Chapter 13
Regulatory Considerations Involved in Imaging

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Abstract Today's revolution in imaging technologies in the biomedical sciences has raised much needed hope for improved diagnostics, therapeutics, and the eventual cure of many debilitating illnesses. Imaging itself has become the seed technology that has fostered the development of many novel diagnostic approaches as well as helping point the way to witnessing the mechanism of action of drugs and biologics. The advancement of new drugs and biologics will be undertaken in the future with surrogate biomarkers, and many of these will be in the form of imaging. Imaging of pharmacodynamic responses to therapies such as changes in RECIST, cerebral glucose utilization, MRI BOLD changes reflecting neurologic activity, and many other novel approaches are opportunities for the imaging community to work with the regulatory community to contribute to the advancement of novel agents. As stated by Dr Steven Larson (2007) "*We are experiencing a paradigm shift from anatomic towards biomarker (molecular imaging) as the primary means for assessing treatment response in oncology*" and as such the regulatory environment for this to happen must be considered and developed to maximize the potential which imaging brings to medical diagnosis and to clinical decision making.

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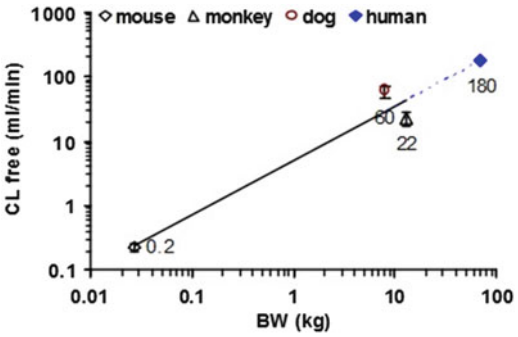

Fig. 13.1 Human clearance of drug "X" relative to other species. Linearity for human and three other species is shown for a log–log relationship of body weight (BW and clearance of free drug Cl-free). A key factor for the best estimation of clearance is the use of the log of the body weight as this provides linearity that covers at least two log range across species. See Chap. 5 in this volume for more detail on the use of clearance in species dose scaling (from Onthank 2005; figure from dissertation; unrestricted)

13.1 The Regulatory Issues in Translational Biology

One of the most confounding issues for the pharmaceutical industry is not at the regulatory approval end of the development spectrum but rather somewhere "in the middle" where costs begin to accelerate, decisions on what is the drug or biologic's market share (potential revenue), what constraints on the indication will be appropriate or required (due to safety findings), and decisions to let go of programs that may have marginal efficacy or too low a therapeutic index (Paul et al. 2010; Muller and Milton 2012).

13.1.1 The Concept of Translational Biology: Predicting Human from Animals

While science rests predominantly on drug development using animal models of disease, including murine genetic knock-in and knock-out models (genetically engineered mouse models; or GEMMs), there has been a long history of skepticism on the relevance of animal models (European Commission, 2010). Although mice share 99% genetic equivalency to man there is still the relationships of gene expressions and the pathologic outcomes may be temporally different from man as well as pharmacologically (receptor affinities, etc). It is important to investigate the prediction of a drug behavior across several species to obtain a linear profile of the drug clearance across those species such that a true estimate of the drug behavior in man may be predicted (Fig. 13.1). Ensuring a range of body weights across selected species is an important factor to consider when applying allometric scaling. If the selected body weights of the species tested have less than a one- to tenfold (1 log)

range, then the value of the extrapolated slope for the estimate is not well defined and the data may skew the determined human value. It is also very important to recognize that in addition to renal flow differences and nephron count in the renal cortex (both are additional allometric parameters for consideration) that can affect rates of drug clearance, some drug elimination rates are a function of *total* drug rather than *free* (unbound) drug concentration in the eliminating region. Changes in drug binding either in blood or in the eliminating region (receptor-mediated clearance) will influence the species clearance from the blood. In the "big picture" of PK across species, it is apparent that tissue binding is far less important in pharmacokinetics than is drug binding to the plasma proteins (Gibaldi and Koup 1981). It thus important to assess protein binding and make corrections to the clearance estimates. In terms of clearance across species, Mordenti (1986) provides a graph showing the linearity of antipyrine clearance versus body weight in 11 species. This relationship across species allows one to do comparative pharmacology and PK studies using this observed relationship as a reference clearance "gold standard." Ritschel and Banerjee (1986) show a similar relationship, as with Mordenti using 11 species, for the volume of distribution (V_β) of antipyrine. Again, a useful "gold standard" for interpreting across species.

From a regulatory perspective, it is prudent to determine the in vitro plasma binding of a drug in several species (including human) in addition to the standard pharmacokinetic parameter estimates as these two considerations form a significant basis for correlation to the human dose. Muller and Milton (2012) describe how to consider plasma protein binding and tissue exposures. We recommend inspection of their paper on the importance of establishing a reliable across species therapeutic index (TI) in drug and especially biologics development. They point out that there is always some likelihood that the in vitro target specificity may not correlate with the therapeutic index. They provide where this is the case where they describe the drug pergolide for Parkinsonism. Pergolide is a dopamine receptor agonist which was found (after approval) to have an additional off-target agonal receptor affinity for the 5-HT_{2b} receptor which was contributing to valvular heart disease complications in some patients. Pergolide has a 36-fold higher affinity for the dopamine receptor than for the 5-HT_{2b} receptor, but in vivo conditions of clearance and overall drug exposure (likely cardiac surface percent flow >> pituitary blood flow) led to an actual therapeutic index of less than 1. For a more current review of dose translation employing body surface area (BSA), we direct the reader to Reagan-Shaw et al. (2007).

Mordenti (1986) provided a log-log plot of multiple species with respect to the logarithm of each species urinary clearance of intrinsic unbound antipyrine (in L/MLP $\times 10^5$), where MLP is maximum lifetime potential in years, vs the logarithm of body weight and demonstrates that this is a highly linear function (r = 0.989) (Fig. 13.2).

Onthank (2005) found in his dissertation that if clearance was taken as the primary PK value, the weight-based allometric scaling, with addition of the protein-binding adjustment, was predictive within 12.5 % based on a retrospective analysis. Work by Tang and Mayersohn (2005a, b) reported predicting human clearance values within 78 % with a method using only rat and human data. They also reported that accuracy using simple allometric scaling was within 323 % and using the rule of exponents

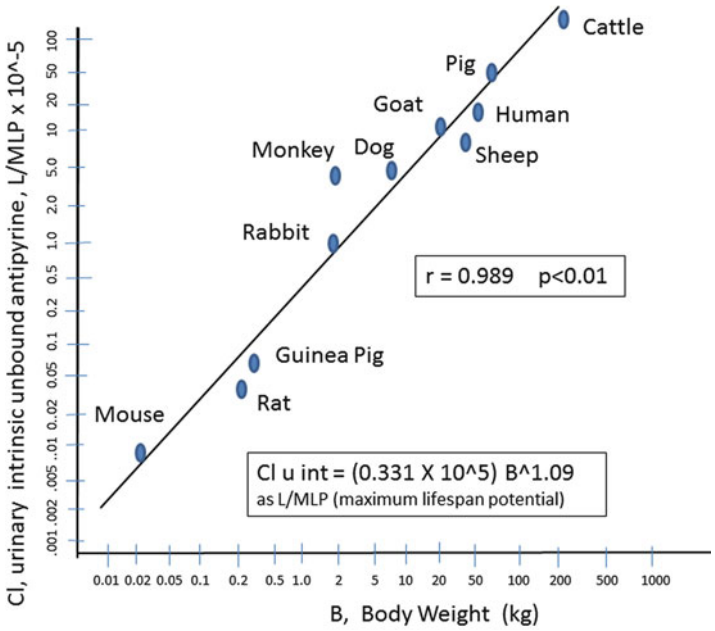

Fig. 13.2 Antipyrine clearance versus BW (kg) versus body weight (BW) over 11 species (log–log plot). Note the similar log–log relationship as was seen for Clearance (from Mordenti 1986; with permission). A similar plot of antipyrine volume of distribution (V_β) versus BW is available from Ritschel and Banerjee (1986)

alone it was within 185 %. Thus, the method of Onthank showing a 12.5 % prediction accuracy based upon clearance and weight-based scaling is an excellent method for providing human clinical dose estimates.

13.1.2 Immunogenicity and Biologics

Immunogenicity, and indeed nearly all drug and biologic toxicologic occurrences, has prompted regulatory attention which has mobilized into specific recommendations and guidance documents (Bass et al. 2011; FDA Guidance for Industry, UCM33856, 2013). Figure 13.3 depicts the history of safety guidance documents over the past 30 years. Imaging is a small part of this as it has generally been in the tracer dose category and thus generally with wide therapeutic indexes. However, of late there has been development of highly biologically active radiotracers and the CT, US, optical, and MR imaging platform industries have been making more biologically active contrast agents which could have deleterious biological activities and thus reasonable suggestion of concern for safety. The development of small radiotracer peptides with exceptionally high (sub-nanomolar) receptor affinities has resulted in products with potentially narrow therapeutic index values. The institution of the Phase "0" trials (see FDA reference: *Exploratory IND studies*, G6384dft.pdf, April

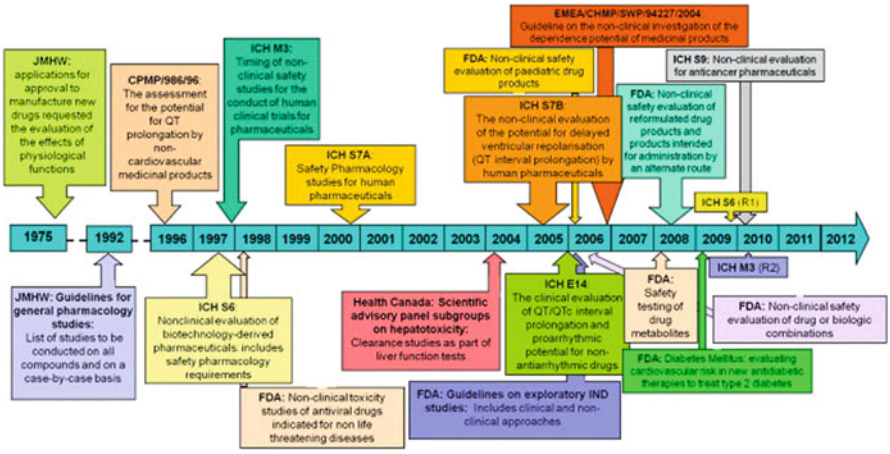

Fig. 13.3 Scope and implementation date of regulatory guidance documents referring entirely or in part to safety pharmacology over the last 30 years. Over the last decade there has been an increase in number and scope of regulatory guidance referring to safety pharmacology end points reflecting increasing regulatory concerns. *FDA* Food and Drug Administration, *ICH* International Conference on Harmonization, *JMHW* Japanese Ministry of Health and Welfare, *FDA* United States Food and Drug Administration, *EMEA* European Agency for the Evaluation of Medicinal Products, *CPMP* Committee on Proprietary and Medicinal Products, *CHMP* Committee on Medicinal Products for Human Use (from Bass et al. 2011, with permission)

2005) allows investigators with purportedly "safe" radiotracers (indeed potentially benign contrast agents as well—documented with GLP toxicology supporting documents) to enter into a dose escalation safety trial. More will be discussed on this post-IND avenue later in the chapter. This kind of early human trial has profound implications in the advancement of new imaging agents and also the potential for use of existing radiotracers and contrast agents with known high therapeutic index values to be employed as companion diagnostics in new clinical indications.

13.1.2.1 The TeGenero Incident: Implications in Imaging

Shankar et al. (2006), as well as Nada and Somberg (2007), has addressed some very important points of scientific as well as regulatory aspects on the immunogenicity of first-in-man (FIM) biologics which have additional implications in their use as diagnostic imaging agents or use as surrogate biomarker end points to explore or defend the efficacy and safety of a biologic. The efficacy and the safety of biologics in human studies has inherent risk with the potential appearance of immune responses. A tragic case of this was the TeGenero TNG1214 incident. Immunogenicity studies are now critical elements of study in the preclinical setting of biologic development following this clinical trial experience. The Nada article is detailed in how clinical trials must change in light of the TeGenero failed FIM dose adjustments.

In 2006 (March 13th) a clinical trial began as a small (<10 patient) Phase 1 trial that was designed based upon preclinical experience. TGN1412 was an agonal

monoclonal antibody (humanized IgG4/kappa) for the human CD28 cell surface marker. As an IgG4 antibody it binds with low affinity to Fc receptors and does not mediate ADCC (antibody-dependent cell-mediated cytotoxicity) or CDC (complement-dependent cytotoxicity) activity. The study was a proposed dose escalation, single IV dose in escalating cohorts covering a 0.1–5 mg/kg dose range. Patients ($n=6$ plus 2 controls) were separated in time for dosing by 10 min. All six patients receiving the lowest dose experienced severe life-threatening toxicities and all within 90 min, and by 21 h all the subjects experienced multiorgan failure (Rellahan 2009).

What are the implications of this biologic, tested in multiple species with general safety assessment sufficient for trial initiation? Clearly this is similar to testing a biologic imaging agent in a Ph "0" trial where the dose is termed "non-efficacious" or even "non-significant" since it binds as a tracer. What are the limits of a safe "tracer dose"? How can we properly test biologics to assure a safe undertaking for a new biologic in the clinic? This is never going to be answered sufficiently for every new product, but there are procedures to give more attention.

The results of the TeGenero incident showed that a 28-day repeated dose study in cynomolgus monkeys gave a NOAEL (no observed adverse event level) of 50 mg/kg—the highest dose to be tested in the clinical setting. Looking closely at the data, however, there were signs of risk. There were elevations in IL-2, IL-6, and IL-5 (an anti-inflammatory) which were dose dependent. There were no signs of TNF-α or INF-γ. The company responsible for the trial saw the rise in IL-2 and IL-6 but was more driven to move the product forward by the observed lack of increases in TNF-α or INF-γ which were considered more important "threat" biomarkers. The long-term consequences of the safety picture were emphasized rather than anything that might occur acutely. Literature sources were known that described the T cell activation in nonhuman primates (NHPs) as muted to that of human but this too was not queried. Lack of toxicity in NHPs does not mean T cell agonists will not be toxic in humans.

An allometric pharmacodynamic response paradigm might well have been useful to consider. There would have been a better prediction of the eventual outcome if the company had not used the NOAEL but rather employed MABEL. MABEL is an acronym for "Minimal Anticipated Biological Effect Level." The intent of the use of MABEL is to more appropriately justify a dose for a biologic effect based upon actual pharmacology –i.e. adjust the dose for anticipated exposure in man by including an anticipated duration of effect which allows for adjustments based upon interspecies differences in product affinity as well as potency. Simms (2009) provides an excellent outline of the TGN1214 analysis for the first dose in man and defined the anticipated safety window based on NOAEL and MABEL appropriate safety factor based on potential risk at 0.001 mg/kg rather than the 0.1 mg/kg (2-log lower) which was the NOAEL-only determination.

Typically, a clinical dose is arrived at as a series of steps (per the FDA Guidances):

- Step 1: Determine "no observed adverse effect level" (NOAEL).
- Step 2: Convert NOAEL to a "human equivalent dose" (HED)—generally normalized to body surface area (BSA).
- Step 3: Select HED from the most appropriate species—additional factors: metabolism, receptors, binding epitopes—*default*: most sensitive species (lowest HED).

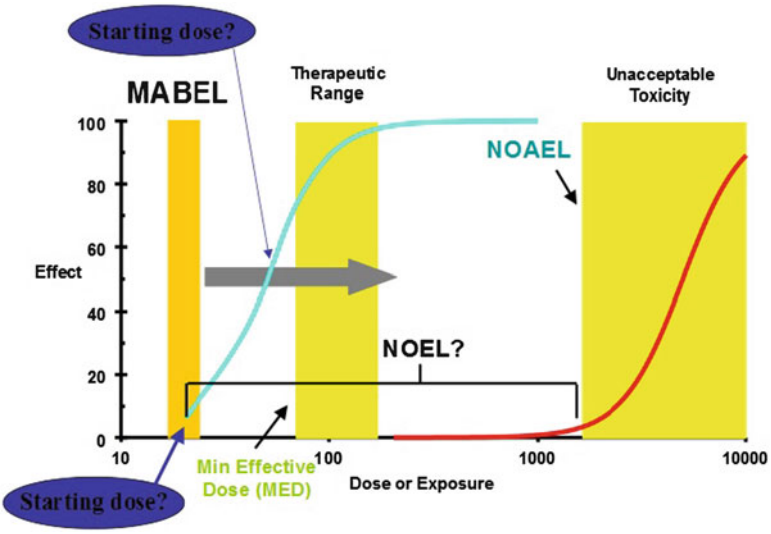

Fig. 13.4 MABEL as an improved paradigm to assist in the decision of a biologic's human starting dose versus the classic approach from NOAEL versus NOEL (no observed event level) methods (from Simms 2009; with permission)

- Step 4: Apply a safety factor (>tenfold) to give a "maximum recommended starting dose" (MRSD).
- Additional NEW STEP using MABEL:
- Step 5: Adjust MRSD based on the pharmacologically active dose.

Clinical first dose, probably more for biologics than drugs, actually needs to change the above paradigm to use the approach provided by MABEL where MABEL asks the question: "why start with the highest dose you think is safe?—Better to start with the lowest dose you think is active." In brief, the decision on the first dose in humans needs to ask about BOTH toxic observations and pharmacologic observations. Figure 13.4 depicts what MABEL actually looks like in the setting of determining the first dose in humans.

13.1.2.2 Companion Diagnostics (CDx) and Imaging

Imaging platforms are fast becoming aids as clinical and non-clinical diagnostic tools for evaluating drug and biologic responses in-vivo (Bocan 2010). In the very near future they will be required as companion tools for identifying and quantifying surrogate endpoints in oncology and a wide variety of diseases (Ellenberg and Hamilton 1989; Carver 2010). Imaging uses in the drug and biologics development arena are being exploited to inform on the risk and benefit of further investment in a candidate drug or in a surrogate biomarker for companion development. An example of a surrogate marker of cancer is circulating tumor cells (CTCs). These cells may offer promise as a surrogate source of representative cells from the

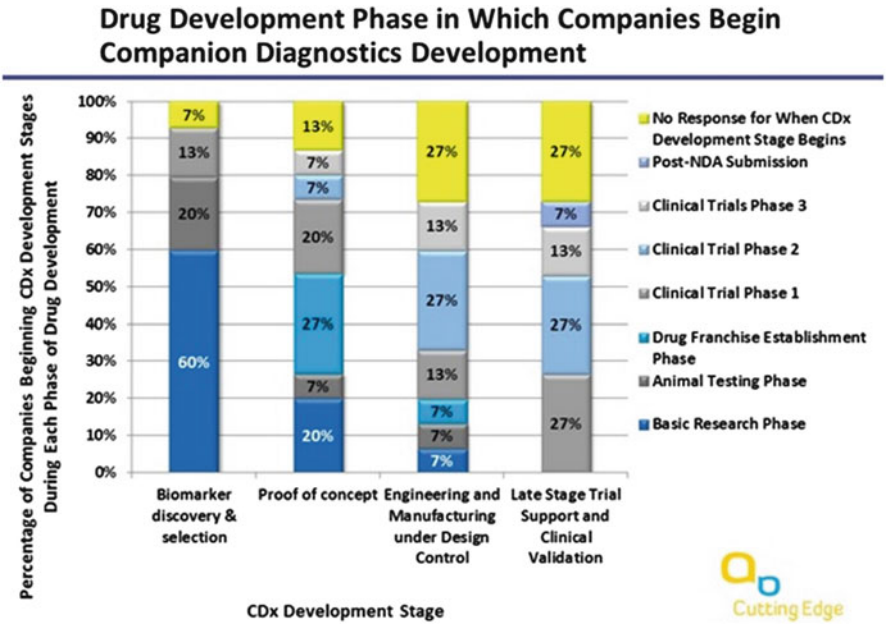

Fig. 13.5 When do companies begin using companion diagnostics? It is apparent that in early discovery 60 % are employing some form of a companion diagnostic for their basic research (likely POS controls), while approximately 40–50 % are using CDx in the animal testing, drug franchising (new companies; or bought by established "Big Pharma"), and thence in Phase 1 (from Cutting Edge Information®, **PH169 Companion Diagnostics and Biomarker Development**; 2012; with permission)

disease that can be obtained in real time and may provide opportunities to evaluate predictive biomarkers, i.e., genetic markers, that can guide treatment decisions. In this review, we consider some of the technical hurdles around surrogate markers such as CTC capture and their analysis platforms for biomarker evaluations but not simply as laboratory assays but as clinically relevant tracking tools that can be employed in imaging and allow the real-time clinical measurements that decide treatment rationale as well as measure treatment success or failure. This chapter will hopefully suggest to the reader novel paths for codevelopment of anticancer therapeutics with image-based diagnostics that could enable clinical validation and qualification of biomarker-based assays as companion diagnostics. Companion diagnostics—tests that provide information about a patient's genetic and genomic characteristics that are used to make therapeutic treatment decisions—hold great promise for "personalizing" medicine and streamlining drug development (Carver 2010).

When are biomarkers explored in the drug development phase as a "companion diagnostics"? In a survey conducted by "Cutting Edge Innovation" (2012), four stages of CDx use were identified: (1) biomarker and discovery, (2) proof of concept (efficacy), (3) engineering and manufacture under design control, and, in (4) late stage trial, support and clinical validation (see web site: http://www.cuttingedgeinfo.com/2012/pharma-stages-new-drug-companion-diagnostic-development/c-5/). The majority of companies begin CDx utilization in early discovery, and this likely is in the form of validating

positive controls. Figure 13.5 depicts the corporate approaches to when they introduce the concept of a companion diagnostic to the primary drug indication.

13.2 Biomarkers and Animal Models: Regulatory Considerations

13.2.1 The Animal Model and Biomarker Qualification Programs at the FDA

It is important to recognize the advancements in regulatory policy at the FDA. Three major "initiatives" over the past several years have made the FDA a true partner in drug discovery, development, and review. The first of these we want to discuss is the "*Critical Path*" *Initiative* dated March of 2004 (and updated 2006; web link: http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/ucm076689.htm). The publication "Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products" identified several reasons for a widening gap in the time between scientific discovery and the appearance of a drug or biologic that changes medical practices. The FDA found that innovations and development of novel medical products were fraught with difficulty and unpredictability (and thus commensurate failure), and the report concluded that the pharmaceutical industry needed to (1) modernize its approaches in the areas of scientific and technical tools and (2) include more advanced information technologies. By implementing actions on these two areas alone, the FDA felt that there would be a significant stimulus to innovation and improve the throughput of drug/biologic evaluations that predict the safety, effectiveness, and manufacturability of medical products.

In March 2006, the FDA's Commissioner announced the release of FDA's Critical Path Opportunities List which resulted from wide public participation. The list described 76 specific areas where the sciences of product development had the greatest need for improvement. The specific areas included genomics, informatics (computer science and statistical techniques), and *imaging*.

Subsequent to the Critical Path Initiative, the FDA has recently launched three important initiatives which have direct connection with imaging. These include qualification programs[1] called the "*Biomarker Qualification Consortium of Best Practices*," the "*Animal Model Qualification Program,*" and the "*Drug Development Tools* (*DDT*) *Qualification Program*." In these initiatives, the FDA actually fosters development in these three directions. The "*Biomarker Qualification Consortium of Best Practices*"[2] offers an opportunity to formally develop and rigorously test a

[1] CDER has developed DDT Qualification Programs directed toward the following types of DDTs: biomarkers, clinical outcome assessments (COAs), and animal models.

[2] Biomarker qualification program: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284076.htm; The Biomarker Qualification

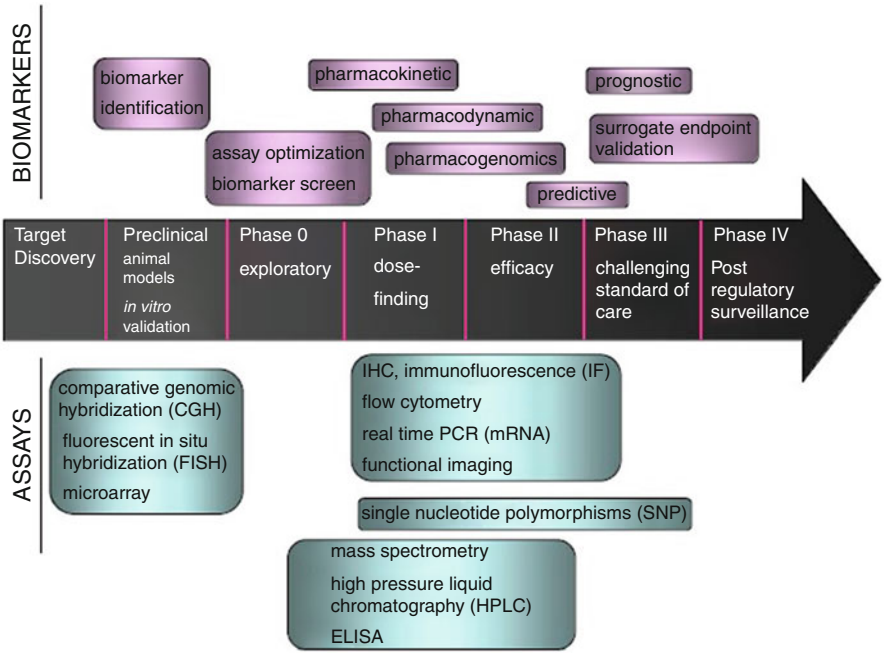

Fig. 13.6 A different view of the regulatory process by viewing a separation of "biomarkers" from "analytical assays." The distinction is not always clear (from Dhani and Siu 2008; with permission)

candidate biomarker for use as part of a candidate drug or biologic's regulatory process. The goals of the CDER Biomarker Qualification Program are to:

- Provide a framework for scientific development and regulatory acceptance of biomarkers for use in drug development.
- Facilitate integration of qualified biomarkers in the regulatory review process.
- Encourage the identification of new and emerging biomarkers for evaluation and utilization in regulatory decision-making.
- Support outreach to relevant external stakeholders to foster biomarker development.

Biomarkers under considered for qualification must be measurable and conceptually independent of the specific test performing the measurement. The distinction of what is a "biomarker"—i.e., a chemical analysis? a "method"? "Biomarkers" are defined differently from "assays" and are more broadly defined as parts of systems which can represent something about the pathology of interest such as being a "predictive" or "prognostic" indicator, i.e., a future trend or outcome versus an advance indication or portent of a future event, respectively. Figure 13.6 depicts

Process is described fully in this link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284621.htm.

this separation of "biomarkers" from "assays" with distinction of biomarkers as terms under larger definitions and assays as specific platforms that can help define a biomarker through the development process. A good reference on how the regulatory authorities have evolved on biomarker qualification is Goodsaid and Papaluca (2010). Another reference discussing "companion diagnostics" is that of Kern and Thomae (2013) and for examples of "surrogate endpoints" in clinical trials see Prentice (1898). A "roadmap for biomarker qualification" can be found in Warnock and Peck (2010).

The Drug Development Tools (DDT) offered by the FDA allows CDER to work with submitters (the public, pharma, etc.) to guide them as they develop or refine a novel DDT for a specific use or indication. Not unlike a grant or contract, CDER then will rigorously evaluate the submission (review) for use in the regulatory process. Qualifying a "tool" (aka DDT) within this FDA program will then allow drug/biologic candidate sponsors to use the "tool" in the qualified context of use during their drug development without requesting that CDER reconsider and reconfirm the suitability of the "tool" for the qualified context of use as it will already be available "off the regulatory shelf." The mission and objectives of the DDT Initiative include the following points:

- To qualify and make DDTs publicly available for a specific context of use to expedite drug development and review of regulatory applications.
- To provide a framework for scientific collaboration to facilitate DDT development.
- To facilitate integration of qualified DDTs in regulatory review.
- To encourage development of DDTs for contexts of use with unmet needs.
- To encourage the formation of collaborative groups to undertake DDT development programs to increase the efficiency and lessen the individual resource burden incumbent with DDT development.
- To encourage innovation in drug development.
- The Animal Model Qualification (AMQ) program is evolving. The program is voluntary and models qualified through this program will be made public. The process described below is subject to change as the Qualification Review Teams (QRTs) work with a number of submitters.

The "Animal Model Qualification" (AMQ) program is sponsored through both CDER and CBER. It is intended to provide added impetus and support for developing improved animal models for drug and biologics. In general, these are sponsored for development under the Animal Rule (21 CFR 314.600 for drugs; 21 CFR 601.90 for biological products[3]), but this need not be an exclusive approach. The AMQ program is to foster animal models of disease which have well-characterized natural histories, reasonably well-understood pathophysiological mechanisms of the disease as related to a pathogen, drug or biologic, and use of the animal model in mitigating or controlling disease. In general, the FDA wishes to see such model interpretations

[3] Concept paper from the FDA: Animal Models—Essential Elements to Address Efficacy Under the Animal Rule http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072214.pdf.

show "translation," or rational species cross over, in more than one animal species for the expected response that is predictive for human benefit. A single animal species can serve as the model if it is sufficiently well characterized for an accurate predictive response in humans. In the Animal Rule, the primary study end point is generally "enhancement of survival" (or prevention of major morbidity). The animal model may also simply serve to define the kinetics and pharmacodynamics of the product in humans and to facilitate in the selection of an effective dose in humans as per the Animal Rule.

Product-independent animal models, i.e., animal models which utilize imaging agents, can be evaluated and qualified as part of the qualification program outlined for Drug Development Tools (DDTs) (see 2010 draft *Guidance for Industry*: *Qualification Process for Drug Development Tools*). In this case "imaging" may have a direct tie to drug success in development. A potentially very good example of this is the utility of F-18 FDG in defining cancer metabolic behavior following drug or biologic therapy (see Chap. 7 for oncology-directed imaging). Figure 13.7 depicts a flow diagram of the process for advancement of a DDT through the FDA qualification pathway.

We will not be covering the "Clinical Outcomes Assessment Tools" (COAT) in much depth in this chapter simply as clinical use of imaging is far too comprehensive a treatise to cover with everything else we need to cover in support of the previous chapters. The reader is encouraged to visit the FDA COAT web site for further information.[4] The primary goal of this book, and indeed this chapter, is to inform the Reader of the *non-clinical* regulatory environment.

13.2.2 Quality Systems Guidance for Imaging Platforms

13.2.2.1 PET, SPECT, MR, CT, and Optical Platforms and the Need for FDA Compliance

In the laboratory setting, imaging platforms are relegated to being simply part of the analytical instruments repertoire—except they are often left out of the formalism tied to quality controls for the corporate analytical services such as ELISA's and other set-aside and managed support services.

Imaging can potentially play a major role in the interpretation of the outcomes depicted in Fig. 13.8 where imaging can (1) provide the initial diagnosis and subsequent additional diagnostic information (on multiple platforms) on the genetics and physiologic character of the cancer prior to treatment (Shields 2008); provide the time rate of change in the RECIST or other measurable property of a cancer whereby a measure of treatment success can be provided (Wahl et al. 2009), and (3) provide a documentation of therapeutic success and resolution of the cancer (Weber 2009).

[4] Clinical Outcomes Assessment Qualification Program (COAQ): http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm.

Fig. 13.7 The Drug Development Tool (DDT) program and a representative regulatory pathway whereby upon full qualification the "Tool" becomes publically available to foster development of future drugs and biologics (from Davis J, FDA presentation at NIH; BARNCATS meeting, Office of Counter-Terrorism and Emergency Coordination, CDER, FDA January 25, 2013; with permission)

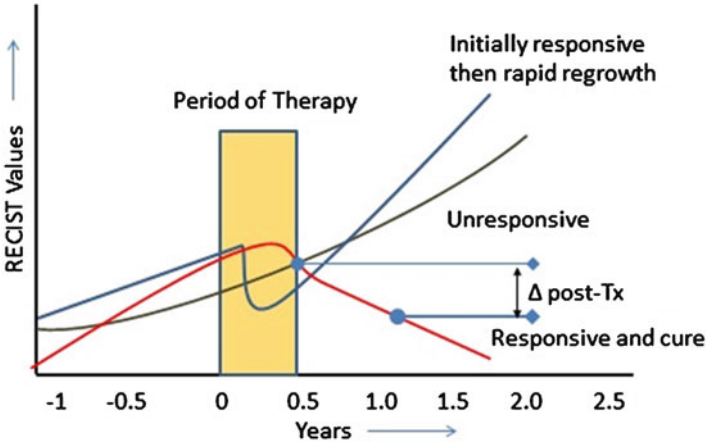

Fig. 13.8 A cartoon depiction of three theoretical cases of cancer development, adjudication with therapy, and the response to the therapy (poor with progression, unresponsive, and successful response with resolution). The change in tumor RECIST values post-therapy can be indicative of success

To achieve these clinical end points and like any analytical system-based laboratory service, there is a requirement of providing validated imaging systems, image collection procedures (time(s) post-administration, acquisition times for statistical purposes, acquisition protocols, other quality assurances), image processing and validated processing algorithms, image interpretation (reader training and interpretation skills), and the appropriate medium to present the findings must also be validated (color maps, windowing of the images, film versus digital screens, etc.). A discourse of these important regulatory concerns is provided below in Sects. 13.2.2.2 and

13.2.2.3. Hoffman (2009) provides a very good walk through of the use of F-18 fluorothymidine (FLT) as an imaging agent for measuring tumor proliferative responses to therapy. He also provides an excellent review of the various IND processes and the role and responsibilities of the physician in using imaging for evaluating new chemical entities (NCEs) in post-IND trials (Hoffman 2012).

13.2.2.2 Image Platform Validations

This topic is too involved to cover adequately in this short section; however, a fine review of an often overlooked aspect of imaging platform validations is provided on medical imaging "processing" by Jannin et al. (2006). The reader is also invited to seek manufacturer guidelines and device applications that are recognized as validated by the FDA medical devices section (see http://www.fda.gov/MedicalDevices/DeviceRegulation andGuidance/GuidanceDocuments/default.htm). The medical devices section covers radiation-emitting devices including MR (for electromagnetic fields), CT, and PET/SPECT with self-contained attenuation correction sources and optical imaging agent sensors (laser sources and near infrared cameras (NIR), etc.). Image platform validations are inherently the responsibility of the manufacturers. However, operationally, the instruments are governed by operating procedures, technical support in the operations, and these all involve operator training and validation of the instruments prior to use in controlled (i.e., FDA acceptable) studies. There are specific limits in performance, and operating the imaging platform will be limited to the inherent resolution of the system, noise of the system (ability to maintain stable electronics), the choices of reconstruction algorithms in 3-D projections, field homogeneity for MR systems as well as coil performance, laser intensity control and reflectivity for optical probes, etc. A "quality control" checklist is appropriate in any imaging platform. Here is an example of a simplified MR system quality operations checklist where there will be a PET imaging correlate. Table 13.1 shows that the aggregate scoring is done through a spider graph representation of the total scores from each topical QC element.

13.2.2.3 Quality Control of Radiotracers, Contrast Agents, and Optical Probes

The Chemical, Manufacturing and Control (CMC) elements of any drug are a critical section of the IND and the NDA/BLA filings. There are multiple guidance documents on the CMC of drugs and biologics,[5] and any imaging agent must in turn satisfy the expectations of stability, purity, stability, excipient control, assay validations of manufacturing processes, starting materials, and composition of the product. There are specific CMC documents which contain sample formats for documentation radiotracers such as for F-18 FDG (cardiac brain and cancer indications), Na F-18

[5] FDA CMC Guidance documents can be found at http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm064979.htm.

Table 13.1 Quality assurance principles for an MR study with a PET (F-18 FDG) correlation

1.0 Staff responsibilities and qualifications
1. Designated operational personnel
2. Designated personnel for patient management
3. Training logs/SOP manual
4. Operational roles defined
5. Contact lists and postings
2.0 Peripheral instruments and devices, reagents, supplies
1. Specifications of peripherals
2. Receipt and login of reagents/controls/devices
3. Radioisotope receipt/RSO controls (PET studies)
4. Storage conditions
5. Drug handling and drug delivery methods
3.0 MRI camera maintenance
1. Specifications of system defined
2. Manufacturer maintenance records
3. Automated equipment controls
4. Table movement and alignment tests
4.0 MRI camera quality assurance testing
1. Specifics from protocol outlined
2. Electronic stability assessments prior to study
3. Safety check prior to study
4. RF field map of room and magnet
5. Quality assurance tests—(weighting factors are adjustable)
Item A. 30 %
Item B. 30 %
Item C. 20 %
Item D. 20 %
5.0 Contrast agent and image ROI correlations
1. MR contrast agent log-in and prescription
2. PET radioactive drugs—RSO involvement
3. Image acquisitions timed for contrast agent
4. ROI selection criteria defined
5. Patient dosing records (non-electronic)
6.0 F-18 FDG-PET correlation option
1. Objective of study defined for fMRI staff
2. FDG blood draw protocol defined for magnet
3. FDG blood sampling procedure training
4. Draw volumes and dead volume corrections
5. Radiation survey procedures for post-study

(continued)

Table 13.1 (continued)

7.0 Image acquisition and archiving

1. BOLD protocol defined

2. Reconstruction methods defined/validated

3. Patient image ROI methodology: study to study

4. Image archiving method security

5. Image registration with other modality (CT, PET)

The resultant spider graph (no scoring entered) provides a snapshot of the overall quality package

injection (bone uptake), and ammonia N-13 injection (see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078740.pdf). The Society of Nuclear Medicine in 2008 also issued a CMC document for radiotracers that is quite useful (Harapanhalli 2008). Nanoparticle contrast agents, particularly for MRI and ultrasound products, that provide improved contrast and favorable biodistribution, i.e., superparamagnetic iron oxide nanoparticles for use as MRI contrast agents and cell labeling, may require additional and different CMC support documentation. Optical imaging agents are entering the clinical arena, and they too will require additional CMC directed at the photostability and the photon decay characteristics of these imaging agents.

13.3 The FDA Review Process: Translational Responsibilities

13.3.1 The Selection of an Imaging Platform to Defend Drug Approval

The FDA approval process is rigorous but not insurmountable. Figure 13.9 describes a full development scenario where a drug enters basic research and finishes with FDA approval and launch (and Phase 4 (not shown)) commitments if there are any post-marketing safety measures the agency wishes to determine after giving their approval to market. In contrast to the average time for the approval for drug or biologic which is 1–13 years, a typical development timeframe for approval of a radiotracer imaging agent may be as little as 7–8 years as it is often supported by a wide therapeutic index (high-dose MR, CT, and other contrast agent face standard safety therapeutic index

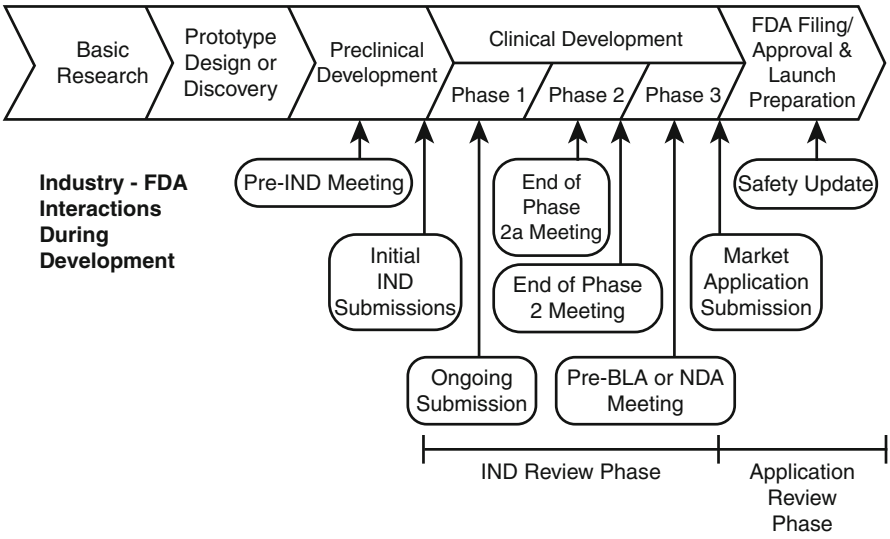

Fig. 13.9 *The FDA Review Process*. A timeline for Sponsor—FDA interaction schedules from early discovery through the NDA/BLA application/approval and launch of product. The paradigm fits any imaging agent as well, but nuclear and very low-dose contrast agents do have the opportunity for the Phase "0" trial (see Sect. 13.2.1) (from FDA, Critical Path Initiative 2004)

concerns). However, this is changing as noted previously due to the advent of biologics as imaging agents and their propensity for immunogenicity. The FDA encourages sponsors to engage with them "early and often," and this can be hugely beneficial in both cost control and study design and outcomes and eventual acceptances for product approval.

13.3.2 Phase "0" Clinical Trials

Prior to entering a clinical study, novel drugs and biologics have been through extensive preclinical safety and efficacy evaluations. Imaging agents, particularly PET and SPECT agents (due to low mass content in the drug), are best studied in a Phase "0" trial where the predictive risk is low due to the less than pharmacologically active concentrations required to produce their clinical determinant (usually uptake over time or relative to a control tissue, i.e., SUV; see Chap. 7). Tomaszewski (2007) provides a very good walk through the process of moving from the preclinical stage into the Phase "0" trial (Fig. 13.10). Marchetti and Schellens (2007) also provide an excellent perspective on FDA versus European (EMEA) regulatory and scientific considerations of Phase "0" trials for drugs and biologics. An important concern they pose is that there are few validated biomarkers for demonstrating anticancer activity. Pharmacological, biological, or imaging measurements at very low exposure levels of novel new anticancer agents (which are often very potent) are required, but unfortunately few reliable and validated assays are currently available. The high potency of new biologic anticancer molecules requires the use of low

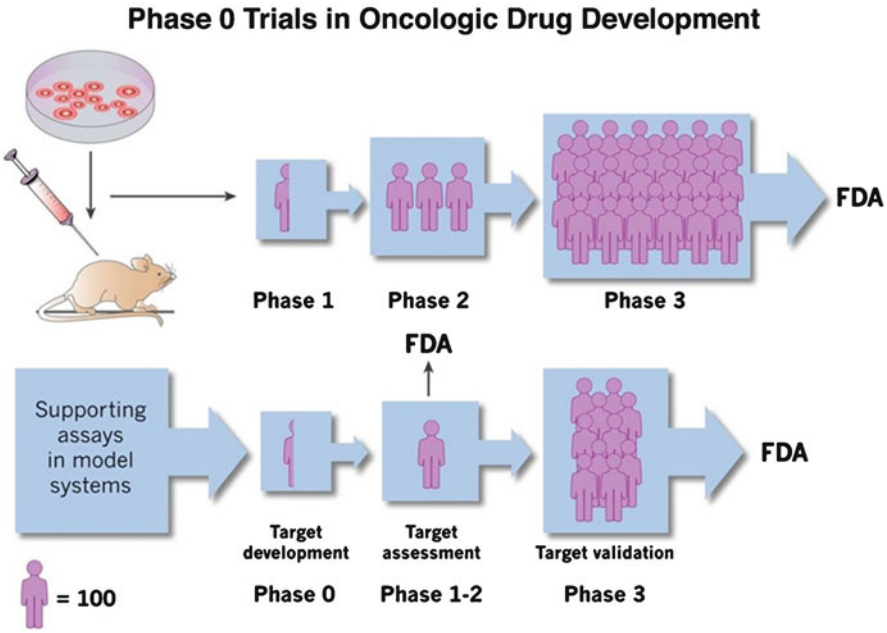

Fig. 13.10 Companion diagnostics, CDx (e.g., an imaging agent): the supporting CDx assays (i.e., and image) represent an agent that is codirected with the investigation of a new drug or biologic as a surrogate biomarker. As a "companion" for the indication, the imaging agent may support changes in a therapeutic approach. The Phase "0" is typically an imaging study with a PET/SPECT or other "tracer" platform but can be done with benign, high-dose imaging agents such as for MR, CT, US, or optical (from Murgo 2007, with permission)

First-In-Man (FIM) doses that are often significantly lower that what had been done for the traditional anticancer agents, potentially as low as three-log lower doses. Micro-dose studies must use very sensitive analytical assays for pharmacokinetic assessments, or may use medical imaging such as PET, SPECT, MR, MRS (magnetic resonance spectroscopy) as "analytical tools". Currently, most imaging techniques are not fully accepted as analytical companion diagnostic tools. Wahl et al. (2009) summarize the emerging considerations for PET imaging as it has become a test venue for imaging as a tool for oncologic response criteria.

The reader is directed to an online series of slide shows from the NCI DCTD (Division of Cancer Therapy and Diagnosis) Programs on Cancer Imaging Programs and Translational Research Programs entitled "Phase 0 Trials in Oncologic Drug Development" (September 5, 2007, Natcher Conference Center, NIH Bethesda, MD) with a web link as http://dctd.cancer.gov/MajorInitiatives/Sep0507Phase0Workshop/workshop.htm. In this series of lectures there is a wealth of reference material with respect to imaging equipment, software and data management, and biostatistical considerations. Imaging examples as well as a series of slides by Dr. Mankoff on the requirements one should anticipate with respect to imaging acquisition and analysis. Figure 13.11 is a selected slide from the NCI series on Phase "0" trials by Dr. Mankoff (2007) where he describes imaging as dynamic

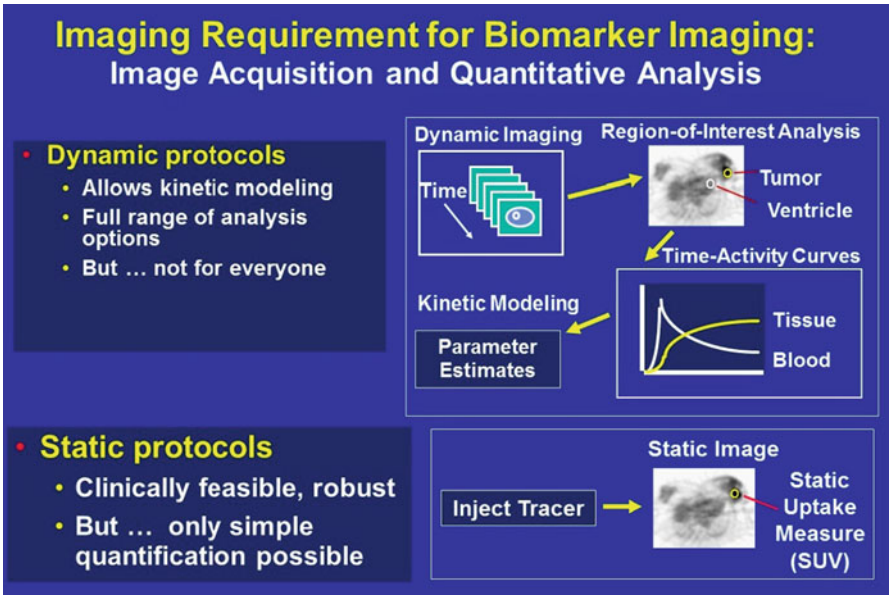

Fig. 13.11 A slide from Mankoff (2007) in the NCI series of talks on the conduct of Phase "0" trial. The figure describes dynamic/static protocols (time series of images), region-of-interest (ROI) analysis of test regions versus control, and kinetic modeling for parameter estimates (time–activity modeling). Each step in the process has critical regulatory implications (from Mankoff 2007; with permission)

protocols (time series of images as well as static imaging), region-of-interest (ROI) analysis (uptake areas vs. control regions), kinetic modeling for parameter estimates, and display of the kinetic data for selected and quantified regions of interest (ROIs).

Medical imaging agents generally are governed by the same regulations as other drug and biological products. In that they must undergo all the scrutiny of CDM, safety, use, and employment under the proper clinical indication, so too is the process one would need to employ an imaging platform on the development of a non-imaging drug or biologic. The imaging system employed will essentially be a diagnostic to govern therapy, a way to visualize a biomarker of either efficacy or safety, and the platform must operate under the rule not unlike a CLIA laboratory certification and validation. Just like a complete blood count, the instrumentation, the training of personnel, the maintenance of the instrument, and the calibration of the instrument at the time of use are critical issues for use of the data for submission toward approval. If a drug or diagnostic imaging agent is to be used in clinical concert, then they need to be developed simultaneously for the indication. The three-part Guidance for developing medical imaging drugs and biologics (FDA, Imaging Guidance Parts 1, 2, and 3, June 2004; see Guidance references) outlines the important aspects and details of imaging agent approval. What this book has been focusing on is a 180° view of this paradigm where the imaging agent is directing the approval of a new novel drug or biologic. Thus, the imaging system

and all associated reagents, platform preparation, platform controls, and platform validation as well as the biomarker (imaging tracer or contrast agent—or simply the physics of an imaging system itself), reagents, chemical preparation, shelf life of a biomarker imaging agent, and metabolic behavior of the tracer or contrast agent in health and disease hold for the use of the platform for associated regulatory documentation.

13.3.2.1 Clinical Trials: Image Analysis via the Blinded Read

Once a drug has moved beyond preclinical to the IND and a human clinical effort, the imaging agent performance must be measurable, quantifiable, and nonsubjective (as much as possible), and readers of the images (radiologists generally) must be consistent and require limited adjudication on the interpretation of the image(s). The performance measures of an imaging agent or imaging system are not different form a therapeutic. An imaging "system," i.e., the device alone or with tracer or contrast, is measured in a clinical trial for its ability to define a pathology, measure a mitigation via a change in pharmacodynamics or metabolism, or change metabolic behavior of the pathology (aka benefit).

Core Labs: Charters, Blinded Reads, Reader Adjudication, and ROC Curves

Before Imaging: Develop a Charter. Before beginning an imaging trial one must first set up the process and statistical analysis plan (SAP) which will provide the overall decisional outcomes from the trial images. The images must be collected appropriately, stored and displayed as required, and read by trained and unbiased readers. To this end the CORE laboratory performing these analyses will need to set up an "Imaging Charter." This is an important document which should comprise a comprehensive, detailed description of the clinical trial imaging methodology. Sponsors of the study should generally regard the Imaging Charter as an integral component of the protocol, much as the SAP. Submit the Charter to the FDA with the complete clinical protocol, including the final SAP, and include important supportive documents. The content of the Charter should include an **Executive Summary** of the trial design and the role of imaging in the trial. This is followed by the **Image Acquisition Standards** which include:

- *Equipment standardization and operation*, i.e., vendor-specific equipment/platforms (e.g., injectors, scanners, software)
- *Equipment technical settings* to be used at each site
- *Role of the technicians* in operation, including identification of faulty or unacceptable images and the need to repeat imaging
- *Phantoms to be used* for site qualification and image quality monitoring
- *Patient preparation*, positioning, and comfort measures
- Imaging *dates and times* and alternatives

- Handling of *off-protocol images*
- Imaging *risks to the patient*
- *Site qualification* process
- *Acquisition quality* control monitoring process
- *Data* storage, transfer, and site display
- Image interpretation (Clinical Trial Standards)
  - *Trained readers*, radiology, and/or nuclear medicine specialists
  - *Image transfer*, *receipt documentation*, *and initial quality assessment*
  - *Image display and interpretation*
  - *Selection of images* for interpretation, display sequence, and randomization
  - *Readers*: background qualifications (reader training)
  - *Timing of image reads* and the read process
  - *Imaging case report forms*; imaging data lock process
  - *Quality control* of the image display and interpretation process

Then there is the "before," "during," and "after" CORE Lab imaging analysis considerations:

- Before imaging—Charter Modifications
  - Charter will describe the process for modification.
  - Charter will describe the process for transfer of information to the sponsor, including needed support activities for the statistical analysis.
- During imaging—Monitoring and Charter Modifications
  - Record of modification of the imaging procedures
- After imaging—QA and documentation
  - Transfer of images (known fidelity of process) and archived as a usual component of patient care and as clinical trial source documents and with limited access
  - Retained for potential inspection and auditing
  - Clinical sites or a core facility analysis (QA/QC; reads and determination of reader interpretation consistency)

The Imaging Charter forms the "rigor" of the study. Within the Charter structure the FDA will find the holes, the gaps in oversight, that will raise questions, and thus, it is imperative that the CORE Laboratory services you enroll in your drug or biologics development have the history, the experience, and the staff that are schooled in these disciplined activities. One should be most careful of the image processing validation within the Charter's oversight. Processor validation is an often overlooked feature as they are frequently "packaged" and called "validated." The processing system employed needs to be tested rigorously with positive and negative control approaches as it is imperative to understand and highlight the intrinsic characteristics and behavior of the method. Critical elements include the evaluation of system performance (i.e., reproducibility, error propagation, especially from image to image

in a kinetic study) and biomarker performance (repeatability in a system and also subject to subject variance using that system), and to fully understand the limitations to the information the targeted imaging objective can convey clinically for the indication of interest (Jannin et al. 2006). Validation is a multifaceted process and it generally is best operationally to include simulated images. Simulated images actually allow for highly predictive outcomes, and if processing becomes askew these images will generally provide reasonable information to recognize the need to realign the software or electronic processors. These kinds of images help define behavior of the method and defend or explain observed intersubject variability.

The Receiver Operating Characteristic (ROC) Curve: Example Using the SUV

The Receiver Operating Characteristic (ROC) curve is a statistical tool of analysis that is utilized to measure the observer (image reader) or to test the performance of the image readings. Duarte et al. (2002) have provided a very useful example in the image analysis setting where the objective was to discern via reading FDG-PET images of bone metastases, that is, to discern malignant versus benign lesion using the observed distributions of the tracer in bone and standardized uptake values (SUV) (see Chaps. 1, 5, and 6) valuations.

In their study they examined ninety-nine bone sites in 33 patients who received F-18 FDG. The "gold standard" reference for the study was "confirmation on a bone scan (PET)" where a positive (POS) finding was a three out of four result. By these criteria the population of 99 lesions were 39 malignant and 60 benign. The SUV valuations from the readers were 61 different grades of uptake from 1.0 to 7.0. The reader valuations were classified as true positive (TP), true negative (TN), false-positive (FP), and false-negative (FN), and the TP and FP fractions were calculated for each threshold value. These comprise the ROC curve (Fig. 13.12) seen below. The optimal SUV of 2.5 produced a true positive (TP) rate (*y*-axis; sensitivity) of ~0.75 and a 1 false-positive rate (*x*-axis; 1-specificity) of <0.1 showing there was little additional benefit (e.g., a sensitivity for malignancy >75 % sensitivity when the SUV is >2.5) from higher SUV values (2.5–7.0) in the ability of a reader to recognize malignancy from benign lesions. An ROC analysis should be an integral part of the Imaging Charter and certainly part of the statistical analysis plan for an imaging clinical trial as it identifies the optimal crossover of scoring that delineates "presence of disease" from that of "no disease."

One must take caution on "statistical significance" when interpreting images (and any other scientific query). Always ask the question "What is the importance of the observed significance?" and then, more critically, assess the actual "significance of importance" (Riegelman 1979). This may read as a "play on words" but these words are indeed a critical point of understanding. The educated (but often subjective) review of an image by a trained reader still has bias and interpretive actions that can quite easily lead to FP and FN readings. The region of interest (ROI) for the assigned or recognized lesion is solely based upon the reader's judgment of edge or the fall off

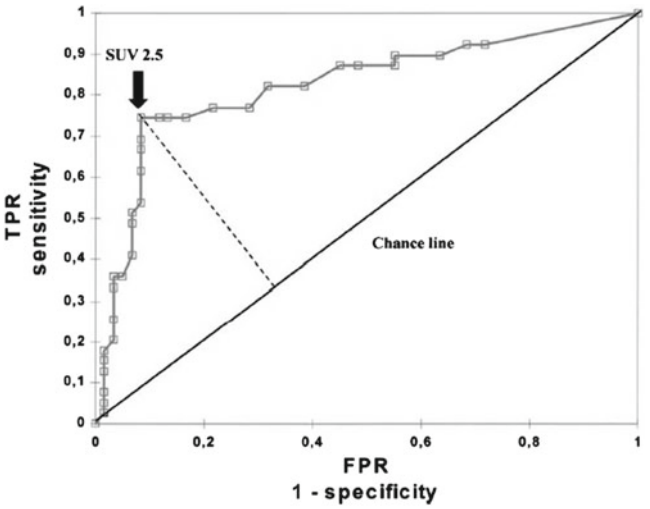

Fig. 13.12 The Receiver Operating Characteristic (ROC) curve depicts the overall performance of readers in terms of their ability to shape the ROC curve to a TPR of 1 and FPR of 0. The AUC of the curve above the "chance line" (50:50 call) improves with reader training. The curve depicts the ability to discern malignancy (>2.5 SUV) from a PET F-18 FDG study. In this case the TPR is nearly a plateau when SUV is >2.5 (from Duarte et al. 2002; with permission)

of intensity of signal. This can add several pixels (picture elements or voxels for PET/SPECT or MR for volume elements; slice volumes) that weaken or strengthen the counts acquired in that ROI, and against the background ROI the standardized uptake value (SUV) for, for instance, an F-18-FDG signal can push or retract an SUV into benign or malignant categorization. This is the inherent "noise" of reader interpretations and is highly dependent on training and common image analysis techniques that need to be harmonized as much possible during the reader trainings. Tests of the readers to attain the required skills need to be performed for reader qualification to actually participate in the blinded read of a trial images. Such training, the documentation of the test images, the reader training, and qualifying examinations of the readers need to be retained for FDA review as part of the Imaging Charter and trial documentation. It is important to remember that one must ask what is the importance of the observed differences (TP from FP and the inverse), especially if any differences are narrow, because finding a difference in small SUV valuations may or may not actually be a true correlation to benign versus malignant and actually represent another contribution to the observed uptake, i.e., infection or differences in regional blood flow. It is important in small imaging trials to remember that the presence of statistically significant difference tells little about the inherent variance expected in each group, i.e., benign uptake versus malignant uptake.

13.3.2.2 Managing the Image Review and Analysis

Effective Management Tools for the Independent Imaging Review Process

Bates and Williams (2007) provided a short but concise article on "effective management" of the independent imaging review process in oncology clinical trials that involve imaging. They key to a successful program is to prospectively define the methodology that will define the clinical outcome. A defined review process must first be implemented, knowledge of the reviewers biases and technical capacity to perform the review, the data that is expected and that the proper reader output will be provided for the statistical analysis and the kind of assessment that the readers will be required to provide. Documentation alone is not sufficient. Unrealistic expectations, lack of experience, and expertise and numerous other issues can make for a waste of investment and may lead to improper conclusions.

There are three key documents that establish the Imaging Core Lab's ability to have success. They include a Project Plan, the Imaging Charter, and the Investigator Site Manual. The Project Plan is a key first document that defines the timelines and the budgets. It can also serve as a guide for the communication plans as well as data management plans. It will aid in the process of qualifying a clinical site, the investigator, and the methodology of sponsor and core lab communications. The first objective of the Project Plan is to identify the risks to the program and establish a risk mitigation strategy to avoid the pitfalls that can be identified.

The Imaging Charter (aka Independent Review Charter, IRC) should be developed in tandem with the Project Plan as it is responsible for the overall review process, image collection and scheduling, types of images (structure/format; i.e., DICOM), the clinical data to be collected, the analysis of the reads, reader training, and reader adjudications (resolution of reader interpretations; partnered reader scoring, image scoring operations). The Charter is often lacking in operational logistics at the sacrifice of getting regulatory or medical issues resolved for the conduct of the trial. Care should be exercised to make sure all participants—clinical, regulatory, data management, statistics, and the core lab for image processing and reading—are included and have opportunities to manage the creation of the document. Very rigorous data collection and management to assure compliance of the "moving parts" often gets "relaxed" after a period of time when specific items become operationally consistent and repeatable.

The Investigator Site Manual is another document that can have severe repercussions if not appropriately constructed and managed. This document goes to the core lab and to the imaging clinical sites. It has a dual purpose: (1) to establish exact imaging protocols and parameters and (2) to provide logistical instructions to the clinical operations team. This document is often far more detailed than the actual clinical protocol. Imaging parameters such as slice size in MR and PET/SPECT, contrast agent or radiotracer administration timing with image acquisition, improper anatomical coverage, and suboptimal baseline image collection or poor attenuation corrections are common imaging trial errors and often cause patient exclusion from the analysis.

Prospectively designing the independent review process is a critical operation for a successful imaging trial. It is imperative that the leadership of the trial demand and

assure the three documents are properly created, clearly written, and vetted with each participating operational entity. The handling of pitfalls in the management of a trial using image analysis is only successful when the operational and communication questions are fully vetted, detailed with solutions with each participant, and a risk mitigation strategy generated.

13.3.2.3 Program Management for Drug and Biologic (and Imaging) Development

Program management is the lead oversight of all operations. Clinical operations, regulatory oversight, statistical planning and analysis, clinical research associates (CRAs) attending to drug or biologic supplies as well as imaging agent or contrast agents and coordination of deliveries with the clinical site (refrigeration required?, etc.), case report form design, technical staff and management communications to the sites, pharmacology and toxicology advisors from the non-clinical IND efforts, the data management team and coordination of the imaging core lab, and selection of talented radiologists (or other appropriate scientists) trained to read the images—all are under the leadership of the program manager. The clinical site principal investigator (PI) should be instructed on trial expectations, anticipated enrollment, scheduling, and expectations of data delivery and data quality. These points are often deferred from clear discussion with the expectation that the PI is either an "expert in the field" and knows what is expected. This is a common mistake as each trial has its own idiosyncrasies and thus requires the program manager and the clinical manager communicate fully and candidly with the clinical site PI.

13.4 A View of "FDA Perspectives" from Outside the FDA

Janet Woodcock has presented a talk on the regulatory (FDA/CDER) perspectives (Woodcock 2010) where she cites the importance of standardization of image acquisition, interpretation (procedure for reading an image), and the management of data through multicenter trials. These elements are critical for accurate diagnosis and assurance to the FDA that the CDx (aka, image) has merit to assess the response of a condition to a therapeutic intervention. Coincident to these requirements is, of course, the requirement of standardization, e.g., of the imaging agent and the imaging platform, and in the non-clinical setting as defense to the agency we need standardization of the routine method of the animal model preparation, the disease model, and imaging parameters that help define the biomarker of interest with respect to the disease, and we need to do this all within corporate and academic budgets which often look at imaging as "that luxury."

Outside the FDA in imaging forums and imaging societies, such as the Radiologic Society of North America (RSNA), scientists and regulatory professionals that support corporate and legal aspects of drug development have formed a task force called the "Quantitative Imaging Biomarkers Alliance" (QIBA) Task Force, and it

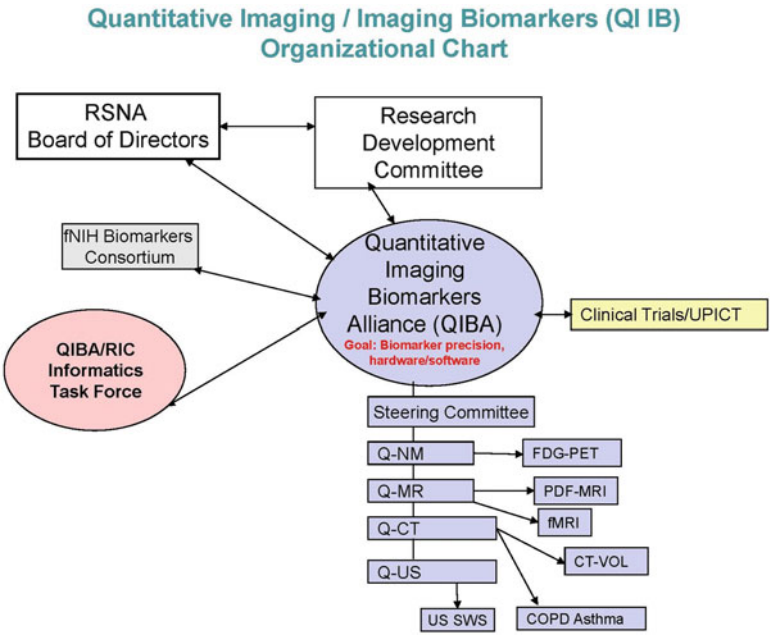

Fig. 13.13 The Quantitative Imaging Biomarkers Alliance (BIQA) within RSNA. A diagram offering a view of the multiple inputs that this organization has recruited to assist the medical community in deriving regulatory acceptance of biomarkers employed in imaging (from RSNA BIQA Report of Aug. 25, 2011, see RSNA in the references)

is comprised of over 20 individuals with active participation in the imaging sciences. Their organizational and FDA-supportive framework is given in Fig. 13.13 as they were set up within the RSNA as a reporting body to the Board of Directors in 2011. As can be seen, the FDA is an important contributor to the QIBA imaging roundtable advisory body feeding into the QIBA feedback from multiple players in the imaging industry on biomarker precision and hardware requirements to achieve regulatory acceptances and validation of biomarkers in imaging. Such organization as the QIBA, as a form of representation as a body to the FDA, has been invaluable toward FDA inclusion and acceptance of imaging in such activities as the DDT and the *Critical Path Initiative*.

13.5 Concluding Remarks

This chapter has been an attempt to introduce the reader to the regulatory environment that surrounds the activities we call "Imaging." The reader must feel, however, the term "imaging" is almost "missed" in the concepts of regulatory activities, and the reader may be correct in that observation. Imaging is a discipline not unlike an

"analytical chemistry toolbox." We "inject on one side and the analysis comes out the other" is not too far from the truth. Imaging is a multidisciplined art and we think the reader has come to appreciate the wide variety of imaging platforms, imaging agents, imaging modalities, imaging quality, image resolution, and "imaging ideas" that all translate to "imagination." "Imagination" is the limiting factor for "imaging" in the pharmaceutical industry, and the advancement of any product can be enhanced through the regulatory process, regulatory rigor, and regulatory oversight. Imaging agents as radiopharmaceuticals (Agdeppa and Spilker 2009; Dunphy and Lewis 2009; SNM 2008; Shields 2008; Zhao et al. 2009), MR contrast agents (Strijkers et al. 2007), and optical probes (Rice and Contag 2009; Boddington 2010) offer the reader excellent reviews on the practical applications and clinical indications of these imaging agents and their respective platforms. Boddington (2010) also discusses cell tracking with optical systems using an FDA alternative for luciferase. Bristow (2008) also provides an excellent overview on the state of the art of biomarkers used in clinical trials.

It is inevitable that imaging sciences will play more of a role in the development of drugs and biologics (Hoffman 2012). Wagner et al. (2006) have pointed out how many "nanomolecular" agents are being developed, and many of these are imaging agents. The ease of monitoring—in a single animal—the pharmacodynamics, the toxicokinetics, and the overall "image" (picture) of a drug as it transits or depots in the body will make drug development much more like an analytic service, more of a step-by-step laboratory operation, and a key way to observe how "a" leads to study "b" which leads to study "c," etc. The availability of small animal imaging platforms (with associated cost reduction from increased market volume), better and more licensed contract service organizations (CROs) that will offer imaging services, and the subcontracting market to provide maintenance of these devices (especially with the advances in novel electronics, detector system, and software), "human" imaging systems are being miniaturized and being implemented as cost-effective laboratory additions. The FDA Initiatives for Biomarkers, Drug Development Tools (aka imaging platforms), and the Animal Models Directives are financially and scientifically creating new opportunities for the imaging sciences. Soon there will be a sufficient number of "off the shelf" validated biomarkers and animal models that will revolutionize clinical medicine and especially drug and biologics development. Companies with products to develop will eventually use these libraries of imaging models and validated imaging tools/tracers/agents, which the FDA is familiar with and possibly co-developed with their "Tools" initiatives. The goal is to avoid "re-invention" of an already validated animal model with a new imaging approach and biomarker—all very likely not validated. The initiatives will actually populate the nonclinical environment with validated and well-characterized models where the disease natural histories are fully defined and imaging tools can be applied appropriately. These tools will be validated across academic institutions and corporate entities, including private CROs, as well as "big" and "little" (one product or venture capital funded) pharma. Table 13.2) is provided as a resource of regulatory approaches, web sites and links, imaging platform tools and and we have also

Table13.2 Regulatory web-based resources important for use of imaging platforms and products in drug and biologics development

Regulatory references and comments on imaging	Web access
Guidance for Industry: Developing Medical Imaging Drug and Biological Products	
• *Part 1: Conducting safety assessments*, FDA—Food and Drug Administration; Center for Drug Evaluation and Research (CDER); Center for Biologics Evaluation and Research (CBER), June 2004	http://www.fda.gov/downloads/Drugs/…/Guidances/ucm071600.pdf; last accessed 25 Apr 2013
Comment: Each of these (Part 1–3) deals with the development and the approval process for an imaging agent (PET tracer, MR contrast, Optical, etc., and thus are not specifically for approval of a combination diagnostic or a surrogate drug or biologic used for approval of another	
• *Part 2: Clinical indications,* FDA- Food and Drug Administration; June 2004	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071603.pdf; last accessed 25 Apr 2013
Comment: as above	
• *Part 3: Design, analysis, and interpretation of clinical studi*es, FDA- Food and Drug Administration; June 2004	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071604.pdf; 25 Apr 2013
Comment: As above	
Carver, KH. "Companion diagnostics: Evolving FDA regulation and issues for resolution." *In Vitro Diagnostics: The Complete Regulatory Guide, 2010,* Chapter 8, pp 149–184	http://www.cov.com/files/Publication/e5c4b3dc-1832-4742-9937-84f965052b44/Presentation/PublicationAttachment/7795d260-621d-4d13-bd29-863acac00254/Companion%20Diagnostics%20-%20Evolving%20FDA%20Regulation%20and%20Issues%20for%20Resolution.pdf; last accessed 27 Apr 2013
Comment: An important guidance to help frame the language of translation of a diagnostic in the analytical laboratory to a diagnostic in the imaging laboratory	
Guidance for industry: *Guidance for industry standards for clinical trial imaging endpoints;* FDA- Food and Drug Administration; June 2011	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM268555.pdf; last accessed 25 Apr 2013
• Comment: A guide on what is expected in reading images. The purpose of the guidance is to assist sponsors in the use of endpoints that depend on the results of imaging tests in clinical trials of therapeutic drugs and biological products[a]	
• This guidance focuses on the imaging standards that are regarded as important *when imaging is used to assess a primary endpoint*, or an endpoint component, in a clinical trial intended to confirm a drug's efficacy[b]	

Guidance for Industry, Investigators and Reviewers: *Exploratory IND studies*, G6384dft.pdf, April 2005 • *Comment: A guide on the Phase "0" trial and what the FDA expects of the CMC requirements as well as animal safety*	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078933.pdf; last accessed 25 Apr 2013
Guidance for Industry and Reviewers: *Estimating the safe starting dose in clinical trials for therapeutics and adult healthy volunteers*; CDERguid/3814dft.pdf; Dec 2002 *Comment: A useful guidance for basic allometry*	http://www.fda.gov/OHRMS/DOCKETS/98fr/02d-0492-gdl0001-vol1.pdf; last accessed 4/25/2013
Guidance for Industry: *Codevelopment of two or more unmarketed investigational drugs for use in combination*; December 2010; *COMMENT: This guidance is very applicable to the use of unapproved, but available, imaging agents for use in the defense of unmarketed drugs or biologics. Imaging agents may be used as defense of (1) finding a pathology, (2) monitoring the treatment success (or failure) of a second product on that acts on the pathology, and (3) where the imaging agent can defend the resolution or progression of the pathology under the treatment product*	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf; last accessed 2 Feb 2013
Feng Q, *Clinical trial efficacy endpoints for molecular Imaging Products Development*, Div. Medical Imaging Products (DMIP), June 11, 2012 *Comment: A useful document which frames the objectives of the FDA's Medical Imaging Products Division (MIPD)*	http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Oncology/UCM314270.pdf; last accessed 25 Apr 2013
John J. Smith, Medical Imaging: The Basics of FDA Regulation Published: August 1, 2006; • *Comment: Device approvals—Imaging platform approval recommendations Devices that use medical imaging are increasingly prevalent. OEMs must know how to navigate the regulatory pathway to get such devices approved. Medical imaging is playing a large and increasing role in modern healthcare delivery. Understanding FDA's regulatory construct that governs medical imaging is crucial to manufacturers operating in this exciting and challenging environment*	http://www.mddionline.com/article/medical-imaging-basics-fda-regulation; last accessed 25 Apr 2013
RSNA, Report on the Quantitative Imaging Biomarkers Alliance Task Force, August 25, 2011 *Comment: A critical assessment on quantitation of imaging biomarkers that the Reader will benefit from in applying to their own systems*	http://qibawiki.rsna.org/images/2/25/QIBA_task_force_report_11-3-11.pdf; last accessed 5 May 2013

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Table 13.2 (continued)

Regulatory references and comments on imaging	Web access
FDA, *Critical path initiative: innovation/stagnation- challenge and opportunity on the critical path to new medical products*, 2004 *Comment: A document on FDA revitalization and change in regulatory approaches*	http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm077262.htm; main page: http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/ucm076689.htm (updated 12/2012); last accessed 28 Apr 2013
Statistical principles for clinical trials—EMEA, Human Medicines Evaluation Division, ICH Topic 9, Note for Guidance, London, 18 March 1998, CPMP/ICH/363/96 • *Comment: a useful reference on statistical approaches which are in FDA favor.*	http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002928.pdf; last accessed 25 Apr 2013
Immunogenity in Animal and Clinical Research —FDA Guidance: Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products • *Comment: Immune responses to therapeutic protein products may pose problems for both patient safety and product efficacy. Immunologically based adverse events, such as anaphylaxis, cytokine release syndrome, so-called "infusion reactions," and nonacute immune reactions such as immune complex disease (see Appendix C), have caused sponsors to terminate the development of therapeutic protein products or limited the use of otherwise effective therapies. Both patient-related and product-related factors may affect immunogenicity of therapeutic protein products. These factors provide the starting point for an immunogenicity risk assessment*	http://www.fda.gov/downloads/drugs/guidancecompliance%20regulatoryinformation/guidances/UCM338856.pdf Feb 2013; last accessed 25 Apr 2013
Simms, J, PAD/MABEL: Calculation of the minimum anticipated biological effect level (MABEL) and first dose in human, 2009 *Comment: This document brings the concept of animal testing and clinical assurance of efficacy and safety in first in human trials where the animal model and pathophysiology play an important role in dose adjustment and selection across species (improved allometry)*	http://www.emea.europa.eu/docs/en_GB/document_library/Presentation/2009/11/WC500010862.pdf; last accessed 25 Apr 2013

Woodcock J, *Medical Imaging: CEDR's Perspective*, Radiologic Society North. America Workshop, Bethesda, MD, April 13–14, 2010 *Comment: A useful treatise on the way the FDA views imaging agents. Not a reference in the context of this book which advocates imaging for the development of other agents*	http://www2.rsna.org/re/TwoTopicImagingWorkshopPresentations/Index%20Files/Woodcock%20CDER%20Perspective.pdf; last accessed 25 Apr 2013
Woodcock J, An FDA perspective on the drug development process, *Food Drug Law J* 1997;52(2):145–161 *Comment: A brief discussion on the rules of law and the drug development process; intellectual property, regulations, pathways to approval*	Not formally available through the web. Seek the Food Drug Law Journal
Woodcock: FDA to Consider Approving Some Drugs Using Just One Phase I Clinical Trial; Latest News | Posted: 12 February 2013; • *Comment: consideration of the new category of* Breakthrough Products *designation. The pathway is intended for any product (*including an imaging product that supports a companion designation, *Editorial comment) that is "intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition and for which preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints."* • *The "Breakthrough Products" designation may provide incentive for companies to develop imaging agents that directly expose efficacious responses in a Phase "0" of other type study. This is category is added to the already in place incentives such as fast-track status, priority review and accelerated approval*	http://www.raps.org/focus-online/news/news-article-view/article/2853/woodcock-fda-to-consider-approving-some-drugs-using-just-one-phase-i-clinical-t.aspx; last accessed 25 Apr 2013
Woodcock J, *Developing a Qualified Biomarker: Regulatory Considerations*; Institute of Medicine of the National Archives, Perspectives on Biomarker and Surrogate Endpoint Evaluation - Discussion Forum; Summary Released: January 18, 2011 *Comment: A surrogate endpoint is expected to predict clinical benefit (or harm, or lack of benefit) based on epidemiologic, therapeutic, patho-physiologic or other scientific evidence*	http://www.iom.edu/~/media/Files/Activity%20Files/Research/NeuroForum/Woodcock.pdf; last accessed 25 Apr 2013

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Table 13.2 (continued)

Regulatory references and comments on imaging	Web access
Brian Malkin and Scot Pittman, The Drug/Biologics Approval Process: An FDLI (Food Drug and Law Institute) Primer**,** January 2013 • *Comment: This publication will help explain the FDA approval processes for drugs and biologics. It describes various FDA premarket requirements and pathways for drug and biologics application reviews, including changes enacted under the Food and Drug Administration Safety and Innovation Act (FDASIA). Topics addressed include the New Drug Application (NDA) process, non-NDA routes to market, generic drugs and the abbreviated new drug application process, as well as over-the-counter drugs and biologics*	http://www.fdli.org/products-services/~/resources/resources-order-box-detail-view/the-drug-biologics-approval-process-an-fdli-primer; last accessed 25 Apr 2013
Phase "0" Trials: Tomaszewski J, The Pre-Clinical Pathway to the Phase 0 Trial, in, Workshop: *Phase 0 Trials in Oncologic Drug Development*, Natcher Conference Center, NIH, Bethesda, MD; Div of Cancer Treatment and Diagnosis; September 5, 2007 • *Comment: A useful reference on moving a pre-clinical candidate toward the IND/NDA through Phase "0" planning and preparation in terms of studies and approaches.* Larson S, Herceptin as a Phase 0 Imaging Example, in, Workshop: *Phase 0 Trials in Oncologic Drug Development*, Natcher Conference Center, NIH, Bethesda, MD; Div. of Cancer Treatment and Diagnosis; September 5, 2007 • *Comment: An excellent example of an imaging Phase "0" trial* Mankoff D, Imaging to Guide Early Drug Trials, in, Workshop: *Phase 0 Trials in Oncologic Drug Development*, Natcher Conference Center, NIH, Bethesda, MD; Div. of Cancer Treatment and Diagnosis; September 5, 2007 *Comment: Also a part of a full meeting at the National Institutes of Health on the Phase "0" Trial approach. The Reader is encouraged to review all the talks form this event and they are web accessible.*	http://dctd.cancer.gov/MajorInitiatives/Sep0507Phase0Workshop/workshop.htm; last accessed 5 May 2013 http://dctd.cancer.gov/MajorInitiatives/Sep0507Phase0Workshop/workshop.htm; last accessed 25 Apr 2013 http://dctd.cancer.gov/MajorInitiatives/Sep0507Phase0Workshop/workshop.htm; last accessed 25 Apr 2013

[a]*drugs* incl. human drugs and therapeutic biological products

[b]A "confirmatory trial" is an adequately controlled trial

provided short summaries of regulatory documents and Guidances. The imaging world is fast expanding from the clinical environment into the early drug and biologic laboratory and it will be important in the future for pharmaceutical developers to contribute their own "imagination" as to how they want to apply imaging tools as potential anaytical tools to provide solutions in answering their scientific questions.

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