Bringing a Product into the Clinic

Handbook for NTR Investigators

Standards and Compliance Core

Network for Translational Research

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Introduction

The translation of bench discoveries to the clinic can be a very long and expensive process. If the process is viewed backwards from a successful IND, the major expense is primarily related to the last preclinical phases of the process. However, the overall time expended on the effort occurs from discovery through preclinical testing. The objective of this handbook is to provide reference materials to NTR investigators who will be developing products for clinical applications. A number of different regulations are involved in demonstrating safety and efficacy of products before they can be introduced into humans. In addition to regulations, Guidance Documents are available to assist in the development process. Standards are also available for certain types of products. The appropriate regulations should be consulted to ensure characterization is sufficient for clinical testing. Following are some of the regulations and Guidance Documents that should be used when developing study plans.

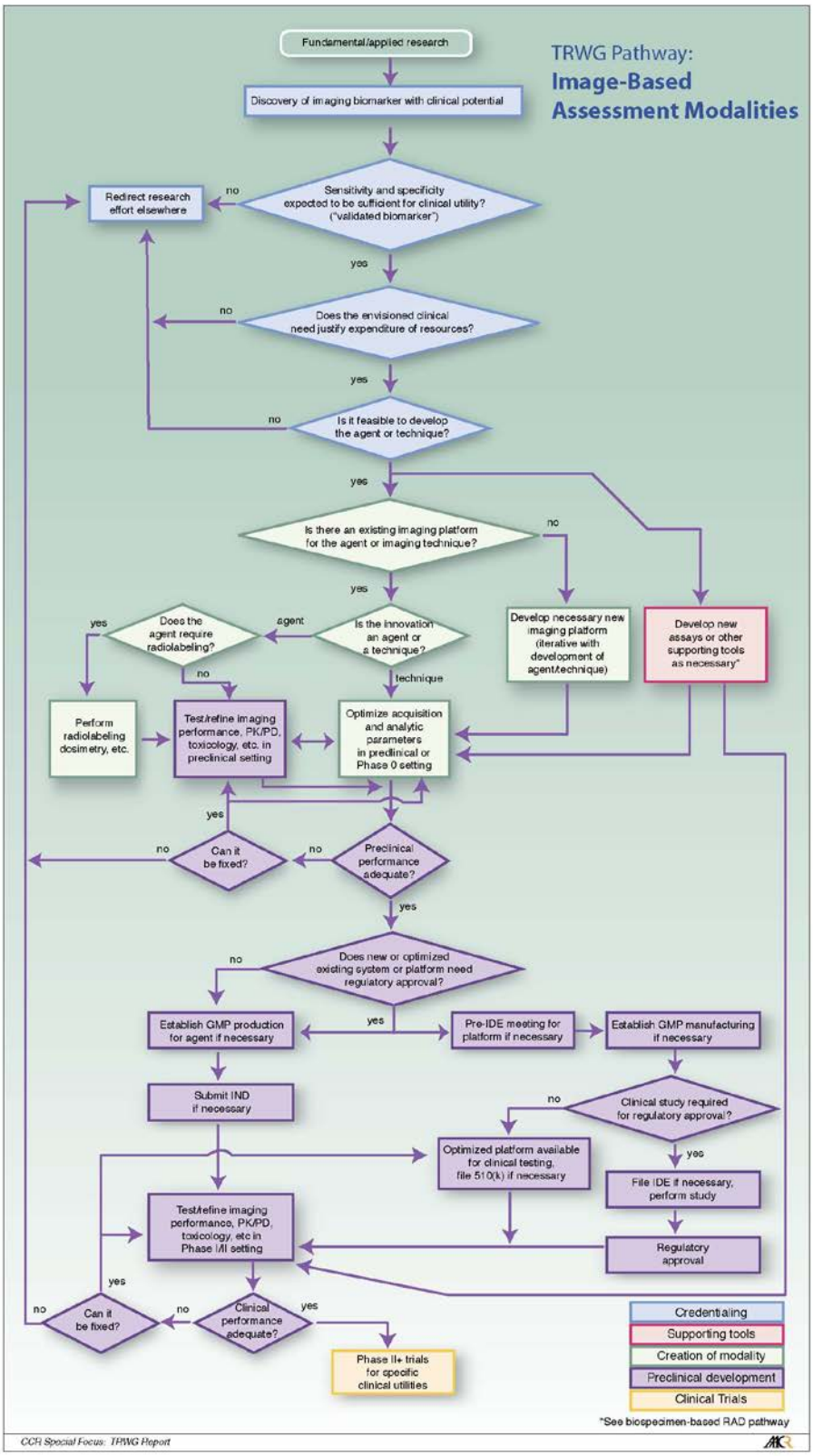
Guidance or Regulation	Description	Usage Area
21 CFR Part 11	Electronic records and computerized systems	Manufacturing, preclinical, clinical
21 CFR Part 50	Human subject protection	Clinical trials
21 CFR Part 54	Financial disclosure by investigators	Clinical trials
21 CFR Part 58	Preclinical safety testing	Preclinical studies
21 CFR Part 210 and Part 211	Good manufacturing practice regulations	Drug or biologic manufacturing
21 CFR Part 312	IND submission requirements	Clinical trials
21 CFR Part 610	Biologic manufacturing requirements	Biologic manufacturing
21 CFR Part 812	IDE submission requirements	Clinical trials
21 CFR Part 820	Quality systems regulation	Device manufacturing
ICH E6 guidance on Good Clinical Practice	Standards for conducting clinical trials	Clinical trials
International Conference on Harmonization S, Q, M, and E guidelines	Safety, quality, multidisciplinary, and efficacy guidelines	Preclinical, clinical
ISO, ANSI, AAMI standards	Device safety and efficacy	Preclinical, manufacturing
U. S. Pharmacopoeia	Validated testing procedures	Preclinical, manufacturing

Current documents in the Code of Federal Regulations can be found online at the following link: http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&tpl=%2Findex.tpl. A good resource for other documents related to clinical trials can be found at: http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/default.htm. The U. S. Pharmacopoeia can be found at: http://www.usp.org/USPNF/; online access can be obtained with a subscription. Additional standards can be obtained from: http://webstore.ansi.org/sdo.aspx and http://www.iso.org/iso/iso_catalogue.htm. Specific to imaging agents, a Guidance Document on new contrast indications for imaging devices used with already approved drugs or biologics

can be found at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM195951.pdf. A link to Guidance Documents specifically for Combination Products can be found at: http://www.fda.gov/RegulatoryInformation/Guidances/ucm122047.htm. A link to general Guidance Documents on the FDA website can be found at: http://www.fda.gov/RegulatoryInformation/Guidances/ucm122044.htm.

An example of the complexities involved in bringing a product from the laboratory to the clinic is illustrated in Figure 1.

Because some sections of this handbook will not be applicable to products under development at a Center, this handbook is arranged in sections to readily locate the necessary information. Contact Core members for information regarding consultants who can provide information on how to perform necessary steps in the translational research process.


TRWG Pathway:
Image-Based Assessment Modalities
Fundamental/applied research
Discovery of imaging biomarker with clinical potential
Sensitivity and specificity expected to be sufficient for clinical utility? ("validated biomarker")
no
Redirect research effort elsewhere
yes
Does the envisioned clinical need justify expenditure of resources?
no
yes
Is it feasible to develop the agent or technique?
no
yes
Is there an existing imaging platform for the agent or imaging technique?
no
yes
Is the innovation an agent or a technique?
agent
technique
Develop necessary new imaging platform (iterative with development of agent/technique)
Develop new assays or other supporting tools as necessary*
Does the agent require radiolabeling?
yes
no
Perform radiolabeling dosimetry, etc.
Test/refine imaging performance, PK/PD, toxicology, etc. in preclinical setting
Optimize acquisition and analytic parameters in preclinical or Phase 0 setting
Can it be fixed?
yes
no
Preclinical performance adequate?
no
yes
Does new or optimized existing system or platform need regulatory approval?
no
yes
Establish GMP production for agent if necessary
Pre-IDE meeting for platform if necessary
Establish GMP manufacturing if necessary
Submit IND if necessary
Clinical study required for regulatory approval?
no
yes
Optimized platform available for clinical testing, file 510(k) if necessary
File IDE if necessary, perform study
Test/refine imaging performance, PK/PD, toxicology, etc in Phase I/II setting
Regulatory approval
Can it be fixed?
yes
no
Clinical performance adequate?
no
yes
Phase II+ trials for specific clinical utilities
Credentialing
Supporting tools
Creation of modality
Preclinical development
Clinical Trials
*See biospecimen-based RAD pathway
CCR Special Focus: TRWG Report

Validation

Introduction

Validation guidelines are needed that are specific for members of the Network for Translational Research. An FDA guidance document describes validation as follows: "Validation involves documenting, through the use of specific laboratory investigations, that the performance characteristics of the method [or agent or instrument] are suitable and reliable for the intended analytical applications [1]." NTR members need guidelines specifically enabling translation of optical markers, targeting agents, instruments, software, and procedures. Specific strategies and examples of validation studies of similar optical imaging products could enable NTR members to negotiate the maze of regulations and work necessary for commercialization of their innovations.

Validation is a necessary and continual process, performed throughout production and testing of agents or methodologies, and validation must be done before any agent or methodology emerges in the clinic. Validation design by the developing investigators is optimal, as these investigators know best the synthesis/manufacturing pitfalls and challenges, as well as potential applications and limits.

Validation needs to occur in the earliest steps – co-evolving with GLP/GMP protocols and SOPs, as well as throughout the development and production of an agent or technology. Validation can apply to the purity, efficacy, and safety/toxicity of an agent, method, or instrument. Validation is necessary to provide data required in a new drug application, premarket approval, or device registration.

Crucial definitions

An understanding of terms used in validation is absolutely essential. To begin with, there are three types of validation.

- *Full validation:* Establishment of all validation parameters to apply to sample analysis for the bioanalytical method for each analyte.
- *Partial validation:* Modification of validated bioanalytical methods that do not necessarily call for full revalidation; for instance, revalidating when a reagent is changed.
- *Cross-validation***:** Comparison of validation parameters of two bioanalytical methods or laboratories.

A short glossary of validation terminology follows, from FDA's Guidance for Industry: Bioanalytical Method Validation:

*Accuracy***:** The degree of closeness of the determined value to the nominal or known true value under prescribed conditions. This is sometimes termed *trueness*.

Biological matrix: A discrete material of biological origin that can be sampled and processed in a reproducible manner. Examples are blood, serum, plasma, urine, feces, saliva, sputum, and various discrete tissues.

Limit of detection (LOD): The lowest concentration of an analyte that the bioanalytical procedure can reliably differentiate from background noise.

Lower limit of quantification (LLOQ): The lowest amount of an analyte in a sample that can be quantitatively determined with suitable precision and accuracy.

Precision: The closeness of agreement (*degree of scatter*) between a series of measurements obtained from multiple sampling of the same homogenous sample under the prescribed conditions.

Process validation: collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products.

Quantification range: The range of concentration, including ULOQ and LLOQ, that can be reliably and reproducibly quantified with accuracy and precision through the use of a concentration-response relationship.

Selectivity: The ability of the bioanalytical method to measure and differentiate the analytes in the presence of components that may be expected to be present. These could include metabolites, impurities, degradants, or matrix components.

Stability: The chemical stability of an analyte in a given matrix under specific conditions for given time intervals.

Upper limit of quantification (ULOQ): The highest amount of an analyte in a sample that can be quantitatively determined with precision and accuracy.

General procedure for validation

1) Plan before the initiation of prestudy validation experiments:
   a) Describe intended use of method (for example, to test the purity of an optical imaging agent). This step is called Design Qualification.
   b) Choose parameters to be validated (precision, accuracy, range, specificity, selectivity, stability, dilutional linearity, robustness, batch size, standard curve, detection limits).
   c) Establish acceptance criteria for each performance parameter—for instance, accuracy described by %CVs less than 20% may be selected as appropriate for a given validation application, and six repeated trials of each standard may be deemed necessary to establish dilutional linearity.
2) Write validation method/SOP. This amounts to simply describing every detail of the test procedure. In addition to procedure steps, reagent supplier catalog numbers and lot numbers should be recorded, or specifications should be provided to allow use of equivalent products from other manufacturers.
3) Perform the validation. Meticulous transcription of all details is required.
4) Calculate limits, linearity, precision, accuracy, and other determinants.
5) Analyze validation, revising as necessary.

The last three steps are considered to be Operational Qualification.

Specific validation needs for NTR researchers:

1) Optical (fluorescent) agents—optical purity, specificity for target
2) Target-binding agents—same as (1)
3) Confocal microendoscopy instrumentation and biomarkers
4) Other Biomarkers
5) Instrumentation and software
6) Pre-cancerous lesion detection
7) Cancer detection and diagnosis
8) Response to therapy
9) Drug development

For each of these products/needs, the committee could devise a list of validation tests and parameters deemed necessary.

For example, for cancer detection using an optical marker validation tests could be designed: *in vitro* (determining purity and specificity of marker for cultured cancer *vs.* non-cancerous cells), *in vivo* (comparing marker specificity to existing, conventional markers), and *ex vivo* (perhaps comparing histology of biopsies to flow cytometric analysis of individual cells from biopsies).

Validation Resources

Basic validation guidance documents are available on the FDA website, and the International Conference on Harmonization has issued guidelines. ICH and FDA documents are often identical and provide basic validation information for many applications. Additionally, some journals publish validation recommendations [1], and validation papers for a procedure will sometimes appear [2, 3]. Following is a table listing validation guidance documents that are relevant to the NTR, along with specific recommendations for validation studies pertinent to optical imaging. Existing FDA and ICH guidance documents and guidelines are not specifically designed for optical imaging, so this chapter of the Investigator's Handbook attempts to identify validation processes that can be used with optical imaging agents.

Table 1: Validation Resources

Description	Source	Reference	Utility
<1058> Analytical Instrument Qualification	USP	USP/NF 33, 2010	To ensure a piece of equipment is suitable for its intended use; includes Design Qualification, Instrument Qualification, Operational Qualification, and Performance Qualification
<1225> Validation of Compendial Procedures	USP	USP/NF 33, 2010	Describes requirements for submission of compendia procedures to the USP
Guidance for Validation of Growth-Based Rapid Microbiological Methods for Sterility Testing of Cellular and Gene Therapy Products	FDA	http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm078696.pdf	Provides a method for rapid batch release sterility testing; approach can be used in other areas
Quality Management Systems – Process Validation Guidance	GHTF	http://www.ghtf.org/documents/sg3/sg3_fd_n99-10_edition2.pdf	Designed to assist in incorporating quality management system requirements for manufacturing, includes sample validation protocol and report
Guidance for Bioanalytical Method Validation	FDA	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107.pdf	Describes ways to validate analytical procedures, including immunologic assays
Process Validation Guidance for Industry: General Principles	FDA	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf	Describes 3 stages of process validation activities using a life cycle approach
Guideline on General Principles of Process Validation	FDA	http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124720.htm	Describes cGMP regulations for pharmaceuticals and medical devices, includes acceptance testing strategy

Table 1: Validation Resources, cont.

Description	Source	Reference	Utility
Development and validation of ELISA for Herceptin detection in human serum	Maple L, Lathrop R, et al.	Journal of Immunological Methods 295:169–182, 2004.	Example of a validation study procedures for an ELISA, provides a procedure and validation report
Annex 15 to the EU Guide to Good Manufacturing Practice Qualification and validation	EUROPA	http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2001/feb/annexe15.pdf	Describes principles of qualification and validation applicable to medicinal products manufacturing under GMP using a risk assessment approach to determine scope and extent of validation required
Validation of Analytical Procedures: Text and Methodology Q2(R1)	ICH	http://www.ich.org/LOB/media/MEDIA417.pdf	Same as FDA Guidance for Industry on validation of analytical procedures
Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products Q6B	ICH	http://www.ich.org/LOB/media/MEDIA432.pdf	Provides information of specifications for biological products rather than validation procedures; validated procedures are required to establish specifications
General Principles of Software Validation	FDA	http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085371.pdf	Includes recommendations for validating Software
Guidance for Qualification Process for Drug Development Tools	FDA	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf	Describes qualification process for tools intended for potential use over time in multiple drug development programs

References

1. DeSilva B., Smith W., Weiner R., Kelley M, Smolec JM, Lee B, Khan M, Tacey R, Hill H, and Celniker A. Recommendations for the Bioanalytical Method Validation of Ligand-binding Assays to Support Pharmacokinetic Assessments of Macromolecules. Pharmaceutical Research 20(11):1885-1900. November 2003.
2. Maple L, Lathrop R, Bozich S, Harman W, Tacey R, Kelley M, and Danilkovitch-Miagkova A. Development and validation of ELISA for Herceptin detection in human serum. Journal of Immunological Methods 295:169-182. 2004.
3. Jamieson D, Cresti N, Verrill MW, and Boddy AV. Development and validation of cell-based ELISA for the quantification of trastuzumab in human plasma. Journal of Immunological Methods 345:106-111. 2009.

GLP Testing (21CFR Part 58)

The regulations developed for FDA Good Laboratory Practice, 21CFR Part 58, came about as a result of fraudulent safety testing that was conducted by a contract research organization. The overall intention of 21CFR Part 58 (Good Clinical Practice for Nonclinical Laboratory Studies) is to provide a framework for conducting studies that ensures the integrity of study data and allows reconstruction of a study from beginning to end. Safety studies are required to be conducted in compliance with 21CFR Part 58 if they are submitted to the FDA. Device studies have been submitted that were not conducted in compliance with GLP regulations, but the FDA has indicated that the same standards for study conduct would apply with the exception of a Quality Assurance audit. Furthermore, justification for not conducting a study in compliance with 21CFR Part 58 must be provided in a submission. 21CFR Part 58 clearly states that safety studies are to be conducted in compliance with GLP regulations in the first section, §58.1. The regulations are intentionally general because they are used for different products – drugs, medical devices, and combination products, and testing requirements will differ for these different types of products. Preclinical safety data must be submitted as part of an Investigational New Drug (IND) or Investigational Device Exemption (IDE) application; INDs are obtained for clinical testing of drugs and biologics, whereas IDEs are obtained for testing medical devices. Combination products will have a determination of the regulatory pathway to follow (IND or IDE) based on the primary mode of action.

Personnel

Subpart B of 21CFR Part 58 describes responsibilities and training required of specific persons involved in GLP studies. For any position, personnel must have education, training, or experience to show that they are capable of doing the work in which they participate in a GLP study, and training records must be maintained according to §58.29. No specific educational requirements are given, just documentation that persons are capable of performing their duties. Steps must also be taken to protect personnel and the test system employed in a GLP study. A person must be identified as Management who has the ability to designate a Study Director and ensure all personnel involved in a GLP study have adequate education, training, or experience to perform their job functions according to §58.31. In addition, a Quality Assurance Unit (QAU) must be established that reports to Management. A Study Director must be designated by Management (§58.33) to be responsible for the overall conduct of the study, and this

person must be capable of analyzing the data obtained and prepare a final report of the study. A GLP study can only have one Study Director, and when parts of studies are contracted out, such as histopathology, the individual responsible for that portion of the study has to have a different designation, such as Principal Investigator or Principal Scientist. The Study Director must also ensure all records are archived at the end of a GLP study.

QAU responsibilities can be contracted out to a qualified person or persons if nobody at the test facility is capable of performing that function. A qualified QAU person would have the necessary education, training, or experience to perform that job function. The QAU is responsible for reporting to Management and the Study Director that protocols, SOPs, and GLP regulations are being followed during the course of a GLP study; if deviations occur, these must also be reported. QAU audit reports are to be kept separate from study records as they are only available to the FDA if a court order has been obtained that allows them access to these records. In addition, the QAU must review the final report for accuracy and provide a statement indicating when inspections were performed and Management and the Study Director were notified of the inspection results. A Master Schedule of all GLP studies conducted at the facility must also be maintained by the QAU.

Facilities

Facilities used to conduct GLP studies must be of adequate size and construction (§58.41). Specific requirements for animal facilities are given in sections 58.43 and 58.45. Other facilities required include an area for handling test and control articles to ensure their integrity before use in a GLP study (§58.47) and provisions for an archive with limited access (§58.51).

Equipment

Equipment used in GLP studies must be of suitable design for the intended use (§58.61). All instruments used to collect data must be calibrated to ensure they provide accurate data, and they must receive periodic maintenance (§58.63). Instructions for use and maintenance procedures must be provided in standard operating procedures (SOPs).

Test Facility Operation

SOPs are required for laboratory procedures, animal care and observation, animal identification, handling of test and control articles, and SOPs must be readily available to people who will be performing the duties specified in a protocol or SOP (§58.81). All reagents and solutions must be properly labeled and used within expiration dates (§58.83). Specific SOPs are also required for animal care procedures (§58.90).

Test and Control Articles

Test and control articles must be characterized before use (§58.105), and stability must be determined for the period of time in which the test and control articles are in use. Characterization of marketed products can be provided by the manufacturer. Additional specifications for handling (§58.107) and mixing test and control articles (§58.113) are also given.

Protocol and Study Conduct

A protocol must be prepared for each GLP study (§58.120), and it must be approved by the sponsor and signed by the Study Director prior to commencing work on a GLP study. Specific requirements for a protocol are given in this section, and provisions for changes in the protocol must be identiified. This is a key component of a GLP study as all protocols must be followed or deviations from them acknowledged. The protocol provides a description of what is to be done during a study, and SOPs describe how the steps to achieve protocol requirements are performed. In §58.130, requirements for study conduct are described, including data collection and correction requirements.

Records and Reports

Each GLP study must have a final report, and minimal elements of a final report for a GLP study are given in §58.185. This section of the GLP regulations also describes steps to follow to amend a report. Reports must also include signed expert reports should they be generated during a GLP study. An example is a histopathology report that is included as part of an overall safety study. These expert reports are easily incorporated into the final report as appendices. A space for an archive with limited access must be provided (§58.190). Minimum retention periods for GLP study records are provided in §58.195. If state regulations for record retention are more stringent, these more stringent requirements must be followed. The minimum retention period of records for a product that is marketed is 5 years from the submission of data for a marketing permit. With drugs and biologics, a marketing permit is a New Drug Application (NDA), and with devices, a marketing permit is Premarket Notification (also known as 510(k)) or Premarket Approval (PMA).

Disqualification of Test Facilities

Unique to FDA GLP regulations, specifications for test facility disqualification and requalification are provided in §58.200-§58.219. Disqualification of clinical investigators can also occur, and this information can be found online at http://www.fda.gov/ICECI/EnforcementActions/DisqualifiedRestrictedAssuranceList/default.htm.

Inspection of GLP studies (as well as manufacturers, clinical investigators, and institutional review boards) is conducted under the Bioresearch Monitoring (BiMo) program. Facilities, clinical investigators, and institutional review boards that receive Warning Letters are identified at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm.

Resources

FDA website www.fda.gov.
Electronic Code of Federal Regulations http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&tpl=%2Findex.tpl. Specific regulations for conducting GLP studies can be found under Title 21, Part 58.
The Investigations Operations Manual is a good resource to find out what FDA looks for during a facility inspection http://www.fda.gov/ICECI/Inspections/IOM/default.htm.
Guidance on the Bioresearch Monitoring program for GLP studies is found at http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133789.htm.

Good Manufacturing Practices – 21CFR Part 211 or 21CFR Part 820

Drugs and biologics come under the current Good Manufacturing Practice (cGMP) legislation, 21CFR Part 211; medical devices are covered by a similar regulation called the Quality System Regulations (QSR), 21CFR Part 820). The regulations are similar in that they both require documentation that the manufacturer controlled the manufacturing process, including raw materials used for manufacturing, and any changes made in manufacturing. Drugs and biologics, and some medical devices also require demonstration of purity and stability. Preclinical testing of a drug, device, or biologic should be done with the final clinical version of the product, manufactured in compliance with cGMP or QSR.

Manufacturing (21CFR Part 212 for PET radiopharmaceuticals)

A Guidance Document for cGMP of PET drug products, PET Drugs — Current Good Manufacturing Practice (CGMP) is specific to PET drug products, and manufacturers have to decide if they will manufacture these products under Good Manufacturing Practices or USP procedure <823> of the U. S. Pharmacopeia, Radiopharmaceuticals for Positron Emission Tomography - Compounding. A link to the FDA Guidance Document is:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070306.pdf.

The final rule for PET Drugs provides for modified cGMP practices that take the unique characteristics of short-lived radiopharmaceutical and very small manufacturing facilities into consideration. Examples of these modifications are permitting self-checking and allowing release prior to sterility results becoming available.

Note that PET Investigational agents (IND) are NOT required to follow the new PET cGMP regulations, but the facility may choose to follow 21 CFR 212 or continue to adhere to U. S. Pharmacopeia (USP) <823>, RADIOPHARMACEUTICALSFOR POSITRON EMISSIONTOMOGRAPHY—COMPOUNDING. Additional USP chapter apply also, particularly <797>, PHARMACEUTICAL COMPOUNDING—STERILE PREPARATIONS and the general chapters within the USP that are referenced by this procedure.

Basic Principles of Manufacturing

As previously indicated for preclinical studies, basic requirements to be followed in Good Manufacturing Practices or the Quality System Regulations are training of individuals, documentation of training, and demonstration that the product functions as it is intended. Documentation of the suitability of raw materials used must be provided. Written SOPS must also be in place to demonstrate consistency between different lots or batches of products. Of primary importance to materials that are injected or implanted are sterility, lack of pyrogenicity, and biocompatibility. Good recordkeeping enables tracking of problems, particularly in the ingredients used or the process of manufacturing. This is analogous to the recordkeeping requirements for preclinical studies that enable studies to be reconstructed once they have been completed.

A link to different documents related to drug manufacturing practices for drugs can be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/default.htm; a good source for information on medical devices can be found at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm. The FDA has issued a Guidance Document of implementing Quality Systems in drug manufacturing, Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations that can be found at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070337.pdf. The Guidance Document for Phase I investigational drugs, including in vivo diagnostics, can be found at the following link: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070273.pdf. Provisions in this Guidance Document do not apply to medical devices or to PET drug products. A specific Guidance Document was developed for Combination Products, Current Good Manufacturing Practice for Combination Products: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070268.pdf.

Manufacturing facilities must be registered with the FDA, and the facilities can expect to be inspected by the FDA before commercial distribution occurs, including devices cleared through the 510(k) process. Guidance on registration of drug and biologic manufacturing facilities can be found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072339.pdf. Regulations for medical device establishment registration can be found in 21CFR Part 807. Useful information on medical device establishment registration can be found at the following link: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/RegistrationandListing/default.htm.

Examples of types of information to be obtained on a drug product, some of which are specific to nanoparticulate-containing products are:

Release specifications for the active pharmaceutical ingredient (API)

1. Appearance
2. Assay/Impurities by high pressure liquid chromatography (HPLC)
3. Identity by HPLC
4. Identity by Mass Spectrometry (MS)
5. Chiral Verification by USP
6. Moisture by USP
7. Organic Volatile Impurities by GC
8. Elemental Analysis
9. Heavy Metals by USP
10. Potency

Final formulated product (as appropriate) release specifications.

1. Appearance
2. API Assay/Impurities by HPLC

3. API Identity by HPLC
4. pH by USP
5. Osmolality by USP
6. Endotoxin by USP
7. Sterility by USP
8. Particulates by USP

Biochemical characterization should be determined and documented:

1. Binding affinity
2. Binding cross-reactivity
3. Matrix effects of plasma

For Nanoparticulate Molecular Imaging agents, the targeting ligand API release specifications prior to formulation into a sterile product may include as appropriate:

1. Appearance
2. Assay by HPLC
3. Impurities by HPLC
4. Identity by HPLC
5. Identity by MS
6. Identity by ^{1}H NMR
7. Chiral Verification by USP
8. Chiral Purity by HPLC
9. Moisture by USP
10. Organic Volatile Impurities by GC
11. Elemental Analysis
12. Heavy Metals by ICP-MS
13. Endotoxin by rabbit assay or Limulus Amoebocyte Lysate
14. Sterility by USP

For Nanoparticulate Molecular Imaging agents, the lipophilic chelate, release specifications prior to formulation into a sterile product may include as appropriate:

1. Appearance
2. Assay by HPLC
3. Impurities by HPLC
4. Identity by HPLC
5. Identity by MS
6. Identity by IR
7. Chiral Verification by USP
8. Chiral Purity by HPLC
9. Free API by HPLC-ICP-MS
10. Moisture by USP
11. Organic Volatile Impurities by GC
12. Elemental Analysis

13. Heavy Metals by ICP-MS
14. Endotoxin by LAL assay
15. Sterility by USP
16. Stability
17. Solubility

Release specifications of a final nanoproduct for preclinical testing:

1. Appearance
2. Topology
3. Molecular Weight
4. Aggregation
5. Purity
6. Chemical Composition
7. Surface Characteristics
8. Functionality
9. Zeta Potential
10. API assay by HPLC
11. Impurities by HPLC
12. Targeting ligand assay by HPLC
13. Targeting ligand impurities by HPLC
14. Egg yolk protein (EYP) lipid assay by HPLC
15. EYP impurities by HPLC
16. Perfluorooctyl bromide (PFOB) assay by GC
17. Particle Size and size distribution
18. Zeta Potential
19. pH by USP
20. Free API by HPLC-ICP-MS
21. Total API by ICP-MS
22. Heavy Metals by ICP-MS
23. API Chiral Purity by HPLC
24. Excipient Purity by HPLC
25. Specific Gravity by USP
26. Osmolality by USP
27. Endotoxin by LAL test
28. Sterility
29. Particulates

Additional information needed before conducting GLP-compliant preclinical studies:

1. Hemocompatibility
2. Complement activation (in vitro or in vivo)
3. Cytokine activation (in vitro or in vivo)
4. Pharmacokinetics of the major components
5. Biodistribution

6. Stability in plasma
7. In vitro cytotoxicity such as a 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay
8. Sensitization
9. Range-finding study and dosage schedule determination
10. Stability and storage conditions

Clinical Studies

Pre-IND or Pre-IDE Meeting

A pre-IND or Pre-IDE meeting should be held to review the proposed work that will go into an FDA submission. This meeting should be held before preclinical studies begin so that the FDA agrees to an approach, although recommendations from Pre-IND or Pre-IDE reviewers are not binding on the FDA. A draft Guidance Document, "IND Meetings for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information" is available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070568.pdf.

Sponsors are encouraged to submit pre-IDE submissions while the sponsor is preparing the formal IDE submission whenever the sponsor requires informal FDA guidance on troublesome parts of the IDE application, e.g., clinical protocol design, pre-clinical testing proposal, pre-clinical test results, protocols for foreign studies when the studies will be used to support future marketing applications to be submitted to FDA. Upon completion of the review of the pre-IDE submission, the reviewing division will issue a response to the sponsor in a timely manner, usually within 60 days of receipt. The response may take the form of a letter or comments provided during a meeting or telephone conference call. If FDA's response is provided via comments during a meeting or a telephone conference call, a memo of the meeting or conference call will be prepared.

A pre-IDE submission must be clearly identified as such, submitted in duplicate, and addressed to:

Center for Devices and Radiological Health
Food and Drug Administration
IDE Document Mail Center (HFZ-401)
9200 Corporate Boulevard Rockville, MD 20850-3223

Additional information on Device Advice for IDEs can be found at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm126600.htm. Information on early meetings with the FDA can be found at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073611.pdf.
A good general description of the device marketing process can be found at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/default.html.

IND or IDE Submission

Information for Sponsor-Investigators Submitting Investigational New Drug Applications (INDs) can be found at:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071098.htm#form1571.

It is important to remember that a Sponsor-Investigator also must assume the role of the sponsor in a clinical trial. This includes all reporting activities such as an annual report to the FDA and any serious adverse events that occur during a clinical study.

General requirements for submission of an IND, including specific information required in a submission can be found in the document, "Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products", which can be found at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071597.pdf

Specific contents of an IND are found in 21CFR §312.23, and include the following:

(1) *Cover sheet (Form FDA–1571).* A cover sheet for the application containing the following:

(i) The name, address, and telephone number of the sponsor, the date of the application, and the name of the investigational new drug.

(ii) Identification of the phase or phases of the clinical investigation to be conducted.

(iii) A commitment not to begin clinical investigations until an IND covering the investigations is in effect.

(iv) A commitment that an Institutional Review Board (IRB) that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation and that the investigator will report to the IRB proposed changes in the research activity in accordance with the requirements of part 56.

(v) A commitment to conduct the investigation in accordance with all other applicable regulatory requirements.

(vi) Name and title of the person responsible for monitoring the conduct and progress of the clinical investigations.

(vii) The name(s) and title(s) of the person(s) responsible under §312.32 for review and evaluation of information relevant to the safety of the drug.

(viii) If a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization (CRO), a statement containing the name and address of the CRO, identification of the clinical study, and a listing of the obligations transferred. If all obligations governing the conduct of the study have been transferred, a general statement of this transfer—in lieu of a listing of the specific obligations transferred—may be submitted.

(ix) The signature of the sponsor or the sponsor's authorized representative. If the person signing the application does not reside or have a place of business within the United States, the IND is required to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

(2) *Table of contents.*

(3) *Introductory statement and general investigational plan.*

(i) A brief introductory statement giving the name of the drug and all active ingredients, the drug's pharmacological class, the structural formula of the drug (if known), formulation of the dosage form(s) to be used, route of administration, and the broad objectives and planned duration of the proposed clinical investigation(s).

(ii) A brief summary of previous human experience with the drug, with reference to other INDs if pertinent, and to investigational or marketing experience in other countries that may be relevant to the safety of the proposed clinical investigation(s).

(iii) If the drug has been withdrawn from investigation or marketing in any country for any reason related to safety or effectiveness, identification of the country(ies) where the drug was withdrawn and the reasons for the withdrawal.

(iv) A brief description of the overall plan for investigating the drug product for the following year. The plan should include the following: (*a*) The rationale for the drug or the research study; (*b*) the indication(s) to be studied; (*c*) the general approach to be followed in evaluating the drug; (*d*) the kinds of clinical trials to be conducted in the first year following the submission (if plans are not developed for the entire year, the sponsor should so indicate); (*e*) the estimated number of patients to be given the drug in those studies; and (*f*) any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs.

(4) [Reserved]

(5) *Investigator's brochure.* If required under §312.55, a copy of the investigator's brochure, containing the following information:

(i) A brief description of the drug substance and the formulation, including the structural formula, if known.

(ii) A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.

(iii) A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.

(iv) A summary of information relating to safety and effectiveness in humans obtained from prior clinical studies. (Reprints of published articles on such studies may be appended when useful.)

(v) A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug.

(6) *Protocol.*

(i) A protocol for each planned study. (Protocols for studies not submitted initially in the IND should be submitted in accordance with §312.30(a).) In general, protocols for Phase 1 studies may be less detailed and more flexible than protocols for Phase 2 and 3 studies. Phase 1 protocols should be directed primarily at providing an outline of the investigation—an estimate of the number of subjects to be involved, a description of safety exclusions, and a description of the dosing plan including duration, dose, or method to be used in determining dose—and should specify in detail only those elements of the study that are critical to safety, such as necessary monitoring of vital signs and blood chemistries. Modifications of the experimental design of Phase 1 studies that do not affect critical safety assessments are required to be reported to FDA only in the annual report.

(ii) In Phases 2 and 3, detailed protocols describing all aspects of the study should be submitted. A protocol for a Phase 2 or 3 investigation should be designed in such a way that, if the sponsor anticipates that some deviation from the study design may become necessary as the investigation progresses, alternatives or contingencies to provide for such deviation are built into the protocols at the outset. For example, a protocol for a controlled short-term study might include a plan for an early crossover of non-responders to an alternative therapy.

(iii) A protocol is required to contain the following, with specific elements and detail of the protocol reflecting the above distinctions depending on the phase of study:

(*a*) Statement of the objectives and purpose of the study.

(*b*) Name and address and a statement of the qualifications (curriculum vitae or other statement of qualifications) of each investigator, and the name of each sub-investigator (e.g., research fellow, resident) working under the supervision of the investigator; the name and address of the research facilities to be used; and the name and address of each reviewing Institutional Review Board.

(*c*) Criteria for subject selection and for exclusion of subjects and an estimate of the number of subjects to be studied.

(*d*) Description of the design of the study, including the kind of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, investigators, and analysts.

(*e*) Method for determining the dose(s) to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug.

(*f*) Description of observations and measurements to be made to fulfill the study objectives.

(*g*) Description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.

(7) *Chemistry, manufacturing, and control information.*

(i) As appropriate for particular investigations covered by the IND, a section is required describing the composition, manufacture, and control of the drug substance and the drug product. Although in each phase of the investigation sufficient information is required to be submitted to assure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, dosage form, and amount of information otherwise available. FDA recognizes that modifications to the method of preparation of a new drug substance and dosage form and changes in dosage form itself are likely as the investigation progresses. Therefore, the emphasis in an initial Phase 1 submission should generally be placed on the identification and control of the raw materials and the new drug substance. Final specifications for the drug substance and drug product are not expected until the end of the investigational process.

(ii) It should be emphasized that the amount of information to be submitted depends upon the scope of the proposed clinical investigation. For example, although stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data can be correspondingly limited.

(iii) As drug development proceeds and as scale or production is changed from pilot-scale production appropriate for limited initial clinical investigations to larger-scale production needed for expanded clinical trials, the sponsor should submit information amendments to supplement the initial information submitted on the chemistry, manufacturing, and control processes with information appropriate to the expanded scope of the investigation.

(iv) Reflecting the distinctions described in this paragraph (a)(7), and based on the phase(s) to be studied, the submission is required to contain the following:

(*a*) *Drug substance.* A description of the drug substance, including its physical, chemical, or biological characteristics; the name and address of its manufacturer; the general method of preparation of the drug substance; the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance; and information sufficient to support stability of the drug substance during the toxicological studies and the planned clinical studies. Reference to the current edition of the United States Pharmacopeia—National Formulary may satisfy relevant requirements in this paragraph.

(*b*) *Drug product.* A list of all components that may include reasonable alternatives for inactive compounds, used in the manufacture of the investigational drug product, including both those components intended to appear in the drug product and those which may not appear but which are used in the manufacturing process, and, where applicable, the quantitative composition of the investigational drug product, including any reasonable variations that may be expected during the investigational stage; the name and address of the drug product manufacturer; a brief general description of the manufacturing and packaging procedure as appropriate for the product; acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of a drug product; and information sufficient to assure the product's stability during the planned clinical studies. Reference to the current edition of the United States Pharmacopeia—National Formulary may satisfy some of these requirements.

(*c*) A brief general description of the composition, manufacture, and control of any placebo used in a controlled clinical trial.

(*d*) *Labeling.* A copy of all labels and labeling to be provided to each investigator.

(*e*) *Environmental analysis requirements.* A claim for categorical exclusion under §25.30 or 25.31 or an environmental assessment under §25.40.

(8) *Pharmacology and toxicology information.* Adequate information is needed about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required varies with the duration and nature of proposed clinical investigations. Guidance documents are available from FDA describing ways in which these requirements may be met. Such information is required to include the identification and qualifications of individuals who evaluate the results of such studies and conclude that it is reasonably safe to begin a proposed investigation and a statement of where the investigations were conducted and where the records are available for inspection. As drug development proceeds, the sponsor is required to submit informational amendments, as appropriate, with additional information pertinent to safety.

(i) *Pharmacology and drug disposition.* A section must be submitted describing the pharmacological effects and mechanism(s) of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if known.

(ii) *Toxicology.*

(a) An integrated summary of the toxicological effects of a drug in animals and in vitro. Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, subacute, and chronic toxicity tests; tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies intended to evaluate drug toxicity.

(*b*) For each toxicology study that is intended primarily to support the safety of the proposed clinical investigation, a full tabulation of data must be suitable for detailed review.

(iii) For each nonclinical laboratory study subject to GLP regulations (21CFR Part 58), a statement must be included that the study was conducted in compliance with the good laboratory practice regulations in part 58, or, if the study was not conducted in compliance with those regulations, a reason for noncompliance must be given.

(9) *Previous human experience with the investigational drug.* A summary of previous human experience with the investigational drug that is known to the applicant must be given. The information must include the following:

(i) If the investigational drug has been investigated or marketed previously, either in the United States or other countries, detailed information about such experience that is relevant to the safety of the proposed investigation or to the investigation's rationale. If the drug has been the subject of

controlled trials, detailed information on such trials that is relevant to an assessment of a drug's effectiveness for the proposed investigational use(s) should also be provided. Any published material that is relevant to the safety of the proposed investigation or to an assessment of the drug's effectiveness for its proposed investigational use should be provided in full. Published material that is less directly relevant may be supplied by a bibliography.

(ii) If the drug is a combination of drugs previously investigated or marketed, information required under paragraph (a)(9)(i) of this section should be provided for each active drug component. However, if any component in such combination is subject to an approved marketing application or is otherwise lawfully marketed in the United States, the sponsor is not required to submit published material concerning that active drug component unless such material relates directly to the proposed investigational use (including publications relevant to component-component interaction).

(iii) If a drug has been marketed outside the United States, a list of the countries in which the drug has been marketed and a list of countries in which the drug has been withdrawn from marketing for reasons potentially related to safety or effectiveness must be provided.

(10) *Additional information.* In certain applications, as described below, information on special topics may be needed. Such information shall be submitted in this section as follows:

(i) *Drug dependence and abuse potential.* If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and experience and studies in test animals.

(ii) *Radioactive drugs.* If a drug is radioactive, sufficient data from animal or human studies must be provided to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject. Phase 1 studies of radioactive drugs must include studies that will obtain sufficient data for dosimetry calculations.

(iii) *Pediatric studies.* Plans for assessing pediatric safety and effectiveness must be included.

(iv) *Other information.* A statement is needed of any other information that would aid evaluation of the proposed clinical investigations with respect to their safety or design and potential as controlled clinical trials to support marketing of the drug.

(11) *Relevant information.* If requested by FDA, any other relevant information needed for review of the application must be provided.

(b) *Information previously submitted.* The sponsor ordinarily is not required to resubmit information previously submitted, but may incorporate the information by reference. A reference to information submitted previously must identify the file by name, reference number, volume, and page number where the information can be found. A reference to information submitted to the agency by a person other than the sponsor is required to contain a written statement that authorizes the reference and that is signed by the person who submitted the information (Letter of Authorization).

(c) *Material in a foreign language.* The sponsor shall submit an accurate and complete English translation of each part of an IND that is not in English. The sponsor shall also submit a copy of each original literature publication for which an English translation is submitted.

(d) *Number of copies.* The sponsor shall submit an original and two copies of all submissions to the IND file, including the original submission and all amendments and reports.

(e) *Numbering of IND submissions.* Each submission relating to an IND is required to be numbered serially using a single, three-digit serial number. The initial IND is required to be numbered 000; each subsequent submission (e.g., amendment, report, or correspondence) is required to be numbered chronologically in sequence.

(f) *Identification of exception from informed consent.* If the investigation involves an exception from informed consent under §50.24 of this chapter, the sponsor shall prominently identify on the cover sheet that the investigation is subject to the requirements in §50.24 of this chapter.

An excellent resource for preparation of an IND is: The Sponsor's Guide to Regulatory Submissions for an Investigational New Drug, which can be found at: http://wwwbdp.ncifcrf.gov/pdf/GuidetoRegSubs.pdf. This document provides an explanation for the contents of each section, and it would be worth reviewing even if an IDE would be submitted.

Specific requirements for an IDE are given in 21CFR §812.20, §812.25, and §812.27:

§812.20 Application

(a) *Submission.*

(1) A sponsor shall submit an application to FDA if the sponsor intends to use a significant risk device in an investigation, intends to conduct an investigation that involves an exception from informed consent under 21CFR §50.24, or if FDA notifies a sponsor that an application is required for an investigation.

(2) A sponsor shall not begin an investigation for which FDA's approval of an application is required until FDA has approved the application.

(3) A sponsor shall submit three copies of a signed "Application for an Investigational Device Exemption" (IDE application), together with accompanying materials, by registered mail or by hand to the address in §812.19. Subsequent correspondence concerning an application or a supplemental application shall be submitted by registered mail or by hand.

(4)(i) A sponsor shall submit a separate IDE for any clinical investigation involving an exception from informed consent under §50.24. Such a clinical investigation is not permitted to proceed without the prior written authorization of FDA. FDA shall provide a written determination 30 days after FDA receives the IDE or earlier.

(ii) If the investigation involves an exception from informed consent under §50.24 of this chapter, the sponsor shall prominently identify on the cover sheet that the investigation is subject to the requirements in §50.24.

(b) *Contents.* An IDE application shall include, in the following order:

(1) Name and address of the sponsor.

(2) Complete report of prior investigations of the device and an accurate summary of those sections of the investigational plan described in §812.25(a) through (e) or, in lieu of the summary, the complete plan. The sponsor shall submit to FDA a complete investigational plan and a complete report of prior investigations of the device if no IRB has reviewed them, if FDA has found an IRB's review inadequate, or if FDA requests them.

(3) Description of the methods, facilities, and controls used for the manufacture, processing, packing, storage, and, where appropriate, installation of the device, in sufficient detail so that a person generally familiar with good manufacturing practices can make a knowledgeable judgment about quality control used in device manufacture.

(4) Example of an agreement to be entered into by all investigators to comply with investigator obligations under this part, and a list of the names and addresses of all investigators who have signed the agreement.

(5) Certification that all investigators who will participate in the investigation have signed the agreement, that the list of investigators includes all the investigators participating in the investigation, and that no investigators will be added to the investigation until they have signed the agreement.

(6) Name, address, and chairperson of each IRB that reviews the investigation and a certification of action concerning the investigation taken by each IRB.

(7) Name and address of any institution at which a part of the investigation may be conducted that has not been identified in accordance with paragraph (b)(6) of this section.

(8) If the device is to be sold, the amount to be charged and an explanation of why sale does not constitute commercialization of the device.

(9) Claim for categorical exclusion under §25.30 or 25.34 or an environmental assessment under §25.40.

(10) Copies of all labeling for the device.
(11) Copies of all forms and informational materials to be provided to subjects to obtain informed consent.
(12) Any other relevant information FDA requests for review of the application.
(c) *Additional information.* FDA may request additional information concerning an investigation or revision in the investigational plan. The sponsor may treat such a request as a disapproval of the application for purposes of requesting a hearing under part 16.
(d) *Information previously submitted.* Information previously submitted to the Center for Devices and Radiological Health in accordance with this chapter ordinarily need not be resubmitted, but may be incorporated by reference.

§ 812.25 Investigational plan.
The investigational plan shall include, in the following order:
(a) *Purpose.* The name and intended use of the device and objectives and duration of an investigation must be provided.
(b) *Protocol.* A written protocol describing methodology to be used must be included and an analysis of the protocol demonstrating that the investigation is scientifically sound.
(c) *Risk analysis.* A description and analysis of all increased risks to which subjects will be exposed by the investigation; the manner in which these risks will be minimized; a justification for the investigation; and a description of the patient population, including the number, age, sex, and condition.
(d) *Description of device.* A description of each important component, ingredient, property, and principle of operation of the device and of each anticipated change in the device during the course of the investigation.
(e) *Monitoring procedures.* The sponsor's written procedures for monitoring the investigation and the name and address of any monitor.
(f) *Labeling.* Copies of all labeling for the device must be included.
(g) *Consent materials.* Copies of all forms and informational materials to be provided to subjects to obtain informed consent must be included.
(h) *IRB information.* A list of the names, locations, and chairpersons of all IRBs that have been or will be asked to review the investigation, and a certification of any action taken by any of those IRBs with respect to the investigation.
(i) *Other institutions.* The name and address of each institution at which a part of the investigation may be conducted that has not been identified in paragraph (h) of this section must be included.
(j) *Additional records and reports.* A description of records and reports that will be maintained on the investigation in addition to those prescribed in subpart G.

§ 812.27 Report of prior investigations.
(a) *General.* The report of prior investigations shall include reports of all prior clinical, animal, and laboratory testing of the device and shall be comprehensive and adequate to justify the proposed investigation.
(b) *Specific contents.* The report also shall include:
(1) A bibliography of all publications, whether adverse or supportive, that are relevant to an evaluation of the safety or effectiveness of the device, copies of all published and unpublished adverse information, and, if requested by an IRB or FDA, copies of other significant publications.
(2) A summary of all other unpublished information (whether adverse or supportive) in the possession of, or reasonably obtainable by, the sponsor that is relevant to an evaluation of the safety or effectiveness of the device.

(3) If information on nonclinical laboratory studies is provided, a statement that all such studies have been conducted in compliance with applicable requirements in the good laboratory practice regulations in part 58, or if any such study was not conducted in compliance with such regulations, a statement of the reason for noncompliance. Failure or inability to comply with this requirement does not justify failure to provide information on a relevant nonclinical test study.

An FDA Guidance on IDE Policies and Procedures document is more than 10 years old, but it can be found at:
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080203.pdf

CRFs and SOPs

Case Report Forms (CRFs) and Standard Operating Procedures (SOPs) should be developed with the study endpoints in mind. Required items that will be used to prepare study-specific CRFs should be discussed during pre-IND or pre-IDE meetings. SOPs are needed for clinical studies to comply with the ICH E6 Good Clinical Practice Guidelines. As SciPort is developed, both CRFs and SOPs can be developed using the software, and data can be entered electronically. Case report forms are to be retained by the sponsor, and a copy should be retained at the study site. Source documentation should also be retained at the study site for review by a study monitor. Some source documents can be generated with SciPort.

Study subject demographic information and medical history will usually be included in CRFs for every study, but other information to be captured in CRFs or source documents will be study-specific and must be developed by each group that conducts a clinical trial. Data obtained from each study should be captured on source documents and transferred to CRFs. Data such as vital signs or clinical chemistry and hematology results should also be included, as well as adverse events. Because SciPort was developed to store image data, imaging results can also be kept in SciPort.

SOPs that support preclinical study needs or GMP procedures performed for a study should be written before the procedure is performed. Many times, this involves extracting information from a protocol. Examples of SOPs include preparation of an imaging agent for administration, QA procedures for devices to ensure they are operating properly before each use, and procedures for development and completion of case report forms. Guidance documents for clinical trials can be found at: http://www.fda.gov/RegulatoryInformation/Guidances/ucm122046.htm; other useful links can be found on this web page. Some examples of case report forms can be found at: http://dcp.cancer.gov/clinicaltrials/management/consortia/step-1/forms.

Clinical SOP examples can be found in the Quality Assurance Journal, where 23 clinical SOPs were published between 1998 and 2005. Examples of the types of SOPs needed for a clinical trial are:

Administrative
Preparation of SOPs
Research Study Personnel Qualifications and Training
Responsibilities of Principal investigators
Responsibilities of Study Coordinators
FDA Audit Procedures

Sponsor/CRO Monitoring Procedures
Sponsor/CRO Audit Procedures
Resolution of Conflicts between Protocols and SOPs
Archives
Reporting Conflict of Interest

Study Conduct
Protocol Development
Regulatory Binder Contents and Preparation
Study Initiation
Study Termination
Subject Identification, Selection, and Recruitment
Obtaining Informed Consent
Subject Confidentiality and Privacy
Emergency Use of Investigational Agents or Devices
Humanitarian Use Devices
Investigational Drug Accountability
Investigational Device Accountability
Completing Case Report Forms
Making Corrections
Adverse Event Reporting
Protocol Deviation Documentation and Reporting
Obtaining IRB Approval for a Clinical Study
Submitting Annual Reports to the IRB
Scheduling Visits or Procedures
Specimen Collection and Preparation
Regulatory Binder Contents
Study Binders
Destruction of Investigational Products
Return of Investigational Products
Blinding and Unblinding

Electronic Records
Computer Validation
Data Collection and Handling
Electronic Signatures
System Maintenance
Data Backup, Recovery, and Contingency Plans
System Security
Change Control
Alternative Record Collection due to System Unavailability
Database Entry
Database Security
eMail Communications

Equipment
Equipment Calibration and Maintenance
Operation of the Blood Glucose Monitor

Procedures
Universal precautions
How to Draw Blood Samples
How to Prepare Plasma Samples
How to Monitor Blood Pressure

IRB approval

IRB approval must be obtained prior to starting a clinical investigation, with few exceptions. IRB requirements differ among institutions, so to obtain specific requirements for an IRB submission, consult your local IRB. The IRB approval letter can accompany the IND or IDE submission if it is obtained prior to FDA issuing an IND or IDE number.

Registering Clinical Trials

Clinical trials must be registered with clinicaltrials.gov, with few exceptions. Form 3674 is used to describe the registration status for the FDA. The PI must register a trial on clinicaltrials.gov. Instructions for trial registration can be found at: http://prsinfo.clinicaltrials.gov/.