Product Development in Tissue Banking: Formal Design Control for Medical Devices

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Product Development in Tissue Banking: Formal Design Control for Medical Devices

Product Development: Taking a product concept with proven feasibility to clinical application

- R&D
- Regulatory
- Manufacturing
- Clinical
- Marketing
- Facilities

Design Control
- A managed, well-defined, gated process for developing products

Medical Devices
- As classified and regulated by FDA
Linear Model of Product Development

- Idea
- Feasibility
- Proof of Concept
- Product Development Project
- Manufacture
- Distribution
Setting the stage

What is Design Control and why should we develop products in this way?

Design Control
- A managed process for developing products
- A gated review process
- A documented pathway
- A communication tool
- An opportunity for management control and input
- A defined checklist

Motivation
- Regulatory
- Project Management
- Management Oversight
- Efficient Product Development
Subpart C--Design Controls

§820.30 Design controls

(a) General.

(1) Each manufacturer of any class III or class II device...shall establish and maintain procedures to control the design of the device in order to ensure that specified design requirements are met.

(b) Design and development planning
(c) Design input
(d) Design output
(e) Design review
(f) Design verification
(g) Design validation
(h) Design transfer
(i) Design changes
(j) Design history file
The purpose of the design control subsystems 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.

Also note: ISO 13485:2003 Quality System Regulation closely mirrors FDA requirements
Product Development Pathway

May be applied to any new tissue product or process improvement
Design Review (DR) Phase Process

- **DC** Project Approval
- **DR-1** Design Inputs
  - Project Team
  - Design Characterization
  - Business Plan
- **DR-2** SOPs
  - Design Outputs
  - Equipment, Machinery
- **DR-3** Design Transfer and Verifications
  - Regulatory Submissions Validations
- **DR-4** Clinical investigation
  - Production Scale-up
- **DR-5** Full clinical release
Why Gate Review?
A: Risk Management
R&D, Marketing, Legal, Regulatory, Clinical, Manufacturing, Finance, Facilities
Director, Product Development
Reason for Gate Review:
What if one function is way ahead?
What if a Project is not managed, controlled, or ‘gated’?

Market Expectations

Technology misaligned with business
Reason for Gate Review:
What if one function is way behind?
What if a Project is not managed, controlled, or ‘gated’?

Designation as Human Tissue?

IP Review?
Product Development Cycle

- **Concept**
  - End user needs
  - Conferences
  - Marketing
  - Synaptic convergences

- **Feasibility**
- **Proof of concept**
  - DR1
  - DR2
  - DR3
  - DR4
  - DR5

- **Manufacturing**
- **Formal Design Control**
Design Control Phase Hallmarks

- DR Phase 1
  - Project and Product Definition/Design Inputs
- DR Phase 2
  - Product Characterization/Design Outputs
- DR Phase 3
  - Manufacturing Scale-up/Design Transfer
- DR Phase 4
  - Validations
  - Verification
  - Regulatory Submissions
- DR Phase 5
  - Manufacturing and Commercialization
Product Development Cycle

-A fictitious example-

[Diagram showing a cyclical process with stages such as Concept, Feasibility, Proof of concept, Formal Design Control, Manufacturing, and End user needs input involving conferences, marketing, and synaptic convergences.]
Let’s work through a fictitious example-I

Again, this is fictitious

• The World Orthopedic Limb Foundation (WOLF, Inc.), a tissue bank and medical device manufacturer, sets up a booth at the AAOS meeting

• Several Orthopedic surgeons approach the booth and express a need for a suitable partial mid-femur replacement for trauma cases.

• Unknown to the sales representative at the booth, WOLF has already been working on a combination product for dental implantation that involved setting metal pins into allograft bone to provide both an anchoring attachment to the jaw as well as a bone plug that would promote healing.

• The WOLF sales representative makes a note to pass the surgeons’ requests along to the WOLF R&D department.
Let’s work through a fictitious example-II

Again, this is fictitious

• Back home, the R&D department discusses the need for the partial femur replacement.

• They further define the user needs, through a literature search and consulting with a staff member who is an expert in orthopedic surgery, that a mid-femur replacement should:
  • Be at least as strong as bone
  • Be able to be physically attached to the recipient bone
  • Fit various size defects
  • Contain fusible elements at the allograft:recipient, end-to-end interfaces
  • Allow weight bearing prior to anticipated allograft:recipient fusion time
Product Development Cycle

Concept

- End user needs
- Conferences
- Marketing
- Synaptic convergences

Input

Feasibility

Proof of concept

Formal Design Control

Manufacturing
Let’s work through a fictitious example-III

• Based on these end user needs, they recall their work on a combination dental product and start to sketch out particular ideas.
  • Human bone allograft component to be weight bearing as well as provide a biological matrix to promote implant to recipient bone fusion.
  • Metal for further structural support and to anchor the bone for implantation
• After developing a few sketches and recording these in a witnessed laboratory notebook, they meet with 2 Orthopedic Surgeons that are members of their Key Opinion Leader panel.
• After the discussion, a single concept is agreed to for further exploration.
Product Concept:
The WOLFinGraft™

An expandable, form-fit structural implant
Product Concept:
The WOLFinGraft™
Product Development Cycle

Feasibility

Concept

Input

End user needs
Conferences
Marketing
Synaptic convergences

Proof of concept

Formal Design Control

End user

Manufacturing
The WolfinGraft™: Feasibility Assessment

• Determined that titanium would be strong enough and be biocompatible (literature)
• Determined that bone with holes drilled in would withstand physiologic compressive and torque challenges
• Preliminary Market Analysis (Focus Group) indicates market acceptance and strong need
• Preliminarily determined not to infringe on any IP and patent application filed
• Regulatory indicates this could be approved via 510K due to the market presence of an all metal femoral shaft replacement, the “MetalloStrut®” from another organization.
Product Development Cycle

Concept

Proof of concept

Feasibility

Input

End user needs
Conferences
Marketing
Synaptic convergences

End user

Manufacturing

Formal Design Control
The WolfinGraft™: Proof of Concept

- Prototype units manufactured
- Compressive and torque strength acceptable with prototype units
- Large animal model pilot study successful
Design Control Process

Proof of concept

Project Approval

Product Development (led by Project Leader)

Manufacturing

Product Review Group
(Executive Leadership)
• Operations
• Finance
• Marketing
• R&D
• QSRA

Design Review Team
(Directors)
• R&D
• Marketing
• Manufacturing
• Engineering
• QSRA
• Independent Reviewer
# Request for DC Project Approval

## Project/Product General Description

**and Purpose:**

**Clinical Product Intended Use:**

**Specific Product Technical Description**

- Design/Drawing
- Measurements (including variance allowed)
- Specific Shape (if applicable)
- Preservation Method
- Treatment Method
- Donor Requirements
- Tissue Processing Origin
- Packaging (inner and outer)
- Qualitative Requirements
- Other Technical Information

## Market Description and Size

- Market Overview
- Market Future Outlook
- Customer Types
- Risk Assessment of Not Processing this Product.

## Pricing Strategy

- Price Points to end-users
- Commission to Partner if applicable

## Distribution Strategy

- Direct
- Co-Marketed
- Private Label
**Request for DC Project Approval**  (p 2 of 3)

<table>
<thead>
<tr>
<th>Competitive Analysis</th>
<th>Regulatory Review</th>
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<tr>
<td>• Current Products Used today</td>
<td>• Would Product Require Medical Device Approval?</td>
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<tr>
<td>• Competitive Review</td>
<td>• Clinical evaluation required?</td>
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<tr>
<td>• Products Competitive advantages compare to existing offering</td>
<td>• Is product considered human tissue under CFR 1271?</td>
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<tr>
<td><strong>Processing Review</strong></td>
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<tr>
<td>• Average Yield per Donor</td>
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<td>• Capacity Review</td>
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<td>• Equipment Needed</td>
<td>• Will product require new tissue recovery?</td>
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<td><strong>Legal Review</strong></td>
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<td>• Right to Use Opinion</td>
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<td>• Right to Patent Opinion (Design, Process, Equipment)</td>
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<td>• Other Legal</td>
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<tr>
<td>• If patented, should we license?</td>
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</table>
**Testing Review**
- Biomechanics
- Toxicity
- B/F testing
- Shelf-life
- Process efficacy testing
- Animal studies
- Others
  - Note: Indicate if any testing must be outsourced.

**Resources & Investment Review**

**Overall ROI of Project/Product**

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**Validation Review**
- Identify all applicable validations that have been performed and are applicable (past or current) to the proposed product/project.
- Identify new aspects of the proposed product/project that may require validation. Validations that may be required are:
  - Process Validation
  - Packaging Validation (to include packaging process, shelf life, etc.)
  - Shipping Validation
  - Design Validation
  - Software Validation
  - Other
Design Review (DR) Phase Process

- **DR-1**: Design Inputs, Design Characterization, Design Outputs, Business Plan
- **DR-2**: SOPs, Equipment, Machinery
- **DR-3**: Clinical investigation, Design Transfer and Verifications
- **DR-4**: Production Scale-up, Regulatory Submissions, Validations
- **DR-5**: Full clinical release

- Project Approval
- Project Team

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Diagram showing the phases of the Design Review (DR) process and the corresponding tasks and milestones.
Product Development Cycle

- Concept
  - Proof of concept
  - Feasibility
- Manufacturing
  - Formal Design Control
    - DR1
    - DR2
    - DR3
    - DR4
    - DR5
- Input
  - End user
    - Needs
    - Conferences
    - Marketing
    - Synaptic convergences
Design Review Phase Elements: DR1

Design Phase 1—INPUTS

“Design input means the physical and performance requirements of a device that are used as a basis for device design.” (§820.30 Design controls)

- Project Authorization
- Project Leader/Team
- Design Inputs/Product Specifications/End user requirements
Product Development Cycle

- Concept
- Proof of concept
- Feasibility
- Formal Design Control
  - DR1
  - DR2
  - DR3
  - DR4
  - DR5

End user needs
Conferences
Marketing
Synaptic convergences

Input

Manufacturing

Feasibility
Design Review Phase Elements: DR2

Design Phase 2—OUTPUTS  “Design output. Each manufacturer shall establish and maintain procedures for defining and documenting design output in terms that allow an adequate evaluation of conformance to design input requirements…” (§820.30 Design controls)

• Project Development Plan
• Standards Review
• Market Analysis: Cost/Revenue/Benefit
• Patent Position
• Preliminary Drawings and Specifications
• Equipment/tooling
• Design Characterization
• Competitive Characterization
• Design FMEA
• Design Outputs
• Clinical Strategy
• Regulatory Strategy
Product Development Cycle

- Concept
- Feasibility
- Manufacturing
- Proof of concept
- Formal Design Control
  - DR1
  - DR2
  - DR3
  - DR4
  - DR5

Input

End user needs
Conferences
Marketing
Synaptic convergences
Design Review Phase Elements: DR3

Design Phase 3—DESIGN TRANSFER

“Design transfer. Each manufacturer shall establish and maintain procedures to ensure that the device design is correctly translated into production specifications.” (§820.30 Design controls)

- Packaging Development
- Sterilization Requirements
- Label Design change/review
- Recovery Plan
- Manufacturing SOPs
- Device Master Record
- Instrument Sterilization Methods
- Process FMEA
- Supplier Review & Approval
- Equipment File Document Review
- QC SOPs
- Health Hazard Evaluation
- Shelf Stock Plan
- Regulatory Submission
Pause from Phase Review Elements to discuss two key review components

Design Input Output Verification Validation (DIOVV)

Failure Mode Effects Analysis

- Design FMEA
- Process FMEA
DIOVV Elements

**Design Input-Example 1**
- Input requirement of the design
  - Sterile

**Design Output**
- Output that addresses each of the Design Inputs
  - Labeling; SOPs-Shipment of Product for Irradiation, Irradiation

**Design Verification (Can I make the product right?)**
- List how the output will be verified to assure output meets input requirements
  - Cross checks, QC check for irradiation completion and dose certs.

**Design Validation (Can I make the right product?)**
- How the design will be validated to ensure it meets user needs
  - Sterilization validation and periodic verification
DIOVVV Elements

Design Input-Example 2
- Input requirement of the design
  - Metal tubes and pins

Design Output
- Output that addresses each of the Design Inputs
  - Titanium Grade 5823 in SOP and Material Specification

Design Verification (Can I make the product right?)
- List how the output will be verified to assure output meets input requirements
  - Receiving inspection; Specification sheet; Training documents

Design Validation (Can I make the right product?)
- How the design will be validated to ensure it meets user needs
  - NA or Functional testing
Design Input-Example 3
   • Input requirement of the design
     – End-to-end fusion interface to recipient

Design Output
   • Output that addresses each of the Design Inputs
     – Allograft bone used to manufacture device; Drawings; SOPs

Design Verification (Can I make the product right?)
   • List how the output will be verified to assure output meets input requirements
     – Inspections; SOPs; Chart review

Design Validation (Can I make the right product?)
   • How the design will be validated to ensure it meets user/needs
     – Animal study to prove fusion
     – Possible surgical investigation
DIOVV Elements

**Design Input-Example 4**
- Input requirement of the design
  - Suitable, intact packaging that allows surgeon to see device

**Design Output**
- Output that addresses each of the Design Inputs
  - Device in transparent PETG Tray; Packaging procedures

**Design Verification (Can I make the product right?)**
- List how the output will be verified to assure output meets input requirements
  - SOPs; Material Specifications; Packaging inspection

**Design Validation (Can I make the right product?)**
- How the design will be validated to ensure it meets user/needs
  - Physical and microbial challenge packaging validation
  - Approval of packaging design by surgeon panel
“Another evaluation technique is Failure Mode and Effects Analysis (FMEA) in which failures are assumed to occur. FMEA is useful for evaluating reliability, safety, and general quality where, for example, the evaluator assumes that:

• each component fails,
• subsystem or subassembly fails,
• the operator makes errors, and
• the power source is interrupted and immediately restarted.

The probability of each failure actually occurring and, if it does, the resulting effect are analyzed. Then, where needed and feasible, hazards and faulty performance are designed out of the device or reduced; or compensated or prevented/reduced by interlocks, warning signs, explicit instructions, alarms, etc. Risks, of course, cannot always be removed from medical devices, but they should be known and controlled to the extent feasible with existing technology.”

(http://www.fda.gov/cdrh/qsr/contnt.html)
Failure Mode Effect Analysis

**Design FMEA**
- Identifies risk if product is made as intended (meets design).
- Assess design inputs

**Process FMEA**
- Identifies risk if product is not made as intended (does not meet design)
- Assess every step in the process of making the device
Failure Mode Effect Analysis

• Assess risk with Risk Priority Number (RPN)
  − Severity (if it does occur)
  − Probability (of occurrence)
  − Detection (likelihood of NOT detecting issue)

  − Quantify risk with Risk Priority Number
    \[ S \times P \times D = \text{RPN} \]

  Different scales are used, often 1-10
  Manufacturer sets limits on actionable RPN values
Failure Mode Effect Analysis

– Design FMEA-Example 1

• Design Input: Metal pins to insert into recipient bone
• Failure mode: Pins come loose, graft becomes dislodged
• Cause of failure: Does not heal in bone properly
• Severity (if it does occur) = 8 (reoperation)
• Probability (of occurrence) = 6 (best assessment)
• Detection (likelihood of NOT detecting issue) = 10 (no way to detect this until implantation)
• \( S \times P \times D = RPN = 480 \) (WOLF cutoff is 200 for action)

• Action: Assess pin-bone healing via larger scale animal or clinical evaluation
Failure Mode Effect Analysis

– Design FMEA-Example 2
  • Design Input: Metal pins set in implant bone
  • Failure mode: Pins work loose
  • Severity (if it does occur) = 8 (reoperation)
  • Probability (of occurrence) = 7 (deemed likely to occur)
  • Detection (likelihood of NOT detecting issue) = 5 (moderate chance that testing in Design Control will detect)

  • $S \times P \times D = RPN = 280$ (WOLF cutoff is 200 for action)

  • **Action:** Perform new fatigue ‘toggle’ testing for pin back and forth in bone to see impact; Reassess RPN
Failure Mode Effect Analysis

Process FMEA-Example 3

• Processing step
  – Metal pins screwed into implant bone
• Failure mode: Pins crack bone
• Severity (if it does occur) = 8 (possible reoperation)
• Probability (of occurrence) = 7 (deemed likely to occur)
• Detection (likelihood of NOT detecting issue) = 5 (moderate)

• $S \times P \times D = RPN = 280$ (WOLF cutoff is 200 for action)

• **Action**: Include graft inspection under magnification; Perform fatigue test on bone to determine if cracking occurs; Reassess RPN
Product Development Cycle

- **Concept**
  - End user needs
  - Conferences
  - Marketing
  - Synaptic convergences

- **Feasibility**

- **Proof of concept**
  - DR1
  - DR2
  - DR3
  - DR4
  - DR5

- **Manufacturing**

End user input
Design Review Phase Elements: DR4

Design Phase 4—VERIFICATION & VALIDATION

**Verification** means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled. (§820.30 Design controls)

**Validation** means confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled. (§820.30 Design controls)

- Design Verification
- Design Validation
- Process Verification
- Process Validation
- Shelf-life Testing
- Transportation & Environmental Testing
- Production Scale Up Plan
- QC Test Methods/Sampling Plan
- Biocompatibility Testing
- Clinical Protocol Initiation
- Clinical Report
Product Development Cycle

Feasibility

Concept

Proof of concept

Formal Design Control

• DR1
• DR2
• DR3
• DR4

• DR5

End user needs
Conferences
Marketing
Synaptic convergences

Input

End user

Manufacturing
Design Review Phase Elements: DR5

Design Phase 5—PRODUCT RELEASE

- Marketing Launch Plan
- Senior Management release for distribution
- Regulatory Release
Design Review (DR) Process

- DR-1: Design Approval, Design Inputs, Design Characterization, Business Plan
- DR-2: SOPs, Equipment, Machinery, Clinical investigation
- DR-3: Design Transfer, Production Scale-up, Regulatory Submissions, Validations
- DR-4: Full clinical release
- DR-5

Project Team

Project Approval
Product Development Cycle

- Concept
- Proof of concept
- Feasibility
- Manufacturing
- Formal Design Control
  - DR1
  - DR2
  - DR3
  - DR4
  - DR5

End user needs
Conferences
Marketing
Synaptic convergences

Input

End user

Manufacturing
Product Development Cycle

Concept

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