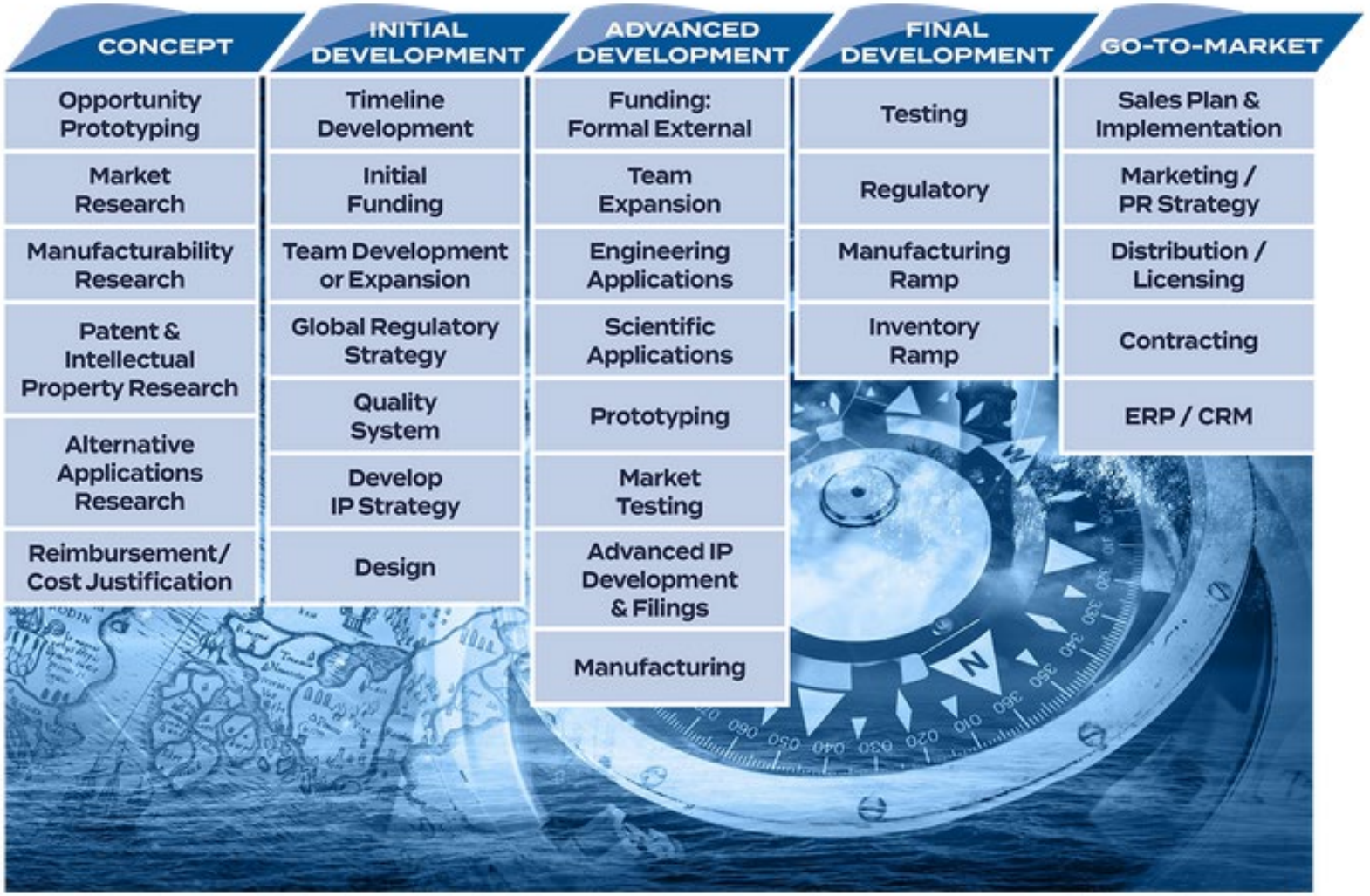
Proven Strategies to Accelerate Regulatory Clearance

NAVIGATING UNCERTAINTY: The Yar Group



MediStrat360 Mission: Enable & Accelerate Access To Disruptive Innovation That Transforms The Lives Of Patients:

- **Strategic Foresight**: Partner With Startups To Build A Holistic, 360 Device Strategy Early In The Development Process To Accelerate Device Commercialization And To Neutralize Unforeseen Risks That Cause Submission Delays/Startup Killers:

- Track Record of Market Access, Regulatory Strategy & Evidence Portfolios That Deliver:
  - Domestic & International Device Clearances & Approvals
  - Promotional Claims With A Competitive Advantage
  - Health Economics Outcomes Research and studies that address Payor Needs & Successfully achieve device Coverage & Reimbursement.
  - Market Leading Positions & Higher Valuations

The Yar Group & MediStrat360

The YAR GROUP
Advise companies to focus on all of the steps to move through development and assist them inn implementing the steps, processes, and teams in order to succeed.

SHARED MISSION

MEDISTRAT360
Enable & Accelerate Access To Disruptive Innovation That Transforms The Lives Of Patients:

AGENDA

NAVIGATING UNCERTAINTY & BRINGING DEVICES TO MARKET

1

- Strategies to accelerate device market access & adoption across the product lifecycle.
- Enabling Visibility to Unforeseen Risks: Startup Killers

R&D

2

- Quality FDA Product Development Phases & Legal Liability
- Design Controls: Implementing early in the development process is important for startups.

REGULATORY

3

- Device Classifications, Regulatory Controls & FDA Submissions
- Global Foresight from Day 1 & Breakthrough Designation

CLINICAL EVIDENCE & REIMBURSEMENT: THINKING BEYOND REGULATORY CLEARANCE

4

- Healthcare Today & the New Value Equation
- Optimizing Clinical Trials Across Stakeholders

STRATEGIC CONSIDERATIONS:

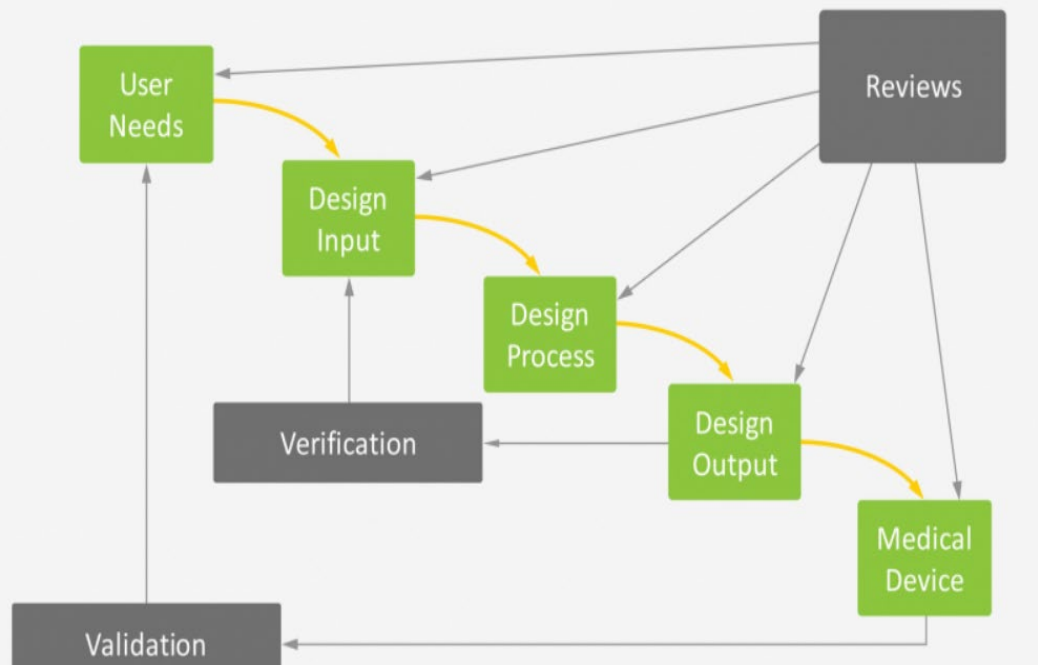
5

- Holistic Device Strategy & Integrated Cross Functional teams lead to successful device commercialization.
- Investor Considerations Across the Product Life Cycle
- Cognitive Biases: avoiding commons traps that lead to failure

QUALITY

DESIGN CONTROLS:

Early Implementation of Design Controls Is Important. ALL DEVICES, *REGARDLESS OF CLASSIFICATION*, HAVE REGULATORY COMPLIANCE REQUIREMENTS ACROSS THE ENTIRE PRODUCT DEVELOPMENT LIFECYCLE .

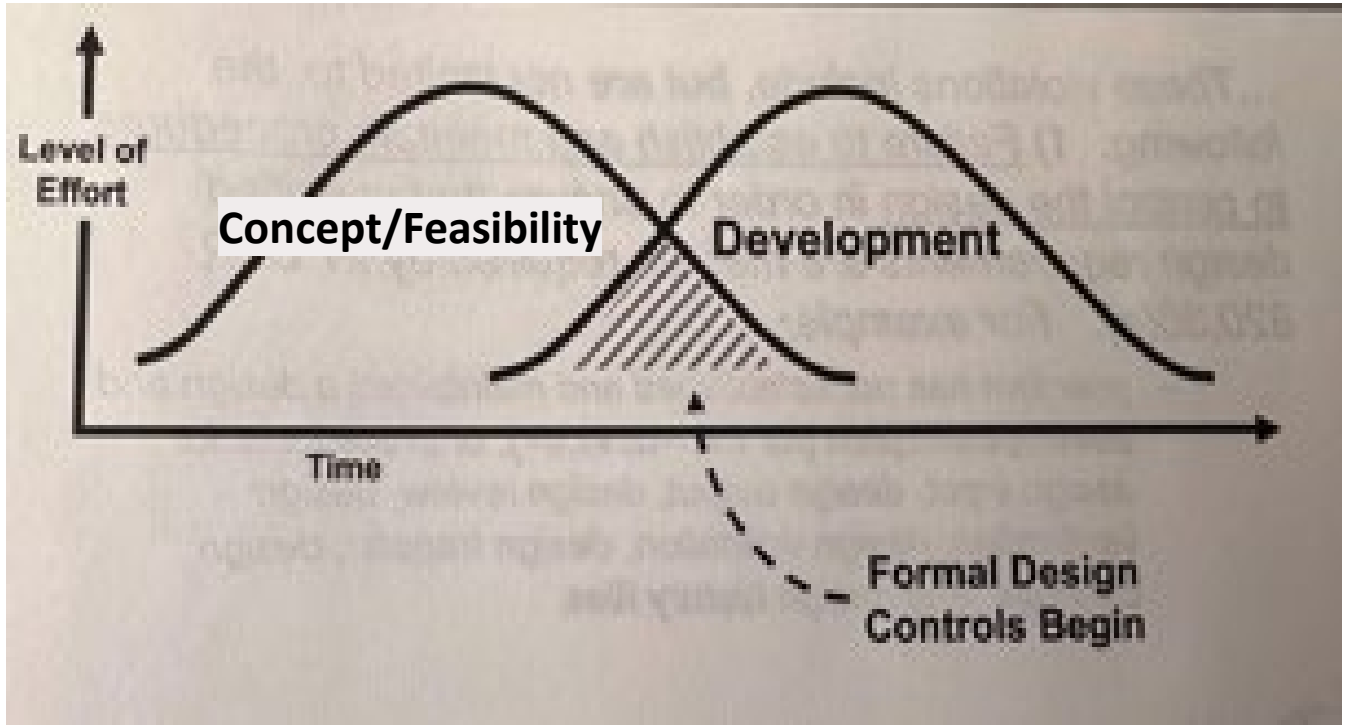


REAL WORLD EXAMPLES

DESIGN CONTROLS: What are they and When do you think they begin and are your assumptions **in line with FDA requirements?**

DESIGN CONTROLS SHOULD STASRT DURING PROTOYPING

Does your expectation match reality?



Warning Letter

Electromagnetic and frequency energizer device

…These violations include, but are not limited to, the following. 1) Failure to establish and maintain procedures to control the design in order to ensure that specified design requirements are met, as required by 21 CFR 820.30(a). For example,

- *your firm has not established and maintained a design and development plan (for the <device>), or procedures for design input, design output, design review, design verification, design validation, design transfer, design changes, and design history files.*

ACCELERATE: REGULATORY CLEARANCE & CREATE HIGHER QUALITY DEVICES

Implementation of an FDA compliant quality management system & design controls early on in the development process - as mandated by FDA - will protect your startup & help you avoid regulatory clearance delays: Much of the content for the regulatory submission comes directly from design controls documents FDA expects you to have in place early on in the product development process.

1 CONCEPT
Device Discovery & Risk Analysis

- Initial Design Development Plan
- Design Inputs
- Risk & Benefit Analysis
- Risk Management Plan

2 PLANNING
Formulation & Feasibility

- Customer Needs
- Feasibility Study
- Risk & Benefit Analysis
- Refined Design Plan

3 DESIGN
Development, Verification

- Design Outputs
- Design & Prototyping Process
- Verification of Design Outputs vs Inputs
- Initial Validation of Working Prototypes vs User Needs: Traceability Requirements

4 VALIDATION , REGULATORY SUBMISSION & PRODUCT LAUNCH

Device Validation:

- Performance Testing
- Clinical Trials

Regulatory Submission:

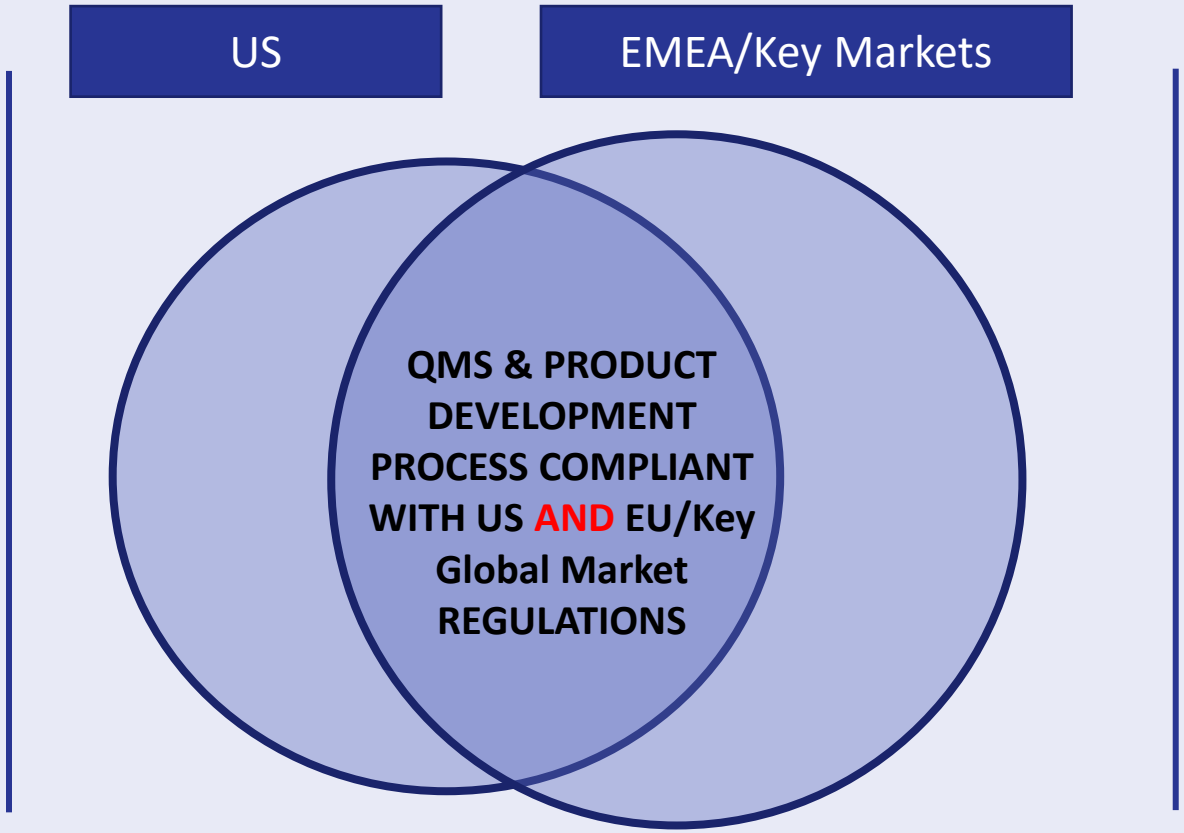
- Process
- Guideline Requirements

5 POST MARKET FOLLOW UP

- Post Market Surveillance & Reporting Requirements

ACCELERATE MARKET ACCESS & VALUATION

Early development of a market access strategy will enable implementation of a design controls & product development process compliant with US AND Key Global Market Regulatory Requirements - enables faster market adoption and saves time & money over the long term.

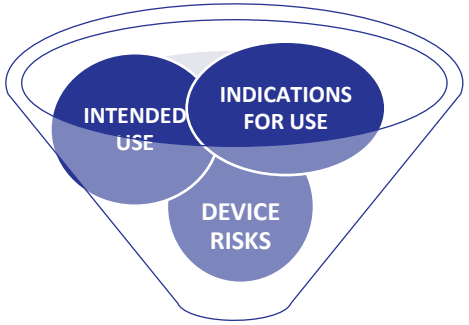


Startups: This can increase company valuation 3-4x

REGULATORY

ACCELERATE: GET REGULATORY GUIDANCE EARLY IN THE DEVELOPMENT PROCESS RECOGNIZING THAT THOSE INPUTS WILL IMPACT ORIGINAL TESTING PLANS & SIGNIFICANTLY ACCELERATE YOUR TIME TO MARKET

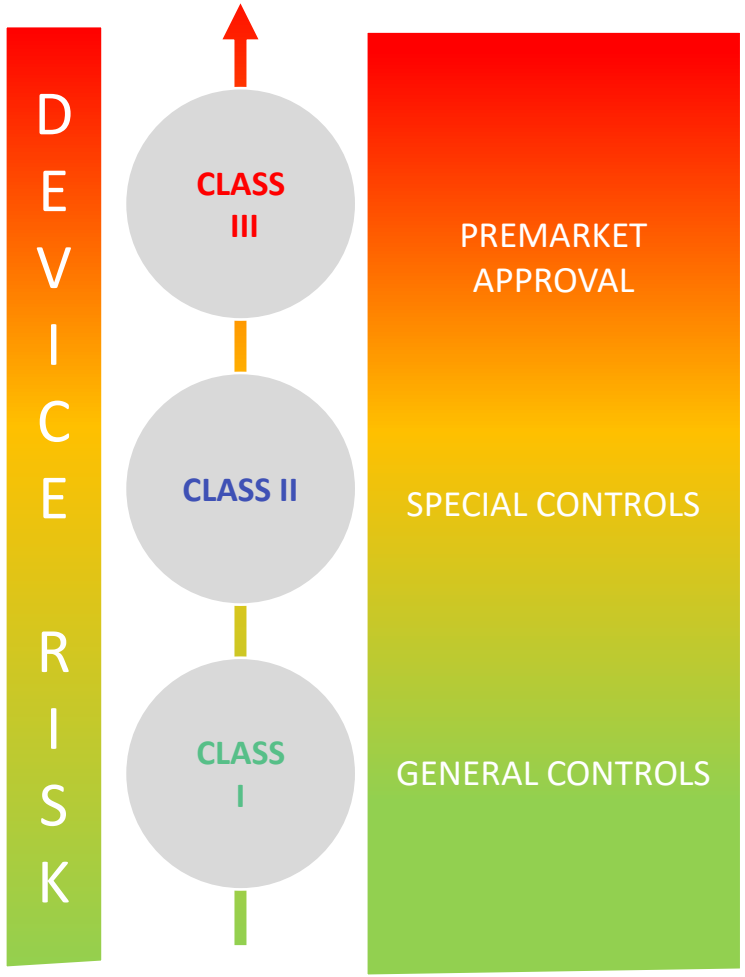
FDA DETERMINATION CRITERIA



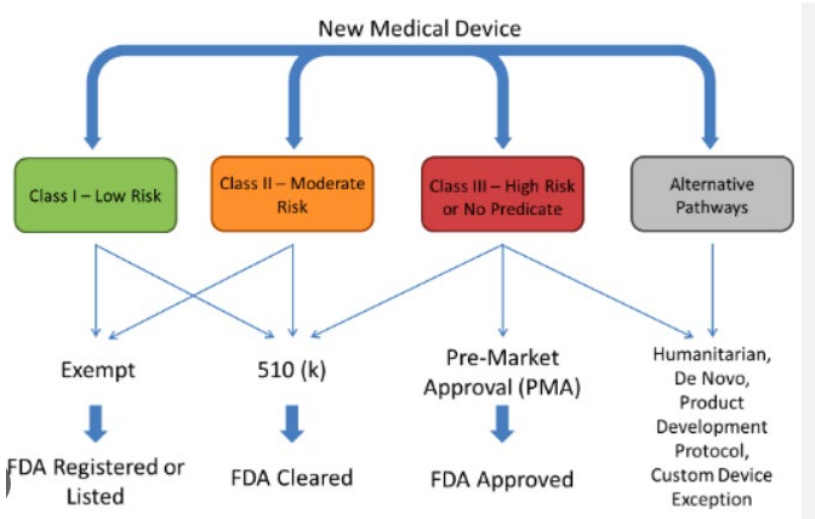
DEVICE CLASSIFICATION

- INTENDED USE : **DEVICE PURPOSE**
- INDICATIONS FOR USE : **DISEASE OR CONDITION THE DEVICE WILL DIAGNOSE, TREAT, PREVENT, CURE, OR MITIGATE, INCLUDING THE PATIENT POPULATION FOR WHICH THE DEVICE IS INTENDED"**
- DEVICE RISKS: **CLASS III DEVICES DEEMED HIGHEST RISK BY FDA → GREATER REQUIREMENTS FOR CLEARANCE VS CLASS I & II DEVICES.**

COMPLIANCE REQUIREMENTS



DEVICE CLASSES



- Class I: 43% General Controls, 91% 510k Exempt
- Class II: 51% Special Controls, 7% 510k Exempt
- Class iii: 6% Premarket Approval
- 1870+ Device Categories

ACCELERATE: GET REGULATORY GUIDANCE EARLY IN THE DEVELOPMENT PROCESS TO NEUTRALIZE UNFORSEEN COMPANY RISKS

Companies are liable for compliance with FDA regulations

Laser Warning Letter, Rick Use Case

The Food and Drug Administration (FDA) has learned that your **firm is marketing the Softlaser under** the trade names of Beurer, Etrans, and Vitalmed in the United States (U.S.) **without marketing clearance or approval**, in violation of the Federal Food, Drug, and Cosmetic Act (the Act).

…The Act requires that manufacturers of devices that are not exempt **obtain marketing approval or clearance for their products from the FDA before they may offer them for sale**. ….
….Further, on November 5, 2007, your website, www.lasertherapy.us, **included new intended uses for the Softlaser. For** example, the website makes medical claims which include, but are not limited to….

A review of our records reveals that **you have not obtained marketing approval or clearance before you began offering your product for sale, which is a violation of the law.** Specifically, the Softlaser is adulterated under section 501(f)(1)(B) of the Act, 21 U.S.C. 351(f)(1)(B), because you do not have an approved application for premarket approval (PMA) in effect pursuant to section 515(a) of the Act, 21 U.S.C. 360e(a), or an approved application for an investigational device exemption (IDE) under section 520(g) of the Act, 21 U.S.C. 360j(g). The devices are also misbranded under section 502(o) the Act, 21 U.S.C. 352(o), because you did not notify the agency of your intent to introduce the devices into commercial distribution, as required by section 510(k) of the Act, 21 U.S.C. 360(k). For a device requiring premarket approval, the notification required by section 510(k) of the Act, 21 U.S.C. 360(k), is deemed satisfied when a PMA is pending before the agency 21 CFR 807.81(b). The kind of information you need to submit in order to obtain approval or clearance for your device is described on the Internet at http://www.fda.gov/cdrh/devadvice/3122.html1. The FDA will evaluate the information you submit and decide whether your product may be legally marketed.

In addition, laser products and medical lasers are subject to other regulatory requirements, including those in the Code of Federal Regulations, Title 21, Chapter 1, Subchapter J. You have failed to comply with 21 CFR 1010.3 because the Softlaser lacks an identification label giving the manufacturing location and date of manufacture. In addition, you have failed to comply with 21 CFR 1002.13 because the Center for Devices and Radiological Health, FDA, has not received an Annual Report for the year from July 1, 2006, through June 30, 2007.

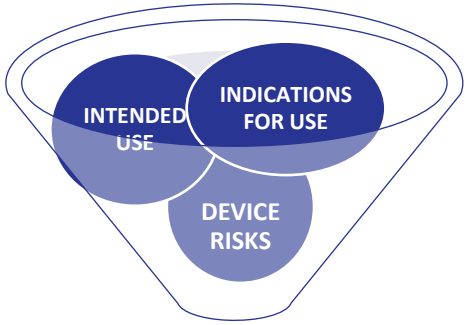
Mutahar S. Shamsi

PROMOTIONAL CLAIMS: WORDS MATTER
Rick Use Case

- FDA issued a Warning Letter to a medical device company that manufactures a facial implant device due to a number of deficiencies found during a 2018 inspection. Based on the inspection, FDA found that the company's marketing materials for the device, including instructional videos and training materials, promoted the product for purposes other than its 510(k)-cleared intended use.

ACCELERATE: GET REGULATORY GUIDANCE EARLY IN THE DEVELOPMENT PROCESS WITH INPUTS THAT WILL CHANGE TESTING PLANS & SIGNIFICANTLY ACCELERATE YOUR TIME TO MARKET

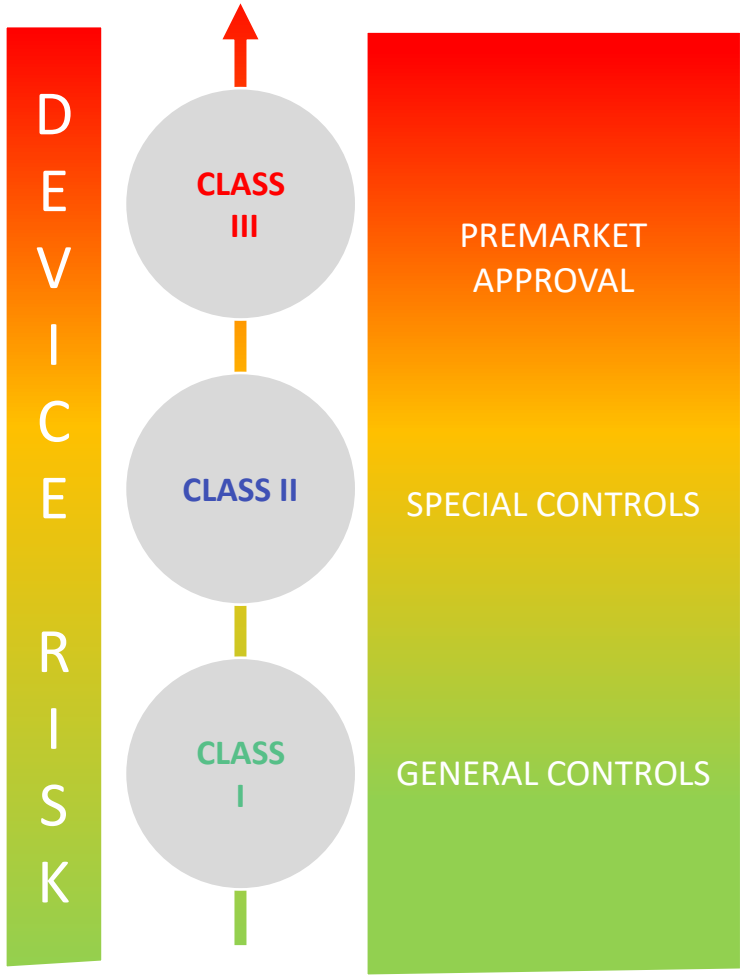
FDA DETERMINATION CRITERIA



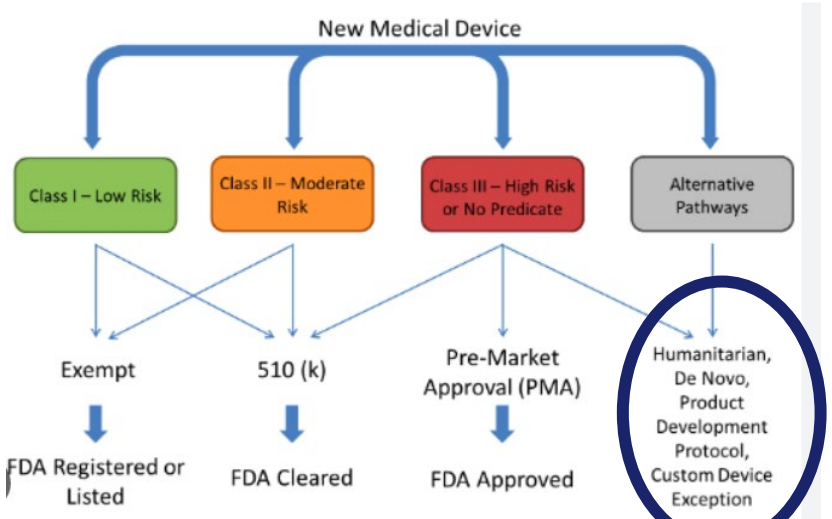
DEVICE CLASSIFICATION

- INTENDED USE : DEVICE PURPOSE
- INDICATIONS FOR USE : DISEASE OR CONDITION THE DEVICE WILL DIAGNOSE, TREAT, PREVENT, CURE, OR MITIGATE, INCLUDING THE PATIENT POPULATION FOR WHICH THE DEVICE IS INTENDED"
- DEVICE RISKS: CLASS III DEVICES DEEMED HIGHEST RISK BY FDA → GREATER REQUIREMENTS FOR CLEARANCE VS CLASS I & II DEVICES.

COMPLIANCE REQUIREMENTS



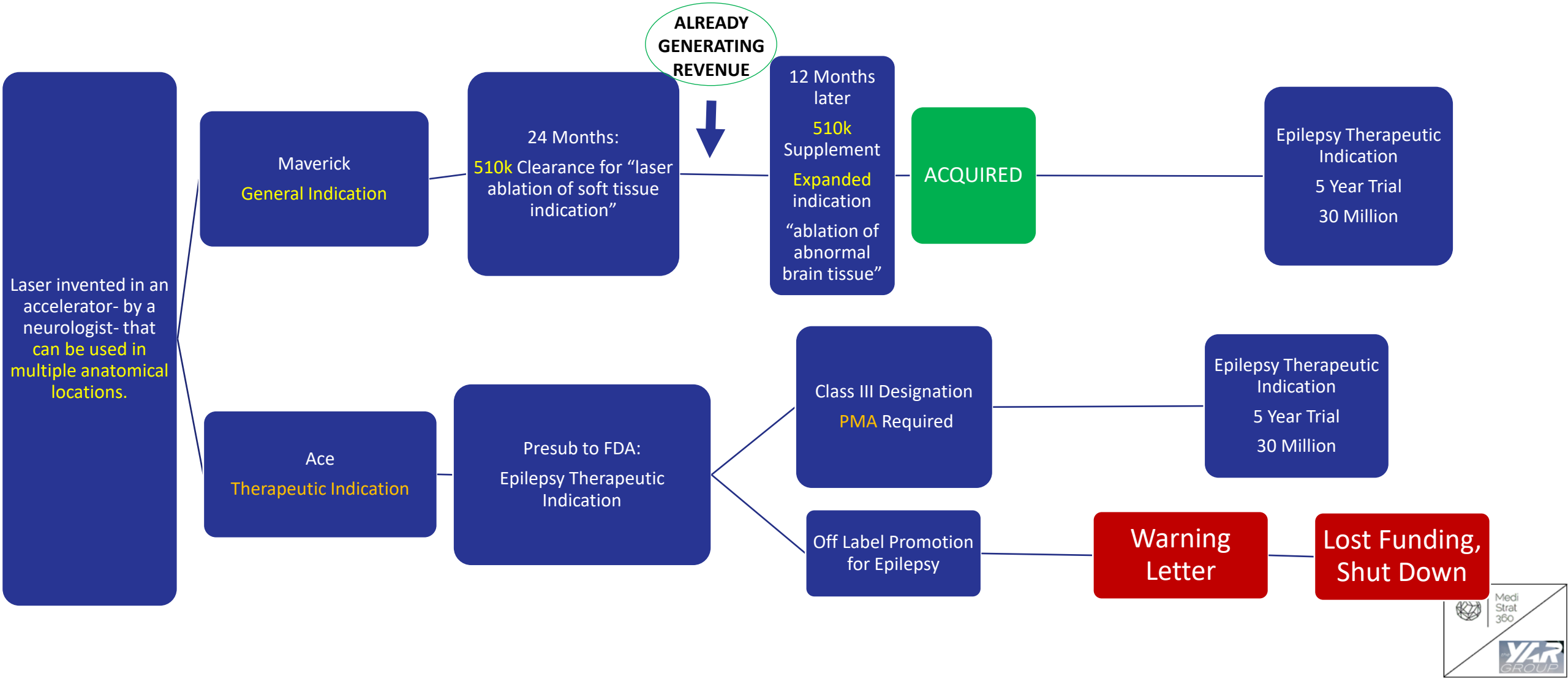
DEVICE CLASSES



- Class I: 43% General Controls, 91% 510k Exempt
- Class II: 51% Special Controls, 7% 510k Exempt
- Class III: 6% Premarket Approval
- **6700+ Device Product Categories**

IMPACT OF REGULATORY GUIDANCE EARLY IN THE DEVELOPMENT PROCESS:
Real World Example

- **Interdependencies Exist That Can't Be Ignored: Early Development activities have long term consequences on what regulatory pathways are available later.**
- **Taking the time to build out a holistic device strategy *from the beginning* will mitigate risk, accelerate clearance/approval → faster revenue generation.**



FDA REJECTION RATES AT FIRST SUBMISSION TO FDA

- 510ks: 75% are rejected at first submission to FDA
- PMA: 83%

REAL WORLD EXPERIENCE

- Development: Multicomponent Medical Device Submission

ACCELERATE: APPLY FOR FDA BREAKTHROUGH DEVICE DESIGNATION TO ACCELERATE FDA CLEARANCE: Does your device qualify under the original program?

Device provides more effective treatment or diagnosis of a life-threatening or irreversibly debilitating disease or condition

Device represents breakthrough technologies

No approved or cleared alternative device is currently marketed in the US OR Device offers significant advantages over existing approved or cleared alternatives

ACCELERATE: APPLY FOR FDA BREAKTHROUGH DEVICE DESIGNATION TO ACCELERATE FDA CLEARANCE: Does your device qualify under the latest revisions?

TOTALITY	To meet more effective element of standard, it will consider totality of information | benefits and risks
ADDRESSES HEALTH CARE DISPARITIES	Reduce barriers to health equity and help to include diverse populations
ADDRESSES CHARACTERISTIC DIFFERENCES	Such as those arising from social factors, phenotypic variations, pathophysiology, and/or response to treatment.
IMPROVED ACCESSABILITY	FDA may favor program eligibility for a medical device that includes user features that are adaptable or more easily used by diverse populations or allow for use in more diverse settings.
NON-ADDICTIVE MEDICAL PRODUCTS	Certain non-addictive medical products to treat pain or addiction may be eligible
DISCLOSURE	The agency generally will not disclose the existence of requests for breakthrough device designation and the associated decisions on such requests until the device receives marketing authorization.

CLINICAL

Clinical: Regulatory Requirements
Device Performance

Trials are Highly Regulated in the Medical Device Industry
21CFR Regulations & ISO14155: 11,50,54,56,803,812,814…and the list goes on

US FDA – Clinical Study Requirements

- 21 CFR Part 11 – Electronic Signatures
- 21 CFR Part 50 – Protection of Human Subjects
- 21 CFR Part 54 – Financial Disclosure by Clinical Investigators
- 21 CFR Part 56 – IRB
- 21 CFR Part 803 – Medical Device Reporting
- 21 CFR Part 812 – Investigational Device Exemption
- 21 CFR Part 814 – Pre-market Approval of Medical Devices
- Applicable Guidances

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER H - MEDICAL DEVICES
PART 812 INVESTIGATIONAL DEVICE EXEMPTIONS

Subpart A - General Provisions
§ 812.1 - Scope.
§ 812.2 - Applicability.
§ 812.3 - Definitions.
§ 812.5 - Labeling of investigational devices.
§ 812.7 - Prohibition of promotion and other practices.
§ 812.10 - Waivers.
§ 812.18 - Import and export requirements.
§ 812.19 - Address for IDE correspondence.

Subpart B - Application and Administrative Action
§ 812.20 - Application.
§ 812.25 - Investigational plan.
§ 812.27 - Report of prior investigations.
§ 812.28 - Acceptance of data from clinical investigations conducted outside the United States.
§ 812.30 - FDA action on applications.
§ 812.35 - Supplemental applications.
§ 812.36 - Treatment use of an investigational device.
§ 812.38 - Confidentiality of data and information.

Subpart C - Responsibilities of Sponsors
§ 812.40 - General responsibilities of sponsors.
§ 812.42 - FDA and IRB approval.
§ 812.43 - Selecting investigators and monitors.
§ 812.45 - Informing investigators.
§ 812.46 - Monitoring investigations.
§ 812.47 - Emergency research under 50.24 of this chapter.

Subpart D - IRB Review and Approval
§ 812.60 - IRB composition, duties, and functions.
§ 812.62 - IRB approval.
§ 812.64 - IRB's continuing review.
§ 812.65 - [Reserved]
§ 812.66 - Significant risk device determinations.

Subpart E - Responsibilities of Investigators
§ 812.100 - General responsibilities of investigators.
§ 812.110 - Specific responsibilities of investigators.
§ 812.119 - Disqualification of a clinical investigator.

Subpart F [Reserved]

Warning Letter

A physician who started an investigator-initiated trial of a significant-risk implanted device failed to get FDA approval before starting the study and did not get signed agreements for himself and the other physicians working as subinvestigators.

Thomas Davis of the Cardiology Division of St. John Hospital and Medical Center acted as both sponsor and clinical investigator in a study of a significant-risk device but failed to submit an investigational device exemption (IDE) application to the FDA, according to the warning letter, which was based on an inspection conducted Nov. 20 to Dec. 12, 2006. In all, five different devices were implanted into 68 subjects without approval.

Davis told the FDA he was not aware that an IDE was required for an FDA-approved device to be used off-label, that there was no risk assessment from the institutional review board and that he was not aware that he met the definition of a sponsor-investigator. However, the letter said, "As a sponsor, you are required to obtain a new IDE if a device that is approved for one indication is intended to be used in a clinical study for a new indication."

The warning letter can be accessed at: http://www.fda.gov/foi/warning_letters/b6324d.htm

ACCELERATE: Seek guidance on FDA performance requirements ***prior*** to starting any studies to ensure compliance with required standards. This applies to clinical trials ***as well as*** feasibility testing early in the development process.

- Real World Example: Foot & Ankle Biomechanical Retesting Post Acquisition
- Clinical Trial: SDV

US HEALTHCARE EXPENDITURE WILL EXCEED 6.8 TRILLION BY 2030

3.8 TRILLION UNITED STATES

8.5 TRILLION WORLDWIDE

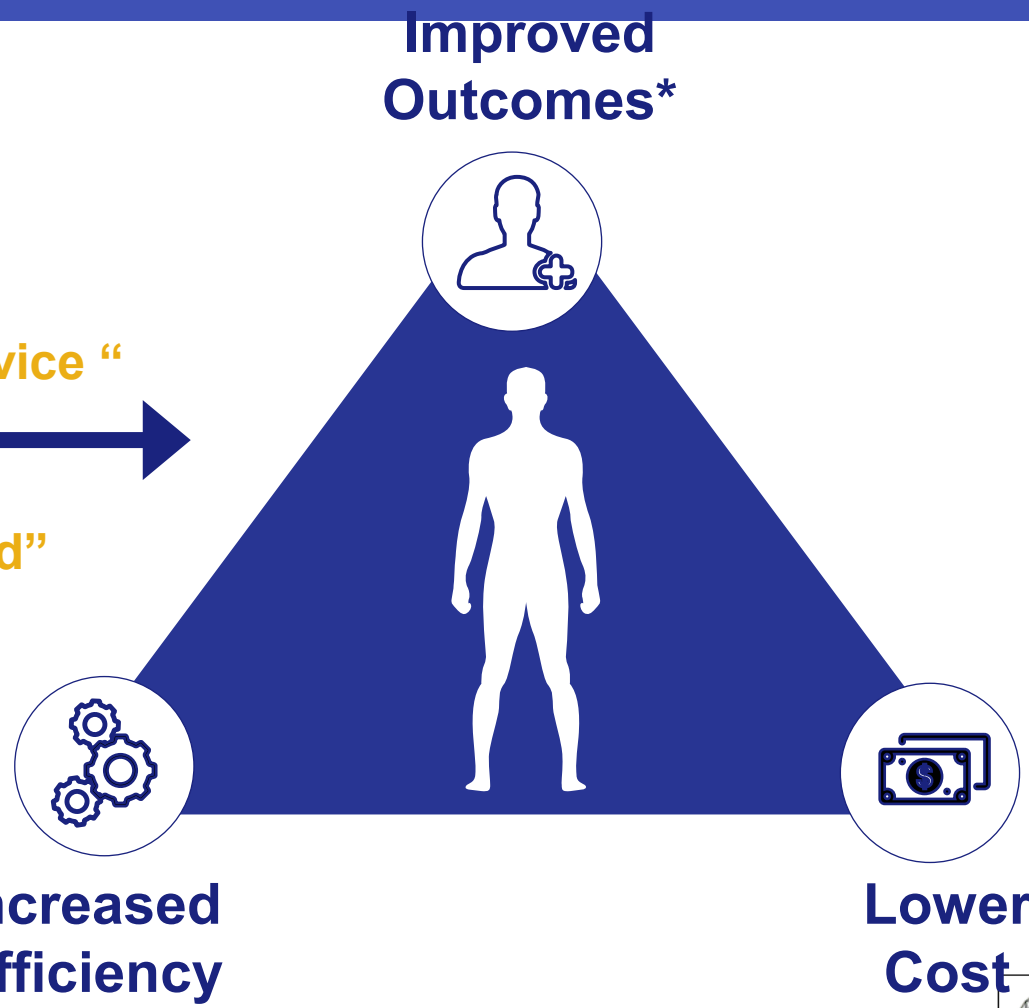
HEALTHCARE REFORM & INDUSTRY: PROVE.YOUR.WORTH
DEFINING VALUE IN THE NEW HEALTHCARE SYSTEM

Massive growth of elderly population with chronic conditions

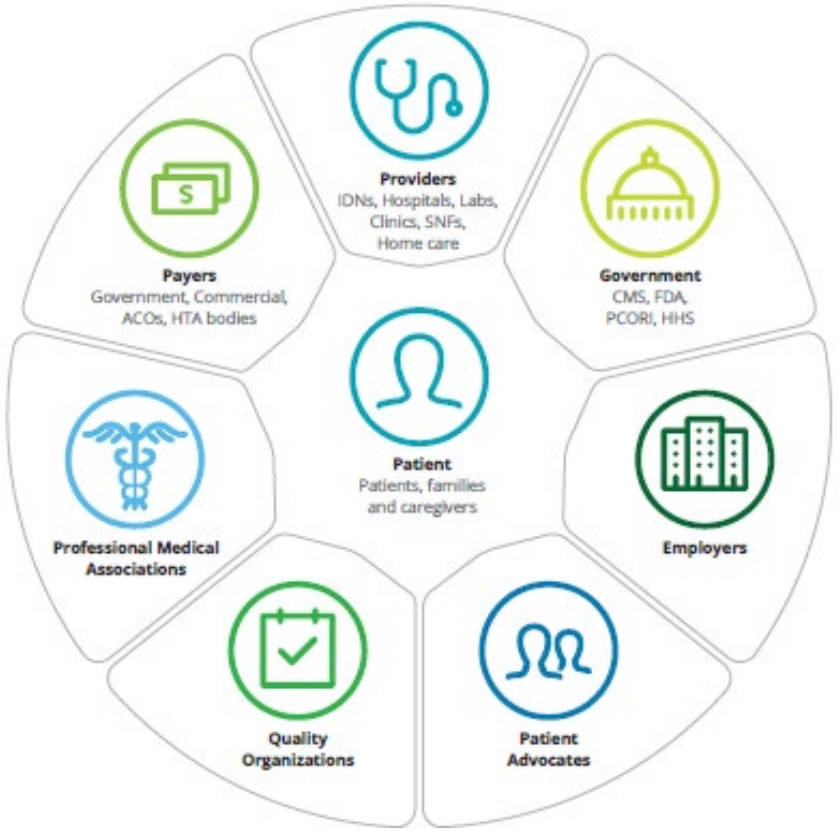
Healthcare system with resource deficit

From
"Fee for Service "

To
"Value-Based" Healthcare



Comprehensive Assessment of Medical Device Technologies
Value Drivers



Clinical Impact

- How does the technology affect clinical outcomes, compared to other treatment options (whether with direct competitive offerings or versus alternative treatments)?
- How does the technology impact patient safety (lower/higher risk of complications, less/more invasive, etc.) relative to available alternatives?
- How does the technology impact quality of life in the short and/or long-term? (physical and social wellbeing)?

Non-Clinical Patient Impact

- Does this technology create more/less preferable options for the patient (e.g., more accessible care settings, less intensive care settings)?
- How does the technology enable patients and their families and caregivers to navigate, coordinate, and manage their care appropriately and effectively?
- How does the technology impact affordability of treatment/out of pocket expense for different patients?

Care Delivery Revenue and Cost Impact

- How does the technology enable the right choice of treatment, for the right patient, at the right time, at the right place?
- How does the technology affect costs related to system throughput, workflows, and care efficiency (site of care, staff)?
- How does the technology help reduce costs associated with variance in clinical outcomes across individual physicians / sites of care?

Public/ Population Impact

- How does the technology impact overall public and population health measures (e.g., life expectancy free of disability)?
- How does the technology help lower unnecessary private and public spending?
- How does the technology impact ability for caregiver to provide care, and address productivity and attendance?

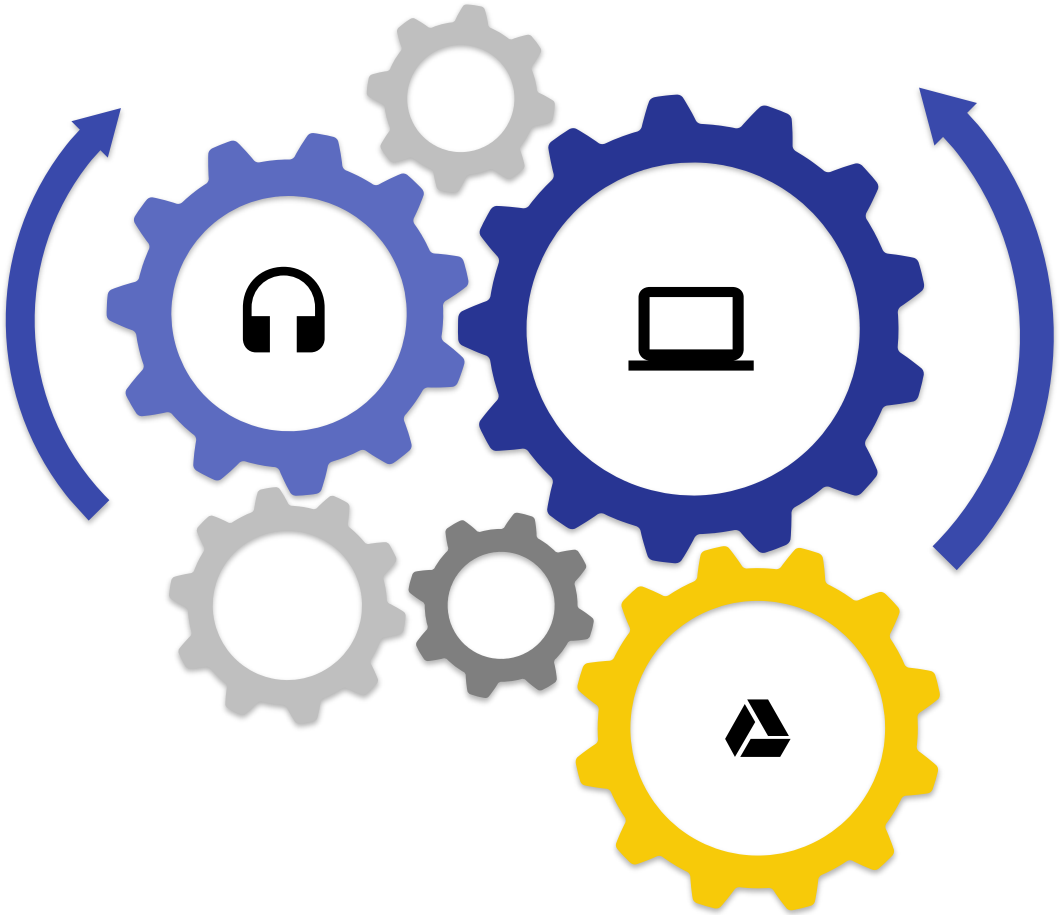
Advamed & Deloitte 2017.
A Framework for Comprehensive Assessment of Medical Technologies: Defining Value in the New Health Care Ecosystem. In BriefMay 2017

REGULATORY SUCCESS ≠ REIMBURSEMENT
REAL WORLD EXAMPLE

Charite ARTIFICIAL DISC

PAYOR POSITION	**CMS and Private Payors (Aetna, Wellpoint, BCBS) cited insufficient evidence of clinical benefit.**
OUTCOME	• **Refused reimbursement** • **Product Fizzled in market followed by negative coverage determination by CMS**

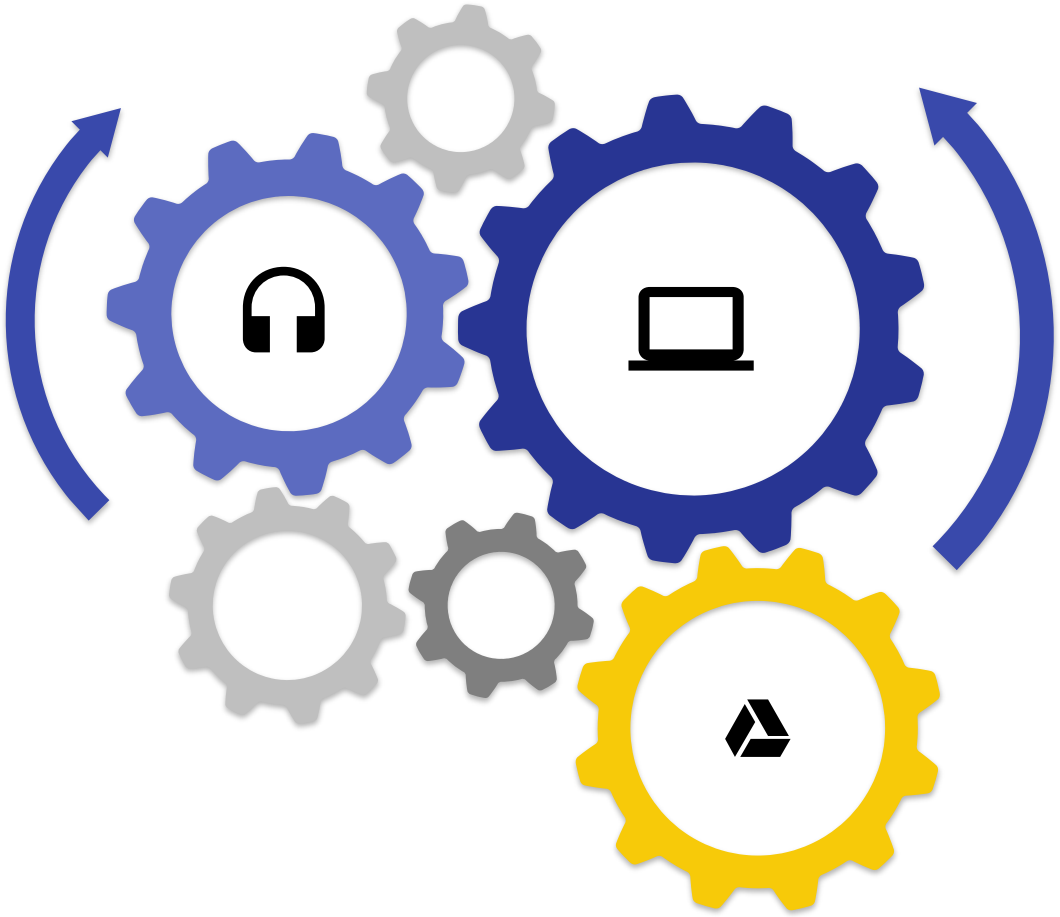
ACCELERATE: OPTIMIZE CLINICAL TRIAL DESIGNS TO GET REGULATORY CLEARANCE AND EVIDENCE DEMONSTRATING KEY VALUE DRIVERS



Think beyond the regulatory clearance: optimize trials with endpoints addressing reimbursement requirements, the new value equation (cost effectiveness), and key stakeholders when possible.

-Economic Value Parameters
-Patient's Payor Designation
*Cost, Outcomes, Efficiency
*Key Stakeholders: Payors, Providers, Patients, Administrators.

ACCELERATE: Leverage Real World Evidence Pathway to Accelerate indication expansion & Establish a robust, compliant, grants program.
Laser example, Rick- Life example



ACCELERATE

Consider FDA RWE Guidance/Real World Evidence Opportunities to strategically accelerate clearances for device indication expansion.

-Grants Programs
-Patient Registries

STRATEGIC CONSIDERATIONS

ACCELERATE: A Holistic Device Strategy & An **Integrated Cross Functional team from the beginning leads to successful device commercialization & accelerated timelines. Rick – helicopter example**

MERGERS & ACQUISITIONS
Ruba- ACQUISITIONS STRATEGIC CONSIDERATIONS
Rick- Questions Investors will Ask as you Progress through the Process

- Medical Benefit
- Strategic Fit Risk

- Cost Effectiveness
- Device Need
- IP

- Market Size
- Revenue
- Investment
- NPV

- Strategic Value
- Platform
- Disease Focus

- Strategic Categories
- Timing
- Markets, etc.

WHY I'M HERE
7 Biases that Kill Startups

- Optimism Bias
- Planning Fallacy
- Sunk-Cost Fallacy
- Overconfidence Bias
- Status Quo Bias
- Confirmation Bias
- Hindsight Bias

Reference: Ron Flavin, Entrepreneur Cognitive Bias: 7 Biases that Kill Startups, https://fi.co/insight/entrepreneur-cognitive-bias-7-biases-that-kill-startups

KEY TAKEAWAYS

- All Devices, *Regardless Of Classification*, Have Regulatory Compliance Requirements Across The Entire Product Development Lifecycle

- Implementation Of An Fda Compliant Quality Management System & Design Controls Early On In The Development Process - As Mandated By Fda - Will Protect Your Startup & Help You Avoid Regulatory Clearance Delays.

- Early Implementation Of A Design Controls & Product Development Process Compliant With Us And Key Global Market(s) Regulatory Requirements - Enables Faster Market Adoption And Saves Time & Money Over The Long Term.

- Get Regulatory Guidance Early In The Development Process: It Enables Access To Strategies You Didn't Know Existed. Interdependencies Exist That Can't Be Ignored & Early Development activities have long term consequences on what regulatory pathways are available later. Taking the time to build out a holistic device strategy *from the beginning* will mitigate risk, accelerate clearance/approval, leading to faster revenue generation.

KEY TAKEAWAYS

- APPLY FOR FDA BREAKTHROUGH DEVICE DESIGNATION TO ACCELERATE FDA CLEARANCE: Does Your Device Qualify Under The Original Program?
- Apply For Fda Breakthrough Device Designation: Does Your Device Qualify Under The Updated Revisions Targeting Healthcare Disparities?
- Prove Your Worth. Optimize Clinical Trial Designs & Evidence Investments Taking Into Account The New Healthcare Environment And Requirements Not Only For Regulatory Clearance, But Also For Payors & Administrators Where Possible.
- Leverage Real World Evidence Pathway To Accelerate Indication Expansion & Establish A Robust, Compliant, Grants Program.
- A Holistic Device Strategy & An **Integrated Cross Functional Team From The Beginning Leads To Successful Device Commercialization & Accelerated Timelines.**
- Stay Diligent And Aware Of Cognitive Bias You Are Susceptible To And Keep It In Check.

THANK YOU!

QUESTIONS? HOW CAN WE HELP?

Rick Thomson
Rick.Thomson@theyargroup.com

Ruba Sarris Sawaya
Ruba@MediStrat360.com