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Bringing Digital Health Products to Market, and Other Relevant Considerations

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Main Takeaways and Lessons

1. The Digital Health landscape is huge, and medical devices are just one part of that ecosystem!

2. There are many different regulatory pathways, but the focus should be on what information and data is needed to support your intended use.

3. Using AI/ML doesn't always mean PMA or De Novo but there are special considerations for AI/ML based devices.

4. Interact with FDA via the pre-submission process especially if you are somewhat different from any potential predicate devices.

Outline

Framework for Device Regulation
- Device Classification and Regulatory Pathways
- How to Determine the Classification of Your Device

The 510(k) Pathway
- Substantial Equivalence
- Predicate Devices
- Changing/modifying a “cleared” device

Other Premarket Pathways
- De Novo Pathway
- Premarket Approval Application (PMA) Pathway

Key Considerations
- Clinical vs Tool claims: When is a clinical study needed?
- My device has AI/ML: What should I considered that differs from other digital health devices?
- Clinical Decision Support Software
- Breakthrough vs. STeP: What is the difference?

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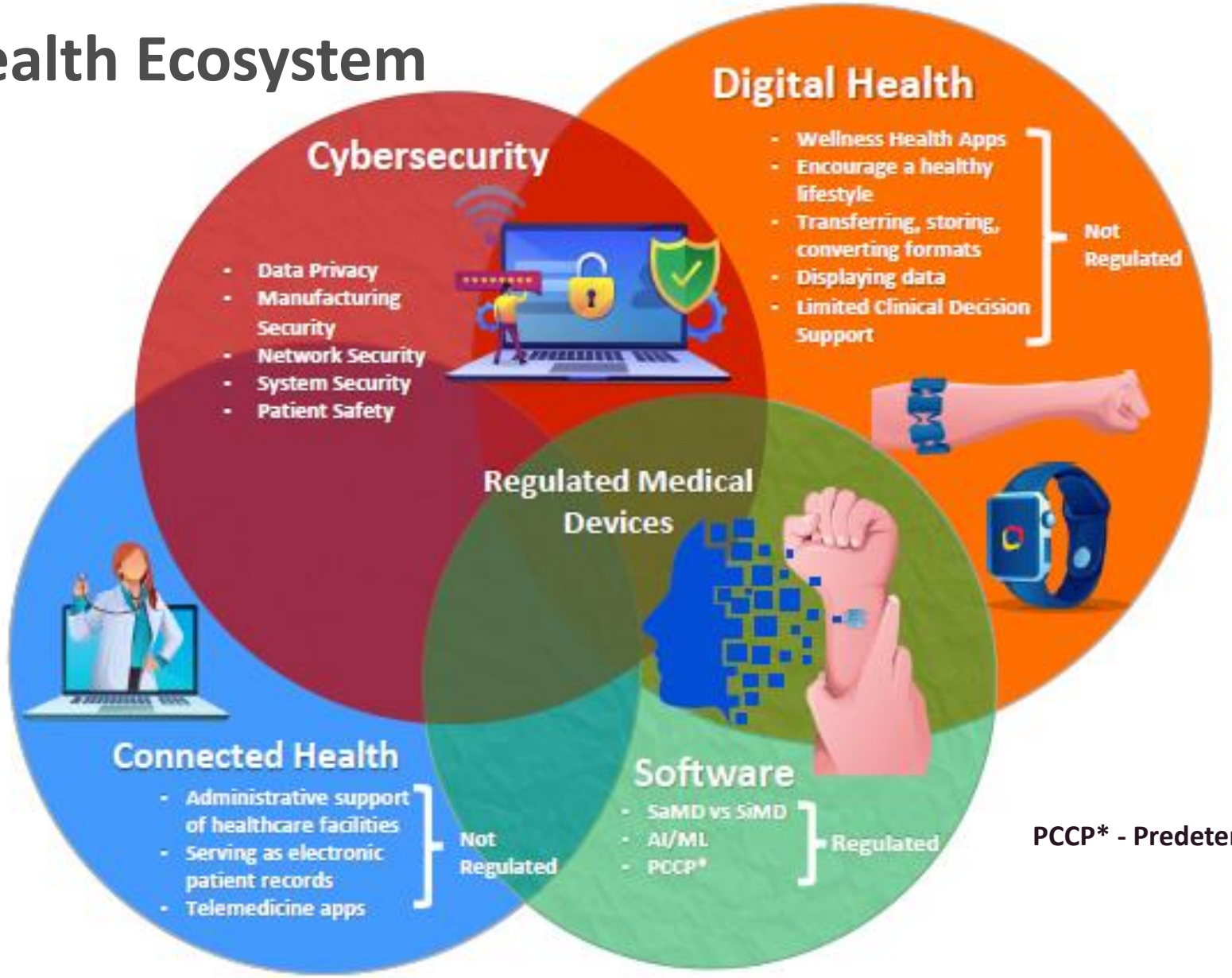
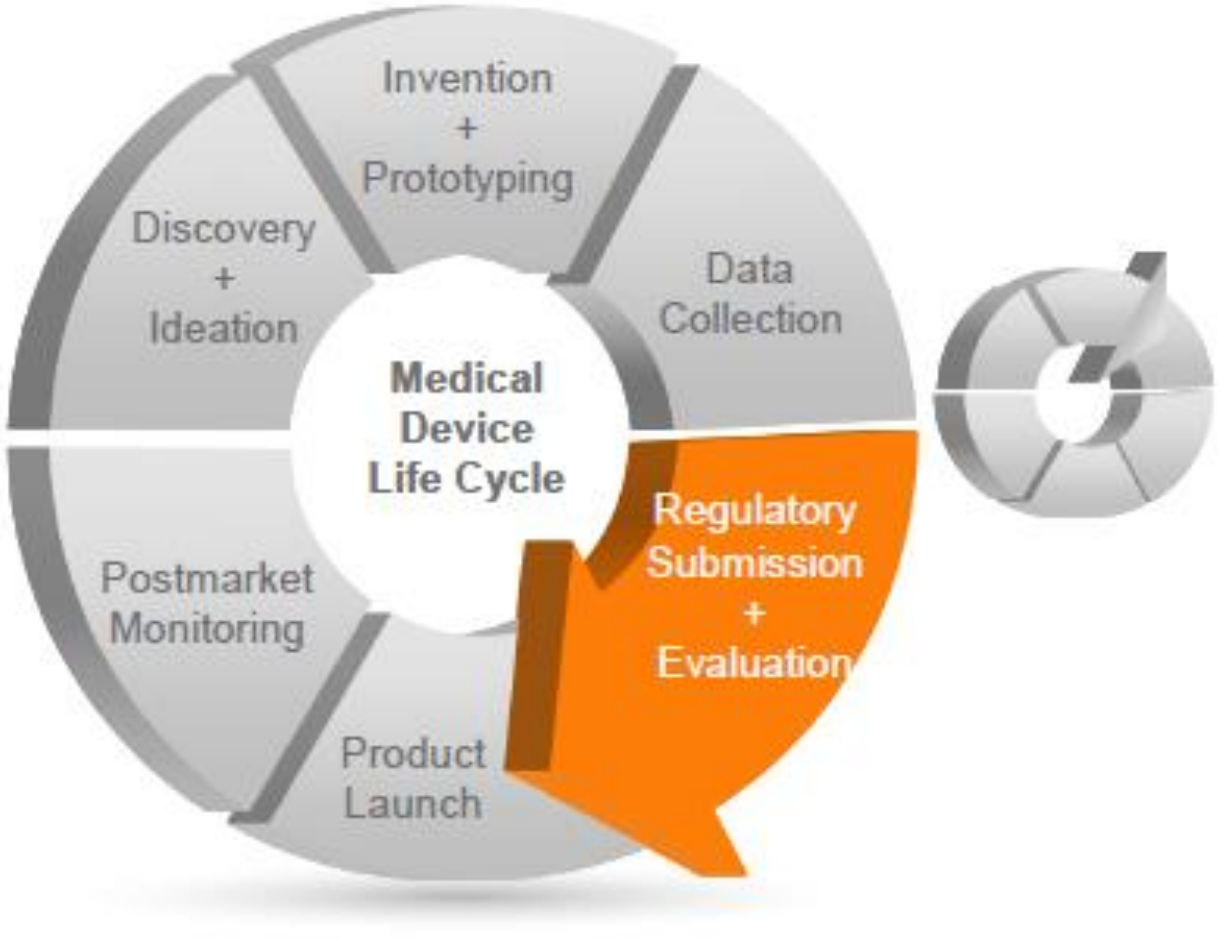
Medical Device Regulatory Framework

Digital Health Ecosystem

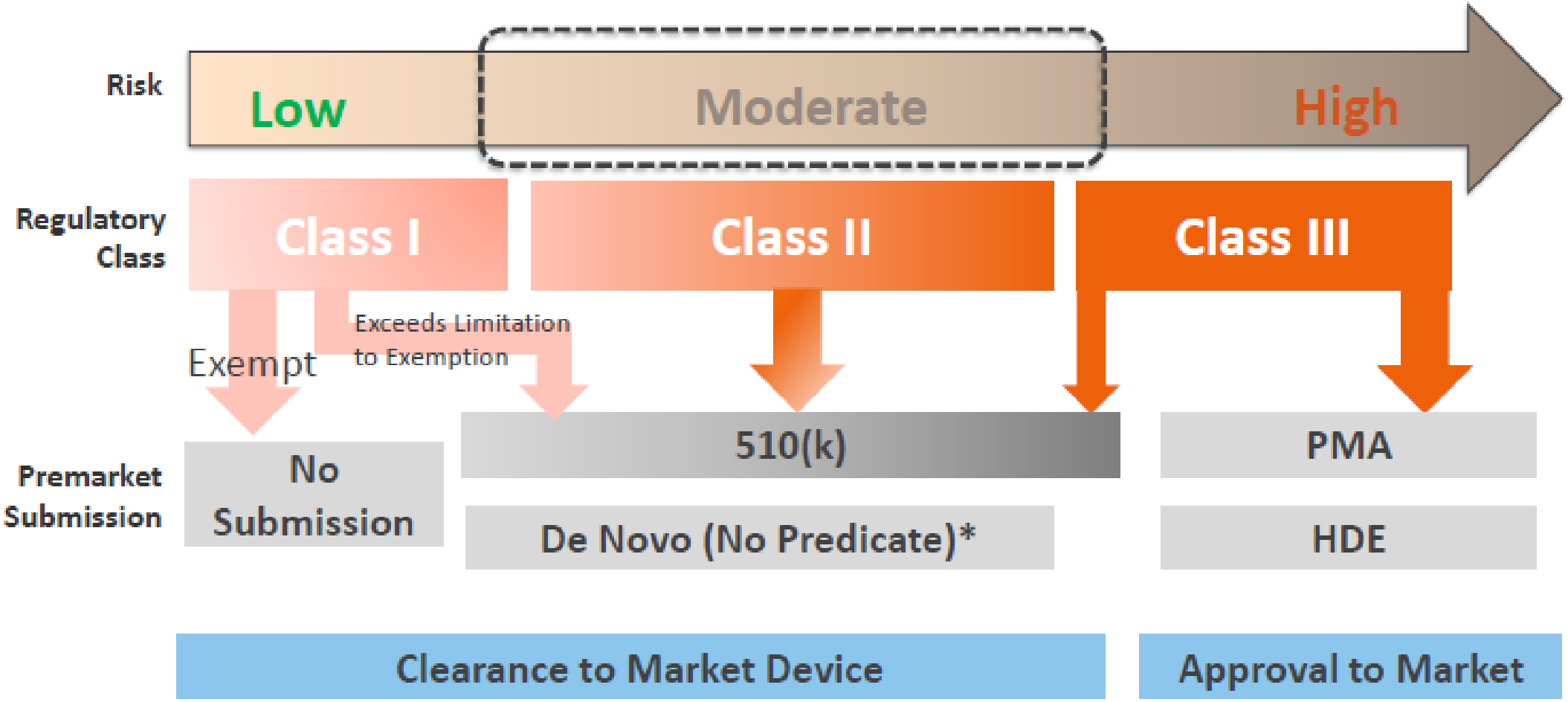


PCCP* - Predetermined Change Control Plan

Submitting to FDA is one phase in the life cycle of a medical device



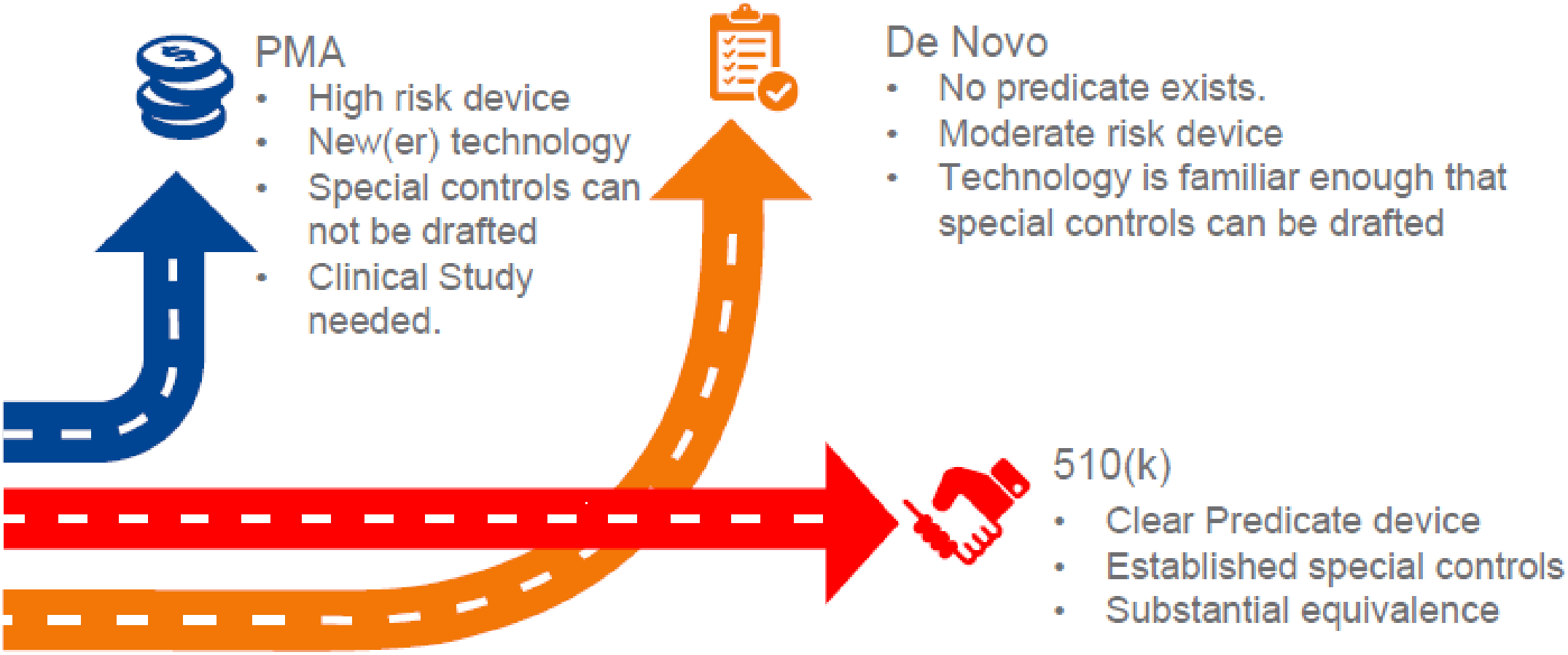
FDA Classification Tree



*De Novos are granted (which allow for future 510(k) clearance)

Indications for use are key for determining regulatory pathway of device.

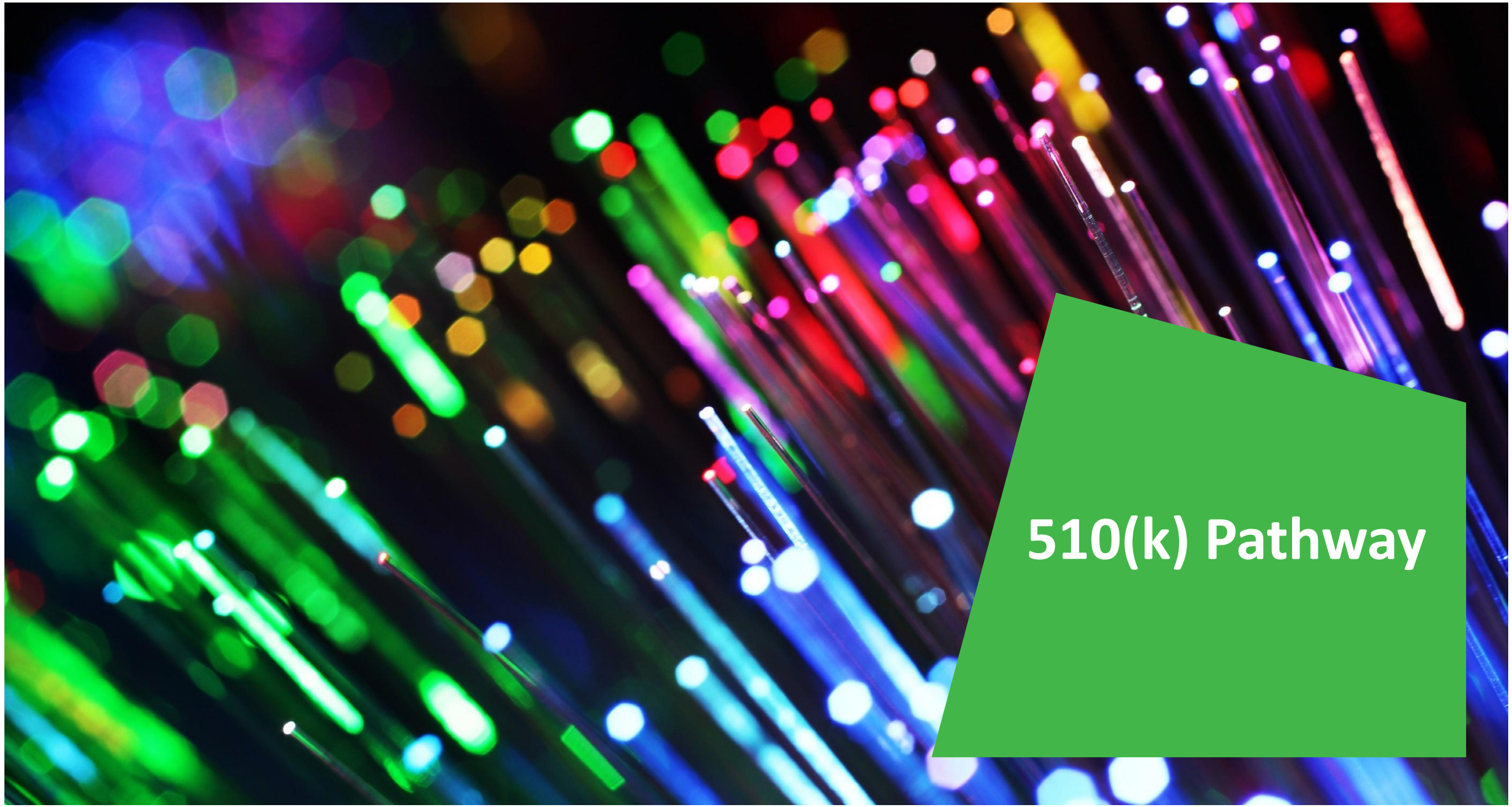
Determining Your Pathway



PMA
- High risk device
- New(er) technology
- Special controls can not be drafted
- Clinical Study needed.

De Novo
- No predicate exists.
- Moderate risk device
- Technology is familiar enough that special controls can be drafted

510(k)
- Clear Predicate device
- Established special controls
- Substantial equivalence


510(k) Pathway

510(k) is the primary path to U.S. market for medical devices

- FDA receives ~3000 original 510(k)s per year
- Most 510(k)s are class II devices
- ~90% are found SE
- Only ~3-4% of 510(k)s receive an NSE decision
- Approximately 10% of 510(k)s include clinical data
- 90 day review timeline

When is a 510(k) Needed?

510(k) Required when…

- Device is introduced to U.S. market for the first time
- New or different intended use
- Modification to a marketed device that "**could significantly affect safety or effectiveness**" or alter product claims

No 510(k) Required if…

- Private Label Distributer
  - who does not modify device or labeling
  - only adds company name or language such as "distributed by__"
- Not marketed in the U.S.
- Manufacturer of parts
- Devices Exempt by Statute or Regulation

Unlike other submission types, 510(k) has a comparative review standard

- A device must be compared to a legally marketed device (apredicate*) that does not require a PMA, i.e.:
  - A pre-amendment device*
  - A device found by FDA to be Substantially Equivalent (SE)
  - A reclassified device*
  - A device classified by a de novo request

- The principles of safety and effectiveness underlie the substantial equivalence determination in every 510(k) review

*21 CFR Part 807.92(a)(3)

You need an adequate predicate to be cleared to market via a 510(k)

= Predicate

✓ Same intended use
✓ Same technological characteristics

vs

✓ Same intended use
✓ Different technological characteristics do **not** raise different questions of safety and effectiveness and demonstrate the device is as safe and effective as the predicate

FDA prefers one primary predicate device; new draft guidance related to how to determine best predicate device

ONE device must meet all the SE criteria to be considered an adequate predicate

Primary Predicate – the identified predicate with indications and technology most similar to the subject device when multiple predicates identified

- Can facilitate a timely review and well-supported decision

Reference Device – a legally marketed device intended to provide scientific information to support safety and effectiveness

- Reference device is not a predicate and cannot be used for indication and technology comparison

Multiples Predicates - can be used to combine features from multiple devices without altering:

- Intended use, and/or
- Risk profile relative to the predicate devices

Multiple predicates example

- A manufacturer submits a 510(k) for a urinary catheter with a thermometer
- The thermometer/temperature-measuring feature is not affecting the intended use or risks of using the catheter (assuming it is integrated appropriately), nor is the catheter affecting the performance or risk profile of the thermometer
- The temperature-measuring feature is a convenience component that is added to the catheter, with the intended use of the device still being that of the catheter to pass fluids to or from the urinary tract, so it is appropriate to have a legally marketed catheter serving as the primary predicate
- Differs from a port that now includes a temperature sensing function where the sensing cannot be integrated in a fashion that does not raise new questions of safety and efficacy.

Reference: See “The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]: Guidance for Industry and Food and Drug Administration Staff” at page 13.

There are different 510(k) types

Traditional (90 Days)	• Most common • Review all relevant performance data
Abbreviated (90 Days)	• Rely on conformance to guidance documents, special controls, and/or recognized standards
Expanded Abbreviated (90 Days)	• a.k.a. Safety & Performance Based Pathway • Rely on objective performance criteria
Special (30 Days)	• Limited to certain changes • Rely on **Summary**-level data focusing on the **modification** via design controls
Third Party (30 Days)	• Can be Traditional, Abbreviated, or Special **for eligible devices** • Review completed by **accredited 3rd party**, FDA performs supervisory review • AI/ML devices not eligible for this pathway

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Other Pathways

Other Submission Types

PMA

- Premarket Approval
- High Risk Products
- 180-day FDA review clock for Original PMA
- FDA typically receives 50-60 PMAs and 180-day PMA supplements each year

De Novo

- Process to be classified as Class II with Special controls
- 150-day FDA review clock
- Establishes 510(k)pathway once granted
- Receive 50 – 70 requests each year

Popular PMA Submission Types

Original PMA (180 Days)	• Review of performance & clinical study data to support safety and effectiveness.
PMA Supplement (180 Days)	• For significant changes in components, design, etc. including a new indication for use of the device.
Real Time Sup. (90 Days)	• For minor changes to the design of the device, software, sterilization, etc. • Must request FDA permission for this pathway.
30-Day Notice (30 Days)	• For modifications to manufacturing procedures or methods that affect the safety and effectiveness of the device.
Special (30 Days)	• For changes that enhance safety of the device, can include labeling and manufacturing changes. • Like an annual report, but submitted at the time of change.
Annual Report (30 Days)	• Typically, a year end review of adverse events, publications and other minor modifications that do not impact safety and effectiveness. • FDA may allow certain other changes to be reported in an annual report.

De Novos–What Does FDA want to see?

- Draft special controls that address and mitigate identified risks through performance testing, labeling, etc.
  - Discuss how each special control was addressed by the information provided in the submission.
  - This is YOUR opportunity to set the bar high for those that follow
- Benefit risk analysis
  - Show how the benefits of the subject device outweigh the risks
  - Detail how the risks have been further minimized with the proposed special controls
- Ultimately the FDA finalizes the special controls for publication into the CFR.

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What Should Be Considered?

Tool Claims & Quantitative Analysis

Automating the measurement of discrete physical quantities either directly or indirectly

- In almost all cases this is not a new task, unless this is an entirely new quantity we are measuring
- There should be a complimentary predicate device for which we can provide a head-to-head comparison of accuracy and precision (possibly our own device?)
- Like with non-AI applications, quantitative analysis IFUs need to remain in the tool claim arena
  - Ex. Automatically calculates LV ejection fraction vs Detects Heart Disease/regurgitation defects
  - Clinical claims will require more extensive clinical data/studies
- If this is the first time the measurement has been automated, then an exact predicate may not exist
  - Do not panic and do not jump to a De Novo
  - Need to establish ground truth
  - Need to clearly define the workflow for the tool and how it complements and fits into the current standard of care

Case Study: Ejection Fraction

- The subject device, an Ultrasound Image analysis AI software device, uses deep learning techniques to automatically evaluate Doppler ultrasound videos of the heart to calculate left ventricular (LV) ejection fraction (EF).
- The predicate device uses simple contrast thresholding techniques for edge detection of the left ventricle to calculate EF.
- Major difference between the subject and predicate:
  - The predicate provides an outline of the volume used to calculate LV EF
  - Subject device only provides the images used and the numerical value.
- Estimated calculation error was decreased from 20% to 5%.
- Was this eligible for a 510(k)?
- See 001 K173780_Response to FDAs 02082018 RAI_05182018222.pdf

Clinical Claims - Detection and Diagnosis

Automating subjective tasks or clinical decision making that will impact patient management and treatment.

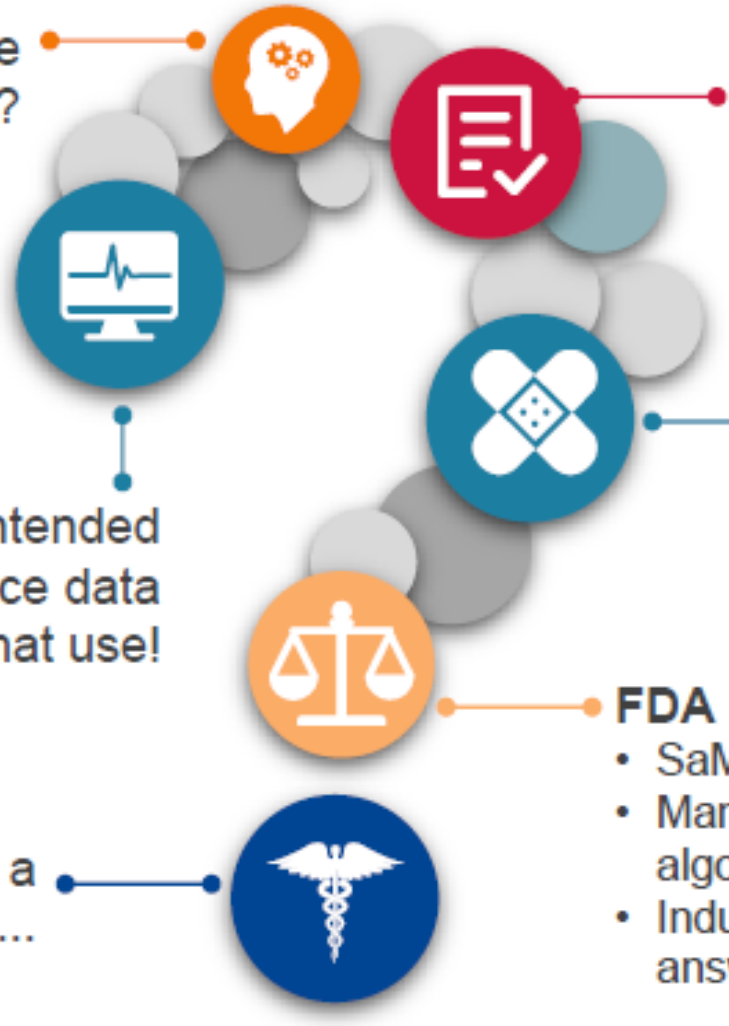
- Historically the first AI/ML applications were repurposing military technology to the health sector for medical image analysis computer aided detection/diagnosis/Triage (CADe/CADx/CADt)
- Most CADe software was approved via PMA
  - Burdensome and longer timelines
  - Almost always required a full Multi-Reader Multi-Case study
- Now the focus has shifted to prioritize performance testing vs regulatory pathway, meaning PMA may not be needed
  - When standalone testing might be sufficient
  - Utilization of real world data and registries
  - Streamlined clinical studies
- Challenge will remain in focusing the scope of the intended use for the device to minimize the amount of testing needed
  - It is easier to expand the IFU after an initial clearance with standalone performance data rather than performing a multi-factorial clinical study.

Does AI/ML = De Novo or PMA?

Is regulatory pathway the right question to start with?

We should start with intended use and what performance data is needed to support that use!

AI/ML may not even be a regulated medical device...



If your IFU and performance plan are done correctly, regulatory pathway should be an administrative question.

Avoid:

- Large/broad Application scope
- Clinical Study design mismatch with IFU/workflow
- RWE that does not have pre-specified endpoints.

FDA Challenges:

- SaMD have a low bar to entry
- Many areas to apply very adaptable AI/ML algorithms
- Industry expects FDA to have all the answers…

AL/ML Devices: Current State, Recent Clearances and Datasets

- Only locked algorithms cleared/approved to date
- FDA clears specific indications, not platform technology
- Many AI/ML devices granted marketing authorization via de novo request pathway due to technological differences
- Clinical data support most marketing submissions
- Many AI/ML devices granted Breakthrough Designation in the past
- CDRH published an Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Device List
  - FDA plans to update this list on a periodic basis

AI/ML Supporting Data

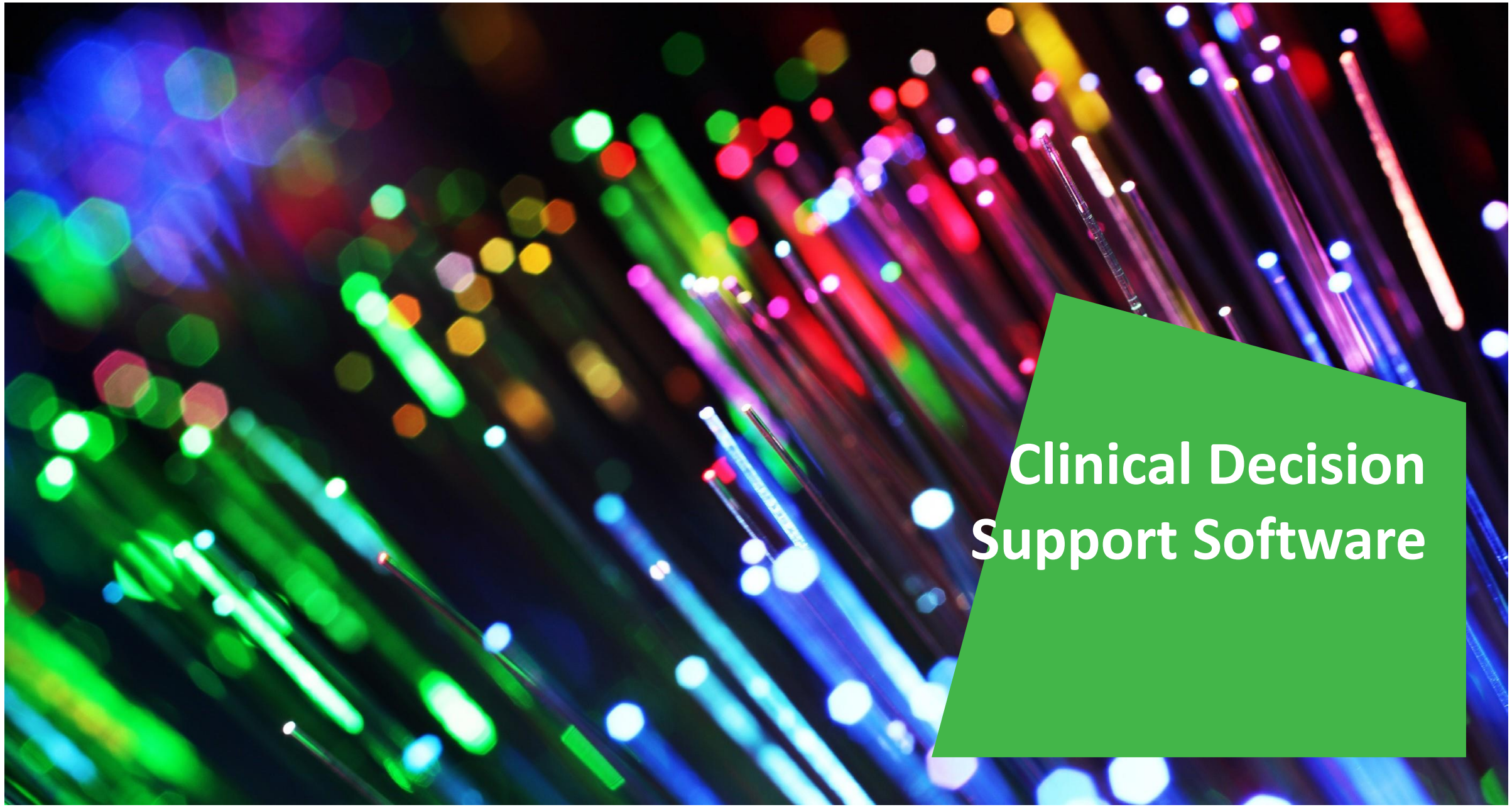
- Ground truthing process to be established
- Separate training and validation datasets
  - By location and/or time
- Training data details needs to be provided to FDA
- Needs to be geographically diverse in US with 3 sites typically required
- Retrospective datasets can be used for certain indications
- Subgroups assessed and need to be powered for certain analyses
- Performance needs to be evaluated at the lower bound of the CI interval

Predetermined Change Control Plans (PCCPs)

- FDA Guidance Document issued
  - Early engagement encouraged
  - Limited changes made via PCCP
    - Review division will determine whether scope of modifications is appropriate for inclusion in a PCCP
  - Includes Description of Modifications, a Modification Protocol, and an Impact Assessment
    - **Modifications**
    - **Modification Protocol**
    - **Impact Assessment**
  - Superiority standard (versus substantial equivalence) to be determined – "improvement" is key

Predetermined Change Control Plans (PCCPs)

- Examples of cleared PCCPS:
  - Caption Health's Caption Interpretation Automated Ejection Fraction Software (DEN220063)
    - **Radiological machine learning-based quantitative imaging software with predetermined change control plan**. A radiological machine learning based quantitative imaging software with predetermined change control plan is a software-only device which employs machine learning algorithms on radiological images to provide quantitative imaging outputs. The device includes functions to support outputs such as view selection, segmentation and landmarking. The design specifications include planned modifications that may be made to the device consistent with an established predetermined change control plan.
    - Special Controls
  - Caption Health 's Caption Guidance (DEN190040; K201992)
  - Medtronic's LINQ II Insertable Cardiac Monitor, Zelda AI ECG Classification System (K210484)
    - "In accordance with the PCCP, market release of any modifications will only occur after the modified algorithms are proven to achieve **superior performance**, increasing sensitivity and/or specificity, while maintaining or improving other performance metrics."


Clinical Decision
Support Software

What is CDS Software?

- Any software function that is intended to support clinical decision-making, such as:
  - Computerized alerts and reminders for HCPs and patients
  - Clinical guidelines
  - Condition-specific order sets
  - Focused patient data reports and summaries
  - Diagnostic support
  - Contextually relevant reference information
- CDS ranges from simple automations of routine clinical calculations to complex, proprietary, machine-learning based algorithms
- With more and more of these products being released, FDA determined a need to clarify which ones are and are not regulated

CDS Exclusion under 21st Century Cures Act

- To fall outside the definition of a medical device, CDS software must meet four criteria:
  - *(1)* *Not* acquire, process, or analyze a medical image, a signal from an IVD, or a pattern or signal from a signal acquisition system
  - *(2)* *Display, analyze, or print medical information* about a patient or other medical information
  - *(3)* *Support or provide recommendations* to a HCP about prevention, diagnosis, or treatment of a disease/condition
  - *(4)* *Enable HCP to independently review the basis* for the software's recommendations so they need not rely primarily on these to make a clinical decision for an individual patient

- To be non-device CDS, the software must be used by an HCP (not a patient/caregiver).

Long-Awaited Final CDS Guidance

- The final CDS guidance (September 2022) added clarity while also seeming to bring additional software functions under FDA's regulatory purview
- *Criterion 4* on independent reviewability of the recommendations remains important.
- *Criterion 3:* Must provide condition-, disease-, and/or patient-specific recommendations to enhance, inform and/or influence a decision, while not intended to replace or direct the HCP's judgment
  - Software issuing an output used in time-critical decision-making FAILS
  - Software issuing a specific preventive, diagnostic, or treatment output/directive FAILS

CDS Guidance *(cont'd)*

- FDA considers such software to exceed "supporting or providing recommendations" because of automation bias
  - If only one option provided, insufficient opportunity for HCPs to input their own judgment into the decision-making
  - If situation requires urgent action, insufficient time for HCPs to adequately consider other information

CDS Functions that May Warrant Enforcement Discretion

- FDA will continue to take a risk-based approach in deciding what clinical decision support software to actively regulate
- Enforcement discretion may apply for software that provides singular outputs to guide patient-specific decision-making, but *in accordance with cited, established clinical guidelines*
  - Must be transparent (basis for recommendation is disclosed to HCP)
- *Example:* Software that performs simple calculations routinely used in clinical practice
  - e.g., BMI, APGAR score, NIH Stroke Scale, delivery date estimator
- In a conversation with the Digital Health Center, FDA stressed that the updated CDS guidance is not meant to erase existing enforcement discretion policies under other guidance documents
  - Just meant to track the Cures Act provisions more closely to limit the ability for companies who should be regulated to take advantage of loopholes
- *Recommendation:* Evaluate CDS products that do not qualify as "non-device CDS" under FDA's *Policy for Device Software Functions and Mobile Medical Applications* for potential enforcement discretion

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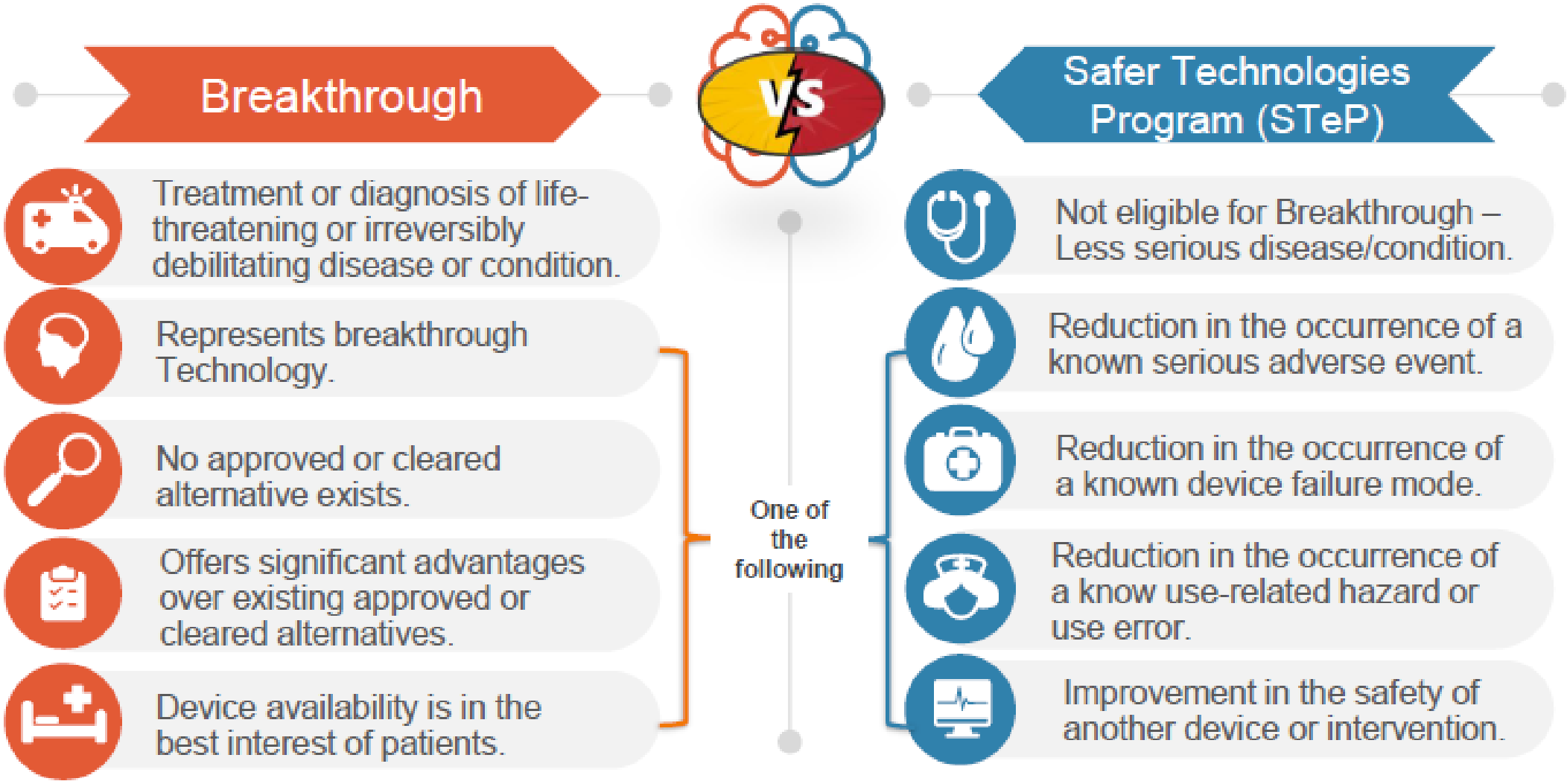
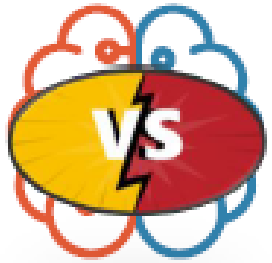
Breakthrough Designation

Breakthrough vs STeP



Breakthrough vs STeP



Breakthrough

- Mandated by statute.
- 60-day review clock.
- Must result in performance improvement.
- Access to sprint discussions as resources permit.
- Potential implications for CMS coverage and coverage.

Safer Technologies Program (STeP)

- Entirely voluntary for both FDA and Industry.
- Aspirational 60-day review clock.
- Focused on safety improvements, performance optional/not required.
- Access to sprint discussions as resources permit.
- Currently no additional coverage or payment advantages.

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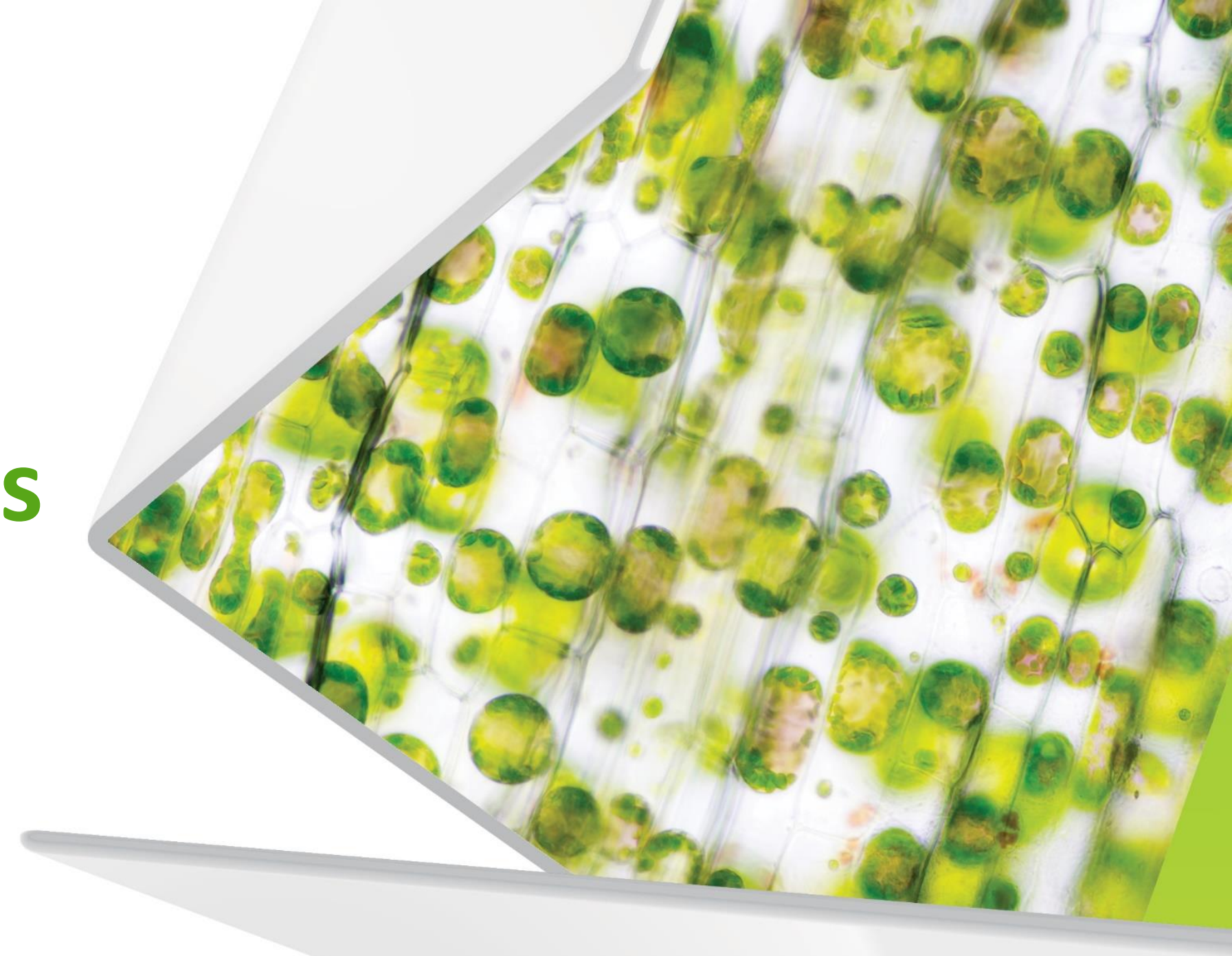
Questions



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