Regulatory Pathways to Clearance: Transitioning University Discoveries

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Clinical Research STRATEGIES

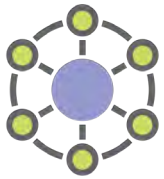
- 2011 – small enterprise consultants
- 2018 – rebranded with consulting team
- 2022 – 11 employees, 15 expert consultants

We specialize in

- Quality, clinical, regulatory and safety over the life cycle of a product
- Risk management, continuous quality improvement paradigm
- Innovation and building companies or products from scratch
- Regulatory science, policy and reform (US and EU)

★ Greatest lessons from companies that failed for a variety of reasons, squandered resources, or refused to look ahead

CRS Services



COMPLIANCE, GOVERNANCE & DUE DILIGENCE

- EU MDR
- SOPs
- Governance
- Trial Master File Management
- Due diligence
- and more…

CRO & SPONSOR STAFFING

- Project management
- Quality assurance
- Clinical monitoring
- Scientific writing
- Medical monitoring
- Regulatory Affairs
- and more…

CLINICAL & REGULATORY AFFAIRS

- Clinical development plans
- Project management
- Regulatory strategy
- Trial planning, efficiency, operations
- Patient recruitment and enrollment rates
- Realistic costs and timetable projections
- Resourcing decisions and recruitment
- Team training on regulatory and ICH-GCP topics
- and more…

RISK MANAGEMENT & QUALITY ASSURANCE

- New quality system implementation
- Improvement of existing quality system
- Internal audits
- Supplier management
- Remediation
- New product development
- Manufacturing improvement
- Post-market surveillance
- Data privacy and safety
- and more…

POLICY & INNOVATION

- Real-world evidence
- Blockchain, AI, etc.
- Intersection of clinical research and value-based medicine
- Emergency use authorization for COVID-19
- Fast-track SBIR grants
- and more…

Modalities: drugs, biologics, medical devices combination products, diagnostics, IVDs, software as medical device, digital therapeutics, and more.

Indications: respiratory, infectious disease, oncology, hematology, immunoncology, CNS, rare disease, pain, opioid-sparing pain, nephrology, transplant, bone marrow transplant, gene and cell-based therapies, diabetes, regenerative medicine, precision medicine, critical care, surgery, orthopedics, ophthalmology, cardiovascular, reproductive health, imaging, biomarkers, and more.

https://clinicalresearchstrategies.com/life-sciences-consulting/

Clinical Research STRATEGIES

Veteran Expertise

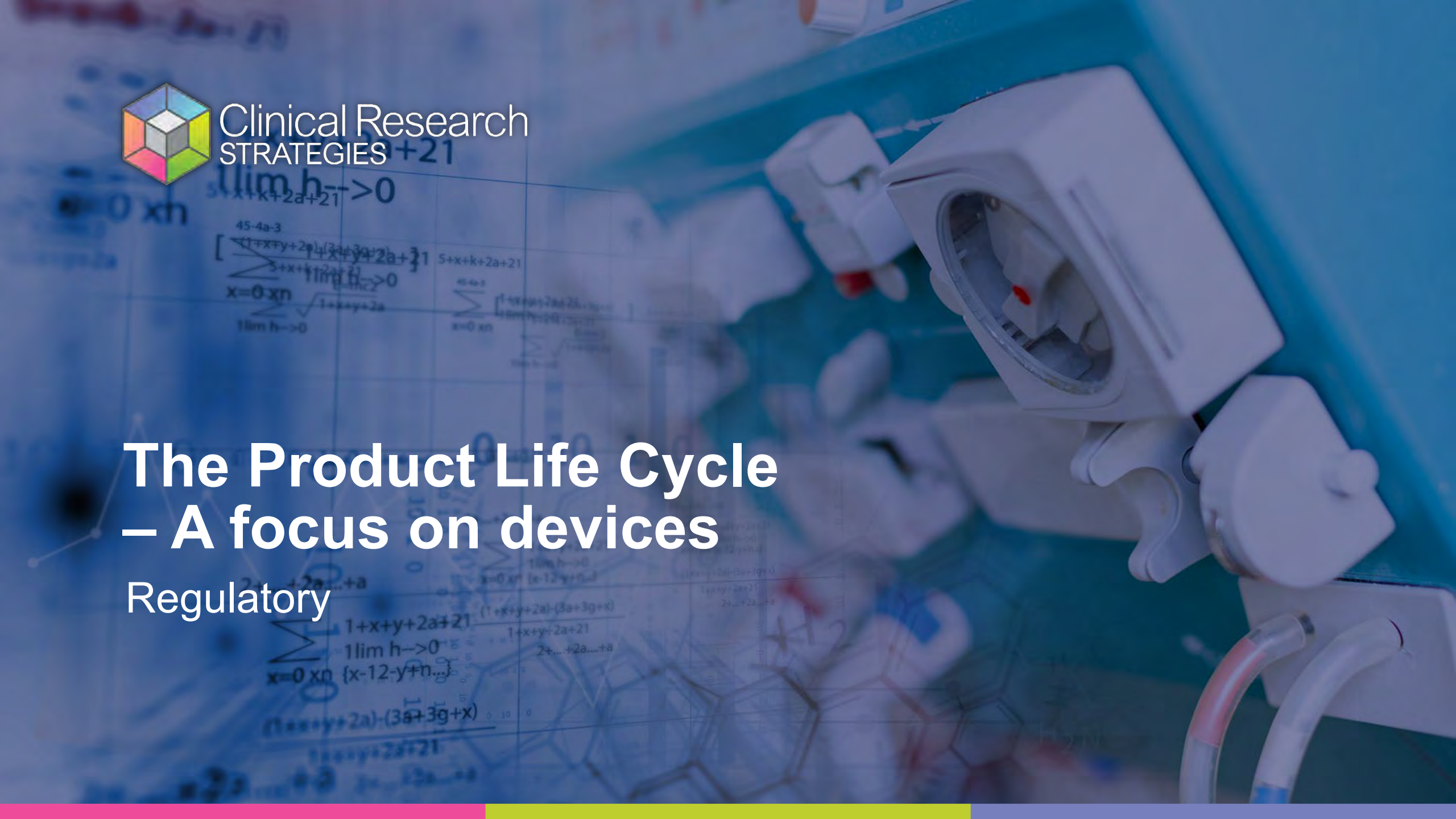
- FDA and EU Meetings and Submissions
- NIH and DoD grants
- Collaboration with regulatory bodies and stakeholders for innovative methods
  - Interoperability, in silico trials, blockchain / data standards in life sciences
  - Statistical experts in adaptive design, master protocols, platform trials
  - Decentralized Trials and Research Alliance (DTRA), RWE/RWD
- Functional Service Provider (FSP) support:
  - Project Management
  - Clinical Monitoring
  - Medical Monitoring and DSMB management
  - Regulatory Affairs
  - Quality Assurance
  - With a variety of partners for Data Management and Statistics

★ CRS recognizes and addresses the gap for those struggling to grasp complex quality and regulatory requirements.

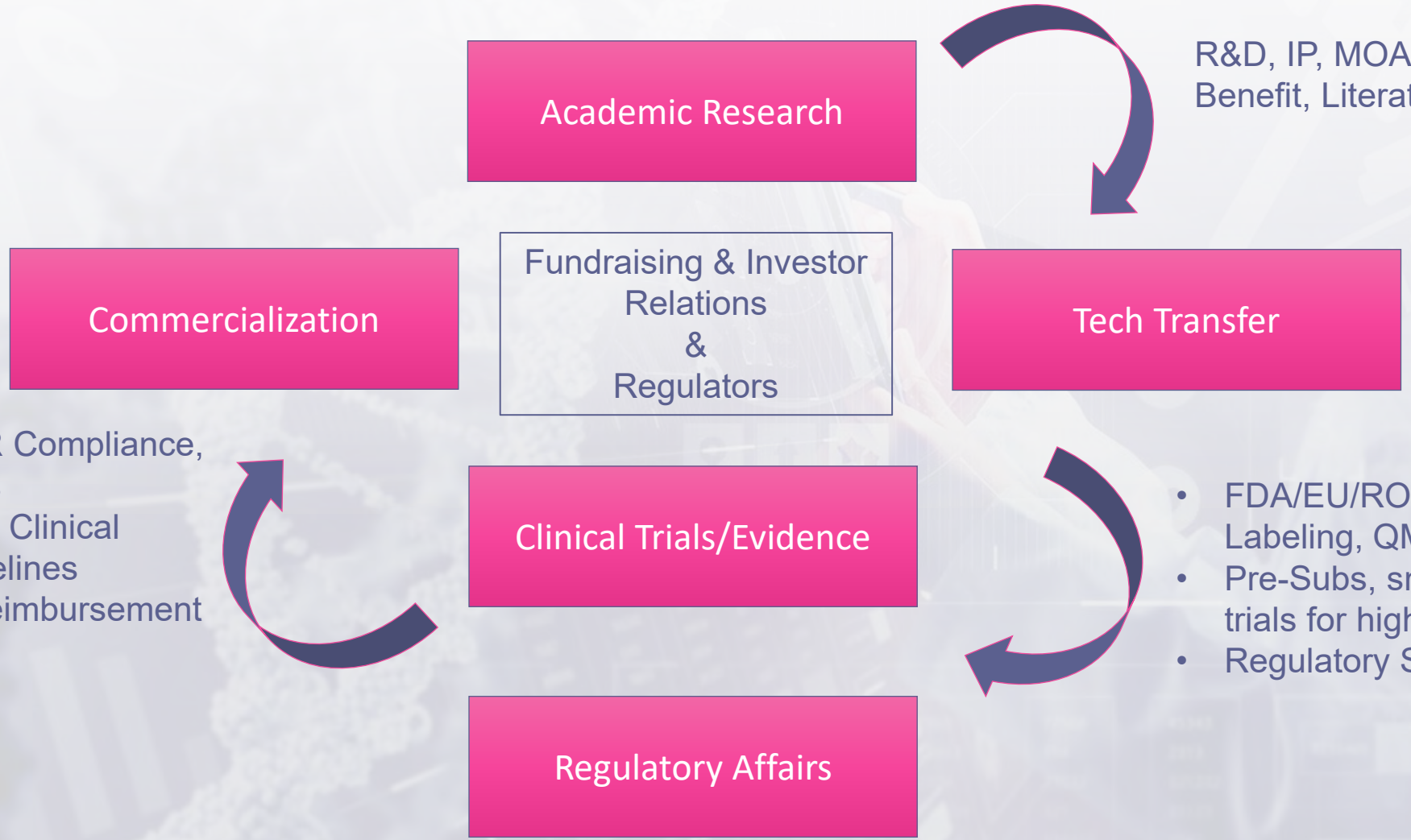
Clinical Research STRATEGIES

The Product Life Cycle – A focus on devices

Regulatory



Product Life Cycle – Where does Regulatory Fit In?



- FDA/EU/ROW Strategy, Labeling, QMS scalability
- Pre-Subs, smallest, innovative trials for highest % of win
- Regulatory Submissions

- QSR/MDR-ER Compliance, Audits & Certs
- Publications & Clinical Practice Guidelines
- Adoption & Reimbursement Decisions
- Due Diligence

Defining my device

- What is my medical product?
- Device Description
  - All the components, accessories, way it is used
- Mechanism of Action (MOA)
  - How it interacts with the patient (treat, diagnose)
- Risk-level and risk-benefit (low, moderate, high)
  - Class I – low risk, self registration or 510(k) (ex: tongue depressor)
  - Class II – medium risk, most 510(k) (ex: absorbable suture, bp cuff)
  - Class III – highest risk, pre-market approval (PMA) (ex: implantable pacemaker)

Intended Use vs Indication

Intended use

- General description of what the device does and what it is used for, its “purpose”
- The use as displayed in the device label
  - Is included in 510(k) submission, must be very "to the point"
- *Example*: Insulin Pen injects insulin to maintain blood insulin levels.

Indication

- Under what specific circumstances or conditions the device will used to diagnose, treat, prevent, cure or mitigate, including a description of the intended patient population
- Conditions or reasons for using the device
  - Can be on the label or explained by doctor
  - Does not have to be "to the point"
- Example: The insulin pen is a home-use reusable pen injector for single-patient use by **people with diabetes** under the supervision of an adult caregiver, or by a patient age 7 and older for the self-injection of a desired dose of insulin.

Types of Device market approval applications

510(k)

- A Premarket notification approval submission.
- A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is as safe and effective, that is, substantially equivalent, to a legally marketed device already placed into one of the three classification categories.
  - Predicate Device
- Compare your device to one or more similar legally marketed devices and make and support their substantial equivalence claims.
  - Same intended use, etc.

PMA

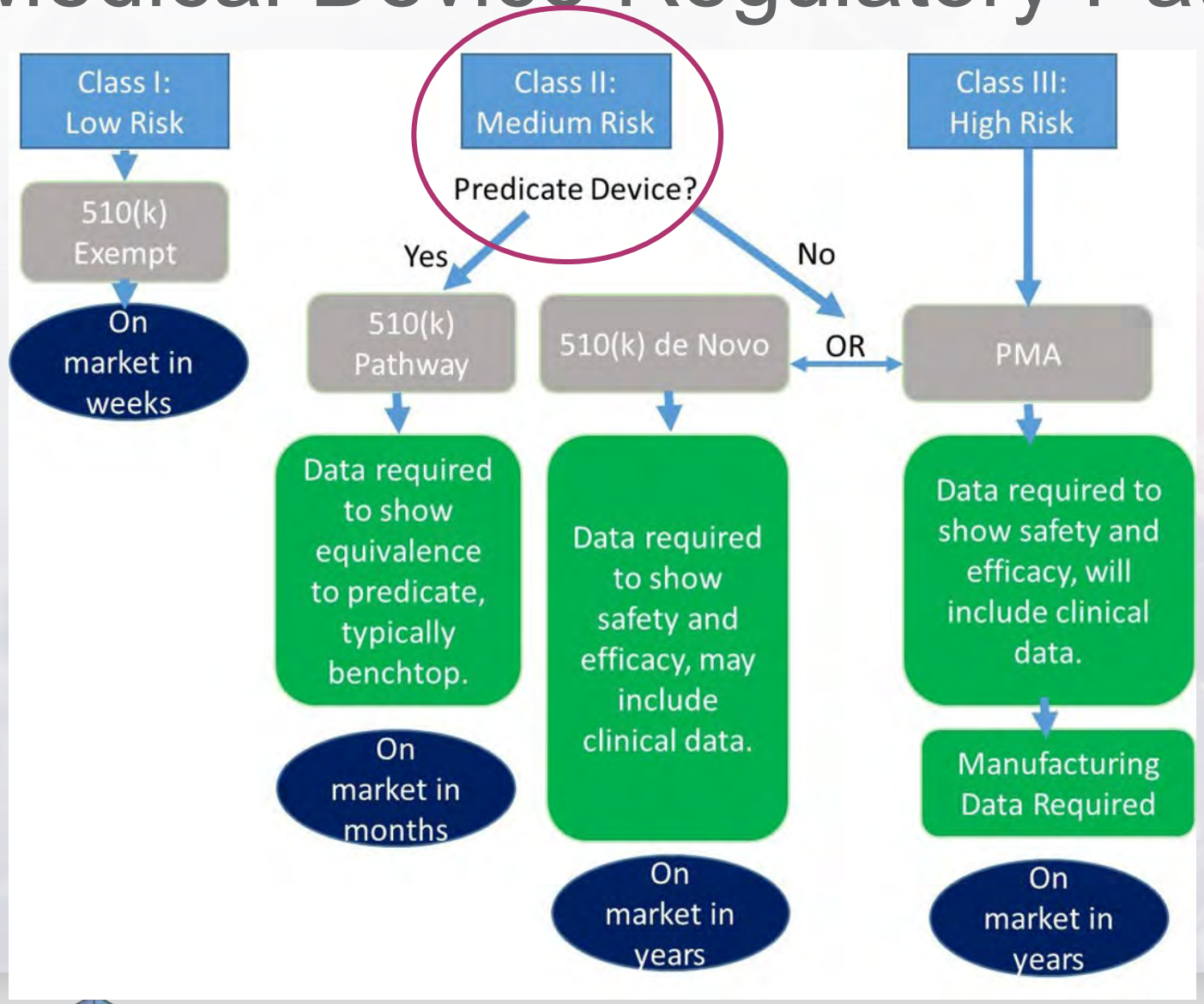
- Pre-market approval
  - Documentation that demonstrates the safety and effectiveness of the device, for its intended use
  - Requirements apply to all class III devices.
    - Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.

Types of Device market approval applications

De Novo

- "De Novo" directly translated from Latin is "from new" which was understood as "from the beginning"
- A pathway for marketing completely novel devices that have no predicates.
- De Novo devices may be used as predicates for future pre-market submissions.
- Initially designated at Class III because it is new, and risks are not established
- There are two ways a device is determined to be De Novo:
  - A 510(K) submission is made and receives a high level "Not substantially equivalent" determination in response to it
  - The requestor can claim there is no substantially equivalent device currently on the market when submitting the request.

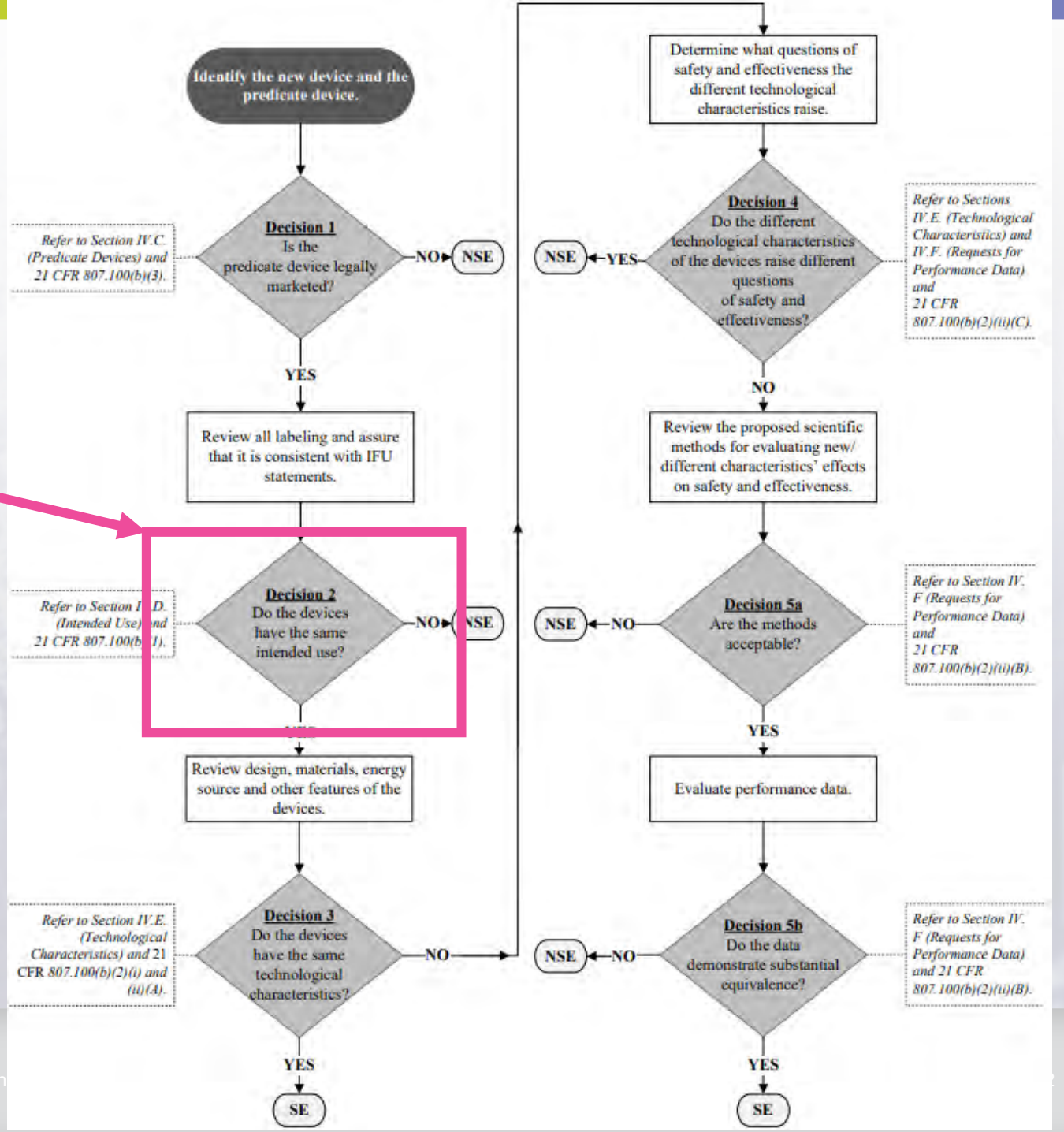
Medical Device Regulatory Pathways



Risk Class:
Getting this right is tantamount to your business

FDA 510(k) Decision-Making Flowchart

- Intended use is a primary decision point in FDA's substantial equivalence decision vs predicate
- Leaves some flexibility on detailed Indications for Use
- Nonetheless the more similar the better



SE = Substantially Equivalent
NSE = Not Substantially Equivalent
IFU = Indications For Use

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How do you get clinical data, without FDA approval?

- Investigational Device Exemption (IDE) (Medical Device, Software): Allows the investigational device, that is not approved for market, to be used in a clinical study in order to collect safety and effectiveness data.
- Clinical studies are most often conducted to support a PMA.
- Only a small percentage of 510(k)s require clinical data to support the application.
- All clinical evaluations of investigational devices, unless exempt, must have an approved IDE before the study is initiated.
- Clinical evaluation of devices that have not been cleared for marketing requires:
  - an investigational plan approved by an institutional review board (IRB). If the study involves a significant risk device, the IDE must also be approved by FDA;
  - informed consent from all patients;
  - labeling stating that the device is for investigational use only;
  - monitoring of the study and;
  - required records and reports.

De-risking the process #1:
Regulatory Pathway Assessments (RPAs)

- Often elucidate state of the art, product codes, predicates or novelty
- **Primary Goal**: Identify optimal regulatory pathway options
  - Shortest time to clearance
  - Lowest risk of FDA refusal
  - Claims that achieve greatest market share
  - Parallel development of data to support CMS coverage

De-risking the process #2:
Pre-submission AKA Q-submission

- Request formal feedback on a device before submitting a PMA, 510(k), De Novo request, IDE, etc.
- Specific questions regarding a planned IDE or marketing submission (e.g., questions regarding cybersecurity considerations for the device; non-clinical testing protocols; design and performance of clinical studies and acceptance criteria).
- Appropriate when FDA's feedback on specific questions is necessary to guide product development and/or submission preparation.
- Early interaction with FDA on planned non-clinical and clinical studies and careful consideration of FDA's feedback may improve the quality of subsequent submissions, shorten total review times, and facilitate the development process for new devices.
- Interactions provided within Pre-Subs are likely to contribute to a more transparent review process for FDA and the submitter.

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Meeting with the Regulators

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Regulators are not adversaries

- Federal and international regulators must protect patients first
- Post-market problems have led to higher scrutiny and policy reform
- Safety and efficacy must be scientifically proven
- Quality and integrity of documentation and data collected must be proven
- Risk-benefit of device must be well-defined and substantiated per the regulations
- Embrace the challenges that lie ahead
- EU is no longer the cheaper and faster location to launch vs US

Meeting with the Regulators

US strategy

- Define your strategy in preparation of your submission
- Read relevant guidance docs for meeting requirements and timing
- View early discussions as a way to de-risk your product and your trial(s) program
- Example questions that are most important to exchange…
  - Pilot trial data protocol
  - Wellness Device vs Medical Device
  - Confirmation of equivalence to marketed product before attempting a 510(k) submission
  - Breakthrough Designation Request requirements

Meeting with the Regulators

US meeting planning

- Once the meeting is planned, prepare brief slide deck
- Assess the personnel who should attend (TC or F2F)
- Rehearse and script out the 1 hour
- Important to be ready unless if written feedback is agreed upon
- The time flies while in the actual meeting
- Sponsor is responsible for meeting minutes
  - Appoint 1-2 team members who are very good at note-taking and not a key participate in the discussion
  - Permanent record

Meeting with the Regulators

EU – Notified Body

- MDR has changed access to the EU
- Strategy should include EU, timing and potential use of US/ROW data
- Risk-benefit profile is still the top consideration
  - Risk management file
  - Early evidence
  - Literature (state of the art - SOA), objective clinical evaluation
- All bets are off – too difficult to predict ease of market access
  - Only several dozen NBs are MDR-certified
  - Deficit of talent in NBs to understand the new regulations

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Considerations for Clinical Evidence Generation

Building a Compendium of Evidence

- Evidence generation is costly
- Stakeholders must see clear proof device does what it's claims say
- Start small: proof-in-concept, early feasibility, training sets, NSR studies
  - Not statistically meaningful
  - Used to attract more investment for larger trials
  - Not enough for reimbursement
  - **Goal is to start publishing**
- Obtain regulator buy-in before spending for larger pivotal trials

Building a Compendium of Evidence

Study types – each provide variable evidence generation

- Human factors
- Training set
- FIM, POC, EFS, Investigator-initiated
- Equivalence (Class I, 510k)
- Pilot-to-pivotal, adaptive
- Pivotal
- In silico
- Post-market: safety surveillance, registry, observational, RWE, cost analysis

Building a Compendium of Evidence

Weighted scale toward gold standard

- Pivotal, RCTs to prove
  - Superiority to other treatments or SOC
  - Non-inferiority to SOC
- Pilot, investigator-initiated
- Increasing use of in silico and RWE studies, *some* for potential regulatory decision-making

Building a Compendium of Evidence

Publications program

- High impact journals – long road
- Lower impact, quick online publications
- White papers
- Voice of customer / testimonials
- Feeds into continuous clinical evaluation and risk-benefit narrative
- Competitor's literature may also prove beneficial

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STRATEGIES

Summary

Summary

Lessons

- Know your intended use, indications for use, device description and MOA
- Meet with regulators for key agreement and understanding ahead of trials
- Establish strategy for clinical evidence generation
- Reflect clinical evidence in publications program
- Consider different stakeholders in order of importance


Thank You for Your Time!
QUESTIONS?
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