical through exclusive and non-exclusive licensing agreements to other institutions or industry are a possibility. This has not yet been a motivation for academic institutions bringing PET radiopharmaceuticals to approval, but it does present a revenue opportunity to channel funds into the institution's research program, and help repay for the cost associated with the NDA submission.

**Patient Access**

At its heart and in its inception, the decision to move forward with the $^{68}$Ga-DOTATOC NDA was about patient access. The clinician-scientists (M. Sue O'Dorisio, MD, PhD and Tom O'Dorisio, MD) primarily responsible for the clinical trials that supported the NDA were passionately driven by the need to help make these state-of-the-art PET radiopharmaceuticals available in the US.

**THE NDA PROCCESS FOR $^{68}$Ga-DOTATOC**

The University of Iowa began performing $^{68}$Ga-DOTATOC scans in clinical trials in 2012. Ultimately three Phase 2 clinical trials were initiated. The first was "Safety and efficacy of $^{68}$Ga-DOTATOC positron emission tomography (PET) for diagnosis, staging, and measurement of response to treatment with somatostatin receptor positive tumors." NCT:01619865. The second was "Comparator study of $^{68}$Ga-DOTATOC PET/CT with Octreoscan + high-resolution, contrast-enhanced CT for diagnosis and staging in neuroendocrine tumors and other somatostatin

receptor positive tumors." NCT:01869725. The third was "Impact of $^{68}$Ga-DOTATOC PET/CT on management of somatostatin receptor positive tumors." NCT:02441062.

The data collected on the research subjects appropriately targeted the scientific aims of the clinical trials, and were not initially collected with the intention of using it in a regulatory filing. As such, only single physician reads were performed, and definitions of reference standard for disease changed from trial to trial. Data collected from each trial was understandably different. For example, in the Change in Clinical Management trial, results of follow-up conventional imaging data were not necessarily collected as part of the protocol, but they proved necessary for our ultimate definition of reference standard for tissue positivity for the NDA.

In 2015, when the research team decided that moving forward with a $^{68}$Ga-DOTATOC NDA was both realistic and an important institutional goal, we needed to develop a strategy to meet regulatory requirements. Our first step was to achieve orphan drug status for $^{68}$Ga-DOTATOC. This was achieved through transfer of the orphan drug designation from SNMMI (original holder) to the University of Iowa.

The entirety of the NDA process took more than four years to complete, beginning with our pre-IND meeting on 30 April 2015 (Figure 1), moving through our pre-NDA meeting fall 2017, and ending with the final approval letter issued on 21 August 2019 (Figure 2). The submission of an NDA is the culmination of a number of steps, some sequential, others performed in parallel. The major steps in the NDA process are outlined in Table 1, and are described in more detail below.

**Step 1: Pre-IND Meeting with FDA**

There are two kinds of NDA application described in FDA regulations. The first and most common is the 505(b)(1) application. This is the standard, prospective Phase 3 trial

approach where the application contains the full reports of the multi-center clinical trials (usually two) of safety and efficacy, non-clinical development (animal and in vitro studies), and Chemistry, Manufacturing, and Control (CMC) information. The second type is the 505(b)(2) application, which is for studies not conducted by or for the applicant, and for which the applicant has not obtained a right of reference. 505(b)(2) submissions rely on information in the public domain to fulfill some of the information required in the NDA application. For the $^{68}$Ga-DOTATOC, the 505(b)(2) pathway was the appropriate approach.

Typically, NDAs require two independent, large multi-center trials to provide data to support the clinical claim of the regulatory filing. Neuroendocrine cancer is an orphan disease with a limited patient population, which makes collection of data from sufficient numbers of patients challenging. This is a recognized regulatory dilemma, and so requirements are relaxed, minimally, in the case of a drug for an orphan disease. FDA has some limited latitude to determine the level of evidence that is required to inform the benefit/risk assessment that underpins orphan drug product approval. This largely means fewer patients are required in the supporting trials, and does not mean a lessening of rigor in other areas.

In February of 2015 the University of Iowa submitted a pre-IND meeting request/ briefing package to FDA with the expressed purpose to review the extensive published data and data generated from University of Iowa clinical trials of $^{68}$Ga-DOTATOC to assess its adequacy for filing a 501(b)(2) NDA. The briefing package is a formal document with a mandated format whose content is sufficient to inform FDA of the salient information about the drug, including its route of administration, proposed indication, summary of peer reviewed literature, and in our case, an update on the current status of our ongoing $^{68}$Ga-DOTATOC trials. Most importantly, it

contained a list of specific questions to FDA regarding the proposed strategy for structure, performance, and content of the clinical trials proposed to support the presumed NDA filing.

The FDA written response and meeting, which took place on the FDA campus on 30 April 2015, was highly productive, with FDA providing substantive guidance on meta-analysis/literature review, and approaches to making our ongoing clinical trials of sufficient rigor to meet expected standards. Additional information was provided to help navigate the nonclinical and clinical pharmacology sections of the NDA.

**Step 2: Clinical Trial Planning**

Based upon the input from FDA and with the aid of external consultants, the University of Iowa created a "new" Phase 3 retrospective clinical trial, which consisted of a rigorous retrospective analysis of the combined subjects enrolled in the original three prospective trials. The single retrospective trial was designed to harmonize the data collected, the reference standard definitions, and the analysis approach. In some cases, additional clinical data was gathered that was not collected in the initial trials. A completely new clinical trial protocol was written describing in detail: inclusion criteria, necessary imaging and clinical data collected, reference standards, primary and secondary endpoints, statistical endpoints, and a statistical analysis plan (SAP).

In the new protocol, patient studies were re-read blindly with standardized case report forms by at least two qualified physicians. Additional clinical data, imaging data, analysis, reference standards for disease positivity and negativity, and safety data were similarly harmonized into a single approach. Under these conditions, some patients from the initial trials were necessarily excluded from the final analysis.

In parallel with the clinical trials, the University of Iowa authored a protocol for a formal meta-analysis of the literature in collaboration with our institution's resident librarian meta-analysis expert. This effort incorporated FDA suggestions regarding the design of the meta-analysis protocol to enhance the probability that it would meet FDA's scientific evidentiary expectations. Statistical endpoints for sensitivity and specificity were pre-defined.

**Step 3: Performance of Clinical Trial(s)**

The performance of the retrospective clinical trial including collection and documentation of all data, generation of completed case report forms, blind re-reads of $^{68}$Ga-DOTATOC studies, re-reading of conventional imaging scans (CT, MRI, In-111 Octreoscan) for the more than 350 subjects took over a year to complete.

In parallel, the formal $^{68}$Ga-DOTATOC meta-analysis was performed and ultimately published in JNM (*2*). Efficiencies were achieved in the writing of sections of the NDA by having the meta-analysis published in peer reviewed literature prior to NDA submission.

**Step 4: Data Lock and Statistical Analysis**

The NDA is a highly-formalized, high stakes process. To maximize the rigor and transparency of the clinical trial process, rigid controls are employed. For purposes of an NDA, data is meant to be collected precisely according to the written protocol. In this way FDA is in a position to know what data is available for inspection/audit. Further, the data must be entered into an FDA mandated database format. The statistical analysis plan (SAP) must be completely and formally pre-specified. The statistical analysis must be performed using a specified SAS

software version such that FDA can duplicate or perform their own analyses. Both the SAS analysis code and the tabulated data are submitted as part of the NDA.

On 5 May 2017 the University of Iowa completed, signed, and dated the final version of the SAP. After a completed internal audit of the clinical trial data, the database lock was initiated on 15 May 2017. A preliminary global analysis of the safety and efficacy data was performed using the statistical analysis described in our SAP. A preliminary assessment of sensitivity and specificity was completed, and we compiled our overall safety data. Within two months of our database lock, the preliminary analyses uncovered two small errors in our clinical data. Twice we initiated database unlock procedures to correct these errors. These database unlocks and associated changes were fully disclosed in the NDA.

**Step 5: Pre-NDA Meeting with FDA**

Following the completion of data collection and analysis of our retrospective Phase 3 trial, and the completion (but not yet publication) of the meta-analysis, a formal Pre-NDA meeting was scheduled with FDA. The explicit purpose of the requested meeting was to agree on the content and format of a complete 505(b)(2) application for marketing approval of $^{68}$Ga-DOTATOC. At FDA's request two separate meetings were scheduled, the first to discuss the clinical, and non-clinical aspects, which occurred on 3 October 2017, with a second meeting for CMC questions on 10 October 2017.

The pre-NDA briefing package was prepared with the help of external consultants familiar with PET radiopharmaceutical NDAs. In the pre-NDA package for the clinical portion of the NDA, summary results of our retrospective trial and meta-analysis were presented. FDA

was asked to judge the initial perceived adequacy of our clinical evidence of safety and efficacy, and were explicitly asked whether additional evidence would be required.

The majority of subsequent questions were related to strategies associated with providing necessary information in the NDA with format and content acceptable to FDA. The primary purpose of these questions was to explore acceptable efficiencies in the presentation of evidence within the constraints of the NDA structure.

**Step 6: Writing the NDA Document**

The NDA is a highly formal document both in content and structure and must be submitted as an electronic Common Technical Document (eCTD). eCTD is a standard interface and international specification for pharma to transfer regulatory information to FDA (or another international agency). It is based on the Common Technical Document format that was developed by the International Council for Harmonization. It is important to understand that the eCTD format is designed not for the convenience of the submitting organization, but to help FDA efficiently review the NDA. Writing, organizing and compiling of the NDA into the eCTD structure with its hierarchical headings and subheadings is a tedious and time-consuming endeavor and requires an external consultant to assemble and submit.

The NDA itself, as illustrated in Figure 3, consists of five Modules. The application is largely drafted from bottom to top, starting with Module 3 - the Quality/Chemistry section, Module 4 – non-clinical data, and Module 5 – the clinical trial data and the trial reports. Each of these sections are independent of one another and can be drafted in parallel.

Module 3 is the Quality section and is where CMC information is detailed. The level of detail expected in a marketing approval application is far in excess of what is typically required

for an IND drug. Drug Master Files (DMFs) from vendors for synthesis modules or cassettes are helpful in simplifying the application. Manufactures of synthesis modules, cassettes, or even chemical precursors are not only subject to FDA inspection, but likely to be inspected by FDA if they have not been previously inspected; this includes overseas manufacturers. The applicant's site will absolutely be inspected by FDA as part of the "pre-Approval Inspection" process. The inspection will be rigorous, and the site will be responsible for adherence to procedures and information precisely as described in Module 3.

Module 4 reports the non-clinical (animal) data that supports the application. Because all animal studies for $^{68}$Ga-DOTATOC came from literature (as was agreed to by FDA in the pre-NDA meeting), the University of Iowa application simply included electronic (pdf) versions of all the original articles that contained the pharmacodynamic, pharmacokinetic, and toxicology data necessary to support the application. All salient article data and results were summarized in the appropriate sub-sections in Module 2, section 2.6.

Module 5, including the Clinical Study Reports, was the most extensive section in the $^{68}$Ga-DOTAOC NDA. It contained not only the clinical trial reports, but the clinical trial protocols, SAP, case report forms, informed consent forms, IRB approval documents, and listing of study team members. Module 5 also contained the full tabulated subject data for all research subjects. The clinical study report body was the longest single document in our NDA, and presented the clinical trial study objectives, the detailed investigative plan, description of all the study variables, safety measures, quality assurance, statistical methods, and sample size determination. It also presented the summarized trial results, including efficacy evaluations (sensitivity, specificity) and safety evaluations, each broken down by subgroups (i.e. race, age, gender).

Module 2 presents high level summaries of the results of Modules 3, 4 and 5 and can only be written after these modules are functionally complete. Critical data, results, and summaries from Modules 3, 4 and 5 are used to populate the summaries in Module 2. The clinical summary in Section 2.7 distills the Clinical Study Report included from Module 5. For perspective, this "summary" was approximately 100 pages in length, which is brief, considering the FDA's 400 page limit for this section. Section 2.6, the non-Clinical Summary, totaled approximately 60 pages, which for our application was a summary of available pharmacokinetic, pharmacology, and toxicity literature for $^{68}$Ga-DOTATOC, with relevant information summarized in the appropriate subsections. One required component of Module 4 is data on repeat exposure dose toxicity, for which no $^{68}$Ga-DOTATOC data existed in the literature. Fortunately, Isotopen Technologien München AG (ITG), a pharmaceutical company with interest in commercializing DOTATOC radiopharmaceuticals, identified the same void and contracted a third-party to perform the necessary repeat dose toxicity study for DOTATOC in rats. ITG graciously provided a letter of reference to this data in support of the $^{68}$Ga-DOTATOC NDA.

Section 2.3, the Quality/CMC summary for $^{68}$Ga-DOTATOC consisted of three sections summarizing the quality of the active drug product (the vial of $^{68}$Ga-DOTATOC), and the Quality Overall Summary (QOS) of the precursor (cold DOTATOC) and the drug substance ($^{68}$Ga-DOTATOC drug itself). The drug substance QOS was brief, as it largely outlined only the molecular structure, $^{68}$Ga decay scheme and emissions, and safety and decay information. The quality of the active drug product was a more extensive document including manufacturing processes, process control, control of excipients and drug product, reference standards, container and closure systems and stability data.

The Non-Clinical Overview, and Clinical Overview (Sections 2.4 and 2.5) are written as very brief high-level description of the data supporting the application and were approximately 10 and 20 pages, respectively. These documents refer liberally to the actual application data from Modules 4 and 5 supporting the proposed indication and clinical use.

Lastly, Module 1 allows for geographically specific and site-specific information to be presented and importantly, it also contains the label. FDA places special emphasis on the label, the significance of which was underappreciated until we proceeded through the NDA authoring process. The label is the quintessence of the NDA, and is the final distillation of the entire application into a single summary document. Unbeknownst at the outset, FDA requires two labels to be submitted in the NDA. One is the clean label/package insert that we are accustomed to seeing. The second is the *annotated* label. The annotated label is identical to the original label except that every statement on the label contains hyperlinks to the specific section of the NDA that contains the specific data that supports that particular entry.

**Step 7: Submission**

The NDA submission to FDA is a process in itself. Each of the several hundred individual documents written for specific entries in the NDA must be to be loaded into eCTD generating software. Each of the individual documents contains both internal hyperlinks to navigate within the document, and external hyperlinks that link to other documents elsewhere in the NDA. There are several thousand hyperlinks, all of which need to be checked for functionality prior to submission. The eCTD software is prohibitively expensive for most academic institutions, and so consultants were used to complete the assembly and testing of the

eCTD formatted NDA. Once the compiled NDA was verified as complete, functioning, and accurate, submission was authorized.

**Step 8: Review and Request for Information**

The submission of an NDA is a momentous event. However, it is also just the beginning of the next phase: the Review.

By Prescription Drug User Fee Act (PDUFA) statute, FDA targets a period of two months to review the application for completeness. They can refuse the regulatory filing if critical information is missing, or the application is of insufficient quality. If accepted, FDA has an additional 6 months for "priority" review, or 10 months for "standard" review of the application. FDA can, and will, file additional "Requests for Information" (RFIs), which may include additional information, clarification, or additional analyses. Because FDA is on a tight review timetable, all RFIs issued also contain an aggressive deadline by which responses must be received. If FDA identifies problems of sufficient magnitude that result in delays in the review, they can and will extend the PDUFA date beyond the original timetable. The University of Iowa responded to 13 RFIs, in total. The most frequent RFIs were related to the Quality/CMC section. The most serious RFI was related to a small algorithmic error in reference standard determination impacting the disease classification of a handful of subjects. The fact that this algorithmic error was discovered is a testament to the detail with which the review is conducted by FDA. Fewer than 5 subjects were impacted by the error, but the delay in correcting and resubmitting the tabulated data and associated statistical analysis was enough that FDA requested a 3-month PDUFA date extension.

There are three benchmark events that FDA is required to schedule during the course of the review. The first is the Mid-Cycle Review, which takes place roughly half way through the review process. During this phone call, representatives of FDA's review subsections are present. In all, 24 FDA individuals attended this call with representatives from CDER leadership, the Division of Medical Imaging Products, Division of New Drug Products, CMC, Division of Clinical Pharmacology, Biostatistics/Division of Biometrics, Division of Epidemiology, and Division of Microbiology. Each Division was given an opportunity to present the status of their review, and ask any questions. The second benchmark is an on-site pre-approval inspection. In our case, this was limited to a Quality/CMC inspection of our manufacturing processes. A clinical inspection of trial data is also likely. The third benchmark event is the Late-Cycle meeting that occurs near the end of the review. This is another large phone meeting attended by the same groups from the mid-cycle call. Any last minute issues are discussed during this call.

**Step 9: Label Negotiation**

The label is the quintessence of the NDA and is the distillation of all the data and information presented in the application. It is the single document that physicians and the public have access to regarding the safety and efficacy of the drug. FDA has gone to great effort to format this document as an organized, concise, presentation of all the critical information from the entirety from the NDA application.

The stakes associated with label language are high, as reimbursement, and therefore, clinical utilization, is inextricably tied to wording used in the label indication. FDA and sponsor must agree on the label indication language. Most critically, the data in the application must unequivocally support the label indication claim.

## LESSONS LEARNED

Through the entirety of the process of planning, drafting, and submitting an NDA, the learning curve was steep and continuous. Lessons were learned through 1) interactions with FDA, who were both patient and professional throughout, 2) listening to our consultants, who had submitted several PET NDAs previously, 3) reading and understanding the regulations surrounding the NDA process, 4) listening to colleagues in academia and industry, and finally, 5) attending SNMMI/FDA organized educational events.

One of the primary lessons learned is that what academicians consider clear and compelling evidence for clinical safety and efficacy does not match the level and detail of rigor demanded by FDA. FDA has a decades-long formal process for drug approval, and although there is some inherent flexibility in approach, it remains a rigid process with requirements to which FDA is necessarily unyielding. Academia is generally unappreciative of the expected rigor.

The critical role of biostatistics in the NDA process, and the central role and work-load assumed by the primary biostatistician was surprising. The NDA is based on data. The biostatistician is the steward of that data. As such our biostatistician was a more critical and active team member than anticipated. The statistical methods used were fundamentally mundane, however the depth of the algorithmic development was substantial. The writing of the SAS analysis code was consuming both during the NDA data analysis process, and also during the review when FDA asked for additional sub-analyses to be performed. FDA reviews the SAS code and variable definitions carefully.

The University of Iowa has submitted many PET drug IND applications, and are no strangers to CMC submissions. However, the amount of additional information necessary and the

overall rigor and detail required in the NDA application was a revelation. Two synthesis modules were initially included in the NDA, but one had neither a DMF submitted, nor the resources to generate a DMF, nor the necessary process control data, and so it was removed from our application.

One final important lesson learned was that the quality of molecular imaging literature describing the investigation of radiopharmaceuticals is fundamentally poor by FDA standards. Peer reviewed literature from well-performed studies can be used to fulfill certain evidentiary requirements of an NDA using the 505(b)(2) pathway, thereby substantially simplifying the NDA process. However, the vast majority of published studies lack either the necessary scientific rigor, or the reporting of simple, yet critical elements of their clinical trial methodology or results. For example, literature can be used to support the safety of a PET drug if the reported literature study includes a simple statement of drug-related adverse events. Most do not, and therefore cannot be included to support safety. Many studies do not perform blinded reads, or use multiple readers for purposes of reader agreement – which is an important FDA metric. Reference standards are often weak or poorly defined. Too many studies are retrospective, and not prospectively designed. Some, but not all, of these issues are related to a lack of funding to perform these trials with the necessary rigor, which is an understandable limitation.

It is important to note that FDA has been actively encouraging a model whereby clinical data for PET radiopharmaceuticals in the public domain might be collected in a more efficient manner for purposes of a downstream regulatory submission. This approach consists of a common foundational harmonized protocol shared amongst academic institutions for a given radiopharmaceutical, probably in a late phase 2 environment. Harmonized criteria might include common radiopharmaceutical end-product specifications, identical injected dose range and

imaging time, a common set of case report forms so that clinical and safety information are collected in a harmonized fashion, and a commonly defined reference standard for disease positivity and negativity. This does not mean that all trials from all institutions must have identical patient populations, or specific aims. Each may have their own study designs and endpoints. But this approach will allow the more seamless combining of data into a potentially powerful multi-institutional trial. (Supplemental Figure 1 and Supplemental Table 1; supplemental materials are available at http://jnm.snmjournals.org). The SNMMI's Clinical Trials Network has performed this function in the past at FDA's request. It is a potentially powerful model, but difficult to implement with limited resources.

Candidate radiopharmaceuticals for additional academic NDAs for PET exist, but certain criteria must be met. The radiopharmaceutical should be in the public domain without intellectual property attached. Ideally, rich literature should exist supporting its safety (including FDA required toxicology studies, pharmacokinetics, pharmacodynamics) and efficacy in prospective, well-controlled trials. The latter data is particularly problematic, and likely additional well-controlled multi-center studies will be required. Finally, the business model for the submitting institution in terms of cost and effort to assemble a full NDA versus downstream revenue needs to make financial sense. Examples of candidate radiopharmaceutical include $^{15}$O-Water (perfusion), $^{18}$F-FLT(proliferation), $^{18}$F-fluoromisonidazole (hypoxia), and $^{18}$F-fluoroethyltyrosine (brain tumors).

## CONCLUSION

Only a handful of PET radiopharmaceuticals are currently FDA approved drugs. However, there are at least five promising PET drugs in the late-development or in the NDA review pipeline. Most are being developed by private industry, but others in the academic/not-for-profit arena. These include $^{64}$Cu-DOTATATE, $^{68}$Ga PSMA, $^{18}$F-DCFPyL, $^{18}$F-Fluoroestradiol, and O-15 Water. What is particularly interesting about this list, including the three most recent PET drug approvals (NETSpot, Axumin, and $^{68}$Ga-DOTATOC), is that their NDA approaches and strategies have all been somewhat different. That is, most have not followed the traditional pathway of two large, controlled multi-center phase 3 trials. It appears that most are using variations of the 505(b)(2) pathway, and the FDA is being open-minded about evidentiary sources to meet the requirements of 505(b)(2). The University of Iowa benefitted substantially from knowledge gained from the previous experiences of both academic and industry organizations that have braved the NDA process. Continued sharing of both successful and unsuccessful strategies amongst partners in this field, combined with continued cooperation and open communication with FDA, is a sound strategy for advancing the field of molecular imaging more rapidly.

**Noteworthy**

- The Division of Medical Imaging Products at FDA, working within a highly restrictive environment, has demonstrated itself to be a responsive mission-driven organization working hard to empower the academic molecular imaging community to navigate PET drugs through the NDA process. (Page 4)
- A better understanding of the NDA structure, content, process, and level of evidentiary expectation in the molecular imaging community is an important component for downstream approval of additional PET radiopharmaceuticals. (Page 19)
- The NDA process is onerous, but will be made more efficient through the open sharing of experiences and resources amongst stakeholders in the molecular imaging community that have submitted NDAs. (Page 22)

**Disclosures:** No potential conflicts of interest relevant to this article exist.

**Acknowledgements:**

Special thanks to the Margie & Robert E. Petersen Foundation for funding.

Appreciation to the University of Iowa NDA team including Sue and Tom O'Dorisio, Michael Graham, Yusuf Menda, Janet Pollard, Nadine Mallak, David Bushnell, Xiaomei Gu, Lisa Dunnwald, Mary Schall, Diane Soulek, Allie Tucker, Shannon Lehman, Kellie Bodeker, Tim Ginader, David Dick, and Facet Life Sciences.

**References:**


1. Nielsen TB, Brass EP, Gilbert DN, Bartlett JG, Spellberg B. Sustainable discovery and development of antibiotics — Is a nonprofit approach the future? *N Engl J Med.* 2019; 381:503-505.
2. Graham MM, Gu X, Ginader T, Breheny P, Sunderland JJ. $^{68}$Ga-DOTATOC imaging of neuroendocrine tumors: A systematic review and meta-analysis. *J Nucl Med*. 2017; 58:1452-1458.


**FIGURE 1.** The University of Iowa $^{68}$Ga-DOTATOC clinical, regulatory, and scientific team at the FDA Pre-IND meeting 30 April 2015. Left to Right: Kellie Bodeker, John Sunderland, Yusuf Menda, Michael Graham, Shannon Lehman, David Dick, M. Sue O'Dorisio, Tom O'Dorisio.

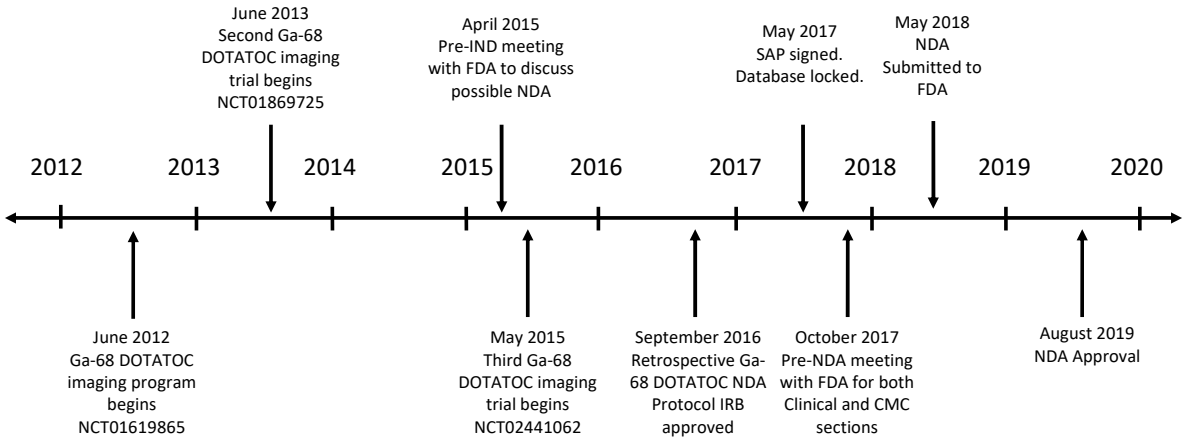



**FIGURE 2.** The timeline for the $^{68}$Ga-DOTATOC NDA project.

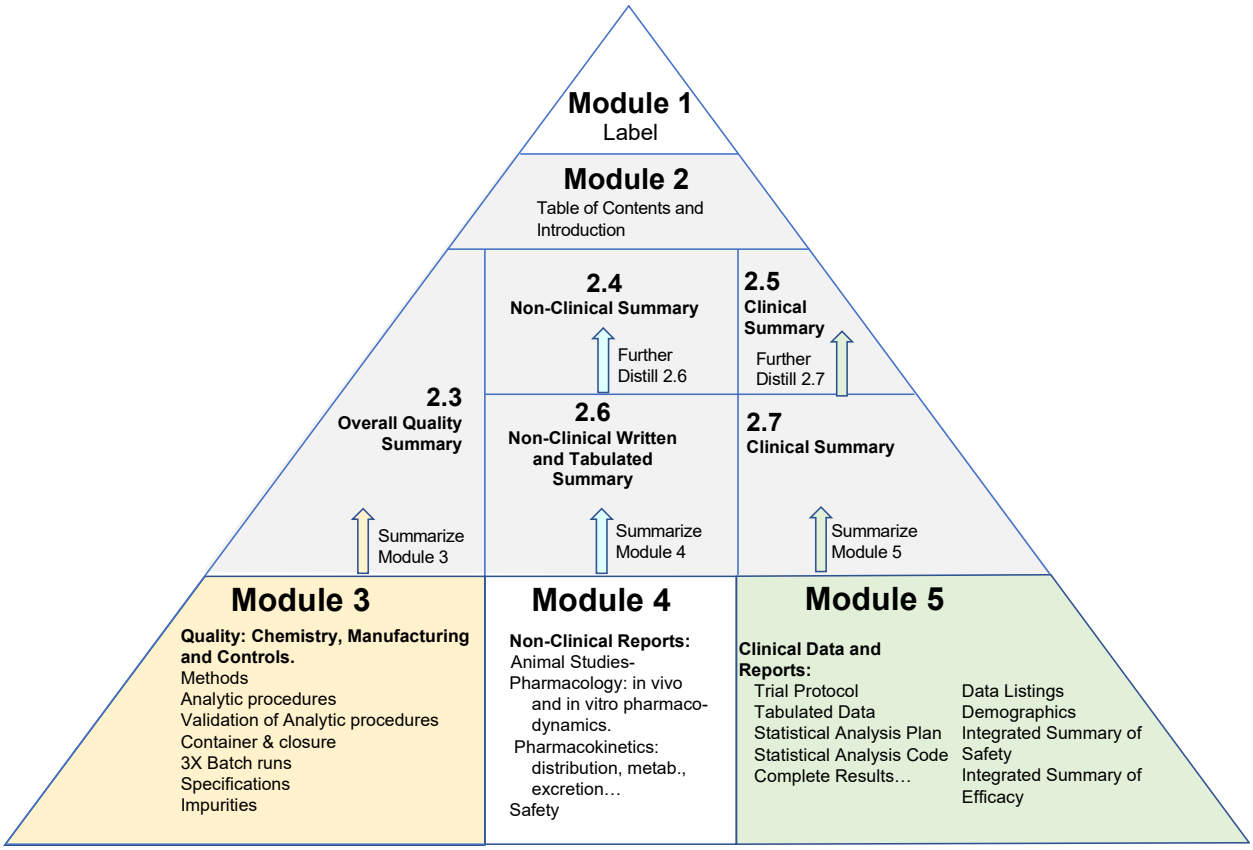



**FIGURE 3.** Pyramid representation of the electronic Common Technical Document (eCTD) format required for use in NDA drug registration submissions – annotated with module contents.

TABLE 1
Steps in the NDA Process

| | Activity | Description | Comment |
|---|---|---|---|
| 1. | Pre-IND meeting with FDA | Discussion of proposed clinical trial and overall NDA approach. Opportunity to ask questions regarding FDA's opinion on any aspect of the trial or NDA strategy. | The meeting request is a lengthy formal document with background material sufficient to familiarize FDA with your product and situation. The *only* topics discussed are related to those questions asked in the package. |
| 2. | Clinical Trial Planning | Writing protocols with aims designed to support your proposed label indication. Statistics are critical. Reference standards must be clearly defined. Data collection must be designed to withstand FDA audit. | The Statistical Analysis Plan (SAP) is a formal, signed, document and must be part of the formal clinical trial. You commit, a priori, the analysis approach and statistical endpoints for the proposed indication. |
| 3. | Performance of clinical trial(s) | Trial data is collected and formally documented. | Internal audits as the trial progresses are important to assure data is collected completely and correctly. |
| 4. | Data lock and Statistical Analysis | All trial data is entered in FDA prescribed data format for statistical analysis. The database is locked. The statistical analysis is performed precisely according to the SAP. | Prior to data lock, all trial data must be reviewed for accuracy and completeness. Statistical analysis is performed using SAS software versions prescribed by FDA. SAS code is submitted in the application. |
| 5. | Pre-NDA meeting with FDA | Preliminary safety and efficacy analysis results are shared with FDA. Questions to FDA regarding adequacy of data and questions regarding structure and content of NDA are discussed. | From the output of this meeting you should understand the likelihood that your data is sufficient to support your indication. You should have all major questions answered regarding the format and content of your application. |
| 6. | Writing the NDA document | The NDA must be written and formatted into eCTD format which consists of five modules. Module 5: clinical trial study reports, clinical trial information, and tabulated data. Module 4: non-Clinical animal data. Module 3: chemistry manufacturing and controls. Module 2: introduction and summaries of Modules 3-5. Module 1: label and other institutional information. | eCTD submissions for NDAs have been required since 2017. Data within the eCTD document has additional FDA required formats, including clinical datasets, statistical code, and label formatting. These standards are changing. Implications to academic institutions submitting NDAs are unclear, but will likely require more expense. |
| 7. | Submission | Submission is via electronic eCTD submission. An electronic receipt will be issued when it passes the FDA Gateway. | |
| 8. | Review and Request for Information | FDA has two months to review the application for completeness. They can refuse the regulatory filing if critical information is missing or is of insufficient quality. If accepted, FDA has an additional 6 months for "priority" review, or 10 months for "standard" review. FDA will file additional "Requests for Information" during the review. | Thirteen "Requests for Information" were received. The most serious addressed an algorithmic error in reference standard determination impacting the classification of a handful of subjects. The delay in correcting and resubmitting the tabulated data delayed the PDUFA date 3 months. |

**Supplemental Data**

**Data Collection Standardization**

Data collection standardization strategies for non-proprietary PET drugs for clinical trials has only recently been contemplated and attempted. This was largely in response to FDA's suggestion that the academic PET community might more efficiently compile imaging and safety data from promising non-proprietary PET radiopharmaceuticals if they accumulated clinical trial data from multiple institutions using standardized methodologies. In this proposed scenario, each site could submit their own IND, with their own protocol and specific aims. However, critical aspects of the trial would be performed using standardized methodologies such that efficacy and safety data may be meaningfully combined to in a downstream drug-registration (NDA) submission. Examples of clinical trial criteria that could be standardized is listed in Supplemental Table 1.

Standardization of methodologies was a critical issue that needed to be addressed in the University of Iowa $^{68}$Ga-DOTATOC NDA submission because it was based upon three non-standardized single institution clinical trials performed over a period of six years. Even with these trials being performed at the same institution, all methods were not prospectively standardized. To remedy this situation, a retrospective re-analysis of the data from the three clinical trials was performed using standardized criteria. This process is simpler than the multi-institutional approach mentioned above.

For example, end-product specifications for $^{68}$Ga-DOTATOC were defined in the IND for each protocol and were identical across all three trials, obviating the need for standardization. For $^{68}$Ga-DOTATOC, the end product specifications were fairly simple and included Appearance (colorless and free of particulate matter), radiochemical identity as defined by iTLC and iHPLC

(against cold Ga-DOTATOC reference standard), radiochemical purity by iTLC and iHPLC (both >90% $^{68}$Ga-DOTATOC), and pH (between 4.0-8.0). In the context of a multi-center trial it would be sufficient to mandate that all $^{68}$Ga-DOTATOC doses synthesized at all sites meet these standards.

With regard to safety, a common standard for Adverse Event (AE) reporting is critical so that data can be combined and properly interpreted by FDA. Within the $^{68}$Ga-DOTATOC trials, AEs were reported using standard Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) terminology. If data was obtained from a different CTCAE version, it was converted to version 4.0 for consistency. AE information included toxicity category information provided by the OnCore® system. This information included toxicity of the AE, grade, attribution to $^{68}$Ga-DOTATOC, and the description for toxicity. Any clinical follow-up information, including the date of clinical follow-up, was collected from the subject chart.

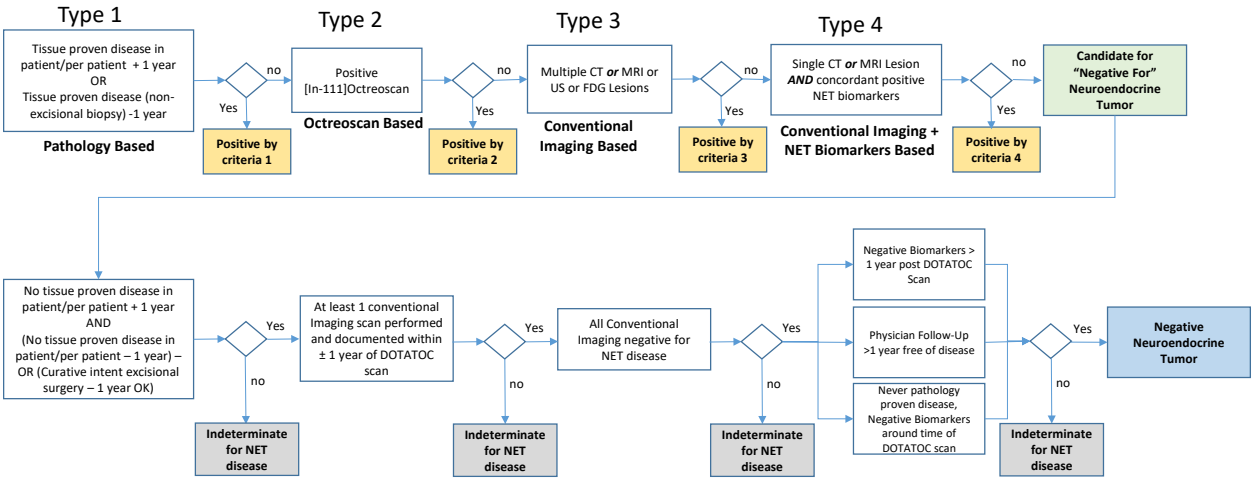
The dose range for the three prospective clinical trials were not identical. However retrospectively defining a range of 111 – 185 MBq (3-5) mCi included virtually all subjects in all three trials. 148 MBq (4 mCi) was common to all trials, and was ultimately the dose accepted for the label. Within a prospective multi-center trial context, defining a common dose range is critical.

Acquisition parameters, to the extent it makes sense, should also be pre-defined. Specific to the $^{68}$Ga-DOTATOC trials, the uptake time targeted 60 minutes throughout the three prospective trials. As uptake levels of $^{68}$Ga-DOTATOC are not static over time, the imaging timepoint is a relevant variable that requires standardization to meaningfully combine data in either a single or multi-center setting.

Image interpretation and analysis in the prospective $^{68}$Ga-DOTATOC clinical trials differed substantially, because the aims of each of these trials were quite different. For purposes of the NDA, in the retrospective analysis of the prospective data, all $^{68}$Ga-DOTATOC studies were reread independently and blindly by two physicians. Disease positivity was assigned by each physician, and sites of disease (organ and region) were tabulated according to a protocol specifically defining rules for positivity. Disagreements between physicians were resolved according to protocol, by a third, independent, physician. Within the context of a multi-center trial, having common reading and reporting criteria is critical to preserving the ability to combine data. Centralized reading in the multi-center setting is a common approach to assure more standard reading of data from multi-center trials. This is possible even in the academic setting if images are uploaded to a common, secure PACS.

Lastly, definitions of the reference standard for disease positivity and negativity for the three prospective $^{68}$Ga-DOTATOC trials were not consistent. In the retrospective analysis, we developed a standardized approach. Overall, a combination of pathology, OctreoScan imaging, conventional imaging, and biomarker data results were used to determine if a subject was positive or negative for NET disease. The positive for NET disease classifications were further delineated into types (Type 1, Type 2, Type 3, and Type 4) based on the strength of the data indicating disease status. By design, Type 1 evidence of NET disease (pathology) was considered more accurate for determination, and superseded Type 2 evidence (OctreoScan or Ga-68 DOTATATE). Type 2 was considered less accurate than Type 1, but more accurate than and superseded Type 3 evidence (multiple sites of disease on conventional imaging). Type 3 was considered less accurate than either Type 1 or Type 2, but more reliable than and superseded Type 4 evidence (single site of disease on conventional imaging coupled with abnormally high

biomarkers). The flow chart provided in Supplemental Figure 1 provides a graphical representation of how this further classification was determined. In the context of prospective multi-center trials, consistent definitions for tissue positivity and negativity should be defined by a common standard or common algorithm to allow for downstream combining of data in a manner similar to that shown.




**SUPPLEMENTAL FIGURE 1.** Flow chart defining tissue positivity and negativity in the $^{68}$Ga-DOTATOC retrospective trial.

SUPPLEMENTAL TABLE 1
Standardized Data Collection Criteria for non-Proprietary PET Radiopharmaceuticals

| Standardized Criteria | Reason | Examples |
|---|---|---|
| Radiopharmaceutical end-product specification | Assure same drug quality across trials | pH range, radionuclidic purity, radiopharmaceutical purity |
| Adverse Event Data Collection | Assure safety standards consistently reported | Same reporting lexicon, same follow-up periods… |
| Dose Range<br>Acquisition Parameters | Assuring same dose<br>Assuring same/similar imaging protocols | 3-5 mCi, with target 4 mCi<br>Scan commenced 55-70 minutes post injection |
| Interpretation criteria | Assure consistent interpretation across trials | Dual blinded reads, Threshold $SUV_{max}$, Minimum size criteria |
| Reference/Truth Standard | Assure true positive, true negative, false positive, and false negative results are reported based on same criteria. | Comparison with histopathology or if no pathology, then conventional imaging. |