Guidance for Industry and FDA Staff

In Vitro Diagnostic (IVD) Device Studies -Frequently Asked Questions

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This document supersedes "Guidance for FDA Staff: Regulating In Vitro Diagnostic Device (IVD) Studies," issued December 17, 1999.

For questions regarding this document, contact Sally Hojvat, Ph.D. in CDRH at 301-796-5455 or the Office of Communication, Outreach and Development in CBER at 1-800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

Preface

Additional Copies

Additional copies are available from the Internet at:
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071230.pdf,

Or, contact:

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Guidance for Industry and FDA Staff

In Vitro Diagnostic (IVD) Device Studies Frequently Asked Questions

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Background

The Investigational Device Exemptions (IDE) regulation, Title 21, Code of Federal Regulations (21 CFR) Part 812, sets forth regulatory requirements for studies of investigational devices. Certain investigational IVD device studies (see the **Glossary**), however, are exempt from most of the provisions of 21 CFR Part 812 (21 CFR 812.2(c)(3)).[1] This guidance document, written in question and answer format, is intended to assist **you**[2] (the manufacturer, sponsor, applicant, investigator and the IVD device industry in general) in the development of IVD studies, particularly those exempt from most of the requirements of the IDE regulation and to provide you with a broad view of the regulatory framework pertaining to the development phase of IVD devices. The information in this guidance document is also pertinent to investigators who participate in IVD studies and to institutional review boards (IRB) that review and approve such studies. The document is intended to facilitate the movement of new IVD technology from the investigational stage to the marketing stage.

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[1] As explained below, even if a particular IVD study is exempt from most requirements of 21 CFR Part 812, studies that will support applications to FDA are subject to 21 CFR 812.119 (Disqualification of a Clinical Investigator), 21 CFR Part 50 (Informed Consent), and 21 CFR Part 56 (Institutional Review Boards).

[2] For the purpose of this document, “you” refers to the manufacturer, sponsor, applicant, investigator and the IVD device industry in general. If the text refers only to one or some of these entities, the appropriate entity is referenced
by its name.

This guidance document outlines FDA regulations applicable to studies for investigational IVD devices, including those regulations related to human subject protection. The guidance also explains data considerations that ultimately will affect the quality of the premarket submission. This document includes a glossary, a reference list with related web addresses, and a quick-reference table.

The Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation and Research (CBER) each have regulatory responsibilities for IVD devices; information included in this document applies to Class I, II, and III IVD devices regulated by either Center.

> Note: Some devices used to test blood donor suitability, and blood donor and recipient compatibility are licensed as biological products under Section 351 of the Public Health Service Act and are subject to the applicable regulations in 21 CFR Parts 600-680 . Examples of licensed biologics devices include blood donor screening tests for human immunodeficiency virus (HIV) and hepatitis B and C tests intended for blood screening and reagents used in blood grouping, antibody detection and identification, and crossmatching for pre-transfusion compatibility testing. This guidance is written to address only IVD devices that are approved or cleared under the Federal Food, Drug, and Cosmetic Act (the Act) and Part 800 of the device regulations, regardless of which Center reviews the submission. If you have questions about a device licensed by CBER, you may go to the CBER website for published guidance (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm) or contact CBER for further information on applicable guidance and regulations. (See **Introduction**, Section II, question # 4, of this guidance for a listing of CBER contact numbers).

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

II. Introduction

1. What is the purpose of this guidance document and how does it differ from other guidance documents related to IVD products?

> FDA prepared this comprehensive document as a resource for you and for its own staff to address issues concerning IVD studies. This guidance document contains information relevant to studies conducted during the development of a new IVD product, as well as other general considerations about applicable requirements and marketing of the new device. It addresses particularly those investigational studies that are exempt from the majority of requirements under 21 CFR Part 812. IVD study investigators and members of IRBs who review and approve such studies

may also find it helpful. There are also device-specific guidance documents available for specific IVD products that can be found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfggp/search.cfm. The use of investigational IVD devices in clinical studies designed to evaluate new drug products falls outside the scope of this guidance.

2. Why are in vitro diagnostics considered devices?

In vitro diagnostics (IVDs) meet the definition of a device under the Act. Section 201(h) of the Act defines a device as:

> "an instrument, apparatus, implement, machine, contrivance, implant, **in vitro reagent**, or other similar or related article, including any component, part, or accessory, which is—
>
> (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
>
> (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
>
> (3) intended to affect the structure or any function of the body of man or other animals, and
>
> which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes." 21 U.S.C. 321(h) (emphasis added).

3. How do IVD devices differ from other devices?

Most other devices function on or in a patient. In contrast, IVDs include products used to collect specimens, or to prepare or examine specimens (e.g., blood, serum, urine, spinal fluid, tissue samples) after they are removed from the human body.

4. Which Divisions at FDA are responsible for review of IVD products?

Center for Devices and Radiological Health (CDRH)

- Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD)
  - **Division of Chemistry and Toxicology Devices** – Phone: **(301) 796-5470**
  - **Division of Immunology and Hematology Devices –** Phone: **(301) 796-5481**
  - **Division of Microbiology Devices** – Phone: **(301) 796-5461**

Center for Biologics Evaluation and Research (CBER)

- Office of Cell, Tissues, and Gene Therapy (OCTGT) – Phone: **(301) 827-5102**

- Office of Blood Research and Review (OBRR)
  - **Division of Blood Applications** (DBA) – Phone: **(301) 827-3524**

DBA schedules all review-related meetings for OBRR
• **Division of Emerging and Transfusion Transmitted Diseases** (DETTD) – Phone: **(301) 827-3008**
• **Division of Hematology** (DH) – Phone: **(301) 496-4396**

5. Whom should I consult when I have questions about the manufacturing regulations or the conduct of a study (e.g., human subject protection issues)?

Center for Devices and Radiological Health (CDRH)

For questions regarding **manufacturing** regulations and IVD-specific conduct of studies, contact:
Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD)
Regulatory Staff, Patient Safety and Product Quality – Phone: (301) 796-5450

For questions regarding the **conduct of studies**, contact:
Office of Compliance (OC)
Division of Bioresearch Monitoring (DBM)
Phone: (301) 796-5490
or
Investigational Device Exemptions (IDE) Staff
Office of Device Evaluation
Phone: (301) 796-5640

Center for Biologics Evaluation and Research (CBER)

For questions regarding **manufacturing** regulations and IVD-specific conduct of studies, contact the appropriate reviewing division identified in the previous answer.

For questions regarding the **conduct of studies**, contact:
Office of Compliance and Biologics Quality (OCBQ**)**
Division of Inspections and Surveillance (DIS)
Bioresearch Monitoring Branch – Phone: (301) 827-6221

III. General Regulatory Issues

1. Which regulations contain provisions relevant to the IVD industry?

Listed below are some of the regulations that implement the Act and that are relevant to IVDs covered by this guidance. See Table 1 (Appendix 1) for additional information. This is not an all-inclusive list.

Title 21, Code of Federal Regulations (21 CFR)
Part 11, Electronic Records; Electronic Signatures
Part 50, Protection of Human Subjects

Part 54, Financial Disclosure by Clinical Investigators
Part 56, Institutional Review Boards
Part 801, Labeling
Part 803, Medical Device Reporting
Part 807, Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices
Part 809, In Vitro Diagnostic Products for Human Use
Part 810, Medical Device Recall Authority
Part 812, Investigational Device Exemptions
Part 814, Premarket Approval of Medical Devices
Part 820, Quality System Regulation
Part 860, Medical Device Classification Procedures
Part 862, Clinical Chemistry and Clinical Toxicology Devices
Part 864, Hematology and Pathology Devices
Part 866, Immunology and Microbiology Devices
In addition, certain sections of Part 610 apply to devices that employ human blood components. For example:
610.40, Test Requirements (Testing Requirements for Communicable Disease Agents)
610.42, Restrictions on Use for Further Manufacture of Medical Devices

2. How do I determine the applicability of the IDE regulation to my IVD study?

We recommend that you begin with the exemptions in 21 CFR 812.2(c). Your proposed IVD study is exempt from most provisions of the IDE regulation if it fits any one of the following three categories:

a. The IVD is a pre-amendments device (i.e., a device that was in commercial distribution prior to the enactment of the 1976 Medical Device Amendments to the Act), other than a transitional device (see the **Glossary** for definition), and is used or investigated according to the indications in the labeling at that time.

b. The IVD is a device, other than a transitional device, that has been found to be substantially equivalent to a pre-amendments device and is used or investigated according to the indications in the labeling reviewed by FDA in determining substantial equivalence.

c. The IVD

- is properly labeled in accordance with 21 CFR 809.10(c);
- is noninvasive (see question #5 below);
- does not require an invasive sampling procedure that presents significant risk (see question #4 below);
- does not by design or intention introduce energy into a subject; ***and***

- is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure (see question # 6 below).

For your study to be exempt from most of the requirements of the IDE regulation under this third category, it must meet **all** of the conditions listed in "c" above. (See also the decision tree in Appendix 1.) You should refer to 21 CFR Parts 50 and 56 for applicable requirements relating to IRBs and informed consent, including for device studies that meet the criteria described in 21 CFR 812.2(c). Additionally, investigators for those studies are still subject to 21 CFR 812.119 (the provision entitled "Disqualification of a clinical investigator.")

If your proposed study does not fit into one of the three categories listed above, you, the sponsor, must have an approved IDE (21 CFR 812.2) before you may begin your investigation, including any shipment of your investigational IVD. (Note: A device that is approved under a premarket approval application (PMA) or cleared under a 510(k) and then used in a study in accordance with the approved or cleared labeling is not investigational and, therefore, is not subject to the IDE regulation.)

The requirements for an IDE depend on the level of risk that the study presents to subjects.

For a significant risk device (see the **Glossary** for definition), the sponsor must apply to FDA for an IDE approval (see 21 CFR 812.1, 812.20). For a non-significant risk device (see the **Glossary** for definition), the sponsor must meet the abbreviated requirements of 21 CFR 812.2(b), including review and approval of the investigation by an institutional review board (IRB) and compliance with informed consent requirements. A non-significant risk study is considered to have an approved IDE when the abbreviated requirements are met.

Note: The requirements of the "Protection of Human Subjects" and "Institutional Review Boards" regulations (21 CFR Parts 50 and 56) apply to all clinical investigations regulated by FDA under section 520(g) of the Act, as well as other clinical investigations that support applications for research or marketing permits. (21 CFR 50.1, 56.101; see also Section V, Human Subject Protection, of this guidance.) Therefore, all studies of investigational IVDs that will support applications to FDA are subject to 21 CFR Parts 50 and 56, even if they are not subject to most requirements of 21 CFR Part 812.

3. How do I determine if the study is a significant or non-significant risk study under 21 CFR 812.2(b)?

A significant risk IVD device is generally one that is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject or otherwise presents a potential for serious risk to health, safety, or welfare of a subject. 21 CFR 812.3(m).

For IVDs, we interpret "potential for serious risk" in relation to the nature of the harm that may result to the subject. Misdiagnosis and/or error in treatment caused by inaccurate test results would be considered a significant risk if the potential harm to the subject could be life-threatening, or could result in permanent impairment of a body function or permanent damage to the body structure.

False positive results can lead to unnecessary confirmatory testing, unnecessary treatment that can be invasive or have harmful side effects, and/or unnecessary psychological trauma when serious or life-threatening diseases or conditions are involved. False negative results can lead to a delay in establishing the correct diagnosis, failure to start or continue needed treatment, false security that may prevent timely follow-up and retesting, and contribute to the potential spread of infectious agents to others. If the potential risk does not rise to the level described above, the study is not considered to pose a significant risk. FDA recommends the sponsor consider all these factors when determining the risk associated with your investigational IVD. (See 21 CFR 812.3(m) and also "Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors," available at http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm, particularly the one on "Significant Risk and Nonsignificant Risk Medical Devices" at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm126622.htm.)

4. How do I determine if an invasive sampling technique presents a significant risk under 21 CFR 812.2(c)(3)?

To determine whether an invasive sampling technique presents a serious risk, we recommend that you base your risk determination on the nature of the harm that may result from sampling. For example, FDA considers sampling techniques that require biopsy of a major organ, use of general anesthesia, or placement of a blood access line into an artery or large vein (subclavian, femoral, or iliac) to present a significant risk.

5. What does noninvasive mean?

A noninvasive device is one that does not, by design or intention:

a. penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra; or

b. enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os.

(21 CFR 812.3(k)).

Blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for noninvestigational purposes is also considered noninvasive (21 CFR 812.3(k)).

6. What does it mean to have "confirmation of the diagnosis by another, medically established diagnostic product or procedure?"

For an investigational study to be exempt under 21 CFR 812.2(c)(3), clinical investigators must use a medically established means of diagnosis (e.g., another cleared or approved IVD or culture) of the disease or condition as the basis for decisions regarding treatment of all subjects participating in the study. 21 CFR 812.2(c)(3)(iv). Additionally, test results from the exempt IVD investigation should not influence patient treatment or clinical management decisions before the diagnosis is established by a medically established product or procedure.

If an investigational test uses a new technology or represents a significant technological advance, established diagnostic products or procedures may not be adequate to confirm the diagnosis provided by the investigational IVD. For example, if an investigational test is designed to identify an infection at the earliest stages of viral infection (before formation of antibodies), established diagnostic products or procedures that rely on the detection of antibodies to the virus would be inadequate to confirm diagnoses. Under these conditions the study would not meet the criteria for exemption under 812.2(c)(3) since the testing could not be confirmed with a medically established diagnostic product or procedure. You may consider whether the device is a non-significant risk device subject to abbreviated IDE requirements (21 CFR 812.2(b)).

7. What if no medically established means for diagnosing the disease or condition exists?

If there is no medically established diagnostic product or procedure and clinical investigators use the results from the investigational study to decide on treatment, FDA would not consider the study exempt from IDE requirements under 21 CFR 812.2. The sponsor would need to obtain FDA approval of an IDE if the results are used in diagnosis without confirmation (e.g., to assist in determining treatment) (21 CFR 812.1, 812.2) and if a significant risk device is involved.

8. Can an investigational IVD device be used outside of the study protocol, in an

emergency situation?

Yes. (See also Chapter III, "Expanded Access to Unapproved Devices," of the guidance document "IDE Policies and Procedures.")[3] A physician may use an investigational IVD device in an emergency situation if:

a. the patient has a serious disease or condition;

b. no generally accepted alternative diagnostic device or treatment for the condition is available; **and**

c. there is no time to use existing procedures to get FDA approval for the emergency use.

FDA recommends that the physician make the determination that the patient's circumstances meet the above criteria, to assess the potential for benefit from the use of the unapproved device, and to have substantial reason to believe that benefits will exist. In the event that a device is used in circumstances meeting the criteria listed above, the physician should follow as many of the patient protection procedures listed below as possible. These include obtaining:

• Informed consent from the patient or a legally authorized representative;

• Clearance from the institution as specified by their policies;

• Concurrence of the IRB chairperson;

• An assessment from a physician who is not participating in the study; and

• Authorization from the IDE sponsor, if an approved IDE exists for the device;

• Authorization from the device company, if no IDE exists.

Although prior FDA approval for emergency use of the investigational device is not required, 21 U.S.C. § 360bbb(a), if an IDE exists, the use shall be reported to FDA in a supplemental IDE by the IDE sponsor within 5 working days from the time the sponsor learns of the use (21 CFR 812.35(a)(2)). The IDE supplement should contain a summary of the conditions constituting the emergency, patient outcome information, and the patient protection measures that were followed. If no IDE exists, the physician should follow the above procedures and report the emergency use to the sponsor and to CDRH or CBER, as appropriate.

[3] This reference can be found at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080203.pdf.

For additional information on the procedures physicians and IRBs should follow in an emergency use situation, please see Chapter III, "Expanded Access to Unapproved Devices" of the guidance entitled, *IDE Policies and Procedures*.

9. Can an unapproved or uncleared investigational IVD device ever be used for nonemergency treatment of patients who do not meet the inclusion criteria of an investigational study?

Yes, in exceptional situations. FDA recognizes that there are circumstances when an unapproved or uncleared IVD is the only available option for a patient or small group of patients who do not meet the inclusion criteria and "compassionate use"/single patient use of the device may be appropriate. Section 561 of the Act. CBER refers to such situations as “single patient exemptions.” Appropriate patient protection measures are needed for these studies.

Use of an investigational IVD device for one or a small group of patients who do not meet the study inclusion criteria would require a change to the investigational plan. 21 CFR 812.35(a). If the study is being conducted under an approved IDE, the sponsor should submit a supplement to the IDE requesting a change to the investigational plan for “compassionate use.” 21 CFR 812.35(a). The review of this supplement can be facilitated by a phone call to the reviewing division and by the submission by facsimile of an advanced copy of the supplement. If the investigational IVD device would require an FDA-approved IDE, but one has not yet been submitted or approved, FDA intends to exercise enforcement discretion where the sponsor submits a compassionate use request to CDRH or CBER, as appropriate, and follows the patient protection measures listed above for emergency use.[4]

If a study is being conducted according to an exemption under 21 CFR 812.2(c)(3), or as a non-significant risk IDE under 21 CFR 812.2(b), the sponsor should obtain prior approval for the specific compassionate use/single patient use for the individual(s) in question from the FDA and the reviewing IRB at the site where the physician proposes to use the device. For CDRH regulated products, the required information can be submitted to the Director of the IDE Program:

Attn: Director, IDE Program
U.S. Food and Drug Administration
Center for Devices and Radiological Health
WO66 Room G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

[4] See Chapter III, "Expanded Access to Unapproved Devices," of the guidance document "IDE Policies and Procedures," http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080203.pdf.

Compassionate use information is available on FDA's web site at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051345.htm#compassionateuse

For CBER regulated products, the required information should be submitted to the appropriate reviewing division (see section II above):

Document Control Center (HFM-99)
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1448

10. Are treatment IDEs and continued access available for investigational IVDs under an IDE?

Yes, both are available. See 21 CFR 812.36 and the **Glossary** for definitions of treatment IDE and continued access.

11. Can my IVD device be considered a humanitarian use device (HUD) and can I apply for marketing approval through a humanitarian device exemption (HDE)?

Yes, it is possible for an IVD device to be approved for marketing under the HDE. See the **Glossary** for definitions, 21 CFR Part 814, Subpart H, and Appendix 1 for more information.

12. Can an IVD device qualify for HUD designation if the affected patient population is fewer than 4,000 per year but each patient may need to be tested multiple times?

IVD devices qualify for an HUD designation when the number of persons tested with the device is fewer than 4,000 per year. FDA recognizes that the number of tests with the device may exceed one per patient. A device that involves multiple patient uses may still qualify for HUD designation as long as the IVD device is designed for diagnosis or treatment of a total of fewer than 4,000 patients per year in the US.

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If a device is being developed to diagnose or to help diagnose a disease or condition with an incidence of fewer than 4,000 patients per year, but there are more than 4,000 patients a year "at risk" who would be subject to testing using the device, then the device may not qualify as a HUD. 21 CFR 814.102(a)(5).

13. Is there a regulation that specifically addresses labeling of IVD products?

Yes. The regulation, "Labeling for in vitro diagnostic products," (21 CFR

809.10), specifies the information required on labeling and in package inserts of marketed products as well as products in development that are distributed for use in studies. We recommend that you design IVD studies so that the results will support the proposed indications for use in the package insert and labeling.

14. Are there different goals for IVD studies compared to other device studies?

No. The goals for IVD studies are the same as the goals for other device studies, even if the IVD study is exempt from most IDE requirements under 21 CFR 812.2(c)(3). We recommend that the sponsor and the investigators conduct an IVD device study with the goals of

- producing valid scientific evidence (for a definition, see 21 CFR 860.7(c)(2) and answer #1 of section IV) demonstrating reasonable assurance of the safety and effectiveness of the product, as described below, and
- protecting the rights and welfare of study subjects. (See **Human Subject Protection**, Section V of this guidance).

15. What regulations describe the content requirements for IVD premarket submissions?

Regulations that describe the basic content requirements by submission type include:

- Investigational Device Exemption (IDE) – 21 CFR 812.20
- Premarket Notification (510(k)) – 21 CFR 807.87
- Premarket Approval (PMA) – 21 CFR 814.20
- Humanitarian Device Exemption (HDE) – 21 CFR 814.104

Currently, there is no regulation describing the contents for a Product Development Protocol (PDP). However, section 515(f)(1) of the Act and the CDRH website at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm048168.htm#pdp describe PDP requirements.

In addition, the FDA 510(k) substantial equivalence determination summaries and FDA PMA summaries of safety and effectiveness are currently available on the CDRH OIVD web page at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/LabTest/ucm126189.htm or for CBER products at http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm089793.htm and http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/510kProcess/ucm133429.htm. We recommend that the sponsor structure submissions

according to the relevant regulations and provide sufficient detail to give the reader an understanding of the scientific data and information supplied. OIVD has issued many device specific guidances that describe FDA's recommendations for premarket submissions for particular types of IVDs.

16. Can published literature be used to support an IVD premarket submission?

FDA has developed a guidance document entitled "Supplements to Approved Applications for Class III Medical Devices: Use of Published Literature, Use of Previously Submitted Materials, and Priority Review," which can be found on the CDRH website at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080183.htm. CDRH and CBER believe that the principles outlined in this guidance are applicable to other submissions, specifically those for a 510(k), PMA, and HDE. (See the **Glossary** for definitions of these submission types.)

17. Can data from studies performed outside of the United States (U.S.) be used to support an IVD premarket submission?

Yes. FDA recognizes that clinical investigations may be conducted outside of the U.S., for example, in order to find adequate numbers of subjects for certain disease states, conditions, or pathogens. The PMA regulation contains information regarding research conducted outside of the U.S. (21 CFR 814.15). FDA can also accept data from foreign studies in support of 510(k)s .

18. Can foreign/international data be used as the sole support of a marketing application?

Yes, but only if warranted. The PMA regulation, 21 CFR Part 814, allows foreign data to be used as the sole support of a marketing application but only if (1) the data are applicable to the U.S. population and to U.S. medical practices, including laboratory practices, (2) the studies have been performed by clinical investigators of recognized competence, and (3) the data may be considered valid without the need for an on-site FDA inspection or, if necessary, FDA can validate the data through an on-site inspection or other appropriate means (21 CFR 814.15(d)).

For IVD devices, FDA would consider differences in population demographics, disease prevalence, disease presentation, laboratory practices, and medical standards of care. If the sponsor plans to submit an application based solely on foreign data, FDA recommends that the sponsor consult with the reviewing division prior to submission of the application.

See **Introduction**, Section II, question # 4 of this guidance for a list of reviewing divisions in both CDRH and CBER.

19. What is a master file and how is one submitted?

A device master file (MAF) is a reference source that a person submits to FDA. In general, it is a file of trade secret or confidential commercial/financial information submitted by a third party (i.e., someone other than the applicant) for use as a reference source in support of at least one application. FDA will accept MAFs from organizations or persons who have not submitted or will not directly submit the information in a PMA, IDE, 510(k), or other device-related submission to FDA. MAFs may include information on the following:

- facilities and manufacturing procedures and controls;
- synthesis, formulation, purification and specifications for chemicals, materials (an alloy, plastic, etc.) or subassemblies for a device;
- packaging materials;
- contract packaging and other manufacturing (such as sterilization);
- nonclinical study data; and
- clinical study data.

We recommend that a MAF include a cover letter, preferably on company letterhead, signed by a responsible company official that identifies the submission as a MAF and provides the name of a contact person at the company or a designated agent. For more information concerning MAFs see the CDRH website at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm142714.htm

20. How do I arrange to reference a MAF?

You, the sponsor, should contact the company that owns the information you would like to incorporate by reference in your premarket submission to FDA, and find out if this information is currently in a master file. If it is, you should obtain a written authorization from the master file holder (or an authorized designated agent/representative) on company letterhead. You should include the original authorization letter in the original copy of the premarket submission to FDA, and a copy of the authorization letter in each subsequent copy of the premarket submission. The master file holder should not send the authorization letter directly to FDA for inclusion in the master file or for inclusion in your premarket submission.

If the information you, the sponsor, would like to incorporate by reference in your

premarket submission to FDA is not already in a master file, you should request that the company that owns this information submit a master file to FDA.

For more information on referencing MAFs see the CDRH website at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm142714.htm.

IV. Investigational Studies

1. What does FDA consider to be valid scientific evidence?

Valid scientific evidence is defined in the "Medical Device Classification Procedures" regulation, 21 CFR Part 860, as:

Evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use (21 CFR 860.7(c)(2)).

The intended use of the IVD, the level and quality of information in the literature relevant to the device use, and FDA knowledge of the technology obtained from reviewing other premarket applications determine the type of study and the level of evidence you may need to demonstrate reasonable assurance of its safety and effectiveness. For example, if you are studying an IVD device that uses a well-characterized technology and has an intended use that falls within a type of device that has been classified into Class I or Class II, the study may consist of a comparison of analytic performance to that of a legally marketed (i.e., predicate) device. On the other hand, if your IVD uses novel or unproven technology or has a new intended use, you may need to conduct a well-planned clinical study of the device in the target population defined by your intended use. You may contact the Division in the appropriate Center if you have questions regarding the type of study you need to conduct for your device.

We recommend that sponsors and investigators of all studies, including exempt studies under 21 CFR 812.2(c)(3), conduct the studies with the following goals in mind: producing valid scientific evidence of the product's safety and effectiveness and protecting the rights and welfare of study subjects. Sponsors and investigators of significant and non-significant risk studies must comply with the regulation requirements in 21 CFR Part 812. FDA recommends that sponsors and investigators of studies exempt from the majority of requirements under 21 CFR Part 812 use the relevant sections of 21 CFR Part 812 regarding the general conduct of device studies as guidance. (**General Regulatory Issues**, Section III of this guidance, discusses how 21 CFR Part 812 may apply to a particular IVD study.)

2. Why should I review the information regarding the conduct of device studies found in the IDE regulation even if, after considering the exemption criteria in the regulation, I determine that my proposed studies are exempt from most IDE requirements?

Some studies are exempt from most of 21 CFR Part 812 because of the low risk they pose to study subjects. However, studies that will support a PMA or other premarket submission should have the same goals as all other device studies: 1) to produce valid scientific evidence to support reasonable assurance of a product's safety and effectiveness, and 2) to protect study subjects. Therefore, the information in 21 CFR Part 812 will also be useful to sponsors and investigators of device studies exempt under 21 CFR 812.2(c). In addition, all studies that will support applications to FDA are subject to 21 CFR 812.119(c) as well as to 21 CFR Parts 50 and 56.

3. Should I review the "International Conference on Harmonization; Good Clinical Practice: Consolidated Guideline" ("ICHGCP") published in the *Federal Register* Vol. 62, No. 90, May 9, 1997, pp. 25691-25709 or the draft ISO 14155, "Clinical Investigation of Medical Devices for Human Subjects," when developing studies for devices that fall within the exemption at 21 CFR 812.2(c)?

Although the ICH document was written for studies of pharmaceuticals, sections of the guidance address study issues common to all investigational products. Thus, these sections of the ICH GCP provide a useful reference regarding the proper conduct of studies.

The draft ISO document specifically states that it does not apply to IVD devices. The draft ISO document is an international document intended to reflect basic practices appropriate to clinical trials worldwide. It does not include all of FDA's specific requirements for clinical studies and is not presently a standard that FDA has officially recognized; therefore, we do not recommend that you rely on it.

4. Is FDA willing to review and discuss a study protocol even if the study is exempt from most of the 21 CFR Part 812 requirements?

Yes. Both CDRH and CBER have developed processes that allow sponsors to obtain early FDA input and review of proposed studies by submission of the protocol and other study materials in the form of a "pre-IDE" document and/or a discussion in the form of a "pre-IDE" meeting. While we refer to this early input as a "pre-IDE" process, it is also available for studies that are exempt from most IDE requirements under 21 CFR 812.2(c)(3) or that will be conducted under the abbreviated IDE regulations for NSR studies (21 CFR 812.2). FDA encourages use of the pre-IDE submission and/or meeting whenever the sponsor desires early feedback for clinical studies, particularly those for novel or high risk (Class III) devices. If you (the sponsor) are interested in submitting a pre-IDE, we

recommend that you contact the Division that will review your device **before** you initiate your studies (See **Introduction**, Section II, question # 4 of this guidance). Use of the pre-IDE process **does not** obligate you in any way to future submission of an IDE. FDA also encourages continued communication throughout the course of the study. This communication can be in the form of an informational meeting/telephone call or status reports to the pre-IDE file.

5. Can I obtain a more formal evaluation of my study design or investigational plan through a determination and/or agreement meeting?

Yes, for Class III IVDs. (See the **Glossary** for definition of terms.) A guidance document regarding these meetings, "Early Collaboration Meetings Under the FDA Modernization Act (FDAMA); Final Guidance for Industry and for CDRH Staff," is available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073604.htm. CBER also follows this meeting guidance document when determination and/or agreement meetings are requested.

6. Under 21 CFR Part 812, what are the sponsor's and investigator's responsibilities for studies of a non-significant risk device conducted under the abbreviated requirements in 21 CFR Part 812?

The majority of the sponsor's and investigator's responsibilities in a study of a nonsignificant risk device are found in 21 CFR 812.2(b)(1) of the IDE regulation and are summarized below:

a. Label the device in accordance with 21 CFR 812.5;

b. Obtain IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintain such approval.

c. Ensure that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under 21 CFR 56.109(c).

d. Comply with the requirements of 21 CFR 812.46 with respect to monitoring investigations;

e. Maintain the records required under 21 CFR 812.140(b)(4) and (5) and make the reports required under 21 CFR 812.150 (b)(1) through (3) and (5) through (10);

f. Ensure that participating investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 21 CFR 812.150(a)(1), (2), (5), and (7);

g. Comply with the prohibitions in 21 CFR 812.7 against promotion and other practices.

All studies should have a written protocol as described in 21 CFR 812.25(b) and a risk analysis as described in 21 CFR 812.25(c), regardless of the status of the study under 21 CFR Part 812.

All sites participating in the study should use identical copies of the protocol and receive protocol amendments simultaneously so that data is collected in a consistent manner. Data collected from different sites otherwise may not be able to be pooled in the final analysis due to inconsistencies in how it was collected. We recommend that protocols describe the study objectives, design, methodology, subject populations, types of specimens, data to be collected and planned data analysis. (See also **Data Considerations**, Section VI, of this guidance). For information on how to monitor the study, you may refer to the FDA guidance document entitled "Guideline for the Monitoring of Clinical Investigations," which is available at http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/UCM133752.pdf

7. What are my responsibilities as the sponsor or the investigator of a study of a significant risk device subject to 21 CFR Part 812?

The sponsor's responsibilities for significant risk device investigations are described in Appendix 3 of this guidance. This information is also included as an enclosure in all IDE approval letters.

The investigator's responsibilities for significant risk device investigations are described in Appendix 4 of this guidance. This information is also included as an enclosure in all IDE approval letters.

8. Is it appropriate to use a quality systems approach in the conduct of IVD studies?

Yes, we recommend that sponsors and investigators follow quality systems methodologies, including accountability and traceability of the investigational device, auditing of data collected and monitoring to make sure the protocol was followed, documentation of training of staff in the use of the device [21 CFR 812.43(a)], and notifying FDA of unanticipated adverse device effects [21 CFR 812.150(b)(1)] in the conduct of IVD studies. Also, 21 CFR 812.20(b)(3) requires "[a] 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 the quality control used in the manufacture of the device." This suggestion is consistent with both the need to provide scientifically valid information in support of premarket submissions and the design control requirements. Manufacturers of Class II and Class III IVD

devices, and some Class I devices, **are required to follow design controls**, as described in 21 CFR 820.30 of the "Quality System Regulation," **during the development of investigational devices**. 21 CFR 812.1(a). See the **Glossary** for the definition of device classes.

9. If a sponsor's 'in-house' laboratory participates in the study of an IVD is the laboratory considered to be a study site?

Yes. All locations involved in an IVD study are considered study sites whether they are located at a sponsor-owned facility or at an independently-owned laboratory. The sponsor should list the laboratory as a study site, and the study should be conducted under the same investigational plan. As a study site, this laboratory can be inspected as part of the FDA's bioresearch monitoring (BIMO) inspection program.

V. Human Subject Protection

1. When does an IVD study involve human subjects?

Under FDA's regulations governing the conduct of IVD device studies, the definition of "subject" includes individuals on whose specimens an investigational device is used [see 21 CFR 812.3(p)]. As a result, an IVD study using human specimens involves human subjects.

2. Am I required to follow the "Good Laboratory Practice for Nonclinical Studies" regulation (21 CFR Part 58) in my IVD study?

Part 58 applies only to **nonclinical** laboratory studies, which are defined as in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. The term does not include studies utilizing human subjects or clinical studies or field trials in animals. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article (21 CFR 58.3(d)).

Moreover, because the safety of IVDs is related to the accuracy of the result, most IVD studies that are intended to establish safety would necessarily use human specimens. As noted above, an IVD study using human specimens involves human subjects and thus is excluded from the definition of nonclinical laboratory studies. Such studies to establish safety are subject to 21 CFR Parts 50 and 56 and 21 CFR Part 812 as applicable, dealing with human subject research, rather than to 21 CFR Part 58.

3. What regulations apply regarding human subject protection in investigational IVD studies?

FDA regulations on “Protection of Human Subjects” and “Institutional Review Boards” (21 CFR Parts 50 and 56) apply to all clinical investigations (investigations involving human subjects) regulated by FDA under section 520(g) of the Federal Food, Drug and Cosmetic Act, as well as other clinical investigations that support applications for research or marketing permits for products regulated by FDA. (21 CFR 50.1, 56.101). As described above, any study using human specimens involves human subjects. FDA has expressed an intent to exercise enforcement discretion regarding informed consent for certain IVD studies, in the guidance entitled, "Guidance on Informed Consent for In Vitro Diagnostic Device Studies using Leftover Human Specimens that are not Individually Identifiable."
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm078384.htm

Some research studies involving human subjects that are conducted or supported by a federal department or agency will be required to follow the Federal Policy for the Protection of Human Subjects (the “Common Rule”). The Department of Health and Human Services (HHS) has codified the Common Rule at 45 CFR Part 46, subpart A. Research involving human subjects that is conducted or supported by HHS and that is not otherwise exempt must comply with 45 CFR Part 46, which contains additional protections for specific populations. For further information about the applicability of 45 CFR Part 46 to your study, refer to http://www.hhs.gov/ohrp/.

FDA regulation and the Common Rule contain some differing requirements. Although FDA and HHS seek to harmonize requirements related to informed consent where possible, certain requirements of the FDA regulation and the Common Rule are different. The same study may be subject to both sets of requirements, either one, or neither. It is the responsibility of sponsors and investigators to comply with all applicable requirements.

4. How do FDA regulations for protection of human subjects, 21 CFR Parts 50 and 56, differ from HHS regulations in 45 CFR Part 46 subpart A?

A general comparison appears in the FDA’s Good Clinical Practice program website, Comparison of FDA and HHS Human Subject Protection Regulations found at http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/EducationalMaterials/ucm112910.htm. For additional information on 45 CFR Part 46 subpart A refer to the Office for Human Research Protections at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm.

5. Can investigational IVD studies receive expedited review (see Glossary for definition) by an IRB?

Yes, in many cases an investigational IVD study is eligible for IRB expedited review (see 21 CFR 56.110), for both initial approval and continuing review. The categories of research that may be reviewed by the IRB through an expedited review procedure are described in the Federal Register notice on expedited review, found at http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm118099.htm. As stated in a Federal Register notice, however, sponsors and investigators may not use the expedited review procedure where identification of the subjects and/or their responses would reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal. (63 FR 60353, November 9, 1998).

6. Can leftover specimens be used in IVD studies without informed consent?

The document entitled, "Guidance for Industry, Institutional Review Boards, Clinical Investigators, and Food and Drug Administration: Guidance on Informed Consent for In Vitro Diagnostic Device Studies using Leftover Human Specimens that are not Individually Identifiable," http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm078384.htm, describes the limited circumstances in which FDA intends to exercise enforcement discretion regarding requirements for informed consent. (See **Glossary** for definition of "leftover specimens".)

7. Can those who routinely conduct studies with IVDs (e.g., research hospitals) use a general informed consent to address future studies using samples collected in their own facility?

To fulfill FDA informed consent requirements for studies of IVDs, a site may develop an informed consent process to address the use of samples collected at the facility (see the **Glossary** for definition) in a specific study or for a broader category of future studies. This general informed consent process may be used for subjects seen at and/or admitted to a specific facility. The informed consent document must contain all of the required elements found in 21 CFR 50.25.

8. Can a human specimen that was initially collected in a study with the informed consent of the subject be used in a later study without a new consent process?

If the original informed consent document contains a statement that excess specimen(s) will be stored for future use in specified types of studies and the new study meets the criteria stated in that consent document, it is possible that no further consent is necessary. This assumes that the original informed consent document contains all of the other essential elements, including notice to the subject that FDA may review their files and an explanation of the purposes and

benefits of the research. (See 21 CFR 50.25.) We recommend sponsors and investigators consult with the IRB regarding the need for a new informed consent process in such a case. The IRB decision should include consideration of any state and/or local requirements regarding informed consent and patient rights. If new testing could expose the subject to previously unanticipated risks (e.g., privacy concerns for the subject and/or his family related to testing for a genetic marker), a new consent may be needed. In addition, if the original informed consent did not address future research use at all, or did not cover the type of study now under consideration, it is likely a new consent will be needed.

Under certain circumstances, for human specimens leftover from specimens originally collected for a previous study, FDA intends to exercise enforcement discretion regarding informed consent requirements. See "Guidance for Industry, Institutional Review Boards, Clinical Investigators, and Food and Drug Administration: Guidance on Informed Consent for In Vitro Diagnostic Device Studies using Leftover Human Specimens that are not Individually Identifiable," http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm078384.htm,

VI. Data Considerations

1. What information should the protocol include to ensure that the investigational IVD study will be scientifically sound?

We recommend that the protocol include a clear description of study design; objectives, estimation of performance goals (e.g., desired confidence interval widths) that are directly related to the intended claims for the IVD device, or hypotheses; and a statistical plan to be applied to the data. (See the **Glossary** for definitions of protocol, statistical hypothesis, and confidence interval.)

2. Is it acceptable to develop new or to revise existing study hypotheses as the study progresses?

We generally believe it would be inappropriate to draw conclusions from after-the-fact hypotheses. We recommend that changes in study protocols be carefully documented and explained. FDA encourages sponsors to contact the appropriate review division to discuss studies before they are initiated and to consult FDA before changes in protocols are made mid-study. (For the FDA divisions responsible for review of IVD products, see **Introduction**, Section II, of this guidance.)

3. How should I determine appropriate sample size for a study?

The sponsor should formulate sample size based on standard statistical techniques and the sample size should account for any unique issues related to intended use(s), device technologies, and/or the biology of the condition being studied.

4. What guidance is available for sponsors to determine how to estimate IVD performance in terms of sensitivity and specificity, how to handle discrepant results, and what to do when a study is performed without a truth standard ("gold standard") (see the Glossary for definitions)?

FDA has recognized a number of Clinical and Laboratory Standards Institute [(CLSI), formerly National Committee on Clinical Laboratory Standards (NCCLS)] standards related to these issues. A list of these standards, but not the standards themselves, can be found through the database on the CDRH web page http://www.accessdata.fda.gov/scrIpts/cdrh/cfdocs/cfStandards/search.cfm
National Committee on Clinical Laboratory Standards
The agency's guidance entitled "Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests" can be viewed at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071148.htm

5. How much leeway is there in deciding on the populations from which human specimens are collected and under what conditions are data on simulated specimens (see the Glossary for definition) acceptable?

Studies should be performed in a representative sample of the intended use population (i.e., representation of both diseased and non-diseased cases, and controlling for subject demographics and morbidity factors that may affect the level of device performance). When a disease is rare or samples are needed specifically to challenge cut-off points, sponsors may use enriched samples, panels of credentialed samples (e.g., Center for Disease Control and Prevention (CDC) panels), and/or spiked or contrived samples. The acceptance of simulated specimens depends on how well they represent specimens from the intended-use population and whether their performance accurately reflects what the IVD device user can expect.

6. Is it acceptable to eliminate data that appear to be out of line with the main body of the dataset (i.e., "outliers")?

An outlier, an observation that lies an unexpected distance from other values, does not in itself prove that an error or violation has occurred. Therefore, the primary data analysis should include all such observations, including "outliers". A sponsor may perform some specific supplemental analyses on subsets of the data, if clinically and scientifically justified, that may exclude outlying data points. Excluding large amounts of data, regardless of the reasons for exclusion, will seriously bias the results.

7. Can I add additional testing on the same subject to the dataset, particularly when it is hard to find study subjects?

In most studies the sponsor should avoid multiple testings of the same subject because it may skew performance statistics and under-estimate standard deviations. When multiple testing is done, the sponsor should explain why it is necessary and choose methods of statistical analysis that allow adjustment for within-subject correlation.

It is appropriate to conduct repeated testing of the same sample to evaluate test reproducibility – i.e., the ability of the test to yield the same or similar readings when expected.

8. How much precision (see the Glossary for definition) is needed for measurement data, e.g., in terms of decimal places?

Study data should contain no more decimal places than the precision of the instrument allows, i.e., if the instrument is only precise to the second decimal place the sponsor should not analyze the data using three decimal places.

9. What records should help to ensure scientific soundness of an IVD investigational study?

Unless a study falls within the exemption at 21 CFR 812.2(c), specific record requirements are listed in 21 CFR 812.140. In general, the records that are needed are those that provide the data for testing the study hypotheses. Records should contain sufficient detail to allow the study to be reproduced when the same protocol is followed. We recommend that investigators maintain detailed records because a review of the study may indicate the need for other analyses of the collected data.

We also recommend that investigators:

a. Maintain records of all data elements captured in the study, including raw measurements and subject co-variables in the form of demographic and morbidity factors;

b. Link every observation recorded to the subject and that person’s co-variable data;

c. Preserve information obtained for all subjects enrolled and for all specimens collected.

Additionally, electronic spreadsheets of study data are useful. Given the possible need to review or analyze study data at the most detailed level, electronic spreadsheets may help to minimize review time. For information on electronic records, see the guidance document, "Part 11, Electronic Records; Electronic Signatures -- Scope and Application," at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072322.pdf. There is also a more general guidance document

available on electronic records for clinical studies that is entitled "Computerized Systems Used in Clinical Trials," which can be found at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126402.htm.

10. What does FDA recommend be included in the final report of the investigation from the sponsor to all reviewing IRBs (and to FDA for significant risk studies) (21 CFR 812.150(b)(7))?

A final report should be a basic scientific report of the studies conducted, including the results of testing the study hypotheses. This report can be a useful means of providing a simple account of the data collection and study outcome. Such a report can facilitate preparation of the eventual submission for regulatory action, particularly when accompanied by the information included in the investigational plan (see the **Glossary** for definition).

The suggested format for the IDE final report, which FDA includes as an enclosure in all IDE approval letters, is found in Appendix 5 of this guidance.

It should be noted that FDA will consider submission of a marketing application (510(k), PMA, or HDE) to serve as the final report for the IDE. When a study sponsor submits a marketing application in lieu of the final report, the sponsor should still submit a supplement to the IDE stating that the marketing application should be considered the final report for the study.

The final report for significant risk device investigations must be submitted to the IRBs and/or FDA within six months after termination or completion of the study. 21 CFR 812.150(b)(7).

VII. Glossary

Note: this glossary is written in plain language and is for use exclusively with this guidance document.

Definitions that have been taken from the Act, other pertinent laws, or in Federal regulations include the relevant citation.

510(k) – See Premarket Notification.

Agreement meeting – a meeting, under section 520(g)(7) of the Act (21 U.S.C. § 360j(g)(7)), that is available to anyone planning to investigate the safety or effectiveness of a class III device (see definition below) or any implant. The purpose of the meeting is to reach agreement on the key parameters of the investigational plan, including the study protocol. The meeting is to be held within 30 days of the receipt of a written request. FDA will document in writing any agreement reached and make it a part of the administrative record. The agreement is binding on FDA and can only be changed with the written agreement of the applicant or when there is a substantial scientific issue

essential to determining the safety or effectiveness of the device. See 21 U.S.C. § 360j(g)(7). A guidance document regarding these meetings, “Early Collaboration Meetings Under the FDA Modernization Act (FDAMA); Final Guidance for Industry and for CDRH Staff,” is available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073604.htm.

Analyte specific reagent (ASR) - ASRs are defined as “antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reactions with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens." 21 CFR 864.4020(a). ASRs are medical devices that are regulated by FDA. They are subject to general controls, including current Good Manufacturing Practices (cGMPs), 21 CFR Part 820, as well as the specific provisions of the ASR regulations (21 CFR 809.10(e), 809.30, 864.4020).

Class I devices – devices for which the general controls of the Act are sufficient to provide reasonable assurance of their safety and effectiveness. They typically present minimal potential for harm to the user and the person being tested. They are subject to general controls, which include registration and listing, labeling, and adverse event reporting requirements (section 513(a)(1)(A) of the Act). Most Class I devices are exempt from premarket notification (see definition below), subject to certain limitations found in section 510(l) of the Act and in 21 CFR 862.9, 864.9, and 866.9. Some are also exempt from the “Quality Systems Regulation” found in 21 CFR Part 820. IVD examples of Class I devices include complement reagent, phosphorus (inorganic) test systems (21 CFR 862.1580), and E. coli serological reagents (21 CFR 866.3255).

Class II devices – devices for which general controls alone are insufficient to provide reasonable assurance of their safety and effectiveness and for which establishment of special controls can provide such assurances. Special controls may include special labeling, mandatory performance standards, risk mitigation measures identified in guidance, and postmarket surveillance (section 513(a)(1)(B) of the Act). Some Class II devices are exempt from premarket notification (see definition below), subject to limitation in 21 CFR 862.9, 864.9, and 866.9. IVD examples of Class II devices include glucose test systems (21 CFR 862.1345), antinuclear antibody immunological test systems (21 CFR 866.5100), and coagulation instruments (21 CFR 864.5400).

Class III devices – devices for which insufficient information exists to provide reasonable assurance of safety and effectiveness through general or special controls. Class III devices are usually those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury (section 513(a)(1)(C) of the Act). Most Class III devices require premarket approval (PMA, see definition below). IVD examples of these include automated PAP smear readers, nucleic acid amplification devices for tuberculosis, and total prostate specific antigen (PSA) for the detection of cancer. A limited number of Class III devices that are equivalent to devices legally marketed before

enactment of the Medical Device Amendments of 1976 may be marketed through the premarket notification (510(k)) process (see definition below), until FDA has published a requirement for manufacturers of that generic type of device to submit PMA data.

Compassionate use – The compassionate use provision allows access for patients with a serious disease or condition who do not meet the requirements for inclusion in the clinical investigation but for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition. There must be no feasible alternative therapies/diagnostics available. Compassionate use is typically available only for individual patients but also may be used to treat a small group. Prior FDA approval is needed before compassionate use occurs.
Further information can be found at
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051345.htm.

Confidence interval – the range of plausible values for a statistical parameter, consistent with the observed data, which is computed with a sample estimate parameter (e.g., mean) and its standard deviation. For example, a "95% Confidence Interval" is computed such that, if the parameter was determined for repeated experiments, the resulting values would include the true parameter value 95% of the time.

Continued access to investigational devices – FDA may allow sponsors to continue to enroll subjects under an IDE, after the trial has been completed, while a marketing application is prepared by the sponsor and/or reviewed by FDA. To continue enrolling subjects, a sponsor should show that there is a public health need for the device, that preliminary evidence indicates that the device is likely to be effective for the indications proposed, and that no significant safety concerns have been identified for the proposed indication. A guidance document, entitled "Continued Access to Investigational Devices During PMA Preparation and Review," can be found at
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080260.htm .

Co-variables – data elements relating to a subject that might affect how well a diagnostic test works, such as demographic status (age, gender, etc.), morbidity, or concurrent therapy.

Determination Meeting – A Determination meeting under section 513(a)(3)(D) of the Act is available to anyone anticipating submitting a PMA or PDP and is intended to provide the applicant with the FDA's determination of the type of valid scientific evidence that will be necessary to demonstrate that the device is effective for its intended use. As a result of this meeting, FDA will determine whether clinical studies are needed to establish effectiveness and, in consultation with the applicant, determine the least burdensome way of evaluating device effectiveness that has a reasonable likelihood of success. The applicant can expect that FDA will determine if concurrent randomized controls, concurrent non-randomized controls, historical controls, or other types of evidence will be acceptable. FDA's determination is to be written, shared with the

applicant within 30 days following the meeting, and is binding upon the FDA, unless it could be contrary to public health. 21 U.S.C. § 360c(a)(3)(D). A guidance document regarding these meetings, “Early Collaboration Meetings Under the FDA Modernization Act (FDAMA); Final Guidance for Industry and for CDRH Staff,” is available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073604.htm.

Device – as defined in the Act, section 201(h): an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is a) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them; b) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or c) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

Excess samples – remnants of human specimens collected for routine clinical care or analysis that would otherwise have been discarded, as well as specimens leftover from specimens previously collected for other unrelated research or investigations. Excess samples are also referred to as “surplus samples,” “residual”, “reserved samples,” "library samples," and "leftover specimens."

Expedited review – review by an institutional review board (IRB) that does not require full board review or a convened meeting. Such a review may be carried out by the IRB chairperson or one or more experienced reviewers assigned by the IRB chairperson from among the members of the IRB. Reviewers may exercise all of the authorities of the IRB except they may not disapprove the study. Disapproval may only result through the IRB’s non-expedited review process. Expedited review is reserved for minimal risk studies. (See 21 CFR 56.110.)

General purpose reagents – chemical reagents that have general laboratory application and that are not labeled or otherwise intended for a specific diagnostic application. They are used to collect, prepare, and/or examine specimens from the human body for diagnostic purposes. (Example: reagents used for general staining in microscopic procedures.) General purpose reagents do not include laboratory machinery, automated or powered systems (21 CFR 864.4010(a)).

Gold standard – see truth standard.

Humanitarian use devices (HUDs) –HUDs are devices intended to diagnose a disease or condition in fewer than 4,000 patients in the U.S. per year. Such devices are regulated under 21 CFR Part 814, Subpart H. If a device receives a designation as an HUD, a Humanitarian Device Exemption request (HDE) can be submitted. HUDs that are

approved for marketing under an HDE have specific labeling requirements. IRB approval is required for use of a HUD (21 CFR 814.124).

Investigation – a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device (21 CFR 812.3(h)). It is often referred to as a clinical trial and is sometimes referred to as a field trial.

Investigational Device Exemption (IDE) – application which, when approved, allows the device to be used lawfully for the purpose of conducting studies regarding the safety and effectiveness of the device, without complying with certain requirements of the Act. (See 21 CFR 812.1 for specific exemptions.) For significant risk (SR) device studies (see definition below), a sponsor must apply to FDA to obtain approval for an IDE. (See 21 CFR 812.20.) For non-significant risk (NSR) device studies (see definition below), an IDE is considered approved when a sponsor meets the abbreviated requirements found in 21 CFR 812.2(b), which include approval from the reviewing Institutional Review Board(s) (IRB(s)).

Investigational plan – sponsor's overall plan regarding the conduct of an investigational study. It includes, but is not limited to, the purpose of the study, a written protocol, a risk analysis, device description, labeling, written monitoring procedures, informed consent materials, and Institutional Review Board (IRB) information. (21 CFR 812.25.) For IVD studies, protocols should describe the study objectives, design, methodology, subject populations, types of specimens, data to be collected and planned data analysis.

Investigational Use in vitro diagnostic (IVD) product – an IVD product being used for product testing prior to full commercial marketing (e.g., for use on specimens derived from humans to compare the usefulness of the product with other products or procedures in current use or recognized as useful). These products must be labeled according to 21 CFR 812.5 for non-significant risk or significant risk devices and according to 21 CFR 809.10(c)(2)(ii) for devices that are exempt under 21 CFR 812.2(c).

Investigator – an individual who actually conducts a clinical investigation, i.e., a person under whose immediate direction the investigational product is administered, dispensed, or used, provided that the investigation involves a subject. In the event of an investigation conducted by a team of individuals, the investigator is the responsible leader of that team (21 CFR 812.3(i)).

In vitro diagnostic (IVD) products – those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. IVD products are devices as defined in section 201(h) of the Act and may also be biological products subject to section 351 of the Public Health Service Act. The regulatory definition of in vitro diagnostic products is found in 21 CFR 809.3(a).

Leftover specimens -- remnants of specimens collected for routine clinical care or analysis that would otherwise have been discarded, or remnants of specimens previously collected for other unrelated research. These specimens may be obtained from a specimen repository -- a common site for storage of collections of human biological specimens available for study. See also **Excess samples.**

Non-significant risk (NSR) device – a device that does not meet the definition of significant risk (SR) device (see definition below). An IDE is considered approved for a NSR investigational device study once sponsors meet the abbreviated requirements found in the "Investigational Device Exemptions" regulation at 21 CFR 812.2(b). The risk determination for an investigational device study should be based on the proposed use of the device in the investigation in addition to the characteristics of the device.

Outlier – a data observation whose value appears to be out of line with the main body of data that has been collected.

Pre-amendment in vitro diagnostic (IVD) tests – IVD tests that were in commercial distribution before May 28, 1976.

Precision – the closeness of agreement between independent diagnostic test results obtained under stipulated conditions. For additional information refer to the Harmonized Technology Database, Clinical and Laboratory Standards Institute, available at http://www.clsi.org.

Premarket Approval Application (PMA) – the application for approval required prior to the marketing of most Class III medical devices (section 515 of the Act, 21 U.S.C. 360e). (See definitions of Class I, II, and III devices above.) PMA approval is based on a determination by FDA that the applicant's submission provides sufficient valid scientific evidence to provide reasonable assurance that the device is safe and effective for its intended use(s). The PMA regulation is 21 CFR Part 814. PMA information is available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/default.htm.

Premarket Notification – also referred to as a 510(k), is a submission to FDA that contains information to demonstrate that a device is substantially equivalent (SE) to a legally marketed (predicate) device. Governing regulations regarding premarket notification procedures are found in Subpart E of the "Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices" regulation (21 CFR Part 807). The 510(k) device advice page is available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm.

Product Development Protocol (PDP) – FDA process of approval for marketing of medical devices, usually reserved for Class III devices (see definitions of device classes

above), by which the sponsor and FDA agree on the product design and testing early in the concept and planning stages of a product (section 515(f) of the Act).

Protocol – a document that contains a description of the objectives and design of an investigational study, methodology(s) to be used, and data to be collected. It may also contain information regarding the planned data analysis and study monitoring. For most studies in the development of an IVD product, it also contains information regarding types of specimens and subject populations.

Reserved samples – see excess samples.

Sensitivity – the probability that a diagnostic test will yield a positive result when the disease or the target analyte is present.

Significant risk (SR) device – an investigational device that presents a potential for serious risk to the health, safety, or welfare of a subject and:

1. is intended as an implant;
2. is purported or represented to be for use in supporting or sustaining human life;
3. is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health; or
4. otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

The risk determination for an investigational device study should be based on the proposed use of the device in the investigation in addition to the device characteristics. Sponsors of significant risk device studies must apply to FDA for an Investigational Device Exemption (IDE) (see definition above). (21 CFR 812.3(a), 812.3(m); 812.20.)

Simulated specimens – specimens made in the laboratory by adding the analyte of interest in known concentrations to a medium that simulates the natural matrix.

Specificity – the probability that a diagnostic test will yield a negative result when the disease or target analyte is absent.

Sponsor – a person who initiates, but who does not actually conduct, the investigation, i.e., the investigational device is administered, dispensed, or used under the immediate direction of another individual. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator (see next definition), and the employees are investigators (see definition above) (21 CFR 812.3(n)).

Sponsor-investigator – an individual who both initiates and actually conducts, alone or with others, an investigation, i.e., under whose immediate direction the investigational device is administered, dispensed, or used. The term does not include any person other than an individual. The obligations of a sponsor-investigator include both those of an investigator and those of a sponsor (21 CFR 812.3(o)).

Statistical hypothesis – a statement about some state of nature that a proposed study or set of studies will either accept or reject on the basis of the experimental data. The hypothesis is usually broken down into a null hypothesis (a statement of what the testing results will hopefully reject) and an alternative hypothesis (a statement of what the testing results will hopefully accept).

Study – as used in this document, covers the systematic evaluations conducted in the development of an IVD product, including the feasibility, analytical assessments, method comparison, and evaluations to determine clinical utility of a product.

Subject – a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease (21 CFR 812.3(p)).

Surplus samples – see excess samples.

Transitional device – a product defined as a device as of May 28, 1976, but previously considered by FDA to be a new drug or an antibiotic drug (21 CFR 812.3(r)).

Treatment IDE – use of an unapproved investigational device for the treatment or diagnosis of patients during the clinical trial or prior to final FDA action on the marketing application, if during the course of the clinical trial the data suggest that the device is effective. A treatment IDE may cover a large number of patients that exceeds the number of clinical sites and patients stipulated in the original IDE. The device must be for treatment or diagnosis of a serious or immediately life-threatening disease or condition; there must be no comparable or satisfactory alternative device or therapy available; the device must be under investigation in a controlled clinical study for the same use under an approved IDE, or such clinical studies have been completed; and the sponsor must be actively pursuing marketing approval or clearance of the device. Requirements for an application for a treatment IDE are found in the Investigational Device Exemptions regulation at 21 CFR 812.36.

Truth Standard ("Gold" Standard) − any medical procedure or laboratory method or combination of procedures and methods that the clinical community relies upon for diagnosis, that is accepted by FDA, and that is regarded as having negligible risk of either a false positive or a false negative result. The truth standard result should be definitive (positive/negative, present/absent, or diseased/non-diseased), and should not give an indeterminate result. As science and technology improve, newer, more reliable standards may replace previous standards, particularly in the case of new disease markers.

VIII. References

Note: this listing is presented in the order that the documents are first referred to in this guidance document.

1. 21 CFR Part 812, Investigational Device Exemptions, found at

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/ShowCFR.cfm?CFRPart=812.

2. 21 CFR Part 312, Investigational New Drug Application, found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/ShowCFR.cfm?CFRPart=312.

3. 21 CFR Part 809, In Vitro Diagnostic Products for Human Use, found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=809

4. 21 CFR 820.30, Subpart C of the Quality System Regulation, found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=820.30

5. 21 CFR 860.7, Determination of safety and effectiveness, in Medical Device Classification Procedures, found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/ShowCFR.cfm?FR=860.7.

6. 21 CFR Part 54, Financial Disclosure by Clinical Investigators, found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/ShowCFR.cfm?CFRPart=54

7. “Expanded Access to Unapproved Devices,” Chapter III, of the guidance document IDE Policies and Procedures. Guidance document found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080202.htm.

8. “Test Requirements,” (21 CFR 610.40), found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=610.40 and the “Restrictions on Use for Further Manufacture of Medical Devices, “ (21 CFR 610.42), found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=610.42

9. Information concerning Master Files for Devices (MAFs) is found on the CDRH website at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm142714.htm

10. “Supplements to Approved Applications for Class III Medical Devices: Use of Published Literature, Use of Previously Submitted Materials, and Priority Review,” which can be found on the CDRH website at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080183.htm.

11. Guidance regarding Product Development Protocol (PDP) applications, found at
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm048168.htm

12. FDA premarket final review summaries and FDA PMA summaries of safety and effectiveness, found at
http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/LabTest/ucm126189.htm

and

http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/PremarketApprovalsPMAs/ucm089793.htm.

13. Guideline for the Monitoring of Clinical Investigations, found at
http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm135075.htm

14. “Preparing Notices of Availability of Investigational Medical Devices and for Recruiting Study Subjects” found at
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073568.htm.

15. International Conference on Harmonization: “Good Clinical Practice” Guideline published in the *Federal Register* Vol.62, No.90, May 9, 1997, pp. 25691-25709, found at
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf.

16. “Early Collaboration Meetings Under the FDA Modernization Act (FDMA); Final Guidance for Industry and for CDRH Staff,” is available at
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073604.htm

17. 21 CFR 814.15, Research conducted outside of the United States, in Premarket Approval of Medical Devices, found at
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/ShowCFR.cfm?FR=814.15

18.FDA’s Good Clinical Practice program website, Comparison of FDA and HHS Human Subject Protection Regulations found at
http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/EducationalMaterials/ucm112910.htm.

19. “Expedited Review of Premarket Submissions for Devices,” found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089643.htm

20. 21 CFR Part 50, Protection of Human Subjects, found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=50

21. 21 CFR Part 56, Institutional Review Boards, found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=56

22. 21 CFR 50.25, Elements of informed consent, in Protection of Human Subjects, found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/ShowCFR.cfm?FR=50.25

23. “Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Test” found at

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071148.htm

24. 21 CFR Part 11, Electronic Records; Electronic Signatures, found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/ShowCFR.cfm?CFRPart=11.

25. Guidance for Industry: Part 11, Electronic Records; Electronic Signatures – Scope and Application, guidance document found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072322.pdf.

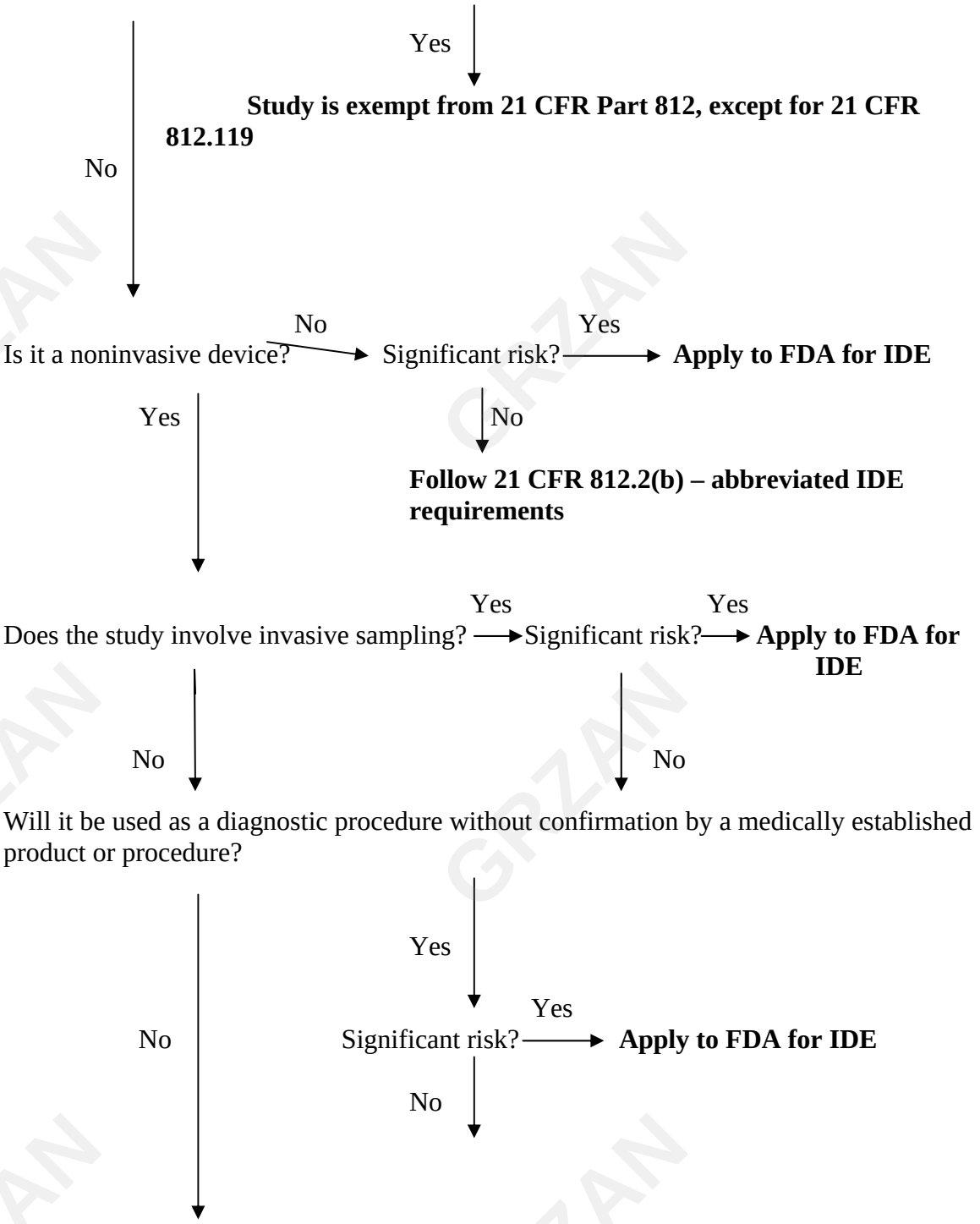
26. Draft Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Exception from Informed Consent Requirements for Emergency Research at http://edocket.access.gpo.gov/2006/E6-14262.htm.

27. The PMA information, found at

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm

28. Food and Drug Administration Modernization Act of 1997; List of Documents Issued by the Food and Drug Administration That Apply to Medical Devices Regulated by the Center for Biologics Evaluation and Research (4/26/99; 64 FR20312) found at http://www.fda.gov/ohrms/dockets/98fr/042699d.pdf.

Appendix 1: REGULATORY DECISION TREE (21 CFR PART 812) for IVD INVESTIGATIONAL STUDIES



Follow 21 CFR 812.2(b) – abbreviated IDE requirements

If the sponsor complies with the applicable requirements of 21 CFR 809.10(c), the study is exempt from 21 CFR Part 812, with the exception of 21 CFR 812.119.

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Appendix 2. Table 1. Regulatory Framework for IVD Products Regulated as Devices[+]

	Registration & Listing	Application	Applicable Labeling 801-Subpart A & 801.119 to all	Limitations	QSRs	IRB & Informed Consent	Adverse Event Reporting
General Purpose Reagents (Class I)	No 807.65(c)	No **864.4010(b)**	**809.10(d)**	'For Laboratory Use' **809.10(d)(1)(iv)**	Only 820.180 and 820.198 (if not sterile) **864.4010(b)**	N/A	Yes **Part 803**
ASR's Class I	Yes **807.20(a)**	No **864.4020(b)(1)**	**809.10(e)** **809.30(c)**	Restrictions on sale, use, distribution, & reporting **809.30**	Yes **809.20(b)**	N/A	Yes **Part 803**
Class II	Yes **807.20(a)**	510(k) **807.81** **864.4020(b)(2)**					
Class III	Yes **807.20(a)**	PMA, **814.1** **864.4020(b)(3)**					
Investigational Use:							
• **Significant Risk (SR)**	No **812.1**	IDE **812.20**	**812.5** [exempt from 809.10(a)&(b)]	Prohibition on promotion and commercialization **812.7**	No (except for 820.30) **812.1** **But see 812.20(b)(3)**	Yes Parts 50 & 56	For SR and NSR: Investigators report to IRB **812.150(a)(1)**
• **Non-Significant Risk (NSR)**	No **812.1**	No **812.2(b)**					
• **Exempt from most requirements of Part 812** Note: 21 CFR 812.119 applies to all investigational devices	No **807.20(a)** (investigational devices are not in commercial distribution)	No **812.2(c)(3)**	**809.10(c)(2)(ii)**	'For investigational Use Only. The performance characteristics of this product have not been established' 809.10(c)(2)(ii)	No*	Yes Parts 50 & 56	Sponsors may need to report to FDA **812.150(b)(1)**
Research Use	No **807.65(f)**	No	**809.10(c)(2)(i)**	'Research Use Only' 809.10(c)(2)(i)	No*	See Parts **50.1 & 56.101** for applicable requirements for clinical research	No **803.19(a)(2)**
For non investigational commercially marketed *in vitro* diagnostic devices: • **Pre-Amendment device**	Yes **807.20(a)**	No [unless 807.81(a)(3) and unless rule requires PMA, 21 U.S.C. 360e(b)]	**809.10** "For In Vitro Diagnostic Use" 809.10(a)(4)	See "labeling"	Yes **809.20(b)**	N/A	Yes **803.1**
• **Premarket Notification* (Class I, II, or III)**	Yes **807.20(a)**	510(k) **807.81** (Exemptions subject to limitations in 862.9, 864.9 & 866.9)			Yes. **809.20(b)**		
• **PMA/PDP (Class III)** *See 21CFR 862-866 (generic device class regulations) for specific-device exemptions	Yes **807.20(a)**	PMA **814.20**			Yes **809.20(b)**		
• **HDE**	Yes **807.20(a)**	HUD **814.102** HDE **814.104**	**809.10** **814.104(b)(4)(ii)**	Labeling & Cost **814.104(b)(4)(ii)** **814.104(b)(5)**	Yes **809.20(b)**	IRB approval **814.124** [no informed consent]	Yes **814.126(a)** **803.1**

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+ All references in table are to Title 21 of the Code of Federal Regulations.
* While investigational IVDs exempt from most of the provisions of 21 CFR Part 812 are not exempt from the QSR requirements, we generally do not intend to enforce such requirements for investigational IVDs that are exempt from most 21 CFR Part 812 requirements; except for design controls.

Appendix 3: Sponsor's Responsibilities for Significant Risk Device Investigations

Sponsors are required to comply with all applicable duties under the regulations. We summarize them below.

1. General Duties (21 CFR 812.40)

a. Submitting the IDE application to FDA
b. Obtaining both FDA and IRB approval for the investigation
c. Selecting qualified investigators and providing them with the information they need to conduct the investigation properly
d. Ensuring proper monitoring of the investigation
e. Ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation

2. Selection of Investigators (21 CFR 812.43)

a. Assuring selection of investigators qualified by training and experience
b. Permitting only participating investigators to use the investigational device
c. Obtaining a signed investigator's agreement from each investigator containing:
(1) investigator's curriculum vitae
(2) statement of investigator's relevant experience, including dates, location, extent, and type of experience
(3) if an investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to the termination
(4) statement of the investigator's commitment to:
• conduct the investigation in accordance with the agreement, the investigational plan, 21 CFR Part 812 and other applicable regulations, and any conditions of approval imposed by the IRB or FDA
• supervise all testing of the device involving human subjects
• ensure that the requirements for obtaining informed consent are met (21 CFR Part 50)
d. Selecting monitor(s) qualified by training and experience to monitor the progress of the investigation in accordance with FDA regulations.
e. Providing investigators with the investigational plan and report of prior investigations of the device. (21 CFR 812.45)

3. Monitoring (21 CFR 812.46)

a. Securing compliance of all investigators in accordance with the signed investigator's agreement, the investigational plan, the requirements of 21 CFR Part 812 or other applicable FDA regulations, or any condition of approval imposed by the reviewing IRB or FDA. If compliance cannot be secured, use of the device by the investigator and the investigator's participation in the investigation must be discontinued.
b. Evaluating all unanticipated adverse device effects and terminating the investigation, or portions of it, as soon as possible if that effect presents an unreasonable risk to subjects (Reporting requirements are listed below.)
c. Resuming terminated investigations only after IRB and/or FDA approvals are obtained, as required by this regulation.

4. Controlling Distribution and Disposition of Devices that are Shipped

Although investigators are responsible for ensuring that investigational devices are made available only to persons who are legally authorized to receive them (*see* 21 CFR 812.110(c)), sponsors also bear responsibility for taking proper measures to ensure that devices are not diverted outside of legally authorized channels. Sponsors may ship investigational devices only to qualified investigators participating in the clinical investigation (21 CFR 812.43(b)). Sponsors must also maintain complete, current, and accurate records pertaining to the shipment and disposition of the investigational device (21 CFR 812.140(b)(2)). Records of shipment shall include the name and address of the consignee, type and quantity of device, date of shipment, and batch number or code mark. Records of disposition shall describe the batch number or code marks of any devices returned to the sponsor, repaired, or disposed of in other ways by the investigator or another person, and the reasons for and method of disposal.

To further ensure compliance with these requirements, sponsors should take appropriate measures to instruct investigators regarding their responsibilities with respect to recordkeeping and device disposition. The specific recordkeeping requirements for investigators are set forth at 21 CFR 812.140(a). Upon completion or termination of a clinical investigation (or the investigator's part of an investigation), or at the sponsor's request, an investigator is required to return to the sponsor any remaining supply of the device or otherwise to dispose of the device as the sponsor directs (21 CFR 812.110(e)).

5. Prohibition of Promotion and Other Practices (21 CFR 812.7)

The IDE regulation prohibits the promotion and commercialization of a device that has not been first cleared or approved for marketing by FDA. This prohibition is applicable to sponsors and investigators (or any person acting on behalf of a sponsor or investigator), and encompasses the following activities:

a. Promotion or test marketing of the investigational device

b. Charging subjects or investigators for the device a price larger than is necessary to recover the costs of manufacture, research, development, and handling

c. Unduly prolonging an investigation beyond the point needed to collect data required to determine whether the device is safe and effective, and

d. Representing that the device is safe or effective for the purposes for which it is being investigated.

6. Supplemental Applications (21 CFR 812.35(a) and (b))

Supplemental applications are required to be submitted to, and approved by, FDA in the following situations:

a. *Changes in the investigational plan*: FDA approval is required for any change that may affect the scientific soundness of the investigation or the rights, safety or welfare of the subjects. IRB approval is also required for changes that may affect the rights, safety or welfare of the subjects. The change in the investigational plan may not be implemented until FDA approval (and IRB approval, if required) is obtained.

b. *Addition of new institutions*: IRB approval is also required for new institutions.

The investigation at the new institution(s) may not begin until both FDA and IRB approval(s) are obtained, and certification of IRB approval is submitted to FDA.

7. Maintaining Records (21 CFR 812.140(b))

A sponsor shall maintain the following accurate, complete, and current records relating to an investigation (also *See* Table I, next page):

a. Correspondence (including reports) with another sponsor, monitor, investigators, an IRB or FDA

b. Records of any shipment, including:

(1) name and address of consignee

(2) type and quantity of device

(3) date of shipment
(4) batch numbers or code marks

c. Records of disposition, describing:
(1) Batch number or code mark of devices returned, repaired, or disposed of by the investigator or other persons
(2) Reasons for and method of disposal

d. Signed investigator agreements

e. Adverse device effects (whether anticipated or unanticipated) and complaints

f. Any other records that FDA requires by regulation or by specific requirement for a category of investigation or a particular investigation

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TABLE I
RESPONSIBILITIES FOR MAINTAINING RECORDS
FOR A SIGNIFICANT RISK DEVICE STUDY

Records	Maintained by Investigator	Maintained by Sponsor
All Correspondence Pertaining to the Investigation	X	X
Shipment, Receipt, Disposition	X	X
Device Administration and Use	X	-
Subject Case Histories	X	-
Informed Consent	X	-
Protocols and Reasons for Deviations from Protocol	X	-
Adverse Device Effects and Complaints	X	X
Signed Investigator Agreements	-	X
Membership/Employment/Conflicts of Interest	-	X
Minutes of Meetings	-	-

8. Submitting Reports (21 CFR 812.150(b))

A sponsor shall prepare and submit the following complete, accurate, and timely reports (also *see* Table II, next page):

a. Unanticipated adverse device effects (with evaluation) to FDA, all IRBs, and investigators within 10 working days after notification by the investigator.
Subsequent reports on the effect may be required by FDA

b. Withdrawal of IRB approval

c. Withdrawal of FDA approval
d. Current 6-month investigator list
e. Progress reports (at least annual) - see attached suggested format for IDE progress report
f. Recall and device disposition (within 30 working days after the request was made)
g. Final report - see attached suggested format for progress reports
h. Use of device without obtaining patient informed consent within 5 working days of receipt of notice of such use
i. Significant risk determinations by the IRB when sponsor had proposed nonsignificant risk within 5 working days of receipt of such IRB determination
j. Other reports requested by the IRB or FDA about any aspect of the investigation

TABLE II

RESPONSIBILITIES FOR PREPARING AND SUBMITTING REPORTS FOR SIGNIFICANT RISK DEVICE STUDIES

Type of Report	Prepared by Investigators for	Prepared by Sponsors for
Unanticipated Adverse Effect Evaluation	Sponsors and IRBs	FDA, IRBs and Investigators
Withdrawal of IDE Approval	Sponsors	FDA, IRBs, and Investigators
Progress Report	Sponsors, Monitors and IRBs	FDA and IRBs
Final Report	Sponsors and IRBs	FDA, IRBs, and Investigators
Emergencies (Protocol Deviations)	Sponsors and IRBs	FDA
Inability to Obtain Informed Consent	Sponsors and IRBs	FDA
Withdrawal of FDA Approval	N/A	IRBs and Investigators
Current Investigator List	N/A	FDA

Type of Report	Prepared by Investigators for	Prepared by Sponsors for
Recall and Device Disposition	N/A	FDA and IRBs
Records Maintenance Transfer	Sponsors	FDA
Significant Risk Determinations	N/A	FDA

9. Inspections (21 CFR 812.145)

Sponsors are required to permit FDA to enter and inspect (at reasonable times and in a reasonable manner) any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records or results from use of devices are kept). FDA may also inspect and copy all records relating to an investigation including, in certain situations, records which identify subjects.

Appendix 4: Investigator's Responsibilities for Significant Risk Device Investigations

Investigators are required to comply with all applicable duties under the regulations. We summarize them below.

1. General Responsibilities of Investigators (21 CFR 812.100)

a. Ensuring that the investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations

b. Protecting the rights, safety, and welfare of subjects under the investigator's care

c. Controlling devices under investigation

d. Ensuring that informed consent is obtained from each subject in accordance with 21 CFR Part 50

2. Specific Responsibilities of Investigators (21 CFR 812.110)

a. Awaiting IRB approval and any necessary FDA approval before requesting written informed consent or permitting subject participation

b. Conducting the investigation in accordance with:

(1) the signed agreement with the sponsor

(2) the investigational plan

(3) the regulations set forth in 21 CFR Part 812 and all other applicable FDA regulations, and

(4) any conditions of approval imposed by an IRB or FDA

c. Supervising the use of the investigational device. An investigator shall permit an investigational device to be used only with subjects under the investigator's supervision. An investigator shall not supply an investigational device to any person not authorized under 21 CFR Part 812 to receive it.

d. Financial disclosure. A clinical investigator shall disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements under Part 54.

e. Disposing of the device properly. Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.

3. Maintaining Records (21 CFR 812.140)

An investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:

a. Correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA
b. Records of receipt, use or disposition of a device that relate to:
(1) the type and quantity of the device, dates of receipt, and batch numbers or code marks
(2) names of all persons who received, used, or disposed of each device
(3) the number of units of the device returned to the sponsor, repaired, or otherwise disposed of, and the reason(s) therefore
c. Records of each subject's case history and exposure to the device, including:
(1) documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances
(2) justifying the failure to obtain informed consent
(3) document all relevant observations, including records concerning adverse device effects (whether anticipated or not), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests
(4) a record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy
d. The protocol, with documents showing the dates of and reasons for each deviation from the protocol
e. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

4. Inspections (21 CFR 812.145)

Investigators are required to permit FDA to inspect and copy any records pertaining to the investigation including, in certain situations, those which identify subjects.

5. Submitting Reports (21 CFR 812.150)

An investigator shall prepare and submit the following complete, accurate, and timely reports:

a. To the sponsor and the IRB:
(1) Any *unanticipated adverse device effect* occurring during an investigation. (Due no later than 10 working days after the investigator first learns of the effect.)
(2) *Progress reports* on the investigation. (These reports must be provided at regular intervals, but in no event less often than yearly. If there is a study monitor, a copy of the report should also be sent to the monitor.)

(3) Any *deviation from the investigational plan* made to protect the life or physical well-being of a subject in an emergency. (Report is due as soon as possible but no later than 5 working days after the emergency occurs. Except in emergency situations, a protocol deviation requires prior sponsor approval; and if the deviation may affect the scientific soundness of the plan or the rights, safety, or welfare of subjects, prior FDA and IRB approval are required.)

(4) Any use of the device *without obtaining informed consent.* (Due within 5 working days after such use.)

(5) A *final report.* (Due within 3 months following termination or completion of the investigation or the investigator's part of the investigation. For additional guidance, see the discussion under the section entitled "Annual Progress Reports and Final Reports.")

(6) *Any further information* requested by FDA or the IRB about any aspect of the investigation.

b. To the Sponsor:

(1) *Withdrawal of IRB approval* of the investigator's part of an investigation. (Due within 5 working days of such action).

6. Investigational Device Distribution and Tracking

The IDE regulations prohibit an investigator from providing an investigational device to any person not authorized to receive it (21 CFR 812.110(c)). The best strategy for reducing the risk that an investigational device could be improperly dispensed (whether purposely or inadvertently) is for the sponsor and the investigators to closely monitor the shipping, use, and final disposal of the device(s). Upon completion or termination of a clinical investigation (or the investigator's part of an investigation), or at the sponsor's request, an investigator is required to return to the sponsor any remaining supply of the device or otherwise to dispose of the device as the sponsor directs (21 CFR 812.110(e)). Investigators must also maintain complete, current and accurate records of the receipt, use, or disposition of investigational devices (21 CFR 812.140(a)(2)). Specific investigator recordkeeping requirements are set forth at 21 CFR 812.140(a).

7. Prohibition of Promotion and Other Practices (21 CFR 812.7)

The IDE regulations prohibit the promotion and commercialization of a device that has not been first cleared or approved for marketing by FDA. This prohibition is applicable to sponsors and investigators (or any person acting on behalf of a sponsor or investigator), and encompasses the following activities:

a. Promotion or test marketing of the investigational device

b. Charging subjects or investigators for the device a price larger than is necessary to recover the costs of manufacture, research, development, and handling

c. Unduly prolonging an investigation beyond the point needed to collect data required to determine whether the device is safe and effective, and

d. Representing that the device is safe or effective for the purposes for which it is being investigated.

8. Annual Progress Reports and Final Reports

The IDE regulations do not specify the content of the annual progress or final reports. With respect to reports to the IRB, the IRB itself may specify what information it wishes to be included in these reports. Because FDA does require the information listed below, it is suggested that, at a minimum, the annual progress and final reports to the sponsor and the IRB also include the following items:

a. IDE number
b. Device name
c. Indications for use
d. Brief summary of study progress in relation to investigational plan
e. Number of investigators and investigational sites
f. Number of subjects enrolled
g. Number of devices received, used, and the final disposition of unused devices
h. Brief summary of results and conclusions
i. Summary of anticipated and unanticipated adverse device effects
j. Description of any deviations from investigational plan
k. Reprints of any articles published by the investigator in relation to the study

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Appendix 5: Suggested Format for IDE Final Report

1. The Basics

a. IDE Number
b. Device name and indication for use
c. Sponsor's name, address and phone number
d. Contact person

2. Study Progress

(Data from beginning of the study should be reported, unless otherwise indicated.)
a. Brief summary of study progress in relation to investigational plan
b. Number of investigators/investigational sites (attach list of investigators)
c. Number of subjects enrolled (by indication or model)
d. Number of devices shipped
e. Disposition of all devices shipped
f. Brief summary of results
g. Summary of anticipated and unanticipated adverse effects
h. Description of any deviations from the investigational plan by investigators (since last progress report)

3. Risk Analysis

a. Summary of any new adverse information (since last progress report) that may affect the risk analysis; this includes preclinical data, animal studies, foreign data, clinical studies, etc.
b. Reprints of any articles published from data collected from this study

4. Other Changes

a. Summary of any changes in manufacturing practices and quality control
(including changes not reported in a supplemental application)
b. Summary of all changes in investigational plan not required to be submitted in a supplemental application

5. Marketing Application or Future Plans

a. Progress toward product approval, with date (or projected date) of PMA or 510(k) submission; or indication that marketing of device is not planned.
b. Any plans to submit another IDE application for this device or a modification of this device.