POINTS TO CONSIDER WHEN PREPARING FOR AN FDA INSPECTION UNDER THE QSIT DESIGN CONTROLS SUBSYSTEM

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1200 G Street NW, Suite 400
Washington, DC 20005–3814
Tel: 202 783 8700
Fax: 202 783 8750
www.AdvaMed.org

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This document was authored by Frederick F. Schweitzer, Welch Allyn, Inc.

Assistance was provided by:

Annette Hillring	Frances Akelewicz	Nancy Singer	Pamela J. Weagraff
Hillring & Associates, Inc.	Practical Solutions, LLC	AdvaMed	MediSpectra, Inc

Many other people also contributed to the ideas contained in the document. We thank the following industry officials for serving as members of the review committee:

Mark Allen, NetRegulus

Richard Andersen, Siemens Medical Solutions

Mary Armstrong, Armstrong Consulting

Edwin Bills, Hill-Rom Company, Inc.

Dia Black, AdvaMed

Franklin Bost, Porex Surgical Inc.

Christine Driscoll, Abbott Laboratories

Richard Franko, MediSpectra, Inc.

Bruce Haggar, MedQ Systems, LLC

Susan Jacobs, QMS Consulting

Betsy Lavin, AdvaMed

Bernie Liebler, AdvaMed

Shelley Looby, Cerner Corp.

Kathleen Lundberg, Guidant Cardiac Rhythm Management

Tony Maganini, Edwards Lifesciences Corp.

Joseph Mertis, Cardinal Health Medical Products and Services

Michael Morton, Sorin-Cobe CV

Regina J. O'Meara, Beckman Coulter, Inc.

George Phariss, Abbott Laboratories

Gary Price, Olympus America, Inc.

Melanie Reeves, Kinetics Concepts, Inc.

Susan C. Reilly, Reilly & Associates

Tim Rew, M.D., Terumo Medical Corp.

Keith Rohrbach, Ph.D., MedQ Systems, LLC

Ahmad Sajadi, Alaris Medical Systems

Michael Santalucia, Bausch & Lomb, Inc.

Ronald Schardong, Ethicon Endo-Surgery

Robert Turocy, Philips Medical Systems

Tim Wells, Wells & Associates

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Introduction

Background

Effective June 1, 1997, the Food and Drug Administration (FDA) revised the Current Good Manufacturing Practice (CGMP) requirements for medical devices and incorporated them into the Quality System Regulation. The FDA conducts inspections of medical device manufacturers to determine if they are complying with the requirements of the Regulation. In an attempt to decrease inspection time and increase the focus of medical device inspections, the FDA, in consultation with the medical device industry, developed an approach for conducting inspections under the Quality System Regulation called the Quality System Inspection Technique (QSIT).

Under QSIT, the Regulation's quality system requirements are divided into subsystems. The FDA, by directing its attention to the subsystems in a firm's quality system, is able to determine more efficiently if the firm's quality system is operating in a state of control. QSIT focuses on four of the major subsystems in the Quality System Regulation: Management Controls, Design Controls, Corrective and Preventive Actions, and Production and Process Controls. **This document only discusses the Design Controls Subsystem.**

The FDA's August 1999 "Guide to Inspections of Quality Systems" (the QSIT Manual) states:

"The purpose of the design controls subsystem is to control the design process to assure that devices meet user needs, intended uses, and specified requirements. Attention to design and development planning, identifying design inputs, developing design outputs, verifying that design outputs meet design inputs, validating the design, controlling design changes, reviewing design results, transferring the design to production, and compiling a Design History File (DHF) help assure that resulting designs will meet user needs, intended uses and requirements."

As with any effective process, it is essential that appropriate methods and controls be established to ensure that critical functions are carried out, including appropriate steps along the way to determine whether resultant outcomes or outputs meet the proposed inputs and requirements. Design control stages should be understood to enable an integral approach rather than being discrete steps in the overall process. Such a planned integrated approach will also allow issues to be identified and addressed earlier, providing a more consistent, predictable end product. Manufacturers that apply such a philosophy and culture in the design and development of medical devices will not only help assure compliance to the design control requirements, but will also help better assure conformance to user and patient needs.

The Design Controls section of the Quality System Regulation, 21 CFR Part 820, Subpart C, Sec. 820.30 outlines the requirements that each manufacturer of any Class II or Class III device, and certain Class I devices, must meet when designing such products or related processes, and when changing existing designs and processes. Although each manufacturer is required to establish and maintain a design controls system, the Regulation does not prescribe specific practices or methods due to the wide variety and diversity of devices and manufacturers; therefore, the Regulation does allow a certain amount of flexibility in the area of design controls.

This document was prepared by AdvaMed to help manufacturers comply with the requirements of Design Controls. The questions and answers herein follow the inspection process outlined in the FDA's QSIT Manual.

References

In compiling this document, we relied principally on the following sources:

- Federal Food, Drug, and Cosmetic Act, as amended
- The Quality System Regulation, 21 CFR Part 820
- The Preamble to the Quality System Regulation (61 FR 52654)
- Global Harmonization Task Force GHTF/FD: 99-9 "Design Control Guidance for Medical Device Manufacturers" June 29, 1999
- FDA guidance "Do It By Design – An Introduction of Human Factors in Medical Devices" December 1996
- "Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management" July 18, 2000
- Trautman, K.A., *FDA and Worldwide Quality System Requirements Guidebook for Medical Device*s, 1997, Milwaukee, Wisconsin
- FDA's August 1999 "Guide to Inspections of Quality Systems"*
- *Compliance Program, Inspection of Medical Device Manufacturers 7382.845**
- FDA's Guidance "General Principles of Software Validation"; Final Guidance for Industry and FDA Staff – January 11, 2002
- ANSI/ISO/ASQ Q9000-2000 – *Quality Management Systems: Fundamentals and Vocabulary*
- 21 CFR Part 11 – Electronic records; electronic signatures
- FDA publications available on their web site at http//www.fda.gov

* FDA's August 1999 "*Guide to Inspections of Quality Systems"* can be accessed at: http://www.fda.gov/ora/inspect_ref/igs/qsit/qsitguide.htm. The Compliance Program 7382.845 can be accessed at: http://www.fda.gov/ora/cpgm/default.htm#devices.

Notes

1) Pertinent definitions can be found in 21 CFR Part 820, Subpart A, Sec. 820.3.

2) The Quality System Regulation does not use the term Risk Management, but uses the term "Risk Analysis". However, as discussed in comment # 83 of the preamble to the Quality System Regulation, the term Risk Analysis is intended to be comprehensive and is meant to include the identification, assessment and mitigation of risk, which are the primary elements of a Risk Management process. For consistency with the terminology in the Regulation, this document will also use the term Risk Analysis in the same context.

Important Information

Please note that manufacturers can comply with the Quality System Regulation requirements in different ways depending on the types of products that the company manufactures, the size of the company and the company culture. The questions and answers included herein are meant to illustrate some of the ways design controls might be implemented. **This document is neither legal advice nor a legal standard**. Companies must ensure that their individual practices and procedures comply with the requirements of 21 CFR Part 820, and may wish to obtain legal advice from a qualified attorney on this topic. Contact Nancy Singer, Special Counsel at AdvaMed, for more information.

Design Controls Subsystem - Questions and Answers

Q.1 During a QSIT inspection, when an FDA investigator requests to inspect a device under Design Controls, what should be considered when a specific device is selected by the investigator, or a firm is requested to assist in the selection of a device to be inspected?

A.1 The firm should consider the following when an FDA investigator requests to inspect a device for adherence to design controls:

- *Devices Subject to Design Controls* – The firm should know whether the devices they manufacture are subject to design controls.
  - Design controls apply to all Class II and III devices, and the following Class I devices:
    - Tracheobronchial Suction Catheter
    - Surgeon's Glove
    - Protective Restraint
    - Manual Radionuclide Applicator System
    - Radionuclide Teletherapy Source
    - Any device automated with software

- *Inspection Jurisdiction* – A firm should refer to appropriate sections of the *Compliance Program, Inspection of Medical Device Manufacturers 7382.845* to determine whether the FDA has inspection jurisdiction.
  - Attachment "D" – Decision Chart for Review of design control records.
  - Part II, Section B., 1b. (R&D Center or Corporate Design Facility).
  - Part III, B., 2 (Special Instructions Concerning Design Controls).

  The program can be accessed on the Internet at http://www.fda.gov/ora/cpgm/default.htm#devices.

- *Eligible Devices* – The firm should provide the investigator with a list of devices eligible for an inspection under design controls.

- *Additional Points to Consider*:
  - Design controls clearly do not apply to devices in concept or feasibility studies, so it is incumbent upon the firm to clearly define the point at which design control begins in its new product development process.
  - Design controls do apply to investigational device exemption (IDE) devices. Normally, the selection of an IDE device for an inspection under design controls would be of a lower priority. Exceptions could include pre-approval inspections (PAI) or inspections related to Class III 510(k) devices. The manufacturer must ensure that the design control requirements for these devices have also been met.
  - If the project was developed internally or under contract
  - If the design was developed at the location under inspection, or at a satellite location, which makes the inspection slower and more cumbersome in providing detailed and timely explanations to the investigator
  - If a firm does not develop new products, e.g. contract manufacturers, then the provisions of Section 820.30(i), Design Changes, apply.
  - The investigator may also consider the quantity of design changes made to newly developed and released devices when selecting a device to be inspected.
  - Typically, an FDA investigator will request a high volume product that has been released to manufacturing and is being shipped to customers. If the company has several equally high volume products, the most representative product should be selected.

- The FDA investigator would usually be most interested in the devices of highest risk, but the investigator's decision may be affected by whether a device has been subject to one or more recalls and/or MDRs.
- The FDA investigator should not be inspecting a device under the requirements of design controls to determine whether the design was appropriate or safe and effective.
- The Quality System Regulation became effective June 1, 1997, including the requirements for design controls. The design control requirements do not apply to distributed devices if the design and development process was completed prior to June 1, 1997. However, Sec. 820.100(a) of the original CGMP Regulation contained requirements for specification controls and controls for specification or design changes.

Q2. What might be shown to indicate when the application of design controls begin?

A.2 Design controls do not apply to research and/or feasibility work, but must be implemented when design and development activities begin.

- *Procedure(s)* – A firm should provide its Quality Manual and/or its product design and development procedure(s) that describes where research and/or feasibility work ends, and where design and development activities and design controls begin. Typically, design controls are applied after the first set of design inputs is approved. A firm should be careful not to confuse initial marketing documents or preliminary concept documents as initial design input requirements.

  Note: *The transition from preliminary concept research to design and development activities should be clearly delineated in the design and development procedure(s). For example, a design review to evaluate and formally approve the initial design input requirements could mark the point at which design controls begin.*

- *Design and Development Plan* – The firm should provide the design and development plan for the selected design project, which should outline when initial design input is approved and/or when design controls begin.

Q.3 How might a firm demonstrate that it has appropriately defined and documented procedures for design controls in accordance with Sec. 820.30 of the Quality System Regulation?

A.3 As required by Subpart C of the Quality System Regulation, manufacturers of any Class II or Class III device, and certain Class I devices, must maintain procedures to control the design of the device to ensure that specific requirements are met.

- *Procedure(s)* – At this point, if a firm has not already provided its Quality Manual and/or design and development procedure(s), then it should show the investigator the relevant procedure(s), and consider having a qualified individual provide an overview of the firm's process. A firm should also consider using terminology that is the same as the Regulation. If terminology is different than that used in the Regulation, the firm should be prepared to discuss how it relates to the Regulation.

- *Required Elements of Design Controls* – A firm should be able to demonstrate that its procedure(s) ensure that specified design control requirements are met. The process for design controls must address the following elements:
  - Design and Development Planning
  - Design Input
  - Design Output
  - Design Review
  - Design Verification
  - Design Validation, including Risk Analysis*
  - Design Transfer
  - Design Changes
  - Design History File

  **Although risk analysis must be completed in design validation, a firm should not wait until design validation to begin risk analysis. Risk analysis should be considered throughout the design process.*

This does not necessarily mean that separate procedures need to be established for each of these elements. Many manufacturers incorporate the specific requirements for each of these elements into one overall design and development procedure.

- *Design Changes* – It is important for a firm to remember that even if it does not design and develop new products, it still must be able to demonstrate that it has defined, documented, and is maintaining procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation. This also applies to companies that utilize contract manufacturers whereas the company that owns the design must review and approve changes to be implemented by the contract manufacturer.

Q.4 What might be the elements of a Design and Development Plan, and what could be included to demonstrate that design and development activities, responsibilities and interfaces were adequately laid out?

A.4 Design and development plans must describe or reference design and development activities and define responsibilities for implementation. Plans must also identify and describe the interfaces with different groups and/or activities that provide input to the design and development process.

- *Procedure(s) and Plan(s)* – The firm should provide the appropriate design and development procedure(s) that outlines the required elements of the firm's design and development plan(s). The firm should also provide the design and development plan for the selected design project to demonstrate that activities, responsibilities and interfaces were adequately laid out.

- *Design and Development Plan Elements* – As well as including the design control requirements that are listed in answer 3, an adequate design and development plan should also include, but not be limited to, the following:
  - Goals and objectives of the design and development program
  - Delineation of organizational responsibilities including internal and external resources, such as contractors and consultants
  - Identification of the major tasks to be undertaken, the deliverables for each task and the staff and/or resources responsible, as well as interfaces with different groups or activities
  - Scheduling of major tasks to meet overall program timing
  - Identification of major design reviews and decision points

- Identification of design review team members, independent reviewers and their qualifications
- Documentation control and clear demonstration of when the plan begins, and what level of detail is needed for review and approval
- The elements that are applicable for each phase of the design within the firm's Quality System
- How management with executive responsibility and team members are kept informed as the project progresses

- *Risk Analysis* – The plan should outline when and how risk analyses will be conducted.

- *Reviews, Updates and Approvals* - A firm must be able to demonstrate that the plan was reviewed and approved. A plan must be updated as appropriate, and subsequently reviewed and approved as the design and development program evolves. Dates of the approvals and a copy of the plan must be maintained in the DHF. The frequency for review and update of the plan can be specified in the plan itself, or on an as needed basis.

- *Additional Points to Consider:*
  - The level of detail in the plan is dependent upon the firm's development process, the complexity of the device and the number of individuals, or functional departments involved in the development.
  - It is very important that the plan explain who holds the lead/responsibility for each phase of the design. Since the approach to design is very complex and involves many team members it is critical that the responsibilities be clearly defined for the various stages of the plan. For example, the Quality Group or the Project Management Group may lead the design review, but as appropriate should involve all of the team members such as R&D, Clinical, Regulatory Affairs, Quality Engineering, Manufacturing and Marketing.
  - The identification of interfaces includes defining the roles of the functional groups involved in the design process, e.g., Marketing, Purchasing, Quality, Manufacturing, Service and describing the information that will be transmitted and received among them. This is especially important when multiple organizations or outside companies/contractors are involved. Flow charts are very useful to identify interfaces.

Q.5 How might a firm demonstrate that Design Inputs (device requirements) were established, and that appropriate sources of Design Input were considered?

A.5 Manufacturers must establish and maintain procedures to ensure that the design requirements relating to a device are appropriate and address the intended use of the device, including the needs of the user and patient. Incomplete, ambiguous, or conflicting requirements must also be addressed and resolved.

- *Procedure(s)* –The firm should first provide its procedure(s) for establishing design inputs. The procedure(s) should indicate how the physical and performance requirements of a device are determined and documented to ensure that the intended uses of the device, including the needs of the user and the patient will be addressed. The firm should also provide the design inputs (device requirements) for the selected design project to demonstrate that the design inputs established for the device did in fact consider the relevant aspects.

- *Relevant Aspects* - It's expected that design input procedures will cover the relevant aspects, which include, but are not necessarily limited to, the following:
  - Intended use
  - User/patient/clinical needs
  - Performance characteristics

- Safety
- Limits and tolerances
- Energy source
- Risk analysis*
- Toxicity and biocompatibility
- Environmental
- Electromagnetic compatibility (EMC)
- Compatibility with accessories/auxiliary devices
- Compatibility with the environment of intended use
- Human factors
- User interfaces
- User competency
- Physical/chemical characteristics
- Labeling/packaging
- Reliability
- Stability
- Statutory and regulatory requirements
- Voluntary standards
- Manufacturing processes
- Sterility
- MDRs/complaints/failures and other historical data
- Design history files

* *It is important to assess the risks and mitigation steps up front at the design input stage. This affords proactive incorporation of the mitigation means during the design process, as well as implementation of appropriate steps during design verification and validations.*

- *Sources* – The sources used to develop design inputs should be provided. One popular approach to determine inputs is through a checklist, which may include, but not be limited to the following areas:
  - Customer input through focus groups, surveys, trade shows, etc.
  - Comparison testing of competitor product for specific performance criteria
  - Benchmarking activities
  - Internal manufacturing and service input obtained through surveys, questionnaires, etc., to determine internal needs or challenges that may be ahead
  - Review of similar product histories to include production data for scrap, rework, testing and inspection failures, warranty/service repairs as well as customer product complaints and CAPA records
  - Review of MDRs, FDA Enforcement Reports, ECRI, USP Reports, and Vigilance Reports on similar products or earlier generations of the product*
  - Performance requirements stipulated by the FDA, voluntary standards, or other regulatory agencies
  - A review of literature within the industry or the medical community
  - Risk analysis used to identify safety and reliability needs
  - Input from R&D, Quality, Regulatory, Marketing, Manufacturing, etc.

**In many cases, manufacturers have similar products and, therefore, many requirements already exist for the device and may be referenced.*

Note: *It is important to document the sources to be able to demonstrate that all appropriate sources of information were utilized in defining design inputs. Human factors are a key area of interest (reference FDA guidance "Do It By Design – An Introduction of Human Factors in Medical Devices" December 1996 and "Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management" July 18, 2000).*

- *Incomplete/Ambiguous or Conflicting Inputs* – The design input, or design requirements, will serve as the basis for design verification and validation; therefore, the firm's design input procedures must define the mechanism that will be utilized to ensure adequacy, and address incomplete, ambiguous and conflicting requirements. This is usually accomplished in a design review, or may be included as part of the design input review and approval process. In any event, the firm should be prepared to demonstrate how design inputs are reduced to measurable terms with appropriate tolerances.

- *Reviews, Updates and Approvals* - A firm must be able to demonstrate that the design inputs were reviewed and approved and also updated as appropriate, and subsequently reviewed and approved as the design inputs evolved. The firm should also ensure that the change history and dates of the approvals are provided in the documentation, and copies of all versions of the plan are maintained in the DHF. The same review and approval requirements apply to updates of the design outputs.

Q.6 How might a firm demonstrate that Essential Design Outputs were established to assure proper functioning of a device?

A.6 Manufacturers must establish and maintain procedures for defining and documenting design output in terms that allow an adequate evaluation of conformance to design input requirements.

- *Procedure(s)* – The firm should first provide the design output procedure(s), which should describe how the design inputs are translated into design outputs, e.g., product specifications, including how essential outputs are determined. In addition, there should be an explanation of how design outputs are traced to design inputs.

- *Design Output* - The firm should provide the design outputs for the selected design project. Design output typically includes, but is not limited to, the following:
  - Drawings
  - Diagrams
  - Specifications
  - Software (source or machine code)
  - Procedures

- *Essential Design Outputs* – Design outputs that are essential to the proper functioning and safety of the device are considered essential design outputs. Using examples of essential design outputs from the selected design project, explain and demonstrate how essential design outputs were identified and documented to assure proper functioning and safety of the device. The use of risk analysis should be one of the prime factors in identifying essential design output. The firm should demonstrate how quantifiable acceptance criteria were established. Establishing clear deliverables for each of the design outputs in a quantifiable manner, such as confidence intervals or other statistical tools, will allow for unambiguous verification and validation.

- *Reviews, Updates and Approvals* - A firm must be able to demonstrate that the design outputs were reviewed and approved prior to being released. It should ensure that the dates of the approvals are provided in the documentation, and approved outputs are included or referenced in the DHF. The same review and approval requirements apply to updates of the design outputs.

- *Additional Points to Consider:*
  - Keep in mind that design output refers to the completed deliverables at the conclusion of a given design phase, e.g., at the end of the specification phase, the design output is the product specifications, at the end of design transfer, the design output includes the device, its packaging and labeling, and a device master record (DMR).
  - Typically, essential design outputs are identified via risk analysis and/or design reviews. Those aspects of the device, whose failure could affect the safety, effectiveness, reliability, etc., are considered essential design outputs. It is key to demonstrate how risk analysis was used to identify essential design output.
  - Manufacturers may document essential design outputs in a variety of ways, including notations directly in the DMR documents themselves, e.g., bold, asterisks, notes, and/or in the risk analysis, e.g., Failure Modes and Effects Analysis (FMEA) may be used to identify hazards at the component level.

Q.7 What might be shown to demonstrate that acceptance criteria were established prior to Verification and Validation (V&V) activities?

A.7 Manufacturers must establish acceptance criteria prior to V&V activities to ensure that the device meets the predetermined requirements of the design input and output. Therefore, V&V must not be an empirical exercise.

- *Procedure(s)* – The firm should provide the procedures for V&V to demonstrate how it requires predetermined acceptance criteria to be established prior to V&V activities.

- *Design Output* – The firm should first provide the design output procedure(s) that describes the process for ensuring that design outputs with appropriate acceptance criteria and/or quantifiable terms have been defined for each product requirement/design input. As objective evidence, the company should provide examples of design outputs for the selected design project to demonstrate that the outputs include acceptance criteria. Ideally, essential design outputs should be provided as examples.

- *Design Input* - As indicated earlier in this document the product performance requirements and design inputs established for the project must be defined in unambiguous, quantifiable terms. It would also be appropriate to demonstrate how the design inputs of the selected design project accomplished this.

- *Verification and Validation Protocols* – V&V activities must be performed in accordance with established procedures and written protocols with clearly defined (or referenced) acceptance criteria. The protocols, as well as the results, must be reviewed, approved and dated. The result should also identify the individuals responsible for performing the verification. In this way, it is clear that the acceptance criteria were identified in the protocol prior to the commencement of the V&V activities. The results will demonstrate that the acceptance criteria were met. Any deviations to the V&V protocol must be documented and reviewed for its impact on the outcome of V&V activity.

Q.8 What evidence might a firm provide to demonstrate that Design Verification activities confirmed that Design Output met Design Input requirements?

A.8 Manufacturers must establish and maintain procedures for verifying the device design. Design verification must confirm that design output meets design input requirements.

- *Procedure(s)* – The firm should provide the appropriate design verification procedure(s) that describes the firm's requirements for design verification, and how they confirm that design output meets design input requirements.

- *V&V Plan* – The firm should provide the V&V plan for the selected design project, which should include detailed information as to how each aspect of the product will be verified and validated to predetermined requirements. The V&V plan should also discuss how traceability has been established to the design input and design output as well as to the risk analyses.

- *Test Protocols* - The firm should provide the V&V test protocols and results that have been completed for the selected project. These, linked with statistical criteria based on the criticality of each feature should provide consistency of approach and clarity for the acceptance criteria.

  Note: *When using statistical techniques, manufacturers must have established procedures for identifying valid techniques as described in 21 CFR, Part 820, Subpart O, Sec. 820.250.*

- *Requirements Traceability* - Traceability can be demonstrated through flow charts or a comprehensive table, such as a traceability matrix, showing the input, output and how the output was measured against established criteria. Each test would link to a test report or study protocol and its final report.

- *Records* – The firm should be able to demonstrate that a record of the results of the design verification, including the identification of the design configuration, verification method(s), the date, and the individuals performing the verification, is documented or referenced in the DHF.

- *Additional Points to Consider:*
  - Though not required by the Regulation, the best way to demonstrate that design verification activities confirmed that design outputs met design inputs is through the use of a traceability matrix. The matrix includes the design inputs, the corresponding outputs that meet the requirements, and references the verification and/or validation activities that demonstrate that the requirements were met. A traceability matrix is also an inherent tool for the development team to track remedial actions following verification to ensure that all open actions have been closed, and requirements subsequently verified.
  - Test methods used in design verification activities should be evaluated to assure that they provide sufficiently accurate, precise and repeatable results under their usual conditions of use. Analytical methods intended for identification, purity or assay should be validated. Physical, electrical, mechanical and performance measurement methods (other than direct measurement by a capable, standard calibrated instrument) should be considered for appropriate validation, especially if the method is for evaluating an essential design output.

Q.9 What evidence might a firm provide to show that design validation data confirmed that the approved design met the predetermined user needs and intended uses?

A.9 Manufacturers must establish and maintain procedures for validating device design. Design validation must confirm that the device conforms to defined user needs and intended uses when tested under actual or simulated use conditions.

- *Procedure(s)* – The firm should provide the appropriate design validation procedure(s) that describes the firm's requirements for design validation, and how they confirm that the device conforms to defined user needs and intended uses when tested under actual or simulated use conditions.

- *Predetermined User Needs and Intended Uses* – The firm should be able to demonstrate that user needs and intended uses were predetermined. User needs and intended uses must be defined at the very beginning of the project and are utilized in defining design input. User needs and intended uses are translated into measurable requirements in the design input document(s). User needs and intended uses may be included in the design input documents or they may be contained in a separate, higher level document, typically owned by the marketing function.

- *Production or Equivalent Devices* - The firm must be able to demonstrate that the design validation was performed on production devices; or, if not performed on production devices, be able to provide evidence that the devices were equivalent to production devices. (Also, refer to question and answer 13)

- *Actual or Simulated Use* – Design validation typically involves functional and/or performance evaluations, but not necessarily actual clinical use. A firm must be able to demonstrate that appropriate evaluations, clinical or non-clinical, were performed. Design validation activities may include, but are not limited to, the following:
  - Clinical studies via Institutional Review Boards (IRBs) and Investigational Device Exemptions (IDEs) or IRB alone for non-significant risk devices
  - Consumer preference testing
  - 510(k) historical database search
  - Bench testing under simulated use conditions
  - Literature searches
  - Review of labels and labeling, packaging and other historical product information

- *Software Validation* – Design validation includes software validation if the device utilizes software. Therefore, as appropriate, a firm should be able to provide software validation protocols and results for the selected design project. (Also refer to question and answer 11.)

- *Requirements Traceability* - As with design verification, a traceability matrix can again be utilized to demonstrate that user needs and intended uses were translated into design inputs and then linked to the validation activities. Each test would link to a test report or study protocol and its final report.

- *Records* – The firm should be able to demonstrate that a record of the results of the design validation, including the identification of the design configuration, validation method(s), the date, and the individuals performing the validation, is documented in the DHF.

- *Additional Points to Consider:*
  - Although verification and validation are associated activities, they do have two distinctly different purposes. Therefore, the firm's V&V plan and procedures should be provided to explain how each purpose is fulfilled. Design verification is intended to provide objective evidence to confirm that specified requirements have been fulfilled. Design validation is intended to establish objective evidence that device specifications conform to predetermined user needs and intended uses.
  - The development of validation protocols can and should begin very early in the design process (i.e., at the same time user needs and design input are being developed). This will help to ensure that user needs, intended uses and design input are adequately defined to enable verification and validation.

Q.10 How might a firm demonstrate that all discrepancies identified during Design Validation were resolved or adequately addressed?

A.10 Discrepancies identified during design validation must be recorded and either resolved or reconciled, and then tracked to completion before commercial distribution of the device.

- *Procedure(s)* – The firm should provide the appropriate procedure(s) for design validation and/or the design and development plan that describes how discrepancies identified during design validation will be resolved/addressed and tracked through to closure. The validation procedure and/or protocol should identify how discrepancies will be documented and resolved.

- *Design Reviews* – The resolution of discrepancies is usually accomplished in design reviews. Action item lists are created and completion/resolution is documented. Once design validation has been completed, the results are typically subject to a design review with appropriate cross-functional representation. During the design review discrepancies/issues are addressed, and action items are determined and assigned to resolve issues/discrepancies. All open discrepancies and/or issues must be adequately resolved or reconciled before the product is released for commercial distribution. A documented review of the residual risks must indicate that the remaining risks are acceptable. Clinicians may be involved to ensure that the resolution/mitigation is appropriate and acceptable. The firm may show the design review minutes/action items, with the subsequent closure reports, as objective evidence.

- *Records* – The firm should be able to trace to closure all identified issues and/or discrepancies. A record of the final resolution, the date and the individuals responsible for the resolution should be documented in the DHF. A traceability matrix is also an inherent tool used by the development team to track remedial actions following validation to ensure that all open actions have been closed. In addition, the matrix is also used to demonstrate that requirements, including those identified in the risk analysis process, are subsequently revalidated.

Q.11 If the device contains software, what evidence might a firm provide to demonstrate that the software was properly validated to ensure that requirements were met?

A.11 Manufacturers must establish and maintain procedures for validating device design. As such, software validation is a required part of design validation. Software validation confirms that all software requirements have been met, while design validation goes further to confirm that the entire device, including its software, meets the user needs and intended uses.

- *Procedure(s)* – The firm should provide the appropriate software validation procedure(s) that describes the firm's method(s) for validating software, and how the process confirms that software requirements will be met.

- *Software Validation Plan* – The firm should start by providing the software validation plan for the selected design project, which should be linked to design input, or to a corresponding software requirements document, and subsequently to a related software specification (output). As with any product specification or design output, all software requirements and acceptance criteria should be traceable to the design inputs or device requirements. Software test plans, test procedures, test cases and results should be documented. Software verification and validation should be a subject of design reviews.

Note: *On January 11, 2002, the FDA issued a guidance document for software validation titled "General Principles of Software Validation; Final Guidance for Industry and FDA Staff", http://www.fda.gov/cdrh/comp/guidance/938.html. The guidance outlines general validation principles that the FDA considers to be applicable to the validation of medical device software or the validation of software used to design, develop or manufacture medical devices. The guidance describes how certain provisions of the medical device Quality System Regulation apply to software and the FDA's current approach to evaluating a software validation system.*

- *Protocols and Results* – The firm should provide the software V&V protocols and results for the selected design project. The V&V protocols should be reviewed and approved, and should describe the software quality assurance activities. The results should demonstrate conformance to the predetermined requirements.

- *Requirements Traceability* – As with any design verification and validation, a traceability matrix, again, can be used to demonstrate that user requirements were translated to software requirements/design inputs and then linked to the validation activities. Each V&V activity would link to a test report or study protocol and its final report.

- *Records* – The firm should be able to demonstrate that a record of the results of the software V&V, including the identification of the software version, hardware configuration, validation method(s), the date, and the individuals performing the validation is documented in the DHF.

- *Additional Points to Consider:*
  - Software presents a unique challenge in terms of the user environment and the mechanics of its interface with the device. The firm can demonstrate the effectiveness of the user interface through user studies or clinical studies, which outline acceptance criteria regarding the performance of the software. A user interface specification may be a useful tool. Additionally, through error testing or fault insertion, the firm can demonstrate that the appropriate defaults and/or warnings are present in the programming.
  - A traceability matrix can be an important tool for software validation. It includes traceability from the system requirements, to the software requirements, to the implementation of the software design, and to the software verification/validation activities. Requirements derived from the risk analysis process can be included in the traceability matrix, which helps to focus the software verification and validation activities.
  - Software used in the manufacturing process or for maintaining quality records for the device must be validated for its intended use.

Q.12 How can a firm demonstrate that Risk Analysis was performed and that identified risks are being or have been addressed during the design process?

A.12 Risk analysis should be pervasive throughout the design and development process, and ideally should begin in the design and development planning phase to ensure the appropriate scope for the plan, as well as to determine at what points in the process risk analyses will be conducted.

- *Procedure(s)* – The firm should provide the risk analysis procedure(s) that describes the firm's methods for performing risk analyses, and how identified risks will be addressed during the design and development process.

- *Design and Development Planning* – If the firm has conducted a preliminary risk analysis during the design and development planning phase, this should be provided along with the plan for the selected project to show how risks were considered during the development of the plan.

- *Design Input Development* – If the firm has conducted initial risk analysis during the development of design input, this, along with the design input for the selected design project, will show how risks were considered during the development of inputs/product requirements.

- *Design Output Development* – If the firm has utilized risk analysis during the development of design outputs, the risk analysis should be provided along with the design outputs for the selected design project to show how risks were considered during the development of the design outputs. Risk analysis input tools, such as Fault Tree Analysis (FTA) for the estimation of failure probabilities and/or FMEA for identifying hazards, are often used to determine essential design outputs.

- *Design Validation* – Risk analysis must be completed in design validation, and is a useful tool in determining V&V requirements to analyze potential risks. This approach also applies to software V&V, which is a part of the design validation process. The firm should provide the final risk analysis for the selected design project.

- *Design Review* – Once risk analysis has been completed, the results are typically subject to a design review with appropriate cross-functional representation. During the design review, unacceptable risks are addressed and action items are determined and assigned in order to resolve and/or mitigate the risks. Action item lists are created and completion/resolution is documented. All open unacceptable risks must be adequately resolved or mitigated by the end of design validation. Clinicians may be involved to ensure that the resolution/mitigation is appropriate and acceptable. The firm should provide the design review minutes/action items for the selected design project, along with the subsequent closure reports.

- *Risk Tracking and Mitigation* – All unacceptable risks identified must be resolved or mitigated through appropriate risk control measures, which are listed as follows in their order of importance: design measures, protective measures, or labeling measures. Once an unacceptable risk is identified, it must be recorded and tracked/traced to closure. Therefore, whether it is design review documentation or other methods, the firm should be prepared to provide appropriate documentation to demonstrate that all unacceptable risks were resolved, and that proposed risk mitigation will not introduce new hazards/risks. A quantitative method such as a Risk Probability Number (RPN) may be useful. A traceability matrix again can be utilized to demonstrate that design requirements identified in the risk analysis process are incorporated into design input and output documentation, and verified and/or validated.

- *Records* – The firm should be able to demonstrate that a record of the results of the risk analyses, the risk analyses methods, updates, the date, and the individual(s) performing the analyses are documented in the DHF.

Q.13 What evidence might a firm provide to prove that initial production devices or their equivalents were used during Design Validation?

A.13 Design Validation should involve devices, which are manufactured using the same methods and procedures intended for ongoing production.

- *Procedure(s)* –The firm should first provide the design verification and validation procedure, which should contain a definition for production equivalent, e.g., devices built using approved manufacturing procedures.

- *Device Identification* – The firm should provide design validation protocols and/or reports that clearly identify the device configuration evaluated, e.g., name, description and/or serial number of the device(s) evaluated.

- *Production Equivalents* – The firm should provide the documented rationale that describes how the equivalent devices were found to be production equivalent, e.g., assembly procedures and test protocols, etc., along with results and/or letter to file outlining the rationale for equivalence. Particular care must be taken to document rationales when personnel other than routine production personnel are utilized to build devices that will be used for validation.

- *Production Devices* – Device History Records (DHRs) documenting the devices' configurations should also be available. By providing the completed DHR and matching it to the approved DMR, traceability can be established. Traceability is usually determined by lot number for the devices used in the validation studies. If dates of manufacture are used to determine whether the lots used in the validation studies were from early production, they must be supported by other quality records.

- *Design Changes* – If design changes are made at some point following design validation, the differences between the devices validated and the "final" production units must be reconciled. Unless the changes are revalidated, it will be necessary to provide a rationale to support the fact that the design changes would not affect the validation results and conclusions.

Q.14 How might a firm demonstrate that Design Changes made during the design process, or after the device was commercialized, were adequately controlled, verified and validated, and if verified only was adequate justification provided?

A.14 Per the Quality System Regulation, design change control applies to both pre-production and post-production design changes. Manufacturers must establish and maintain procedures for identifying, documenting, validating, or, where appropriate, verifying, reviewing, and approving design changes before their implementation.

- *Procedure(s)* – The firm should first provide its design change control procedure(s) that cover both pre and post-production design changes. Pre-production design change control typically begins when the initial design inputs have been approved and continues on through the life of the product. Design change control procedures should indicate when only verification of changes is allowed in lieu of validation and the procedures should describe how the justification is documented.

- *Pre-production Design Change Control* – Pre-production design change control can be accomplished with the same procedure as post-production design change control. However, firms usually establish a less stringent, more flexible approach for pre-production design change control to allow the development process to flow more freely. The firm should provide examples of pre-production design changes that were made to the selected design project.

- *Post-production Design Change Control* – The firm should provide examples of post-production design changes. The firm should ensure that the design change documentation indicated how verification and validation were handled, including the rationale if validation was not performed.

- *Review and Approvals* - A firm must be able to demonstrate that the design changes were reviewed and approved prior to being released. The firm should also ensure that the dates of the approvals are provided in the design change documentation.

- *Additional Points to Consider:*
  - It is important for a firm to remember that even if it does not design and develop new products, it still must be able to demonstrate that it has defined, documented, and is maintaining procedures for the identification, documentation, validation, or, where appropriate, verification, review and approval of design changes before their implementation.
  - All post-production design changes will require verification. The level of verification can vary greatly, and can include activities such as reviews of specifications, visual examination and actual testing. If it is determined that validation is not required, then a rationale must be documented. The design change procedure should include guidelines, e.g., a material or component change that does not affect user needs or intended uses may not require validation.

Q.15 What might a firm provide to demonstrate that appropriate Design Reviews were conducted and documented, and that resultant action items are being or have been resolved?

A.15 A firm must be able to demonstrate that formal documented design reviews were conducted at appropriate stages during the development cycle, and that appropriate representatives conducted the review.

- *Procedure(s)* – The firm should first provide its design review procedure(s) that describe its requirements for design reviews. The procedures must ensure that participants at each design review include all responsible functions for the stage being reviewed and a representative(s) who does not have direct responsibility for the stage being reviewed. The procedure(s) must also describe how design reviews are planned and documented.

- *Design and Development Plan* – The firm should provide the design and development plan for the selected design project to demonstrate where design reviews were planned throughout design and development. The number of design reviews is dependent on the complexity of the design project, but at least one formal design review must be conducted prior to final product release for distribution.

- *Design Review Results* – The firm should provide the result(s) of a design review for the selected design project. The results should include the agenda of the design being reviewed, the date, the individuals performing the review (including at least one reviewer who doesn't have direct responsibility for the stage being reviewed), and the follow-up meeting minutes indicating the issues, action plans and responsibilities determined during the design review.

- *Design Review Records* – The firm should also provide evidence that design review records are being documented in the DHF, and that the records demonstrate that all issues and action items were resolved/closed prior to the release of the product. A record of the steps taken to close the action items, the individual(s) responsible and the completion dates should also be part of the record.

- *Additional Points to Consider:*
  - In almost every case it is recommended to conduct a formal design review of the design inputs prior to their approval, and at the conclusion of the design process before design transfer. A review of risk analysis is also highly recommended.

- Action items are usually documented and tracked separately from the design review meeting minutes. A traceability matrix is a good tool for the development team to track action items following design reviews to ensure that all open actions have been closed. Some manufacturers track action items under their change control procedures. Action items are typically reviewed at subsequent design reviews to ensure that all items are adequately addressed.
- The firm should ensure that the independent reviewer is qualified to perform the review of the specific portion of the design.

Q.16 What evidence might a firm provide to prove that the design was correctly transferred into production specifications?

A.16 Each manufacturer must establish and maintain procedures to ensure that the device design is correctly translated into production specifications.

- *Procedure(s)* – The firm should first provide the design transfer procedure(s) that describes the transfer of design outputs from design and development to manufacturing. The procedure(s) should ensure that all product specifications are qualitatively assessed to ensure completeness and adequacy, and that all documents and articles which make up the production specifications are reviewed and approved at the time of transfer.

- *Device Master Record* – The firm should provide the DMR for the selected design project along with some corresponding design outputs to demonstrate that the design outputs were transferred correctly and are complete, adequate and approved.

- *Additional Points to Consider:*
  - Process validation is the key activity associated with design transfer to ensure that the design was correctly translated into production specifications. Process validation encompasses the assessment of the completeness and adequacy of the production specifications. Design validation may also be accomplished concurrently with process validation. Both process and design validations are performed in accordance with written protocols, which, along with results and conclusions, are documented and/or referred to in the DHF.
  - Software used in the manufacturing process or for maintaining quality records for the device must be validated for its intended use.
  - It is not necessary for design transfer to occur all at once and it may occur at separate intervals over time.
  - Other design transfer activities may include the "final, release-to-production" review and approval of the DMR and a review of the DHF to ensure that all the requirements of the design and development plan and the Regulation were met.

Q. 17 What documents or quality records might be maintained in the Design History File and what evidence might be provided to demonstrate that the DHF is being maintained?

A.17 Each manufacturer must establish and maintain a design history file for each type of device being developed under design controls. The DHF must contain or reference the records necessary to demonstrate that the design was developed in accordance with the approved design plan and the requirements of Subpart C of the Regulation.

- *Procedure(s)* – If the firm has a procedure(s) that describes how the DHF is established and maintained, it should first provide the procedure. It would also be appropriate to provide the DHF Index. The procedures for record retention should demonstrate what records are kept, and for how long, as well as where they are kept.

- *Records* – The records or documents that should be found in the DHF or referenced as to their location include, but are not limited to, the following:
  - The design and development plan
  - Design input documents
  - Risk analyses documents
  - Design output
  - Pre-production design change control records
  - Engineering notebooks, which contain relevant information recorded after Design Control began
  - Records of product builds and testing
  - V&V protocols and results*
  - Design review records
  - Design transfer records
  - Copies of controlled documents used during the design process
  - The initial DMR
  - A DHF index
  - Issues tracking matrix

  ** Raw data may be stored in another location, which should be referenced. Software program names and versions should be referenced in reports and the electronic data backed up and stored in a secured location with additional backups provided at an additional location to prevent loss in case of disaster.*

- *DHF and Plan* – The firm should also provide the DHF and the design and development plan for the selected design project to demonstrate that the DHF contains the necessary elements to substantiate that the device was designed in accordance with the design and development plan and Subpart C of the Regulations.

- *Additional Points to Consider:*
  - Many firms have found that organizing the DHF in a manner consistent with the elements of the Regulation is convenient and facilitates future FDA review.
  - A firm may choose to organize the files in whatever manner makes the most sense for its business, keeping in mind that the goal of the DHF is to demonstrate compliance to the design and development plan and the requirements of the Regulation.
  - Design and development plans typically describe how DHFs will be established and maintained for a specific device. A DHF must be established for each type of device. The firm may decide upon the types of devices to be addressed in a single DHF. The files are usually consistent with the types of devices and accessories covered in the marketing submission, i.e., 510(k) or PMA. If more than one device shares a common DHF, the firm must be able to identify each device that has common design characteristics, such as a catheter design that has different sizes.
  - A firm should strongly consider organizing the DHF in a manner consistent with how data will be submitted in a 510(k) or PMA.
  - DHFs are typically "frozen" after final design transfer. When design changes are made post-production, then addendums can be created, or the supporting documentation is maintained in accordance with the firm's change control process. The original DHF should be the embodiment of the new product as it was released for commercial distribution.

- The DHF should be established early and updated as the design process evolves and documents are created. Design transfer should include an audit of the DHF to ensure all the documents are present to demonstrate conformance with the design plan and the Regulation.
- The DHF should be maintained in a manner that is easily accessed at the time of an inspection. The investigator usually expects that documents requested be available on the same day of the request. Any unusual time delay may result in a more extensive inspection of the file, or inspection of additional files.

Q.18 What evidence might a firm provide to demonstrate that post-production changes made during a product's life were/are reviewed for potential impact on the design and application of Design Controls?

A.18 Post-production design changes require a firm to revisit the Design Controls section of the Regulation to ensure that the appropriate elements of design controls have been addressed. (Also refer to question and answer 14)

- *Procedure(s)* – The firm should first provide its change control procedure(s) that describes how post-production design changes are made and managed throughout the life of the product. The procedure(s) should indicate how changes are reviewed to consider how they might impact design input requirements and intended uses, or risks of the device. Change control procedures should indicate when only verification of changes is necessary in lieu of validation.

- *Post-production Change Control* – The firm should provide examples of post-production changes. The change documentation should provide evidence that the firm considered the appropriate aspects of the device's design, which should be indicative based on the verification, validation and evaluation of the risk analyses that were performed, or by the rationale that was provided if validation was not performed.

- *Review and Approvals* - A firm must be able to demonstrate that the design changes were reviewed and approved prior to their implementation. The firm should also ensure that the dates of the approvals are provided in the documentation.

- *Additional Points to Consider:*
  - All elements of design controls must be considered and individuals knowledgeable about the product design must be involved in the review and approval of post-production changes to determine the extent to which the change will impact the device design. Seemingly insignificant changes can have significant product effects. The significance and timing of the change determines the level of documentation required and how far back into the design process the firm must investigate. The firm should use the risk analysis process to help determine the impact of the change.
  - All post-production design changes will require verification. The level of verification can vary greatly, and can include activities such as reviews of specifications, visual examination and actual testing. If it is determined that validation is not required, then the rationale must be documented. The design change procedure should include guidelines, e.g., a material or component change that does not affect user needs or intended uses may not require validation.