Diagnostic and intraoperative targeted molecular imaging for pancreatic cancer

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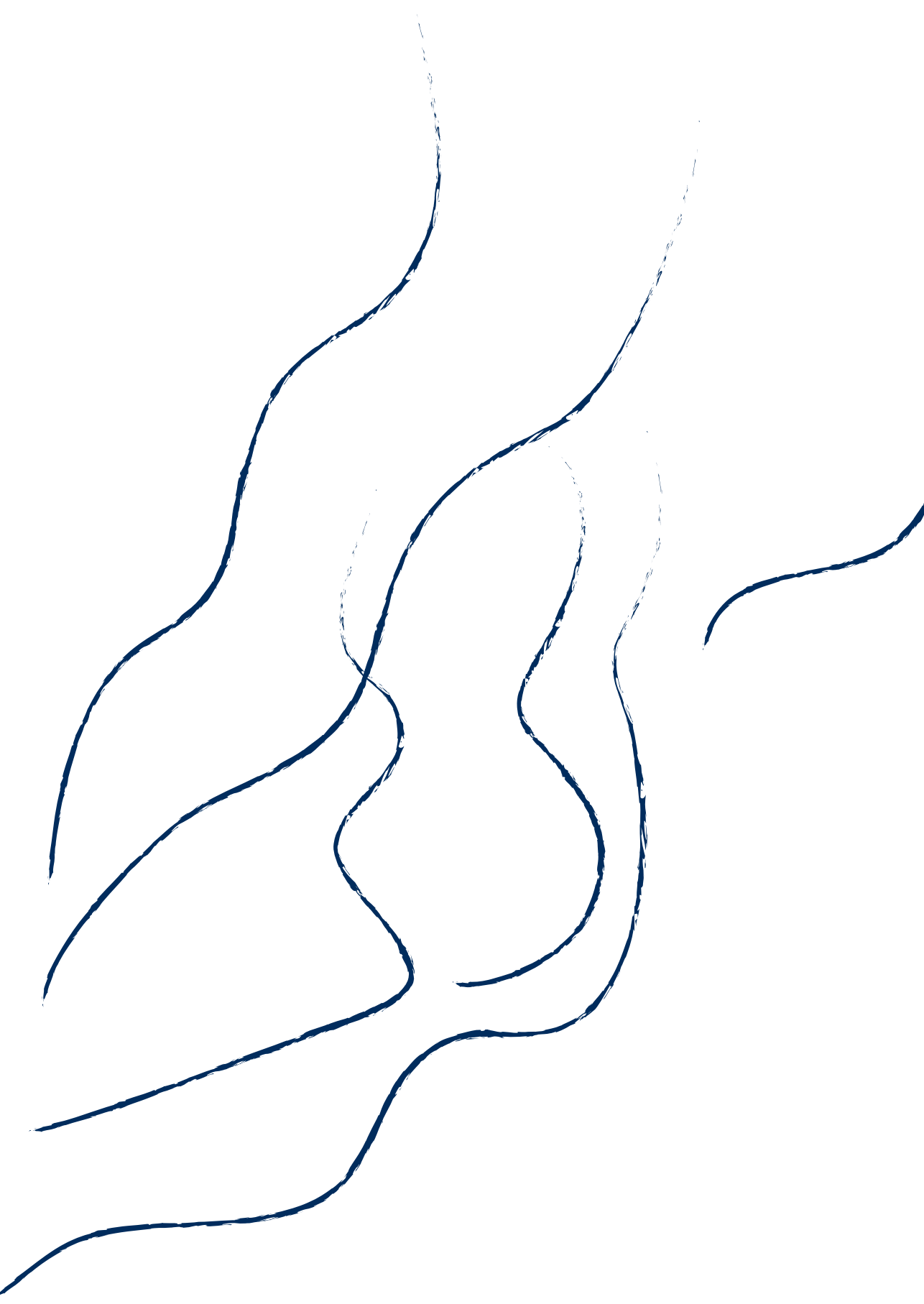
Part | III

Clinical Translation of Targeted Molecular Imaging



Chapter | 7

Regulatory Aspects of Optical Methods and Exogenous Targets for Cancer Detection

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ABSTRACT

Considerable advances in cancer-specific optical imaging have improved the precision of tumor resection. In comparison to traditional imaging modalities, this technology is unique in its ability to provide real-time feedback to the operating surgeon. Given the significant clinical implications of optical imaging, there is an urgent need to standardize surgical navigation tools and contrast agents to facilitate swift regulatory approval. Because fluorescence-enhanced surgery requires a combination of both device and drug, each may be developed in conjunction, or separately, which are important considerations in the approval process. This report is the result of a one-day meeting held on May 4, 2016 with officials from the National Cancer Institute (NCI), The Food and Drug Administration (FDA), members of ASIGS (American Society of Image-Guided Surgery) and members of the World Molecular Imaging Society (WMIS), which discussed consensus methods for FDA-directed human testing and approval of investigational optical imaging devices as well as contrast agents for surgical applications. The goal of this workshop was to discuss FDA approval requirements and the expectations for approval of these novel drugs and devices, packaged separately or in combination, within the context of optical surgical navigation. Additionally, the workshop acted to provide clarity to the research community on data collection and trial design. Reported here are the specific discussion items and recommendations from this critical and timely meeting.

INTRODUCTION

Surgery with negative margins is the foundation for curative treatment in many solid cancers.[1] While conventional imaging modalities such as magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), and ultrasound (US) facilitate surgical planning, they are generally difficult to integrate into the surgical environment. Most importantly, however, these traditional modalities do not reliably communicate real-time feedback to the surgeon except for ultrasound. Therefore, surgeons must depend on subjective palpation and subtle visual changes for achieving complete tumor clearance. Although intraoperative frozen tissue sectioning, staining, and microscopic visualization are routinely used for achieving negative margins, this is time-consuming, costly, and samples only a small proportion of the wound bed, which may lead to sampling error with false-negative results. Positive or close margins directly correlate with poorer outcomes, often necessitating post-operative adjuvant therapy and, in some instances, a second operation.[2] Conversely, aggressive radical resections can remove normal tissue, leading to excessive morbidity and/or disfigurement. Thus, real-time surgical guidance for differentiating tumor and healthy tissue is crucial to both improved overall survival in addition to preservation of tissue function and appearance.

The recent advances in optical contrast imaging have brought forth a myriad of cancer-specific agents that have the ability to expand the information required for the surgeon to make informed clinical decisions. These optical imaging techniques are highly variable with a wide range of imaging wavelenghts and spatial scales.[3] Together, these developments offer tremendous advantages to the field of surgical guidance, with an unparalleled ability to transform surgical oncology. In fact, due to their potential for high signal to noise ratios (SNR) and sensitivity to a broad range of spatial resolution, optical fluorescence imaging has the potential to impact patient care in multiple arenas. For example, in comparison to shorter wavelengths, the penetrating deep tissue properties of near-infrared (NIR) fluorescence has led to a focus on similar long-emitting fluorophores for this and many other optical imaging applications (see NIH Research Portfolio Online Reporting Tools (RePORT) for details).[4] Nevertheless, there are a number of variables that impact the success of intraoperative optical imaging that are intrinsic to the imaging hardware or the molecular probe itself.

Perhaps the greatest variable, however, is inter- and intratumor heterogeneity. Despite three decades of research to identify tissue-specific targets and develop effective imaging agents, 5-aminolevulinic acid (5-ALA) is the only real-time, cancer-specific agent available in the clinic today. Administered orally or topically, 5-ALA is converted intratumorally to fluorescent protoporphyrin IX. Currently, 5-ALA is approved for oral administration in Europe, Canada, and Japan to highlight brain tumors during cytoreductive surgery. The 5-ALA ester derivative hexaminolevulinate (HAL) is approved for topical use for bladder cancer detection in both the United States and Europe.[5, 6] The use of 5-ALA was shown to be successful during intracranial tumor resection[5] by achieving more complete resection and improving progression-free survival in patients with malignant glioma, which suggests that it carries the potential for use in other cancer types with similar favorable outcomes.[7-9]

There are a number of additional tumor-specific molecular probes that are widely applicable to several cancer types that have been described,[10] and an increasing amount of clinical trials are being conducted to evaluate both their safety and efficacy. Favorable safety data from non-human primates allows antibody-based optical imaging to build on the advances in immunotherapy and immunoPET imaging.[11] For example, cetuximab conjugated to IRDye800 (cetuximab-IRDye800) has been studied in phase 1 clinical trials and has demonstrated the ability to identify subclinical tumor in patients with head and neck cancer.[12] However, successful regulatory approval for the widespread use of this technology requires additional clinical trials. These trials must be designed and performed according to the standards of the FDA Investigational New Drug Application (IND) recommendations to demonstrate safety and patient benefit as well as the Centers for Medicare & Medicaid Services (CMS) for cost-effectiveness. Over the past few years, the number of FDA submissions for IND or Investigational Device Exemptions (IDE) related to optical imaging has doubled annually, with 26 clinical trials currently planned or already underway.

A unique feature of fluorescent optical imaging is that it facilitates real-time decision-making by guiding surgeons to potential areas of microscopic disease in a macroscopic setting. From a regulatory standpoint this deserves special considerations since real-time feedback not only fosters dynamic decision

making but also permits adjustments to the treatment plan, which is not possible with current pre-operative imaging modalities.

In February 2015, the American Society of Image Guided Surgery (ASIGS) held a meeting with surgeons and scientists in the field of Image Guided Surgery to critically evaluate imaging platform technologies and optical imaging agents. The goal of this meeting was to provide recommendations regarding trial development and the regulatory approval process, and come to an agreement on how this technology could be used to meet the needs of cancer patients.[13] Since then, several new clinical trials have incorporated major elements from the resulting ASIGS consensus report. However, the appropriate clinical trial endpoints that meet FDA requirements for successful device and/or drug approval remain ill-defined due to a lack of precedence and diagnostic/therapeutic crossover inherent to this technology. As such, these potential setbacks formed the basis of the one-day workshop on May 4, 2016, which included representatives from the National Cancer Institute (NCI), the FDA, members of ASIGS and members of the World Molecular Imaging Society (WMIS). The primary aim was to define consensus methods and endpoints for FDA-regulated human testing and approval of investigational optical imaging devices and contrast agents (drugs) in surgery. The first step was to report FDA considerations for evaluation of any new device or drug, and obtain their guidance on how devices, drugs, or their combination, would most effectively obtain market approval. Recognizing that there is significant controversy regarding this topic, we have summarized to the best of our ability the findings and recommendations from this meeting. This report can critically assist in the development of optical imaging products, and the regulatory pathways for their approval. The meeting was recorded and can be viewed online at URL https://videocast.nih.gov/PastEvents.asp.

PRECEDENCE

When approving imaging devices and agents for clinical use, the FDA relies on data supplied by marketing applications and regulatory bodies. Taking this into consideration, the field should identify clinically meaningful endpoints as well as surrogates of clinical benefit to aid the approval pathways of any new promising

technologies, including optical imaging. However, this task is confounded by the paucity of clinical data on contrast-enhanced oncologic imaging agents, which consequently results in limited or lack of regulatory precedents. Therefore, it is critical to identify clinical developmental pathways for optical imaging in oncological surgery using similar yet appropriate modalities and companion agents that can be used for FDA's consideration. For instance, the use of MRI-guided surgery in brain cancer is analogous to fluorescence-guided surgery, where enhancement is used to influence surgical decisions and has previously shown benefit in patient outcome.[14] However, MRI procedures do not use products that have been specifically approved by FDA for surgical intervention; hence, FDA does not consider MRI-guided surgery an established predicate for fluorescence-guided surgery. Until these approaches have been thoroughly evaluated by the FDA, we will not have any certain guidance documents to clearly define the principles of study design and appropriate outcome measures based on safety and benefit to the patient.

IMAGING DEVICES

A wide range of intraoperative fluorescence imaging devices have been developed by academic and commercial institutions that use similar illumination strategies, light sources, detectors, device architectures and collection geometries. Systems for use in open surgery, laparoscopic, thoracoscopic, and robot-assisted procedures have all been described, and likely represent a broad range of sensitivities to a given set of fluorophores, and differences inherent to their background noise levels. Because they have been developed with a specific usage in mind, they differ significantly in their fields-of-view, resolution, and wavelengths. Although the concept of these devices is relatively straightforward in that they simply require a light source, filters, detector(s), and display, there are specific challenges intrinsic to the system design. These include having appropriate light sources with a variety of wavelengths but within the prescribed safety standards for illumination,[15] adequate filter design to eliminate excitation and ambient light for use with one or more fluorophores, detectors with the appropriate spectral range and sensitivity with good SNR, real-time readout superimposed on a reference image, and ultimately, a user-friendly and ergonomic design. The ideal optical imaging system for the OR

should have additional characteristics, such as seamless operation with room lights, quantitative pattern recognition, and favorable ergonomic characteristics for use in a demanding environment. For a more detailed overview of the different characteristics imaging systems should possess and the challenges for development we would to refer to the review paper by DSouza et al.[3] While many of the current systems include these features, there is considerable variation among these devices, and industry standards are only just emerging. Most of these instruments possess a broad range of wavelength imaging capabilities, which translates to a potential for imaging several distinct fluorophores. This imaging potential is further compounded by the fact that any fluorophore can be conjugated to a number of targeting moieties. For these reasons, many different molecular formulations could be used with the same instrument. The FDA will review an application for a new drug intended for use in combination with a specific instrument or intended for use with multiple instruments as designated by the applicant drug manufacturers who need to carefully consider instrument design and capabilities before undertaking clinical development of a new drug.

FDA regulatory pathways for Device approval

For imaging devices, the FDA regulatory process is directed by the Center for Devices & Radiological Health (CDRH). This process begins with an optional pre-submission meeting with the FDA after a "Q-submission" request to the Agency has been requested. This meeting serves as a forum for individual sponsors and the FDA to discuss the planned Investigational Device Exemption (IDE) or marketing application/clearance submission. The subsequent route to regulatory clearance or approval for devices depends primarily upon the level of risk associated with the clinical application of the device. When the goal is simply anatomical, such as locating lymph nodes or blood vessels, the FDA typically views optical imaging systems as relatively low risk. Optical imaging systems used to visualize anatomy in clinical investigations could be considered "non-significant risk" (NSR) devices, and an IDE is not required. Upon establishing safety and efficacy through the completion of such a clinical investigation, a sponsor can subsequently submit a traditional 510(k) application for market clearance if "substantial equivalence" to a predicate device is claimed.[16]

Optical imaging systems used in the diagnosis, prognosis, and/or treatment of diseases, however, are by default designated significant risk devices (SR) by the FDA regardless of disease severity. If the study sponsor intends to use such devices during an investigational human study, the FDA requires the study sponsor to file an IDE application.[17] For combination drug and device products, an Investigational New Drug (IND) application for the associated molecular agent being used may be filed in place of an IDE, if the Center for Drug Evaluation Research (CDER) is assigned as the lead review center.

Depending on the intended use of the imaging system, the sponsor presents the appropriate NSR or SR designation to the local Institutional Review Board (IRB) for review. Once IRB *and* IDE (for significant risk devices) are granted, the sponsor is free to proceed with the investigation. The issue of NSR/SR designation has been discussed and documented in detail previously.[18] The required elements for an IDE application can be found on the FDA website and are summarized in Table 1.[19] Ultimately, a pre-market approval (PMA) application is filed for market approval of Class III medical devices. The information requested by the FDA for PMA approval depends upon its intended use and any specific claims about the device that have been made by the sponsor. Evidence must support the intended use claim. For device approval under a PMA, information on device labeling, performance specifications, valid scientific evidence, tissue effects of the product, mechanism-of-action, and clinical outcomes will be required.[20] Guidance documents for PMA submissions can also be found on the FDA website.

Currently approved devices

Currently, there are several optical imaging devices that have been cleared by the FDA mainly for non-cancer indications. All 510(k) cleared devices can be found in the FDA database.[21] A recent review by dSouza et al. compares the existing fluorescent imaging devices and provides basic criteria for the comparison of different images for specific applications.[3] To summarize these devices, a tabular overview detailing currently cleared devices are shown in table 2 along with more detailed information included in supplemental materials. For the main advantages and disadvantages of these devices we refer to the following reviews.[3, 22, 23]

Table 1. Different types and characteristics of Investigational Device Exemption (IDE) studies

	Early feasibility study	Feasibility study	Pivotal study
Sample size	• Small number of patients, < 15 (approximate).	• More patients than EFS.	• Number of patients determined by statistical needs.
Criteria	• Fundamental questions about device performance & safety exist • Expected changes to design of prototype device. • Limited nonclinical data available.	• Sufficient information is known about the design, procedure or indication to justify clinical studies with more patients than EFS.	• Device is the final design and there is significant information known about the design, procedure and indication.
Purpose	• To demonstrate a proof of concept. • Early look at safety/efficacy. • Examine human factors and work flow. • Determine what design or procedure changes could optimize the therapy. • Determine patient characteristics that may impact device performance.	• Capture preliminary safety and effectiveness. • Plan an appropriate pivotal study.	• Demonstrate safety and effectiveness to support a marketing application.

Standardization of Devices and Device Performance

Best practices for evaluating safety and performance of medical imaging devices are regularly published in the form of standards documents. While performance standards are commonly used in established medical imaging fields, such as the FDA-recognized PET imaging standards published by NEMA,[24] only safety standards currently exist for optical imaging. Standards that address performance typically recommend phantom-based test methods. Specifically, these documents identify relevant characteristics (e.g., spatial resolution, uniformity, sensitivity, dynamic range), provide guidelines for testing (e.g., phantom material property range/geometry, methods for calculating metrics), and describe viable test methods for a performance characteristic. Standardization improves FDA's ability to understand device working mechanisms and overall effectiveness, for benefit-risk assessments and substantial equivalence determinations. They also help to facilitate device development, standardize clinical trials and ensure product quality.

Table 2. Tabular overview detailing the currently 510(k) cleared devices.

Fluorescence imaging system	Company	Year approved/510(k) cleared	FDA 510(k) number	Predicate device(s)
SPY™ Intra-operative Imaging System	Novadaq Technologies Inc.	2005	K042961	The Philips Integra Series 2 Systems (K984545) Heidelberg Retinal Angiographic System (K944261)
PDE Fluorescent Angiographic system	Hamamatsu Photonics K.K.	2012	K110480	Novadaq Technologies Inc.'s SPY Imaging System SP2000 (K063345) SPY Fluorescent Imaging System SP2001 (K073130)
Fluobeam 800 Clinic® Imaging Device	Fluoptics	2014	K132475	Hamamatsu Photonics K.K., PDE Fluorescent Angiographic System (K133719)
da Vinci® Firefly™ Imaging System	Intuitive Surgical	2014	K141077	da Vinci Xi Surgical System device (K131861) da Vinci Fluorescence Imaging Vision System (K101077)
The Artemis Handheld Imaging System	Quest Medical Imaging	2015	K143474	PDE of Hamamatsu (K110480) Fluobeam of Fluoptics (K132475)
VS3-IR-MMS System	VisionSense Ltd	2015	K150018	Novadaq Technologies SPY Imaging System (K063345)
PINPOINT Endoscopic Fluorescence Imaging System	Novadaq Technologies Inc.	2016	K161792	PINPOINT Endoscopic Fluorescence Imaging System (K150956)

The use of a phantom or physical standard to ensure device performance is well accepted, yet the idea of requiring device developers or manufacturers to adhere to an equivalent standard remains somewhat controversial. This is largely due to the fact that optical imaging and fluorescent probes represent innovative, rapidly changing areas. Therefore, in addition to adhering to basic principles of image quality assessment, methods should be applicable to a wide range of devices and contrast agents. Furthermore, testing should be as "minimally burdensome" as possible, which includes factors such as complexity of preparation/execution and ability to assess multiple image quality characteristics simultaneously, or in relatively rapid succession.

Establishment of performance standards begins with research on phantom-based test methods. While much progress has been made in this area, more work is needed to optimize methods addressing key characteristics. Professional

societies can use this research as the basis for generating publications that outline scientific consensus on best practices. Finally, authorship of a standard is performed by a standards organization (e.g., IEC, NEMA) committee that can draw on published consensus documents. Therefore, members of academia and industry are strongly encouraged to participate in optical safety and performance testing research, scientific consensus building and standards development that will inform and impact the regulatory process.

Unlike PET, which relies upon annihilation events to produce photons at a specific energy (all emissions lead to 511 keV gamma rays), optical imaging must consider its interactive properties with regards to the wavelength or frequency of the tissue being imaged. In many respects, each of the 16 regions of the optical imaging spectrum falling between 500 and 1300nm is unique. However, the specific parameters to be used to define these tools and the community designated to regulate these optical instruments has yet to be determined. The onus may lie on both the FDA and device manufacturers to determine such characteristics and whether they are better suited for regulation at the industry or federal level. For other imaging modalities, there are established testing parameters like spatial resolution, uniformity, distortion, sensitivity, linearity, and field of view, all of which may be applicable to optical imaging but with additional considerations for optics.[24] These may include dynamic range, spatial resolution, background collection, and sensitivity. To date, no accepted standard phantom for optical imaging or minimum requirements for device performance exist.

Preclinical Safety Testing

Light safety standards typically used to ensure optical device safety do not address the increased potential for injury when light interacts with an exogenous agent present in tissue.[15] Many fluorescence contrast agents (e.g., protoporphyrin IX, IR700DX, Cy5) are known to produce photochemical damage in DNA and other cellular components due to light-induced generation of reactive oxygen species. While beneficial for photodynamic therapy and photoimmunotherapy,[25] this behavior presents a potential safety risk for imaging products. Contrast agents exhibiting strong absorption may intensify local energy absorption, increasing the risk of photothermal or mechanical (cavitation) damage.[26] Furthermore, novel nanoparticles may introduce unique hazards – such as highly localized fluence

"hot spots" due to plasmon resonance effects. While no guidance documents have been developed to address testing of optical imaging contrast agents, a recent guidance published by FDA/CDER provides general recommendations for preclinical testing of medications' photochemical safety[27] through the use of chemical assays for evaluating production of reactive oxygen species as well as *in vitro* and *in vivo* assays for assessing damage to cells and tissues. In the absence of standards or even well-validated best practices to clarify potential issues with novel contrast-enhanced optical products, preclinical testing, which may include in vitro cellular, phantom or tissue testing, or *in vivo* animal studies, is often warranted on a case by case basis to ensure patient safety.

IMAGING AGENTS

The challenge for cancer imaging agents is the detection of small lesions while maintaining a high tumor-to-background ratio (TBR). There are two major classes of optical agents: targeted and non-targeted probes. The targeted probes consist of a signaling moiety, a vehicle, and a targeting ligand. These can be further divided into "always-on" and "activatable" probes.[28] Probe diversity further adds to the complexity of the approval process. Pharmacokinetics plays an important role in regulatory issues; for example, the longer an agent stays in the body the more significant the safety issues. Properties like molecule size, composition, and relative mass of signaling and targeting moieties result in different biodistribution and clearance rates. Not only toxicity should be taken into account when developing targeted contrast agents, but also other design considerations such as stability in human serum, specificity and sensitivity for the target.[29] Additionally, the route of administration will influence safety issues, such that topical application may be more favorable from a safety standpoint due to low systemic absorption as compared to intravenous (IV) administration. However, there are practical considerations when using topical formulations not encountered with IV administration, such as an inability to wash off unbound probe, non-uniformity of delivery, local tissue toxicity and barrier effects of the tissue surface (e.g. the stratum corneum of the skin). These different elements affect data collection and interpretation, and must be considered in pursuit of regulatory approval and subsequent clinical studies. Therefore, a more standardized process for imaging agents could help improve

development and approval. This would improve the FDA's ability to understand safety, working mechanism and overall effectiveness. However, the field also points out concerns regarding standardization in agent development, since this can slow down the rapidly changing chemistry in this field. A full review of these issues for imaging agents can be found elsewhere.[30]

Currently only the non-specific NIR imaging agent indocyanine green (ICG) is approved by the FDA for imaging purposes. However, at this point novel NIR fluorophores are developed with a substantially higher fluorescent yield compared to ICG and in contrast to ICG, these molecules can be conjugated to a targeting ligand, leading to targeted imaging agents.[3] An example of such a fluorophore that is already tested extensively and shown safe in humans is IRDye 800CW (LI-COR Biosciences, Lincoln, NE). Additionally, ZW800 (Curadel, Marlborough, MA) is another advanced NIR fluorophore that is nearing clinical testing.[31]

Due to unique physiological and mechanical characteristics of these agents, all will require distinct safety and toxicity studies. The range of wavelengths combined with the range of agent types makes this area of imaging different than PET, MRI, or single-photon emission computed tomography (SPECT). Using an approved drug as an imaging vehicle that can be coupled to a fluorescent molecule, analogous to incorporating a radionuclide into a drug for PET imaging, might seem like a way to improve the efficiency of the clinical translation process due to known biodistribution, targeting and safety profiles. However, since fluorophores are often large in comparison to the approved pharmaceutical agent, the new entity may confer significant differences from the approved drug, and the FDA considers this a New Molecular Entity (NME), which limits many of the predicate drug advantages.[32] The NME will be reviewed as a novel compound and require NME-specific safety and efficacy data. In diagnostic imaging, there is an option to perform a traditional dose-ranging Phase I clinical trial, or if the agent is likely to be visualized at very low doses, an exploratory IND can be initiated when the intended dose is limited to a microdose level (⩽ 100 μg and 1/100 of the therapeutic dose or ⩽ 30 nanomoles of a protein). Using this pathway, the early safety testing should demonstrate that the safety profile of the NME is similar to the previously approved parent compound. This approach will provide early information on biodistribution and streamline the testing and

approval process. For radioactively labeled agents, the FDA has developed a specific mechanism to facilitate early data acquisition through the Radioactive Drugs Research Committee (RDRC) mechanism, whereby radioactively labeled agents can be used to perform certain clinical research without IND approval. Information regarding metabolism, pathophysiology, or biochemistry can thus be obtained through early phase studies. The most important difference between an eIND and the studies conducted via the RDRC mechanism is that the RDRC can only review basic science research proposals for the use of radioactive drugs in humans, but is not intended for therapeutic or diagnostic purposes, nor for determining safety and efficacy.[33]

Nonclinical safety and toxicity studies

The potential toxicity for investigational agents needs to be balanced by potential benefits. For traditional diagnostic imaging agents undergoing early clinical testing serious or clinically important adverse reactions are generally not acceptable. Nonclinical safety and toxicity studies should be designed to establish a wide safety margin. However, because many new agents are being proposed for surgical resection of malignancies, which inherently involve major procedures for life-threatening diseases, higher levels of risk may be justified by the nature of the procedure's anticipated benefits. When diagnostic imaging agents are evaluated for use to guide therapeutic decisions, there may be some flexibility (see below in Early Phase Clinical Trials). At this point current studies, both in humans and in preclinical setting, have not raised any specific safety issues for human use of NIR fluorophores since they have shown low or completely absent toxicity.

Nonclinical drug studies require identification of drug-target organs, characterization of pharmacology and toxicology, starting dose determination with dose escalation scheme, and study-tailored drug usage information. For NME, there are specific studies typically required prior to the onset of a Phase I trial (Table 3).[34] However, it is important to note that with appropriate scientific justification, the FDA may allow trials to proceed without some of the required studies after thorough discussion in a pre-IND meeting. The criteria mentioned are for targeted contrast agent and focus specifically on the physiochemical properties of the agent, biodistribution, and clearance pathway. It is the opinion of the field that it is crucial to analyze these properties at this point of the

approval process. For modified existing agents, the requirements are variable and, in some instances, no new preclinical studies are required. Bridging toxicity studies may be required. When a change is made to the route of administration, dose, or population of an already approved agent, the FDA encourages early discussion since they will individually evaluate the need for any additional preclinical studies. Moreover, for certain nonclinical studies (e.g. reproductive toxicology), the sponsor may submit a waiver request to the FDA.[35] For certain agents like nanoparticles, which are known to accumulate in off-target organs, the FDA might request chronic toxicology studies.

Table 3. Non-clinical studies needed for New Molecular Entity (NME) before Phase I trial can be conducted for optical imaging agents

Study	Explanation
Proof-of-concept	Studies showing proof-of-concept of the NME.
Safety Pharmacology	To measure functional indices of potential toxicity. The aim of the safety pharmacology studies should be to reveal any functional effects on major physiological systems.
Pharmacokinetics and Toxicokinetics	Single and multiple dose pharmacokinetics, toxicokinetics, and tissue distribution studies. Information on absorption, disposition, and clearance in relevant animal models should be collected.
Expanded single dose toxicity study (can be combined with repeat dose toxicity study)	Single dose studies should generate useful data to describe the relationship of dose to systemic and/or local toxicity. Repeated dose toxicity must be done when there is a chance for a secondary dose.
Special toxicology	e.g. phototoxicity, route irritancy, blood compatibility.
In vitro genotoxicity study	The use of standard genotoxicity studies for assessing the genotoxic potential of biotechnology-derived pharmaceuticals is not considered appropriate.

*Note that FDA may permit delaying or omitting some of these studies during a pre-IND meeting

FDA regulatory pathways for drug approval

When a sponsor considers development of a broad-range optical imaging agent with use for multiple cancer types and subsequent FDA approval, a study can be conducted to demonstrate generalization of efficacy across a number of cancers, by extrapolating data when similar methods are applicable for the proposed cancer types. In this setting, the trial design typically does not address a therapeutic indication and instead seeks approval as a contrast agent. Lymphoseek,[36] which is widely used for sentinel lymph node biopsy, followed a similar process for approval. These studies additionally serve to establish differences in pharmacokinetics and biodistribution among a range of tumor types and disease states. However, early phase trials should continue to focus on safety followed by efficacy. As such, it may be preferential to begin studies in a well-defined population, as this better facilitates successful completion of desired trial endpoints and further minimizes variability in results. Conversely, one benefit of feasibility testing in a variety of tumor types is the ability to confirm the proposed mechanism of visualization. For example, if the feasibility of an imaging agent has been demonstrated in the imaging of diseased blood-brain-barrier (BBB), which is typical of brain cancer, there is no additional need to show efficacy in subsequent brain cancer histologies. Another example is 2-deoxy-2-(^{18}F)fluoro-D-glucose (FDG), an agent approved for imaging glucose metabolism upregulation, which is known to occur in multiple cancers; therefore, FDG is amendable to imaging multiple types of cancer. To be successful in drug development, the FDA encourages early interaction to optimize the efficiency of clinical data development and, therefore, optimize data usefulness, enhance communications with regulators, and expedite the drug development process. The intended indication of the product must be clear in the strategic plan and well-known at the onset of development. Therefore, this “target” indication should be a leading consideration in the trial design.

Case-by-case evaluation by the FDA

The FDA believes that open discussion of the scientific and clinical considerations regarding optical imaging agents and devices will successfully advance this field. The agency further recognizes that each case requires individual assessment and that strict regulatory guidelines do not uniformly fit all products due to the complex nature of optical imaging. Additionally, the FDA has regulatory flexibility to meet the needs of any specific product when necessary. If the

science and rationale of an investigational optical product are sound, the FDA will perform an individual analysis of the studies that should be conducted to collect safety and efficacy data for approval.[34]

COMBINATION DRUG AND DEVICE PRODUCTS

Optical imaging technologies for intraoperative imaging tend to be device and drug combinations,[37] which may be beneficial for commercialization. The decision of whether or not to submit a combined application is entirely dependent upon the sponsor, not the FDA. Nevertheless, the FDA will examine each device and/or drug submission to determine the appropriate product designation (combination or individual) based on desired labeling.

When a specific medical device is to be used with certain drug products, labeling for either product may be accomplished in a number of ways. For example, it may fall under general labeling, whereby the medical device (or drug) has a broad indication and without restrictions for use with a specific drug (or device). Additionally, one-way labeling may be applicable when a drug (or device) is for use with a specific device (or drug), but the device (or drug) can be used with multiple drugs (or devices). Lastly, two-way labeling or cross-labeling where the drug and device are tied together and seen as a combination product.

By definition, a combination product refers to 2 or more different regulated components (such as a drug with device).[38] Optical imaging usually includes two products that are sold separately but labeled for use together.[38] An e(3) product is one that is developed for use with another already approved product, which according to the investigational plan, are both necessary for its intended use. If used with a device, labeling of a previously approved product will be seen as a combination product. An e(4) product has both an investigational drug and an investigational device component and specifies that both are required for their intended use. The assignment of the combination product to a lead FDA center (e.g. CDER, CBER, or CDRH) is based on the primary mode of action (PMOA) of the product. The PMOA is defined as the single mode of action of a combination product that provides the most important therapeutic action.[38] The assignment algorithm considers precedence (i.e. where has similar technology

been assigned) in assigning a lead center. The lead center will become the point of contact for the sponsor and will communicate with other centers for the purposes of regulatory review. Consequently, there is a need for only one marketing application for most combination products, either an NDA or PMA. However, a sponsor can choose to submit two marketing applications.

If the sponsor wishes for a drug to be indicated for use with multiple devices, it does not automatically imply that it will be a combination product. This is especially true when said devices are already approved. Regardless, there must be technical and clinical data available to support the use of multiple devices in addition to one-way or general labeling.

The best examples of this approach are PET agents, which can be used on a range of PET imaging devices. When a PET scanner is cleared for human use, it is not indicated for a specific PET agent but rather for positron-emitting radionuclides, which is a broad label. The reason for this is that the FDA has evidence that PET devices operate with sufficient similarity. For optical imaging, however, this is not yet the case. As such, the FDA must continue to develop a similar level of experience when using an optical imaging agent with multiple devices. When comparing optical imaging devices to PET or MRI, there are several aspects to consider. First, there are orders of magnitude variations in signal levels, which makes it difficult to draw a parallel with the other techniques. Secondly, there is a wide variety of devices, large dynamic range differences (causing as much as 6 orders of magnitude variation in sensitivity), wavelength variation, and varying performance with room lights that will change background sensitivity, and intensity variation due to distance.

CLINICAL TRIAL TYPES AND IMPORTANCE OF DESIGN

Early feasibility studies - Devices

For the development of medical devices, it can be valuable to use the Early Feasibility Study (EFS) program as a regulatory tool, which is similar to a phase I study for drug development.[39] The goal of the EFS program is to enhance patient access to beneficial technology and supporting innovation in the clinical sector.

A sponsor can conduct an EFS IDE trial when there are significant unknowns regarding device performance, because the device is early in development or is intended for a new use. Therefore, a small number of subjects are permitted for clinical investigation. The differences between the different types of IDE trials are shown in Table 1. Also part of the EFS guidance are recommendations on the optimal path for filing a pre-submission for an IDE.[40] Early discussion with the FDA can be very helpful to agree on a test plan that will support the IDE and can help avoid unnecessary testing, which can be time consuming and expensive.[19] Additionally, it may be possible, in some instances, to use novel devices for certain preliminary clinical studies without formal FDA approval, which would only require local Institutional Review Board (IRB) approval.

Pharmacology in clinical trials - Drugs

The pharmacology requirements during the clinical drug development process are primarily divided into safety and efficacy considerations (Table 4). Safety issues are based on what is being delivered to the patient (manufacturing), dosing, and appropriate monitoring during the trial. Recommendations on trial design, which are made by the FDA, can aid in making the process successful. The primary goal for efficacy trials is to determine a "near-optimal" dose, a process that is often finalized in Phase II. For the FDA, the definition of near-optimal is a dose regimen and imaging condition that are superior to alternatives, which have been studied for safety and pilot efficacy. This will require the investigation of a dose escalation scheme with 3 imaging windows, and the ability to conclude whether or not more will be better or fewer will be just as good. Early on, pharmacokinetic assessment can assist in the selection of optimal imaging window, timing of repeat dosing, and amount of repeat dosing. The goal should be to correlate concentrations to clinical outcome, which is typically performed in Phase III studies.

Phase I and II trials for Imaging Agents and Combination Products

As stated previously, potential risk vs. potential benefit considerations for investigational diagnostic tests require that the test products (drug and associated cameras/devices) have relatively low safety risks. However, when agents are developed to have an effect on therapeutic decisions, are supported by proof of concept data, and trials are designed to show improvement in clinically important outcomes it may be justifiable to adjust the safety threshold

Table 4. Safety and Efficacy requirements at all different phases of drug development

Study	Requirements
First-in-human	Minimum requirements for conducting study to establish safety data. Safety: • Collect early dosing information. • Determine entry criteria; e.g. renal impairment. • Monitoring cardiac safety; at baseline and after imaging. • Adverse event collection during imaging and follow-up. Important data set to obtain • Sufficient PK sampling. • Drug interactions on concentration. • Imaging characteristics at various doses and time points
Phase-II trial	Controlled clinical study to collect early effectiveness data and generate hypotheses. Safety: • Same as Phase I, but supported by evidence obtained previously. • Gain early understanding of the expected adverse event profile. Efficacy: • Refine dosing to determine "near optimal" dose. • PK sampling for assessment of PK linearity. • Develop imaging interpretation standards.
End-of-Phase II meeting	Generally considered the most important meeting between sponsor and FDA. • Near optimal dose is determined, both in safety and efficacy manner. • Determine what needs to be measured in future studies. • Acquire input from FDA on how specific populations will be addressed in the label.
Phase III trial	Safety: • Same as Phase II, but supported by evidence obtained previously. • Sufficiently powered for statistical determinants. Efficacy: • Clinically meaningful primary endpoint success. • Sufficient PK sampling to inform dose adjustment during or at end of trial for a typical patient and specific populations.
Pre-NDA/BLA meeting	• Review data to fulfill recommendations made at end-of phase 2. • Review organization of future application: study reports and datasets.

in order to match potential benefits. For those agents or product combinations that claim improvement on patient survival, the safety requirements may be less

stringent than those agents that claim a lesser benefit. The main focus of trial design for phase I and II trials should be to collect sufficient safety data and information to define achievable endpoints for clinical benefit and also collect data that supports the intended clinical use and indication statement (Table 4). When conducting Phase I and early Phase II studies, it is important that the standard of care be maintained to protect patients from imaging products that have not yet been provided preliminary evidence of effectiveness.

Efficacy endpoints in clinical trials

During design of clinical trials, endpoints need to align with the proposed drug/device labeling indication and, therefore, high standard clinical claims will require more clinically meaningful evidence. The FDA works with a risk-benefit approach such that any risks must be outweighed by increased benefits. The variety of potential efficacy endpoints is demonstrated in Table 5 and includes clinical therapeutic outcomes as well as measures of diagnostic performance.

Table 5. Types of efficacy endpoints

Endpoint	Explanation
Exploratory	Used for development of hypotheses, pharmacodynamics measurements.
Primary	Used to demonstrate efficacy.
Secondary	Support efficacy, provide information on safety and efficacy in specific subpopulations.

To gain FDA approval for new drug applications (NDA),[41] the study needs to show benefit to the patient. Endpoints that simply correlate fluorescence with the location of a known tumor are not considered sufficient for approval; rather evidence must be shown that imaging will have a positive benefit for the patient. An example discussed was the identification of positive tumor margins in a defined clinical setting. For example, if after standard surgical resection additional malignant lesions are identified, then this would indicate the potential benefit of the imaging, assuming that a more complete removal of malignant tissue for this type of cancer is directly correlated with survival or other clinical benefit such as reduced need for reoperation. This means the FDA does not specifically require direct measurement of survival endpoints for this

indication. It can be sufficient to show improved detection of positive margins when the new technology is used, since the correlation between clear margins and survival is already well established for many types of cancer. The same may be true for debulking surgeries. For example, if prior evidence indicates that debulking correlates to better outcomes, it may be sufficient to show that the optical technique improves the surgical safety and effectiveness of debulking procedures.

One of the important considerations for the conduct of imaging studies what procedures will be used to minimize bias. There was little consensus to better understand which clinical trial methodologies would be most efficient, cost effective and scientifically reproducible. Trial randomization increases the number of patients required for studies in several cancer types. Additionally, it is impossible to effectively blind the operating surgeon, who would most certainly realize when optical imaging was being utilized. An intra-patient controlled study can be adequately designed to test the hypothesis that the optical technique provides additional information that contributes to the tactile or visual information provided by standard of care. To tackle these problems the FDA established a recommendation panel. An example of a clinical setting where an intra-patient control study can be used successfully is a study of primary breast cancer resection. A pre-specification of optical agent diagnostic performance and definition of the meaningful improvement to be achieved by the investigational product in the clinical trials need to be defined in the clinical protocol before study initiation.

FUNDING AND RESOURCES AT NCI FOR MOLECULAR IMAGING AGENTS

The NIH and NCI have resources available to support molecular imaging research. Only funding specifically for imaging will be discussed here. Some grant opportunities for early phase clinical trials are available for image-guided drug delivery, for combination of pre-clinical and clinical studies, and for collaborations between academia and industry to translate imaging systems for cancer imaging. Additionally, there are the SBIRs and STTRs for industry support. More extensive information can be found at the NIH website[42] and special imaging grant opportunities are listed at: http://imaging.cancer.gov/

researchfunding/fundingopportunities/currentcip. The NCI also has the NExT program for alleviating the substantial resource strain required to translate experimental therapeutics into the clinic. This program provides access to NCI recourses and expertise.[43]

For late Phase II and Phase III trials, the NCI has the NCI National Clinical Trial Network (NTCN) to conduct large-scale clinical trials. The ECOG-ACRIN group is specialized in imaging.[44] Lastly the NCI can provide help in regulatory issues and provide resources during pre-submission phases. It is also important to note that the nanocharacterization lab (NCL) can be a useful resource for nanoparticle based agents and is an important resource within the NIH.[45]

CONSIDERATIONS

Reimbursement by the CMS for optical imaging is an important consideration for industry investment. Traditionally, this is initiated after FDA approval has been granted. The goal of CMS is to assess whether new technologies are reasonable and necessary. Therefore, they may require patient and cost-effectiveness outcome data. In contrast, the FDA has a different responsibility when evaluating new technologies, namely assessing safety and effectiveness. However, the FDA can assist in designing trials in collaboration with CMS to additionally assess those outcomes.

There was consensus that target-specific imaging agents are the most likely to have a long-term benefit when compared to non-specific agents like indocyanine green. However, the general opinion was that the field should first focus on more generalizable agents so as to expand the technique using fluorescent guidance beyond purely surgical applications. Clinical translation must be efficient, but it is rather unlikely that multiple agents will be approved in a timely manner. It is important to note that continued education of the CMS is likely necessary in considering molecular imaging agents, which has been the case for many years with the FDA regarding such agents. Lack of CMS reimbursement will be a key factor in hindering the widespread use of molecular imaging agents for intraoperative imaging. Thus, a consortium that includes professional societies, industry, NIH, and private foundations will be important to better educate

the CMS and ultimately obtain reimbursement for specific molecular imaging agents.

When considering improvement of the approval process for devices and agents, regulatory and commercial incentives must be taken into account. While decoupling agents and devices would certainly aid in the advancement of optical imaging, this may not be in the economic interests of the manufacturers. The reason for this may not be solely financial, but also safety driven. When devices and drugs are coupled, a rigorous safety profile must be established, which is further associated with a higher regulatory burden.

CONCLUSION

The ultimate goal of NIR-fluorescent contrast-enhanced oncologic surgery is to provide information to the surgeon that lies beyond that of the visible light spectrum and amplify contrast enhancement in different tissue types. By improving visual detection of tumors, the surgeon gains critical information that can translate to improved overall outcomes for the patient. Since optical imaging techniques lead to real-time feedback, there is a direct and instantaneous effect on patient care and decision-making. While this is one of the main advantages of contrast-enhanced oncologic resection, it nonetheless requires proof of benefit to the patient. Thus, the field must clearly demonstrate the benefit in clinical trials and thoroughly assess relevant outcomes. The investigational imaging agent/device's proposed "indication for use" will direct all future studies needed for approval and, therefore, should be chosen carefully. Lastly, the use of predicate devices and agents, when available, should help accelerate the eventual approval of new optical imaging technology.

Summary statements
1. Contrast-enhanced surgery should be considered a complementary technique for the surgeon rather than a diagnostic tool. This technique is used to provide additional information to assist the surgeon in making clinical decisions to improve procedural outcomes.
2. Proving performance equality in different imaging devices (as in PET imaging) is critical to demonstrate so that imaging agents may be used on multiple devices.
3. Identifying a predicate device can help guide the approval pathway for a new or equivalent device.
4. If an optical imaging system is intended for the diagnosis, prognosis, or treatment of cancer during an investigational human study, such use is determined to be "significant risk" and FDA requires the study sponsor to file an Investigational Device Exemption (IDE) application.
5. Optical imaging products are traditionally viewed as combination products by the FDA.
6. Additional toxicity of imaging agents should be well justified by the benefit since the invasiveness of procedure does not factor into the FDA classification considerations.
7. Clinical trials must be designed to obtain safety and efficacy data for the intended indication of use.
8. If the sponsor wants a drug to be indicated for use with multiple devices, there must be technical and clinical data available to support the use of multiple devices.
9. Clinical trials must prove patient benefit before FDA approval can be obtained since optical imaging inevitably influences patient care and decision making in real-time.
10. The FDA does not specifically require direct measurement of survival endpoints to show benefit for the contrast-enhanced surgery indication. It can be sufficient to show improved detection of positive margins when the new technology is used, since the correlation between clear margins and survival is already well established for many types of cancer.

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