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The views expressed in this handbook are those of the authors and do not necessarily reflect the views of their organizations or IVT Network.

Preface

When the Institute for Validation Technology approached me in the spring of 2017 with an idea for a validation handbook, we agreed that despite a wealth of validation information available online and in numerous industry publications and seminars, medical device professionals continue to struggle to apply a subset of validation concepts in their day-to-day work. In spite of evolving regulatory standards and industry guidances, in my professional practice I am regularly asked for help with the same list of integrated principles. As I reflected on my contribution to this handbook, I realized the best way to be of service to our industry is to dedicate one chapter to each of those overarching concerns, then seek out the top subject matter experts in those areas for their perspectives and best practices on the topic. This Medical Device Validation Handbook is the result of the efforts of the contributing authors over the months since we began this odyssey. I am particularly indebted to the subject matter experts with whom my organization has worked over the years, for volunteering to share their immense and practical knowledge in making this Handbook a reality.

Particularly as the medical device industry faces the emergence and convergence of several co-integrated standards and regulations, this Handbook serves to provide readers with practical tools and guidance on risk management, process validation, test method validation, six sigma design concepts, and more, with a healthy dose of real-life case studies to aid in the application of the principles herein to your daily practice.

Each of us is a citizen of this industry. During the courses of our careers, we have been privileged to design, produce and qualify medical devices to improve the quality of life for our customers' patients. It is our combined hope that the information provided in this Handbook will increase your confidence as you continue your important work to bring health and vitality to our fellow citizens.

With gratitude,
Roberta D. Goode
Editor and Author

At-A-Glance Steps for Bringing Medical Devices from Concept to Commercialization

William Knab

Introduction

This chapter is intended to provide a quick reference guide for developing a medical device. This is a complex process, but the requirements are well defined in the regulations and quality guidelines. What follows is a list of the key steps in sequence, and references to the current guidance documents. If the path delineated below is followed, it will result in the successful launch of a new medical device.

Concept to Commercialization Key Steps

1. Feasibility — Will it work?
    - What are the key features and benefits needed for success?
    - Is it feasible/possible to build? (Is the science sound?)
    - Can it be manufactured?
        - Using existing, proven technology/methods
        - Requiring new systems/technology and validation
    - Can it be protected?
        - Patent
        - Copyright
    - Is there a clear market need?
        - Market size
        - Competitors
    - Who is going to pay for it and how?
        - Reimbursement strategy
            - Target Customer
                - Hospital
                - Physician
                - Allied health professional
                - End user
            - Payor
                - End User — Direct
                - Hospital
                - Insurer
                - Public (i.e., Medicare/Medicaid)
    - How will financial returns be realized?
        - What is the exit strategy? (Begin with the end in mind.)
    - Develop a two to four page executive summary and an eight to ten slide deck to present the concept to initial stakeholders for buy-in
        - Obtain feasibility approval for the concept

2. What market will it serve?
    - Is the market new or existing?
    - What is the market size?
    - How will the product get to the market?
        - Distribution strategy
            - Direct
            - Indirect
            - OEM third-party

3. What will be the regulatory path?
    - What agencies will need to be involved? (Market region driven)
        - FDA, CE Mark, etc.
        - Choose the most comprehensive path to maximize global application
    - Will a clinical or market trial be required?
        - What class will the device be?
            - FDA Class 1, 2, 3
            - EU Class I, IIa, IIb, III

4. What are the quality system requirements?
    - Market and regional requirements
        - Choose the most comprehensive requirements to maximize global application

5. Demonstrate technical feasibility
    - Prove that the concept will work (build prototype)
    - Develop tangible data that supports feasibility

6. Build a business case (five year plan)
    - Market size
        - Unit volume
        - Market penetration
        - Key competition
        - Local, regional, global market penetration strategy
    - Manufacturing assumptions
        - Build in-house
            - Investment cost to build and qualify the manufacturing line
            - Leverage existing in-house capacity
        - Contract manufacture
            - Cost of partnership
    - External influences
        - Governmental regulatory changes
        - Governmental funding/coverage changes
        - Market competitors
    - Unit cost assumptions
        - Development cost assumptions
            - Clinical trial (if required) cost assumptions
        - Project timing /cost assumptions
        - Product launch cost assumptions
        - Return on investment (R.O.I) assumptions
    - Business strategy assumptions
        - Market launch
            - Region priority
            - Clinical performance data trials/studies
            - Timing
            - Training requirements
        - Market support
            - Technical support
            - Clinical performance data publication
            - Training
            - Customer service
        - Exit strategy
            - Define investor returns
            - How is the investment monetized?
            - What is the timing of the R.O.I.?

7. Obtain Project Funding
    - Private in-house
        - Present business case and obtain funding
    - Public
        - Government grant or research
        - Small Business Innovation Research (SBIR) grant
        - Write grants and applications
    - Private investor /equity
        - Friends and family
        - Physician
        - License partners
        - Supply chain partners
        - Angel funding
        - Venture capital funding

8. Design and build
    - Develop comprehensive project plan
        - Design requirements definition
            - User requirements (human interface)
            - Performance requirements
            - Technical requirements
            - Manufacturing requirements
            - Legal/patent requirements
            - Regulatory path requirements
            - Quality system requirements
            - Risk Management requirements
            - Reimbursement path requirements
            - Market introduction plan and timing target
    - Design path sequence
        - Hardware
            - Molded parts (long lead parts first)
                - Purchased
                - Molds/mold design
            - Custom fabricated parts
                - Frame, cabinet/housing
                - PC boards and electronic controls
                - Cable, connector and active component selection
                    - Sourced
                    - In-house designed and fabricated
            - Packaging
            - Validation
        - Software
            - Operating and development system
                - Public domain purchase
                - Custom embedded or combination
                - Update methods
                - Validation
        - Disposable design
            - Molded parts
                - Sourced
                - In-house designed/molded
            - Extrusions
                - Sourced
                - In-house

- Custom metal/wire or specialty plastic items
- Acceptance and assembly methods
  - Validation
- Packaging
  - Validation
- Sterilization method
  - Validation

- Complete master plan sequence and resource all key activities
  - Sequence all key activities based on known and assumed lead times
  - Resource plan to meet timelines
  - Update comprehensive Risk Management plan

9. Review plans with stakeholders and document approvals
   - Business plan and deliverables
   - Project funding, timing and key milestone deliverables
   - Comprehensive project plan and key milestone deliverables
   - Risk plan and management notification requirements
   - Staff project team and links to supporting departments and /or suppliers

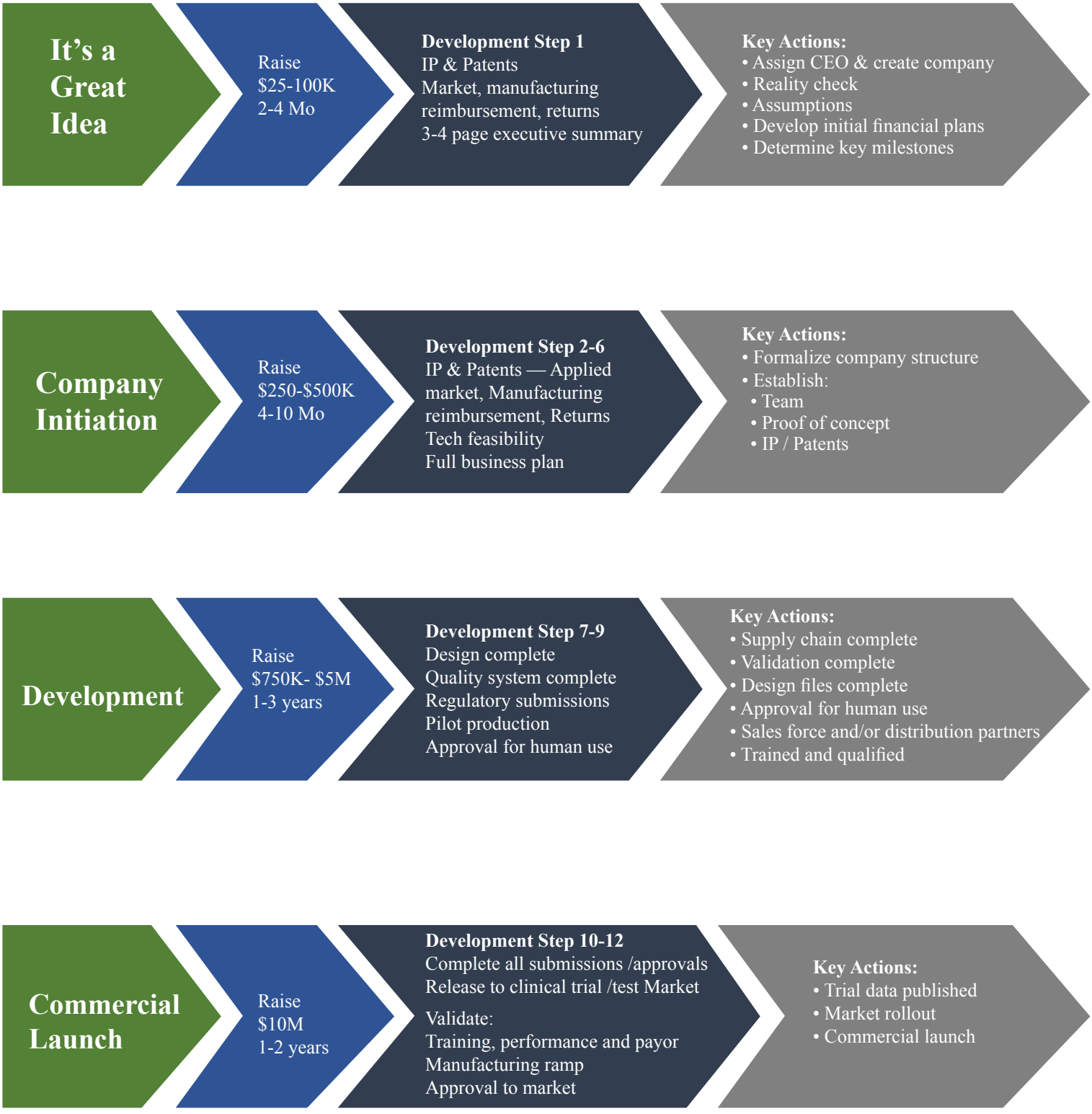
10. Kickoff project, establish management and key milestone reporting
    - Modify and adjust plan as needed and approved by management/key stakeholders
    - Build and test prototypes
    - Verify design requirements
    - Obtain approval for verification/validation and full manufacturing build
      - Build first run production
        - Verify
        - Design requirements
        - Validate
          - Manufacturing systems
          - Quality monitoring and reporting
          - Sterilization
          - Packaging
          - Update risk plan
        - Develop a comprehensive release package for approvals
          - Design files complete per prevailing regulatory and quality requirements
          - Validation files complete per prevailing regulatory and quality requirements
          - Risk plans complete and ready for market launch
          - Prevailing regulatory agency “Approval to Market” is complete
          - Market introduction plans are complete
    - Obtain project approvals to enter test market from key stakeholders

11. Release product into limited test market or clinical trial sites if required
    - Validate design requirements
      - User training and acceptance
      - Product performance/reliability
        - Complete clinical trial protocol (if required)
        - Develop publishable clinical performance data
      - Payor and reimbursement
    - Adjust launch plans as needed

12. Obtain approval from key stakeholders and regulatory agencies for general market launch

13. Launch product into intended markets
    - Implement quality system and market monitoring per prevailing regulatory and quality requirements

Startup Model for New Device Company Formation and Growth



Robust Design Methodology Using Attribute Data in Product/Process Design

Matt Hedrick

Abstract

Attribute (pass/fail) data are very common within medical device processes to describe defect rates and other qualitative characteristics. Assessment of this data type generally occurs in validation activities using acceptance sampling through lot tolerance percent defective limits, representing confidence and reliability levels. This entails large sample sizes and occurs in the final stages of development. Considering attribute-based characteristics early in product/process design has a considerable advantage due to more flexibility in design and/or specification changes. Robust Design, or Taguchi Methods, represents a tool that can be effectively applied using attribute data to optimize results and dampen the impact of uncontrolled noise factors commonly encountered in manufacturing.

Introduction

There is a famous saying that has been attributed to a few people, including Lou Holtz and Tony Robbins: "If you're not growing, you're dying." Competing on the global stage for low cost manufacturing while also meeting the demands of a sophisticated customer base compels organizations to adopt a culture of learning. We each have a responsibility for our contribution to this culture. Within the product and process development communities of medical device manufacturers, the application of statistics and sound engineering judgement are cornerstones for a culture of continuous learning.

The following discussion is an attempt to share the tools brought to industry by Genichi Taguchi in the area of robust design. Robust design bridges the gap between One-Factor-At-A-Time (OFAT) and statistics-heavy Design-of-Experiments (DOE) analysis. With experimental cost and time being dominant factors in decision making, OFAT can be appealing, where traditional DOEs can seem overwhelming and impractical. An organization too heavily focused on OFAT is left learning very little and the cost on the organization is a slow drain of resources accompanied by inconsistent results. This can erode the confidence the organization has on the teams involved. Robust design offers an OFAT alternative which allows for the simultaneous assessment of nominal performance and variation. It relies on minimal statistical knowledge and the analysis does not require extensive use of statistical software programs. The resulting output and process leading to it can be more easily described and understood by a wider audience.

Attribute data, such as visual defect inspection results, are very common among critical-to-quality characteristics in both product and process design for medical devices. As Robust Design is an approach less concerned with statistical theory and more focused on engineering judgement, the application can be applied to attribute data without the same level of concern for large sample sizes. It has some of the same appeal provided by the OFAT method in terms of cost and time, but will provide a sounder basis for analysis and decision making.

Genichi Taguchi mentions that, "The broad purpose of the overall quality system is to produce a product that is robust with respect to all noise factors."[1] Conducting experiments early in the design phase of a project which take into consideration presently uncontrolled sources of variation ensures that the learning process has a holistic view. Including "noise factors" in a robust design activity improves the accuracy of yield projections by exposing the testing to more sources of natural variation. It may identify an uncontrolled factor that has an unacceptable level of influence and either must be controlled or its effect designed out of the product/process. Because there is less statistical rigor involved, Robust Design is not conducive to find validation activities, but should not be overlooked for its importance in characterization activities associated with product and process design (e.g. challenge testing, operational qualification).

Areas to Apply Robust Design

Before describing how an attribute-based robust design experiment would be carried out, a brief description of where the use of this tool fits into a new product development roadmap or problem solving process is needed. Since robust design is a type of designed experiment methodology, it can be effectively applied to any area in which is would be approriate to use DOE.

Organizations applying a Design-for-Six-Sigma (DFSS) approach to their product development process would follow a roadmap similar to the one presented below referred to with the acronym DMADOV (see Figure 1). It should be noted that DFSS roadmaps vary much more than the Six Sigma problem solving roadmap. There are many variants and a thorough explanation goes beyond the scope of this review. The DMADOV process is the most common model used at around 62% [2]

Figure 1: Role of Robust Design in DFSS Process using DMADOV Approach

Using robust design to identify noise (uncontrolled) factors in the design stage of new product development allows for consideration of design changes early in the process, saving time and money. This could lead to decisions that alter the design to be insensitive to any significant noise factors involved. In the Optimize phase, this method can allow for parameter or tolerance settings which dampen the effects of the noise factors involved and improve the probability of successful validations in the Verify phase. Care needs to be taken with any modifications to evaluate the potential cost impact.

Having the noise factors included early in the process (pre-validation) is critical to enabling changes before validation and commercialization begins, due to extensive change approval processes and regulatory considerations. Once the Verify phase begins, a more traditional approach to validation is required to demonstrate appropriate confidence and reliability levels. For attribute data, the established Lot-Tolerance-Percent-Defective (LTPD) criteria will dictate acceptable product or process performance. The probability of passing these larger sampling plans is enhanced by the mitigations taken from understanding the role of uncontrolled factors in the product or process characterization phase.

When troubleshooting manufacturing issues or embarking on a continuous improvement initiative, the DMAIC process or a variant thereof is often applied. Robust design can be applied anywhere that a DOE would be used in identification or optimization of key factors. This corresponds with the Analyze and Improve phases.

Figure 2: Role of Robust Design in DMAIC Process

Robust Design

During this process, key factors may be identified which either cannot be controlled or controlling them would be cost prohibitive. This can be especially true if the key factor is a raw material or supplier related characteristic of which there is little influence or customization available. If this occurs, other process variables or process design changes can be evaluated to determine if the influence of these uncontrolled factors can be minimized or eliminated altogether. Robust design techniques support the process of establishing parameter limits reducing the effects of uncontrollable variables and optimizing the output. This generates more long term reliability demanding fewer resources for commercial support and higher levels of customer satisfaction.