

Development and Seeking Regulatory Approval for New Contrast Agents

Peter Caravan

caravan@nmr.mgh.harvard.edu

Martinos Center for Biomedical Imaging
Massachusetts General Hospital
and Harvard Medical School



Financial Disclosures

P.C. has equity in Reveal Pharmaceuticals,
Factor 1A, LLC and Collagen Medical, LLC.
Research support from Pfizer, Pliant, Indalo
Consulting income from Guerbet, Bayer

Drawing Heavily From

<https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/ucm092895.htm>

Guidance for Industry

**Developing Medical Imaging Drug and
Biological Products**

Part 1: Conducting Safety Assessments

Guidance for Industry

**Developing Medical Imaging Drug and
Biological Products**

Part 2: Clinical Indications

Guidance for Industry

**Developing Medical Imaging Drug and
Biological Products**

**Part 3: Design, Analysis, and
Interpretation of Clinical Studies**

Types of Medical Imaging Agents

- Contrast agents: compounds that increase the relative difference of signal intensities in adjacent regions of the body to improve visualization of tissues or processes
 - Iodinated compounds used in radiography and CT
 - Paramagnetic complexes (Gd, Mn) or particles (Fe) used in MRI
 - Microbubbles used in diagnostic ultrasonography
 - Detected indirectly
- Diagnostic radiopharmaceuticals: radioactive drug or biological product that contains a radionuclide that emits a gamma ray, and that typically is linked to a ligand or carrier
 - Directly detected by planar imaging, single photon emission computed tomography (SPECT), or positron emission tomography (PET)

General Requirements for Approval

- Medical imaging agents generally are governed by the same regulations as other drugs or biological products.
- Under section 505(d) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(d)), FDA cannot approve a new drug application (NDA) unless adequate tests demonstrating safety are shown.
- All drugs have risks: from intrinsic properties of the drug, the administration process, and incorrect diagnostic information.
- Even if risks are found to be small, all drug development programs must obtain evidence of drug effectiveness
- Simply generating an image, for which the implications to the patient are not understood, does not confer benefits to the patient.

Indications for Imaging Agents (FDA)

- Structure delineation
 - Locating and outlining normal anatomic structures or distinguishing between normal and abnormal anatomy in a defined clinical setting.
- Disease or pathology detection or assessment
 - Detection of disease (diagnosis) or monitoring disease progression
- Functional, physiological, or biochemical assessment
 - E.g. organ perfusion, cardiac wall motion, metabolism of a radiotracer
- Diagnostic or therapeutic patient management
 - Improve patient management decisions, e.g. rule in/out a more invasive diagnostic test
 - Improve patient outcomes when used in a defined clinical setting, such as predict which patients would respond to a particular therapy

Demonstrating efficacy

1. Establish accuracy of the test

- Need sufficient numbers of subjects with and without disease
- Need to test in presence of other conditions that could influence the result or affect the interpretation of the result
- Generally need some sort of truth standard for comparison
- Establish sensitivity, specificity, positive and negative predictive value, and reproducibility of the test
- Data usually analyzed by blinded readers who have no knowledge of the subjects' medical history

2. Establish the clinical value of the test

- May already be established if improving or replacing an existing test
- How would the imaging test change patient management?

Proving efficacy

All truth standards are imperfect

Differences between readers (pathologists or radiologists)

Inherent accuracy of the method

Example: Liver biopsy with histology as truth standard for fibrosis stage (Bannas, Hepatology. 2015; 62:1444–1455)

- MRI of explanted human liver to determine fat fraction

- Comparison to core biopsy in each segment of the liver, 45 biopsies per liver

- High variability in steatosis across the liver. 6.3% of biopsies falsely characterized the steatosis stage

- Higher variability in histology readers than in MRI

Impact of an imperfect truth standard

	True AKI (i.e., tubular injury)		Total
	AKI	No AKI	
AKI according to SCr	180	80	260
No AKI according to SCr	20	720	740
Total	200	800	1000

sensitivity = 90% specificity = 90%

	AKI according to SCr		Total
	AKI	No AKI	
New biomarker positive	180	20	200
New biomarker negative	80	720	800
Total	260	740	1000

apparent sensitivity = 69% apparent specificity = 97%

Abbreviations: SCr, serum creatinine; AKI, acute kidney injury

$$\text{Sens} = \text{TP} / (\text{TP} + \text{FN})$$

$$\text{Spec} = \text{TN} / (\text{TN} + \text{FP})$$

Waikar et al. *Clin Trials*. 2013; 10: 696–700.

(Pre)Clinical Development

- Preclinical safety and efficacy assessments to support an investigational new drug (IND) application
- Phase 1: pharmacokinetic and human safety assessments of a single mass dose, and increasing mass doses
- Phase 2: (i) dose optimization and regimen; (ii) optimizing the imaging protocol and criteria for analysis; (iii) preliminary evidence of efficacy and expanding the safety database; (iv) specific pharmacokinetic and pharmacodynamic questions
- Phase 3: Confirming the principal hypotheses developed in earlier studies, demonstrate efficacy and safety, and validate instructions for use in the intended patient population
- At least 5 years to get to New Drug Application and approval

Contrast Agents vs Radiopharmaceuticals

- Both typically single administration products
- Mass dose to a human is grams for MR contrast agents versus micrograms for radiopharmaceuticals
- Microdose for greatly reduces cost
 - Can make one batch of precursor (few grams)
 - Very abbreviated preclinical safety assessment for acceptance of IND
 - Clinical development requires smaller database (200 – 300) since safety risk is very low
- (Relatively) low barrier to evaluate radiopharmaceutical in patients

Contrast Agent Preclinical Development

- Require expanded acute single dose toxicity in rodent and non-rodent before Phase 1
- Require short term (28 day) repeat dose toxicity in rodent and non-rodent before starting Phase 2
- Depending on the dose, will typically need several kilos of contrast agent manufactured, formulated, and analyzed in a few batches
- High cost to get to human proof of concept

\$2 – 4 Million to initiate human studies

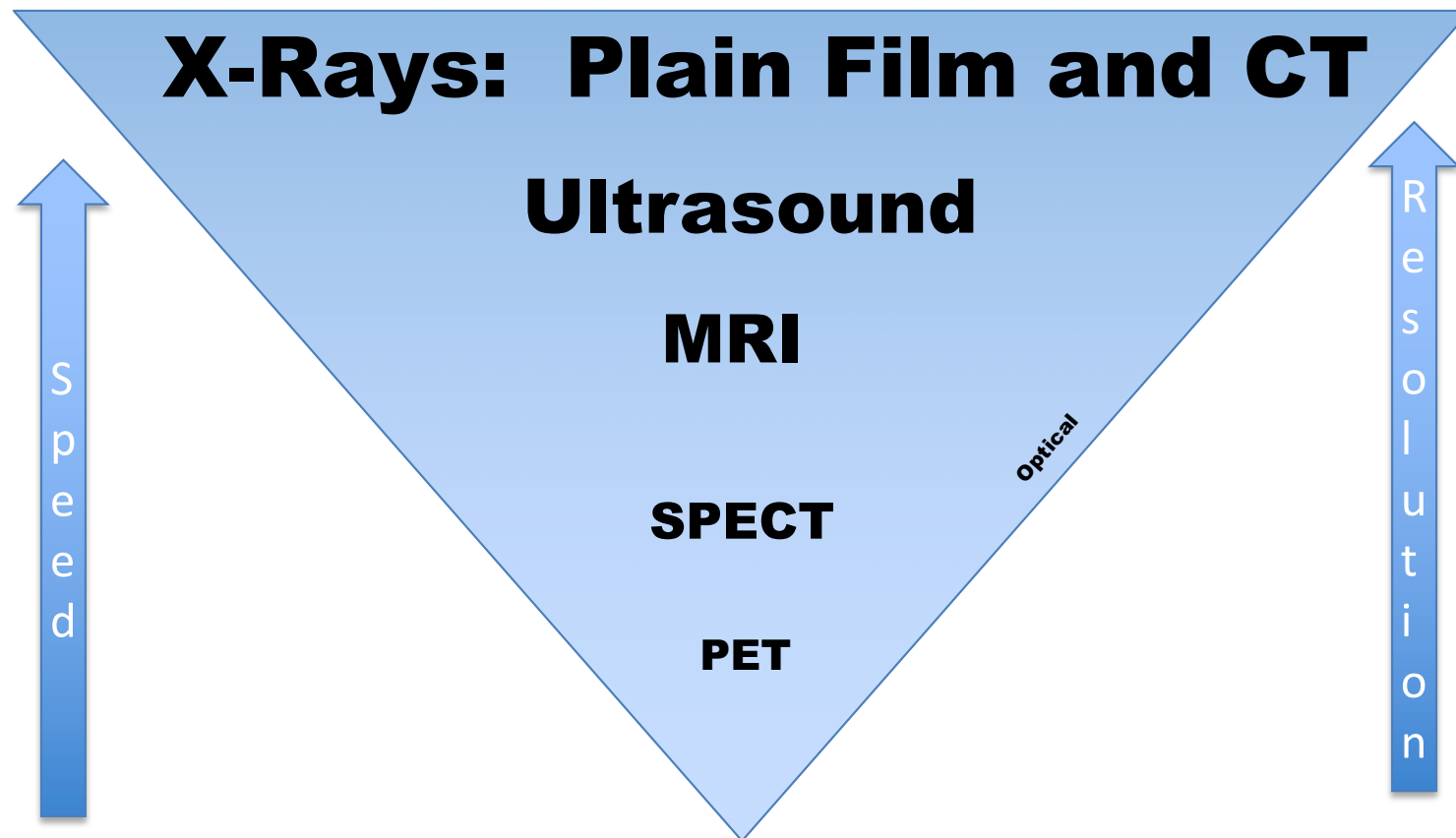
Lack of Private Investment

- Venture capital does not flow to imaging agents
 - Limited number of procedures, typically used once
 - Diagnostic test so a low limit on what payers will pay
 - Generally lower potential market size vs therapeutics
 - Regulatory risk – challenges of imperfect truth standards, increased cost if clinical value must be established
 - Clinical trial risk
 - Lack of recent success stories
- Potential for clinical development partnership with Pharma, e.g. to incorporate the imaging agent into a Phase 2 trial
 - Won't fund preclinical development
- Human POC is a requirement for investment

Why not just focus on PET/SPECT

- Easier path to human POC, lower overall development cost
- Same issues with demonstrating efficacy and viable market
- Fewer procedures, smaller scanner base vs MR, CT, US
- Radiation
- Low resolution in imaging compared to other modalities

Clinical Imaging Utilization



How do we cross the translational chasm?

- Human proof of concept data is key to driving investment
- Preclinical development to obtain an IND for a contrast agent is too costly for traditional academic funding mechanisms
- Development skills generally outside academic know-how
- Directed, milestone driven public funding, that recognizes the need for adequate safety and manufacturing studies?
- Adequately funded bioengineering research partnership (BRP) grants that require multidisciplinary expertise
- SBIR contract funding for specific development
- More effective deployment of programs like SMARTT