FORTIS LIFE SCIENCES

White Paper
NCXQUALLFA_WP2023306v1

Quality Considerations for a Successful Diagnostic Assay Launch

nanoComposix

The increasing prevalence of infectious diseases has heightened demand for an *in-vitro* diagnostic (IVD) that is low complexity, portable, rapid, and inexpensive to manufacture. Lateral flow immunoassays (LFA) have helped to address this demand as demonstrated by the use of COVID-19 rapid tests to combat the global pandemic. LFAs are capable of being used at the point-of-care (POC) without training and expensive instrumentation while still being able to provide clear and accurate results. Given that it typically takes large capital investment to develop an IVD device like an LFA, companies often rush through product development to reduce development costs and expedite the time to market to begin recouping their investment. However, taking time to build quality into the device allows not only an increased chance of successful launch by assuring that the device meets the user needs and intended uses, but also increases the longevity of the product in the market by avoiding issues with product quality or consistency. When IVDs are designed with quality in mind, chances that a safe and effective product is developed are increased. This is achieved through proper control of the product design, methods for planning the production process, and adequate risk management strategies throughout the product lifecycle.

About the Author

Kristina Pike is a Design Control Senior Scientist at Fortis Life Sciences with over twenty years of comprehensive IVD Development, Quality Control, Quality Assurance, and Regulatory Affairs that includes nine years of hands-on laboratory experience and over twelve years of design control and project management. Kristina received a Bachelor of Science in Biochemistry from University of California, Los Angeles and began her career as a Research Associate in R&D at an IVD Development company. She enjoys working with cross functional teams to facilitate the definition of project scope, goals, and deliverables, while promoting conformance to customer, regulatory and site-specific requirements.

What is design control and how can it streamline product development to bring products to market faster?

Design controls have been a Quality System requirement for ISO 13485 and FDA Code of Federal Regulations 21 CFR 820.30 since the late 1990s. The addition of design control to FDA regulations was based on findings from a report entitled "Device Recalls: A Study of Quality Problems" wherein "the FDA found that approximately 44 percent of the quality problems that led to voluntary recall actions during a 6-year period were attributed to errors or deficiencies that were designed into particular devices and may have been prevented by adequate design controls".[1] New IVD products developed must comply with these regulations to market and sell these medical devices.

When framed as a regulatory requirement, design controls are often viewed as an afterthought, a hindrance that detracts and slows the progress of the science, or superfluous documentation to be checked off on a task list. As a result, it becomes easy to overlook the potential for design controls to synergize the development and decrease time to market. The cost to correct a design error is lower the earlier it is detected and corrected, and if performed properly, design controls hasten time to market as less time is spent on re-design and performing additional studies. Along with risk management, design controls also have the potential to prevent recalls, which may incur additional development costs, lost revenue, and damage to product or company reputation.

nanoComposix

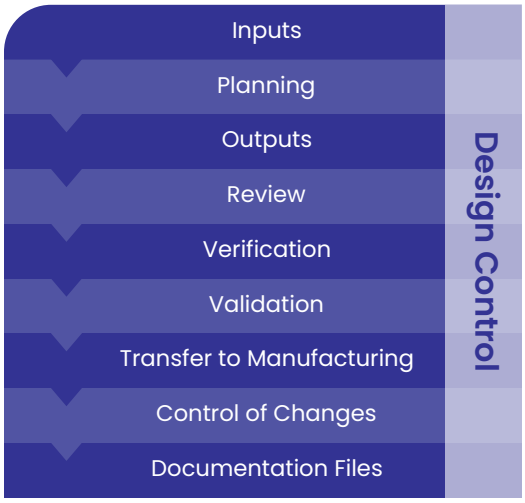
In general design controls:

- Ensure documentation that provides evidence that the developed product is safe, effective, and performs to meet intended use and established user needs.
- Are required to conform to FDA 21 CFR 820.30, and ISO 13485 Section 7.3 regulations prior to marketing a medical device.
- Provide a basis for measuring conformance to quality system objectives and builds quality into the device.
- Are best practice to develop successful product output that meets the defined input requirements.
- Are incorporated into product development to provide a system of checks and balances.

And provide mechanisms to:

- Identify the user population, objective of the new product, and general purpose of the IVD
- Reduce product risk in production, distribution, and use by mitigating foreseeable issues
- Ensure that product meets specified requirements, user needs, and intended use
- Ensure the product developed is manufacturable
- Provides identification and traceability
- Improve communication and coordination among teams involved in the development process

The 9 Elements of Design Control



1. Design and Development Inputs - When is the best time to start design controls?

Once the product concept is defined and determined to be feasible, design control should begin. The Design Inputs Phase should describe the product specifications and must include requirements that detail what the device will do, how and by whom it is regulated, and how it should perform. Requirements should describe the user needs such as purpose of device, intended use, intended market, and indications. This set of requirements allows the design team to effectively plan, manage, and guide the project and resources to launch the product.

Development can begin as soon as the project is greenlit, however it is more resourceful to set the targets from the beginning. The developers require design inputs to begin work designing the right product. Documenting the product requirements uncovers incorrect assumptions that detrimentally effect timelines and cost.

One way to influence the timeline is to define inputs as soon as possible. This sets the development team up for success as there will be less iterations and changes throughout the development cycle. Design inputs should be clear, discrete, and actionable. They should be used to identify features that cannot be lived without and ones that can be compromised on if necessary. While input requirements will evolve and can be changed throughout development, it is crucial to document and evaluate those changes to ensure that they don't negatively affect other aspects of the product.

Risk management begins with the development of design input requirements: identify, reduce, analyze acceptability of potential risks to product, process, distribution, and use of the product. Then determine acceptable solutions to reduce those risks.

The input requirements act as a blueprint that guide development and provide an objective set of specifications that can be verified. Every iteration of the design will be tested, analyzed, or developed to conform to functional, characteristics, performance, useability, safety, regulatory, and labeling/packaging requirements.

nanoComposix

2. Design and Development Planning - How do project leads align stakeholders with different priorities?

IVD contract development and manufacturing (CDMO) services continue to rise with the shift in focus to point of care testing. The emergence of COVID-19 opened the market to companies ready to fulfill the high demand, but whom may not have established quality systems. One of the drivers for outsourcing development is improving efficiency through access to experts, equipment, facilities, and manufacturing technology. With outsourcing, however, it becomes increasingly important to have well-defined interrelationships and division of responsibilities between several parties, which may include suppliers, CDMOs, outside consultants, and independent auditors. Close cooperation between groups is essential and a well-defined plan opens the lines of communication, sets expectations, and assists in aligning the goals of each of these stakeholders.

The development plan assists in controlling the design process through documentation of the development stages along with the activities and deliverables required to meet quality objectives and product goals within each of those phases. A typical product development lifecycle includes development, verification/validation, and transfer followed by product launch and manufacturing. Design reviews are required at the end of each phase. The plan can delineate if there are any additional triggers or key decision points such as freezing parts of the design or resolution to significant issues.

Target dates for milestones and reviews should be established in the plan as a high-level overview of timeline. A Gantt chart can be created to track deliverables and provide granularity for expectations from each phase.

In addition to detailing what is required and when, the plan must also describe who is responsible. Delegating organizational responsibilities such as quality assurance during the development; qualification of facilities and equipment; evaluation of manufacturability; control of materials and suppliers; compliance with regulatory requirements; and establishment of branding, labelling, and packaging all contribute to the effectual management of a project. The plan must also detail who has the signature authority to approve documentation, studies, design, and transitions to subsequent phases.

The efficiency of product development and launch depend on the alignment, communication, and coordination among participants, especially when working with consultants and CDMOs. A documented plan interconnects the product development goals, which will be actualized by scientists and manufacturing teams, ensuring that results are meeting both stakeholder expectations and regulatory and quality requirements

The plan acts as a roadmap to scientists developing the product. The explicitly listed milestones and goals focus the activities for the project team, illuminating when a product meets requirements versus when it requires more iterations of development. In an ideal world, with unlimited time and money, many development scientists would be happy to iterate development in an attempt to perfect a product, but this is not realistic. The development plan fosters a balance between what is ideal and what is practical.

In summary the plan:

- Establishes roles, responsibilities, milestones, deliverables
- Goals and objectives of design and development program (what is to be developed)
- Major tasks including deliverables and responsibilities (with respect to design and development activities)
- Scheduling and time constraints
- Reviews and decision points
- Team composition
- Controls for documentation and notification activities

nanoComposix

3. Design and Development Outputs - How do developers design a product to ensure requirements are met?

Developers must ensure that their product is consistently reproducible, from the first lot produced through the last lot ever made. Product specifications are a type of development output that ensure the product is reproducible by measuring the conformance of every lot made against the performance of the lot that was used to set assay characteristics and validate assay design. Other development outputs include drawings, materials, components to build the device, and procedures and process instructions.

Design and development outputs must allow for verification against the design and development inputs defined at the start of the development process. In other words, the outputs must contain, or reference product acceptance criteria, which measure conformance to the input requirements.

Design outputs are the results of each design phase and the total design effort. They are the culmination of development activities where specifications are established. From raw material receipt and verification, through in-process activities, to release testing—requirements for materials, subassemblies, and finished goods are detailed in the outputs. They are the basis for the device master record, which serves as an index to the standard operating procedures that were established to manufacture the product. The completion of the design effort signifies that the project is ready to be verified and validated.

Outputs function to:

- Establish specifications
- Provide a way to measure if the product is made correctly
- Prove design input requirements have been met/addressed
- Meet the input requirements for design and development
- Provide appropriate information for purchasing, production and service provision
- Specify the characteristics of the product that are essential for its safe and proper use

4. Design and Development Review - How do project leads keep stakeholders informed on the design effort, make decisions, and resolve conflicts?

Product design efforts are complex undertakings with many elements moving quickly. Mistakes, omissions, and mistimed efforts can delay project efforts along its critical path. In-depth design reviews can be invaluable in identifying issues before product release. A typical design review will use a design checklist to provide framework for the systematic assessment of design results and to verify project requirements are being addressed.

Design reviews provide opportunities to make critical, well-informed decisions on the direction of the development. Reviews are used to evaluate or confirm choices and to monitor resolutions, corrective actions, and risk mitigation efforts. During the initial phases, concerns related to design input requirements prevail. The following phases tend to focus on issues surrounding verification and validation activities. The design reviews supply a stage to voice and resolve conflicts.

Design reviews provide the following benefits:

- An opportunity to review and systematically evaluate the design and process to ensure the project is on track
- Risks/red flags before issues compound later
- Opportunity to provide feedback on emerging problems and risks
- Guide next steps and development focus
- Provide evidence that the project is ready to move to the next phase of development

The participants at each review must be comprised of representatives from all functions concerned with the aspect or stage of development being reviewed. The qualifications of reviewers, including technical competence, experience, and expertise should be considered when establishing a review panel. The reviews must include an individual who is independent of the design work being reviewed (assuring an objective review) who can provide a fresh perspective, ensuring that design errors are not overlooked by those too close to the design.

nanoComposix

5. Design and Development Verification - Was the product developed correctly?

When the product enters design Verification and Validation (V&V) the importance of the earlier design control activities becomes evident. During design verification, the project team must show that the product developed is the product that was asked for. The outputs must be verified against the product requirements and/or product specification. This can be accomplished through lab testing, bench studies, and prototype/pilot production units. Design verification provides evidence that the design outputs (device made by the development team) meet the design inputs (product requirements and/or design specification). Products used for design verification can be produced by the R&D team, rather than the manufacturing team. Following successful verification, however, production of validation products will utilize the manufacturing team and will require qualified equipment and approved processes.

Design controls ensure that verification activities are explicit, methods are approved and measures the effectiveness of their results. Verification activities are conducted throughout development and can include worst case analysis, failure modes and effects analysis, and comparison of a design to previous products with a history of successful use.

Verification objectively presents stakeholders with evidence that the development effort produced product that meets established requirements.

Verification summary:

- Testing to ensure that the product (design output) is as expected and made right.
- Verification often happens on raw materials, piece parts, and prototypes of the final assembly. These can be manufactured under any condition.
- Confirms that the product does what it is supposed to do as per the client.
- Discloses any product deficiencies that must be resolved through design iteration, or accepted through a design review.

6. Design and Development Validation - Was the correct product developed?

The purpose of design validation is to prove that the device meets the intended use and user needs. This is often done through clinical testing and or direct user testing. It can also incorporate inspections and analysis. Scientific literature or historical evidence from similar design or materials can be used to support that the device is safe.

In addition to establishing performance claims, validation testing can determine stability, biocompatibility, electrical safety, and shipping conditions.

Elements to consider during validation:

- The product being validated should be as close to the final product that will be marketed as possible. Product must be manufactured using the same conditions as commercial product including process, environment, and scale.
- Devices tested should have been made by the manufacturing group with qualified equipment. They should be manufactured using drawings, specifications, work instructions, and QC plans that are released and controlled.
- The tested product should be in the final form factor. Final packaging and labeling such as instructions for use have significant human factor implications and can affect product performance.
- The product should be tested in actual or simulated use i.e. (health clinics, reference laboratories, or at home). This includes real-use environments such as lighting, temperature, humidity, and timing.
- Validation studies can be used to support regulatory filings.

nanoComposix

7. Design and Development Transfer - When does design transfer begin?

Transfer is one of the last stages of design control. It is finalized after demonstrating that verification and validation of the device are complete and successful. Transfer is not simply a documentation exercise but a critical transition wherein R&D hands off the knowledge of how to consistently produce a device. The transformation of a R&D design (R&D personnel, equipment, environment, and scale) to a product that is scaled and manufacturable spans multiple phases and involves a cross functional team. Looping in team leaders, manufacturing, and process development scientists early on is key to establishing procedures that produce a reproducible and scalable product.

CFR 820.30 subpart (h) defines the Design Transfer requirements as such, "Each manufacturer shall establish and maintain procedures to ensure that the device design is correctly translated into production specifications."[2]

This can be broken down into two requirements, starting with establishing procedures to ensure design is translated into production specifications. As written in the Design and Development Outputs Section, production specifications are outputs of design that ensure that the product is reliably and consistently produced. The knowledge transfer from the development team is captured in the specifications. This is essentially the Device Master Record (DMR), or the procedures and specifications used for making the finished device, testing it, and releasing it for distribution. The DMR contains the specific details (the recipe for the device) including materials used, equipment used, environmental requirements, and the production order. This includes a final review of the design documentation, raw materials and their specifications, supplier qualification, process methods, final risk assessment, and production capability.

The second part of the regulation is that the procedures are maintained, which are basic principles of document control and configuration (change) management. Documents and changes to documents must be reviewed for adequacy and approved prior to issuing. The manufacturer must maintain documentation for the approval, date (both approval and effective) and in the case of changes, description of change.

Design transfer documentation must include:

- Production facility and equipment qualification
- Process Validation
- Training
- Inspection and test procedures (from raw material to final device)
- Manufacturing procedures
- Risk analysis
- Post market surveillance plan
- Drawings and specifications
- Bill of Materials
- Packaging and labelling specifications (including Instructions for Use, Certificate of Analysis, Safety Data Sheets)
- Design History File (described in subsequent section)
- Final Certificate of Conformance or Certificate of Analysis that is agreed upon

nanoComposix

8. Control of Design and Development Changes - Do products that have been transferred to manufacturing require design controls?

All changes to a device are design changes whether they occur in development or following transfer. Changes must be evaluated from a risk and regulatory standpoint to determine if verification and validation of change are not required. If a design change is made early in the development process, prior to verification and validation activities, then an inspection may be all that is needed to approve the change.

Design controls don't end with the transfer to manufacturing. The primary focus of good manufacturing practices (GMP), and a central theme in design control, is to create a system or process that ensures products are consistently produced and controlled according to quality standards. The manufacturer must ensure that the production team builds the same product every time. This requires control planning in manufacturing, the ability to identify the product at all stages of manufacturing, and control of changes to design, processes, equipment, or documentation. Data is collected on the success of production efforts and may trigger a change request.

Document control and change control were described in the Transfer section as requirements for maintaining procedures. There two elements are also required for controlling changes to design. Document control ensures that employees are working with the latest version of the documents, such as SOPs, production specifications or at the highest level of Quality System, the Quality Manual. Change control ensures that changes are evaluated and approved prior to implementing. Before a document is revised and made ready to review and approve, the change request must go through the rigors of change control to assess the impact on the design input requirements and the product's safety and effectiveness.

The objectives of Change Control:

- Track any corrective actions assigned via investigation or re-development.
- Implement changes to resolve problems and confirm that no new issues are created as a result of the original change.
- Update design documentation such as risk analysis, design input requirements, verification, and validation reports to reflect the change.

9. Design and Development Files - How do developers and manufacturers provide evidence that the product was developed in accordance with the design plan and requirements?

The Design History File (DHF) or records that went into developing a product provide evidence that design control procedures were appropriately adhered to. The DHF is a compilation of the deliverables from every design control requirement. Other documents that may be stored in the DHF are laboratory notebooks, memoranda and electronic mail correspondence. These documents do not need to be stored in one place, rather the manufacturer must have access to the information when it is required.

The knowledge of how and why a product was designed is advantageous to the developer/manufacturer. These files can aid in selection of alternative raw materials, help to determine if a design change may affect the safety and performance of a device, or assist in CAPA investigations.

- DHF is typically required as part of the device submission package
- DHF should contain or reference records for Design Plan, Design Inputs, Design Outputs, Design Reviews, Design Verification and Design Validation
- Demonstrate that the device was developed following a design and development plan using the design control process
- Records of design and development are a regulatory requirement

Conclusion

Getting a product to market quickly may be an important driver for initial sales, however, building quality into the product increases the longevity of a product in the market. Design controls are a subset of a quality system that spans the life of the device, from concept through product obsolescence. The requirements detailed in both ISO 13485 Section 7.3 and FDA 21 CFR 820.3 were implemented as an attempt to reduce recalls due to design deficiencies by integrating quality considerations into device development. The requirements serve to communicate, align, and to provide traceability with checks and balances.

Design control is not meant to interfere with research or development, instead it de-risks and augments these processes, saving time and money in the long term while assuring regulators that the product is safe and effective. Although mandatory, design control in lateral flow assay development is also both practical and beneficial when performed correctly. Documenting and controlling the design in parallel to the product development streamlines the project and provides opportunity to recognize and reduce risk. Companies often make the mistake of starting design controls too late in the process, or even retrospectively, exposing themselves to unnecessary risk and missing out on the benefits to product design.

For more information, visit fortislife.com

nanoComposix

References

1. Center for Devices and Radiological Health. Device Recalls: A Study of Quality Problems. HHS Publication FDA 90-4235. January 1990. Rockville, MD 20857 USA.

2. Quality System Regulation, Subpart C—Design Controls, 21 C.F.R § 820.30. https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-820/subpart-C/section-820.30

nanoComposix