Developing Drugs for Optical Imaging
Guidance for Industry

DRAFT GUIDANCE

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to provide recommendations to sponsors regarding clinical trial design features that support development and approval of optical imaging drugs that are used in conjunction with imaging devices and intended as intraoperative aids for detection of pathology such as tumors or to enhance the conspicuity of normal anatomical structures.[2]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Optical imaging is defined in this guidance as the use of light in conjunction with imaging drugs and devices during medical procedures to aid in the detection of tumors or other pathology and delineation of normal anatomical structures. This guidance is necessary because of the burgeoning interest in the development of novel optical imaging drugs and imaging devices to assist standard surgical procedures in a variety of clinical contexts. Surgeons use these imaging drugs with imaging devices during surgery to assist the direct visual inspection and palpation of tissue in the surgical field. The imaging drugs, for example, enhance the ability of the surgeon to distinguish tumors from normal tissue. Therefore, the drugs can increase the likelihood of safe and complete removal of cancers and can minimize the risk of unintended injury to normal anatomical structures. The increasing use of minimally invasive and robotic surgical approaches is a contributing factor driving the development of optical imaging

[1] This guidance has been prepared by the Division of Imaging and Radiation Medicine in the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health at the Food and Drug Administration.

[2] For purposes of this guidance, unless otherwise specified, references to *drugs* include drugs submitted for approval or approved under section 505(b) or (j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and biological products submitted for licensure or licensed under section 351 of the Public Health Service Act, other than biological products that also meet the definition of a device in section 201(h) of the FD&C Act (21 U.S.C. 321(h)).

products because of the loss of tactile perception and a more limited field of view with these procedures.

Optical imaging uses light of a wide spectral range spanning from visible to near-infrared (NIR). Some optical imaging drugs (e.g., indigo carmine) are dyes that can be directly visualized under white light, whereas others contain a fluorescent moiety called a fluorophore that must be excited by specific wavelengths of light before they emit light that can be visualized. Some optical imaging drugs target cancers or the associated microenvironment through mechanisms including ligand binding to specific receptors that are overexpressed by neoplastic cells or accumulation in tumors due to a unique microenvironment attribute, such as lowered pH or increased proteolytic activity. In other circumstances, optical imaging drugs delineate normal or abnormal anatomy by excretion in the urine or bile or by physiological transit through the vascular system, lymphatic system, or gastrointestinal tract.

Optical imaging during oncologic surgery aims to optimize tumor resection by enabling enhanced tumor removal while minimizing resection of normal tissue. For primary solid tumors, complete resection with negative tumor margins is often necessary for curative treatment. In this setting, incomplete resection with positive margins or close margins (i.e., cancer cells within a certain distance from the edge of resected tissue) is associated with poorer clinical outcomes. In clinical settings where surgical debulking is indicated (e.g., metastatic ovarian cancer or high-grade glioma), optical imaging–guided surgery can aid the removal of an optimal amount of tumor tissue while minimizing resection of normal tissue.

This guidance focuses on the use of optical imaging for the following purposes:

- Detection of tumor
    a. Surgery with curative intent (e.g., breast-conserving surgery (BCS))
    b. Surgery for debulking and cytoreduction (e.g., metastatic ovarian cancer, high-grade gliomas)
    c. Endoscopic resection of neoplasm (e.g., nonmuscle invasive bladder carcinoma)
- Lymph node staging
    a. Lymphatic mapping
    b. Sentinel lymph node identification
- Enhanced delineation of normal anatomy to decrease risk of injury
    a. Ureters or bile ducts in abdominopelvic surgery
    b. Nerve structures in head and neck surgery

Optical imaging drugs generally are governed by the same regulations as other drugs. FDA recommendations intended to assist developers of other medical imaging drugs in planning and

coordinating their clinical investigations and preparing and submitting their investigational new drug applications, new drug applications, biologics license applications, abbreviated new drug applications, and supplements to new drug applications or biologics license applications are also applicable to optical imaging drugs.[3] Optical imaging drugs are generally used with an optical imaging device. The Center for Devices and Radiological Health has oversight of imaging devices.

III. KEY CONSIDERATIONS FOR CLINICAL TRIALS

A. Trial Population

The trial population should be consistent with the intended clinical use (i.e., patients who are candidates for the medical procedure in which the optical imaging drug is used) with adequate characterization of disease status (e.g., clinical tumor staging and expression of tumor markers).

B. Trial Design

1. Intrasubject Control Design

In some clinical contexts, an intrasubject study design may be considered. An intrasubject control for efficacy trials can be used to test the hypothesis that optical imaging provides additional information beyond the tactile and visual perception achieved with standard-of-care (SOC) practice. This approach is efficient because it internally controls for variability due to individual subject characteristics, including pathology or anatomy. For an intrasubject control trial design, the surgical procedure is typically performed using the SOC procedure, with tumor status assessed by SOC methods at that point, and then completed with the aid of optical imaging. Examples of clinical settings suitable to evaluate the added value of optical imaging include detection of residual tumor in BCS or cystoscopic detection of nonmuscle invasive papillary cancer of the bladder (see sections below).

An intrasubject control design may also be applicable for drugs intended to improve visualization of normal anatomy (e.g., visualization of the urinary tract during pelvic surgery, see section III.C.2.c.i. below) when assessment of the level of visualization is possible using quantitative or qualitative scales and a parallel-arm study to show a decrease in injury is infeasible due to the rarity of surgical complications.

[3] See the guidances for industry *Developing Medical Imaging Drug and Biological Products Part 1: Conducting Safety Assessments* (June 2004), *Developing Medical Imaging Drug and Biological Products Part 2: Clinical Indications* (June 2004), and *Developing Medical Imaging Drug and Biological Products Part 3: Design, Analysis, and Interpretation of Clinical Studies* (June 2004). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

2. Parallel-Arm Control Design

Settings in which a parallel-arm control design should be considered include those in which:

- The value of enhanced conspicuity of tumor or normal structures is not established in a general clinical setting and clinical outcome data are needed.
- Demonstration of decreased complication rate with the optical imaging drug relative to SOC is feasible (e.g., nerve injury following radical prostatectomy or surgery for head and neck cancers).
- Sequential SOC evaluation followed by optical imaging is otherwise infeasible.

Clinical data collected in parallel-arm control studies might include adequacy of tumor resection, acute and delayed surgical complications, tumor recurrence, re-resection rate, and patient-reported outcomes such as cosmesis in BCS.

In a parallel-arm control design, the safety profile of a drug can be directly compared with a placebo or SOC. Although the safety profile of a drug can also be assessed in an intrasubject control design, comparison to placebo or SOC is recommended if serious safety risks posed by the investigational drug are anticipated and need to be rigorously characterized to make benefit-risk assessments.

C. Efficacy Considerations

1. General Considerations for Efficacy Endpoints

Evidence of effectiveness is intended to show that the imaging drug will provide a clinically meaningful benefit in a well-defined clinical setting and patient population. For example, an investigational optical imaging drug may be able to detect additional sites of metastatic tumor or residual primary tumor that result in changes in surgical results (e.g., extent of tumor resection) and can affect patient outcomes (e.g., recurrence rates, disease-free survival, overall survival).

Additional considerations for efficacy endpoints of optical imaging drugs intended to detect pathology include the following:

- Early in development, the false positive and false negative rates of the optical imaging drug against immunohistochemistry (IHC) or histopathology should be measured to establish performance thresholds.
- In settings where IHC is being proposed to confirm the expression of tissue targets for optical imaging drugs, FDA-cleared or similarly validated IHC methodology should be used.[4]

[4] See the guidance for industry *Guidance for Submission of Immunohistochemistry Applications to the Food and Drug Administration* (June 1998).

- Evaluation of tumor targeting should be performed in patients with various histological subtypes of cancer and correlated to the degree of target expression. Studies of the drug should be limited to subtypes with adequate imaging characteristics.

- The diagnostic performance to be achieved by the investigational drug in phase 3 trials should be prespecified in the clinical protocol and the statistical analysis plan. The prespecified performance thresholds should be clinically meaningful and scientifically justified.

- Histopathology is generally used as the standard of truth for measuring diagnostic performance. In the absence of a histopathological truth standard, a combination of clinical testing data and patient follow-up can be used as a reference standard. For example, when a biopsy of lesions is not feasible to verify tumor detection, follow-up of lesion size on imaging, monitoring serum biomarkers levels such as prostate specific antigen, and clinical outcome data can be used as a reference standard.

- An assessment of the nonmalignant tissue removed as a result of optical imaging with the investigational drug should be made to determine a false positive rate measured at a lesion level and a subject level. Generally, lesion-level analyses provide a direct estimate of drug performance, whereas subject-level analyses provide estimates of harm (or benefit) in an individual patient.

2. Specific Considerations for Efficacy Endpoints

The following considerations take into account common types of surgical oncology procedures where optical imaging drugs might be used to improve current SOC procedures.

a. Tumor resection

For indication as an aid in tumor resection, the study should aim to show that detection and removal of a tumor with optical imaging is significantly improved as compared with SOC procedures. Examples of procedures to remove a tumor in which optical imaging may be employed are described below with recommended endpoints.

i. Decrease in the positive tumor margin rate

In clinical settings where the presence of positive margins directly affects patient management, the trial should aim to show a reduction of the positive margin rate with use of the optical imaging drug as compared with SOC resection. One such clinical setting is BCS, where positive margins may result in a second surgery for the patient or a radiation therapy boost.

The following co-primary endpoints are recommended for drugs being developed to detect residual cancer in the BCS cavity using an intrasubject design:

- Conversion rate defined as the proportion of patients who had one or more positive margins after SOC surgery who then have fully negative margins after use of the optical imaging product, among all patients imaged.

- Tissue-level sensitivity and specificity (diagnostic performance) of the optical imaging assessments performed during surgery. Imaging assessments of particular interest are those performed immediately after the completion of SOC surgery and after the completion of surgery with the use of optical imaging.

Patient-level sensitivity and specificity are also recommended as endpoints of interest. In BCS, histopathology results are generally reported by orientation or the anatomical location of a given margin within the patient. Therefore, in the BCS setting, patient-level diagnostic performance should be based on the imaging and histopathological results of all the margin orientations of the resection cavity. The outermost face of tissue resected from a margin determines whether a corresponding margin orientation is positive or negative. A method of converting tissue-level data to patient-level data should be proposed and justified.

Capture of the average volume of tissue excised with SOC or optical imaging is recommended to evaluate the extent of the optical imaging-guided procedure.

ii. Tumor debulking for cytoreduction

The use of optical imaging for tumor debulking is well-established in a number of clinical settings where tumor identification enhances adequacy of safe resection and debulking to maximize the efficacy of adjuvant treatment (e.g., metastatic ovarian cancer or high-grade glioma). In these settings, the aim is to optimally and safely reduce tumor burden. The role of intraoperative optical imaging is to identify fluorescence-positive tumors that can be resected without compromising normal tissue or function. If prior evidence demonstrates the clinical benefit of debulking surgery, it may be sufficient to show that resection with optical imaging adds value over SOC surgery without compromising safety.

As such, the recommended primary efficacy endpoint in the tumor debulking setting is the proportion of patients undergoing cancer removal surgery with at least one evaluable pathology-confirmed cancer lesion detected using an optical imaging drug that was not detected by SOC such as palpation and visual inspection. The proportion of study subjects with only false positive detections out of all subjects imaged is recommended as a secondary endpoint. This endpoint is intended to assess the potential for incorrect identification of normal tissues in the surgical field as tumor.

iii. Endoscopic detection of neoplasms

In the setting of endoscopic detection of neoplastic or preneoplastic lesions (e.g., colonic adenomas or bladder nonmuscle invasive papillary cancer), an intrasubject or parallel-arm trial design may be considered. An intrasubject design is suitable if SOC procedures can be assessed first and then followed by optical imaging procedures.

In an intrasubject control design, consider an efficacy endpoint that captures additional detections by optical imaging beyond those identified by SOC at the lesion level or subject level. The numbers of lesions and the percentages of patients with lesions detected by SOC only, by optical imaging only, and by both SOC and optical imaging are also endpoints of clinical interest.

In a parallel-arm control design, patient-level detection rate (e.g., proportion of patients with lesion detection) is the recommended primary efficacy endpoint based on comparison between arms.

b. Surgical evaluation of lymph node metastasis

For many cancer types, the presence of regional lymph node metastases has a major influence on clinical management of a patient and patient outcome. Regional lymph node dissection (LND) to detect clinically occult nodal disease can cause significant morbidity (e.g., nerve injury, lymphedema). In some cancer types, such as breast cancer and melanoma, sentinel lymph node biopsy (SLNB) has replaced elective LND as the initial procedure for staging of nodal disease. In an SLNB procedure, a radiotracer or an optical imaging drug is locally injected at the site of the primary tumor with the goal of identifying the first draining lymph node(s), as these lymph nodes have the highest likelihood of harboring tumor metastases. A positive SLNB (i.e., lymph node removed during the procedure is found to contain cancer by histopathology) may affect patient management.

Two indications may be considered for optical imaging products intended for use in the intraoperative evaluation of lymph node metastasis: (1) lymphatic mapping and (2) guidance of SLNB.

i. Lymphatic mapping indication

For this indication, the recommended primary efficacy endpoint is the node-level detection rate, defined as the proportion of excised, histologically confirmed lymph nodes identified by the lymphatic mapping drug among the total number of histologically confirmed lymph nodes excised using all identification methods combined, including lymph nodes excised due to clinical suspicion. The patient-level detection rate, defined as the proportion of patients in whom at least one node is detected by the lymphatic mapping product among all patients in whom lymphatic mapping is performed, is recommended as a secondary endpoint.

For the primary efficacy analysis, the performance of the investigational optical imaging drug can be demonstrated by hypothesis testing against a prespecified and clinically justified performance threshold. Alternatively, the node-level detection rate using an investigational optical imaging drug can be compared with the rate using an approved lymphatic mapping drug.

The false detection rate is recommended as a secondary efficacy endpoint. This endpoint is intended to capture the potential for incorrect identification of other tissues in the surgical field as lymph nodes with use of the optical imaging drug. It can be defined as the proportion of histologically confirmed non-lymph nodes identified by the lymphatic mapping drug among the total number of collected specimens identified by the drug. Other recommended secondary endpoints include the mean number of nodes detected by the lymphatic mapping drug per patient and the proportion of patients without node detections.

ii. Indication to guide SLNB

For this indication, the investigational optical imaging drug performance is evaluated against the reference standard of histopathology (i.e., presence of cancer) from regional LND. Evaluation of optical imaging performance against a comparator is not needed.

The recommended primary endpoint is the patient-level false negative rate for cancer, defined as the proportion of patients for whom the optical imaging drug did not detect any cancer-positive nodes out of those patients with cancer-positive nodes identified by regional LND.

c. Delineation of vital anatomical structures

The role of optical imaging for this type of indication is to minimize inadvertent injury to vital organs and tissues by facilitating their identification during surgery. Support for an indication of delineation of anatomy generally involves intrasubject comparison of the conspicuity of the normal structure of interest without and with optical imaging. A specific indication for prevention of injury would require additional patient outcome data.

i. Delineation of ureters or bile ducts in abdominopelvic surgery

For this indication, an optical imaging drug is excreted in urine or bile to improve visualization parameters such as border delineation of ureters or bile ducts relative to SOC visualization. Conspicuity of urinary efflux from the ureteric orifices when observed through cystoscopy is another potential visualization parameter. These parameters are assessed using ordinal scales and an intrasubject design. All scoring should include a comparison between conspicuity without (baseline) and with the optical imaging. Standardization of ratings can be achieved by developing a training manual with examples of various levels of conspicuity of the structure of interest for each point in the scales. Evaluation of the level of agreement in scoring between different raters (e.g., operating surgeon and blinded central rater and intra-rater agreement) is useful to validate the scoring method.

Additional considerations for delineation of ureters or bile ducts in abdominopelvic surgery include the following:

- For minimization of bias, use of blinded, independent, central rating with access to digital images is recommended. Based on the context of use, either the assessment by the operating surgeon or the blinded raters may be designated as the primary efficacy endpoint. In either case, a formal assessment of the level of concordance between the two should be prespecified in the study protocol.

- Assessment of the level of conspicuity between the anatomical region of interest and the surrounding tissue by measurement of the signal-to-background ratio is recommended.

- Examining the duration of structure visualization with optical imaging over multiple time points during surgery is recommended.

- Where feasible, based on the incidence of iatrogenic injury, parallel-arm studies could be designed to evaluate the rate of surgical complications by comparison between SOC surgery and surgery with the use of the optical imaging drug. The assessment of injury should be performed in the intra- and postoperative periods. Patient follow-up evaluations to capture late manifestations of surgical complications are recommended.

ii. Delineation of cranial and peripheral nerves

During surgery in any anatomical region, accidental injury to critical nerves might occur resulting in immediate or late nerve dysfunction. This is particularly important in surgeries involving the head and neck region and is not exclusive to oncologic surgeries. The rates of acute and chronic dysfunction can vary based on the anatomical region and the specific nerve. For example, facial nerve dysfunction rates following parotidectomy can be sufficiently high to permit comparison of complication rates in a parallel-arm trial.

With optical imaging drugs that show uptake in nerve tissue, delineation of the nerves in the surgical field can be assessed not only by conspicuity but also extent (length) and branching patterns. Intrasubject comparison of SOC surgery and surgery with the use of an optical imaging drug is recommended using a composite ordinal nerve-visualization scale that assesses the contrast between nerve and surrounding tissue and the ability to measure the length and delineation of nerve branching.

In addition, see discussion in section III.C.2.c.i. of this guidance regarding visualization scales and documentation of injury, as these recommendations also apply to delineation of cranial and peripheral nerves.

d. Intraoperative fluorescence angiography

The intraoperative delineation of vascular structures and assessment of tissue perfusion might assist the surgical oncologist as well as the plastic and reconstructive surgeon to minimize risk of surgical complications. Examples of the adjunctive use of fluorescence angiography would be the assessment of anastomotic perfusion following bowel resection for malignancy and assessment of perfusion of surgical flaps in certain oncologic reconstructive procedures. The surgical complications include anastomotic leak in the former case and tissue or flap necrosis with wound dehiscence in the latter. A parallel-arm randomized study comparing complication rates in the fluorescence-guided arm to the SOC surgery alone arm would be necessary if the utility of intraoperative fluorescence angiography in a specific setting is not well established.

3. Other Trial Design and Statistical Considerations

This section includes important statistical considerations for the design of adequate and well-controlled clinical trials for optical imaging drugs.

At the time of study planning, the primary estimand that addresses the clinical question of primary interest should be defined. Randomization and blinding are critical aspects of an adequate and well-controlled study that facilitate minimization of potential bias, particularly in intraoperative optical imaging drug development for surgical oncology, where the site of interest is visually identified.

a. Randomization and blinding considerations

Blinding an imaging rater to the use of an optical imaging drug is generally not feasible. For instance, the surgeon or operator performing the procedure is typically aware that they are using SOC methods, active comparators, or investigational optical imaging techniques. The below randomization techniques

can reduce potential bias during imaging evaluation despite lack of blinding to the optical imaging drug.

In an intrasubject control design, randomization aims to minimize the potential of surgeons underperforming using SOC methods (the first part of the procedure) due to knowledge of another opportunity to intervene in the second part of the procedure using optical imaging.

- In an intrasubject trial design in which SOC resection of tumor occurs before optical imaging, for the purpose of minimizing bias, subjects should be randomized to either an SOC arm or an SOC plus optical imaging arm. Rationale should be provided for the proposed randomization ratio. All eligible subjects receive the study drug before the start of surgery, and the surgeon should open the randomization code only after the SOC procedure is complete to determine whether to perform further surgery that relies on optical imaging. Alternatively, for the purpose of minimizing bias, randomization to either a group receiving optical imaging drug followed by SOC and then optical imaging or a group receiving placebo followed by SOC only may be considered.

  In more complex settings where the surgeon needs to alternate between the optical imaging technique and SOC, sponsors are encouraged to communicate with FDA early in product development.

- In an intrasubject trial design that employs an active comparator, the sequence of the imaging drug administration can be randomized. However, if randomization of the imaging drug administration is not feasible, randomizing the sequence of the imaging drug evaluation should be considered. The order of administration or evaluation should be guided by the pharmacokinetics and pharmacodynamics of both drugs. If none of these randomization approaches is feasible, a fixed order of evaluation should be employed such that the investigational imaging drug is not given an advantage.

For a parallel-arm control design, simple randomization, blocked randomization, and stratified randomization are some commonly used approaches. When an important confounding factor exists (e.g., longer procedure times with the investigational imaging technique possibly contributing to improved detection of pathology), exploratory analysis to evaluate the impact of differential procedure time between the two study arms is recommended. In such cases, a carefully planned statistical analysis based on the confounding factor may provide additional information on the efficacy of the investigational imaging drug.

Additionally, blinding to patient clinical information can be achieved through use of an independent rater who does not perform the procedure but assesses imaging captured from selected aspects of the surgical procedure without access to other patient data. Review of histopathology or other reference standard data by personnel blinded to the investigational imaging results is also recommended to minimize potential bias and ensure the objectivity of the reference standard assessment.

b. Reader agreement

For trials with primary efficacy analysis based on images assessed by surgeons, the images should also be assessed by independent raters blinded to patient clinical information; similarly, for studies with

primary efficacy analysis based on image reads by independent raters, images should also be assessed by the operating surgeon. The agreement measures with mathematical details and the threshold criteria to be achieved for successful inter- and intra-reader agreement should be prespecified with supporting justification.

c. Intercurrent events and missing data

All subjects who are planned to be imaged with an investigational optical imaging drug should be included in efficacy analyses. However, there may be intercurrent events or missing data that occur after the start of study treatment and affect the interpretability of the study results. For example, not all subjects in this intent-to-image set may have undergone image-guided surgery or may have reference standard data collected or interpretable. In addition, there may be an incomplete administration of an imaging drug due to a serious adverse reaction (e.g., anaphylaxis or other hypersensitivity reaction), unevaluable imaging scan results, limitation of biopsy (e.g., imaging might inform about the need or feasibility of a biopsy), or failed or uninterpretable histopathology evaluation for a reference standard. Intercurrent events affect the interpretability of the treatment effect estimates. Missing data are data that would be meaningful for the analysis of an estimand of an imaging drug effect but are not collected.

The primary strategy for handling intercurrent events and the primary method for imputing missing data should be prespecified as part of the primary analysis for evaluating the optical imaging drug effect on the primary efficacy endpoint. The intercurrent events handling should be based on event type. The missing data approach should incorporate the reason for missingness. Optical imaging drug sponsors are encouraged to prespecify one or more sensitivity analyses in addition to the primary analysis to assess the robustness of the imaging drug effect estimate.

d. Sample size

Sample size planning for a parallel-arm control design is generally based on the postulated effect size of an investigational imaging drug relative to its comparator on the primary efficacy endpoint. With an intrasubject control design, the effect size of interest is the average effect of adding an investigational imaging drug to SOC for all subjects studied in the investigational arm. The sample size of the SOC-alone arm depends on the proposed randomization ratio.

When the primary efficacy endpoint is at a more granular level than patient-level (e.g., node-level detection rate), sample size planning and planned statistical analyses can account for the correlation within a patient. For efficacy endpoints intended for labeling consideration, sample size should be sufficiently powered at the design stage.

B. Safety Considerations

The following are points to consider regarding potential toxicities and the maintenance of standard surgical management of study subjects in early phases of optical imaging product development.

- Optical imaging drugs with potential for phototoxicity (e.g., aminolevulinic acid hydrochloride) necessitate special risk-minimization procedures in the clinical trials, including reducing exposure

of subjects to ultraviolet and room lights, avoiding concomitant use of other phototoxic drugs, and monitoring for dermatologic and systemic phototoxic reactions.

- Other potential optical imaging drug toxicities include photothermal effects and light-induced generation of reactive oxygen species that may cause genotoxicity and mutagenicity. These risks are evaluated during nonclinical studies.

- In phase 1 and phase 2 studies, the investigational optical imaging drug should not guide clinical decisions and should not interfere with established practice standards. Following the demonstration of acceptable performance of the investigational product, efficacy studies are designed to assess the clinical performance and utility of the drug.

GLOSSARY

Immunohistochemistry (IHC): Immunohistochemistry uses antibodies to selectively stain for the presence of certain targets in tissues (e.g., estrogen receptors on cells, enzymes in the tumor microenvironment, etc.). Staining intensity is graded and reflects the density of target molecules in tissues.

Near-Infrared (NIR) Fluorescence: NIR fluorescence relies on the NIR region of the electromagnetic spectrum (from 780 nm to 2500 nm) for excitation and emission of certain optical imaging drugs. Intraoperative exposure to NIR light allows the identification and localization of such drugs.

Reference Standard: When a truth standard is not available, a reference standard may be used to validate the imaging results of an investigational drug through measures including clinical assessments and other testing results.

Standard of Care (SOC): Standard of care is defined by the National Cancer Institute as treatment that is accepted by medical experts as proper treatment for a certain type of disease and that is widely used by healthcare professionals.[5]

Truth Standard: A truth standard is an independent method of measuring the same variable being measured by the investigational drug and is known or believed to give the true status of a clinical condition. Truth standards can be used to assess the diagnostic performance of optical imaging drugs. Histopathology is typically used as a truth standard.

White Light: White light is normal room light that is composed of a variety of electromagnetic waves, each with different wavelengths or frequencies. White light is typically used in the operating room. Certain optical imaging drugs (e.g., indigo carmine) are visible under white light without special devices or filters.

[5] Definition from the National Cancer Institute, available at https://www.cancer.gov/publications/dictionaries/cancer-terms/def/standard-of-care.

APPENDIX: OPTICAL IMAGING DEVICE CONSIDERATIONS

Labeling of optical imaging drugs can refer to a specific imaging device or can be device agnostic. A wide range of imaging devices are available that use similar illumination strategies, light sources, detectors, device architectures, and collection geometries, but some are developed for specific surgical uses, and there may be significant differences among them. It is important that all devices used for a specific intraoperative imaging use have adequate performance characteristics for its particular use. At a minimum, imaging device characterization should address the following:

- Field of view
- Focal length and depth
- Illumination and detection wavelength ranges
- Illumination intensity
- Spatial uniformity of the illumination field
- Minimum detectable fluorescence signal
- Spatial uniformity of fluorescence detection
- Clinically meaningful limits of detection of the imaging drug
- Target-to-background ratio as a function of fluorescence signal intensity

Imaging device characterization can be accomplished in most cases by using a phantom for quality control and assurance. If multiple imaging devices are permitted in a clinical study, case report forms should capture the specific device used to allow related subgroup analysis.

For the identification and delineation of fluorescent structures, establishing objective criteria is necessary to standardize use of intraoperative optical imaging technology whether using real-time, intraoperative imaging alone or combined with ex vivo specimen mapping. Through semiquantitative assessment of images with metrics such as target-to-background ratio, optical imaging devices may be used to complement the surgeon’s visual and tactile perception. Semiquantitative analyses are particularly useful for exploratory evaluation purposes and for demonstrating substantial equivalence between optical imaging devices. There should be clearly defined approaches for the semiquantitative assessment of imaging system performance, such as real-time and post-acquisition image analysis, to enhance objectivity.