

Pediatric Devices for Rare Diseases

Clinical Trials Issues Panel

Trial Design Considerations

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FDA CDRH – Dual Mandate

→ Protecting the Public Health

Safe and Effective Medical Devices

→ Promoting the Public Health

Facilitating Device Innovation

Current State of Medical Device Therapy for Pediatric/Orphan Diseases

- Few are supported by randomized clinical trials
- “Off-label” use supported by:
 - Expert opinion
 - Single institution observational studies
 - Extrapolations from adult cardiovascular medicine
 - Evolutionary – historical literature based comparisons
- Desire for innovative less-invasive treatments are
 - Driving a need for more targeted therapies which require disease/lesion specific devices and more vigorous comparisons
 - Demanding assessment of hybrid approaches

Randomized Clinical Trials: Barrier to Orphan Device Development

Device Company Perspective

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- High Costs often Prohibitive

- R & D – growth, long term durability
- Trial
- FDA - PMA
- Marketing

- Small end market limits return

Medical Device Approval Risk-Based Paradigm

Medical Device Classes:



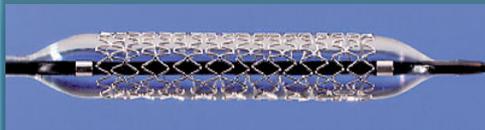
Class I

General Controls
Most exempt from
premarket submission



Class II

Special Controls
Substantial Equivalence
Premarket Notification
[510(k)]



Class III

Significant risk
devices

Safety and Effectiveness

Pre-Market Application [PMA]

Additional Classifications:



De Novo

Device "types" that have
never been marketed in
the U.S., but whose
safety profile and
technology are now
reasonably well
understood



Humanitarian Use Device (HUD)

Significant risk devices

Orphan diseases (< 4,000
US patients per year)

Safety and Probable Benefit

Humanitarian Device Exemption [HDE]

Alternative Device Regulation Process for Pediatric/Orphan Diseases

Humanitarian Use Device (HUD) Designation:

- Purpose: To encourage the discovery and use of devices intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the United States. Office of Orphan Products Development (OOPD)
- Disease manifested in < 4000 patients per year in US
 - Includes medically plausible subsets for either the population or condition
- Device is used to diagnose or treat < 4,000 patients per year in the United States

What is an HDE Application?

An HDE application is a PMA application that is not required to contain clinical data demonstrating "effectiveness"

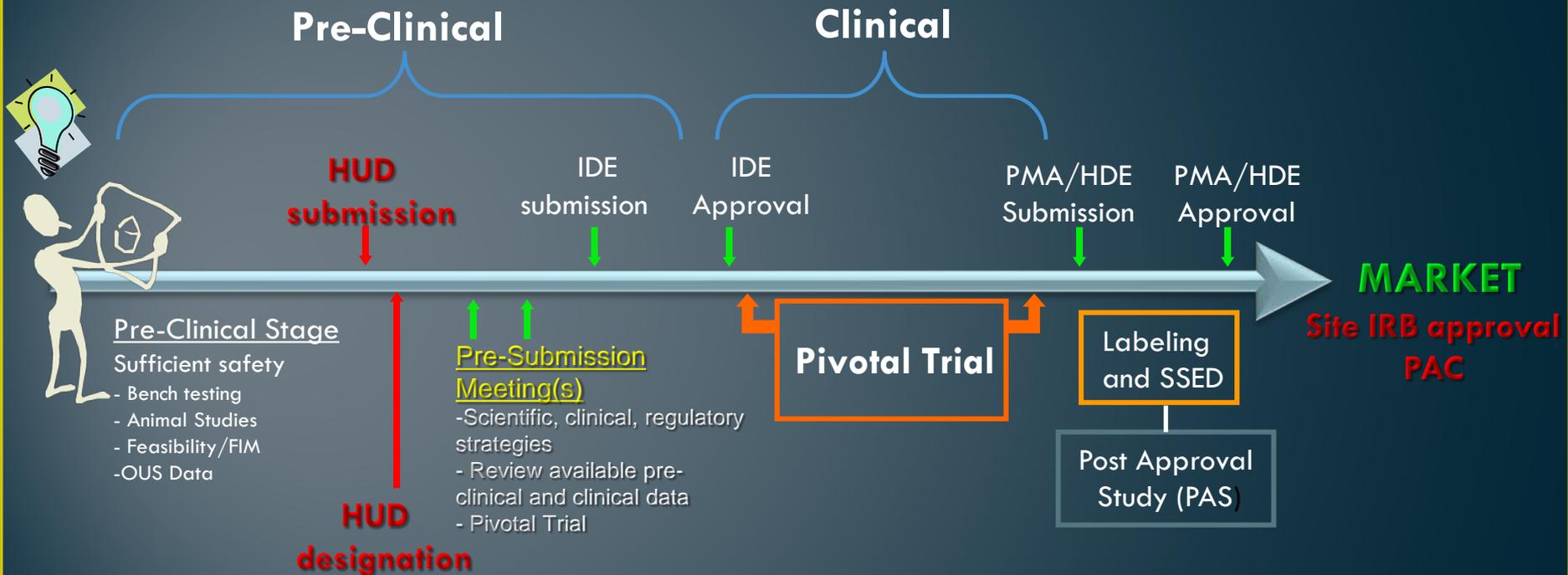
HDE Application

- Similar in form and content to PMA Application
- Significant risk devices – require an IDE for US clinical study
- Must contain information allowing FDA to conclude:
 - Device would not be otherwise available
 - No comparable device available for Rx
 - Justification for why a PMA application is not feasible/ cost prohibitive

Other post-approval provisions:

- PAC – 12-18 month intervals
- Can be sold to recoup all costs (Profit allowed for Pediatrics)
- Administered at sites with Local IRB - approval needed for device use

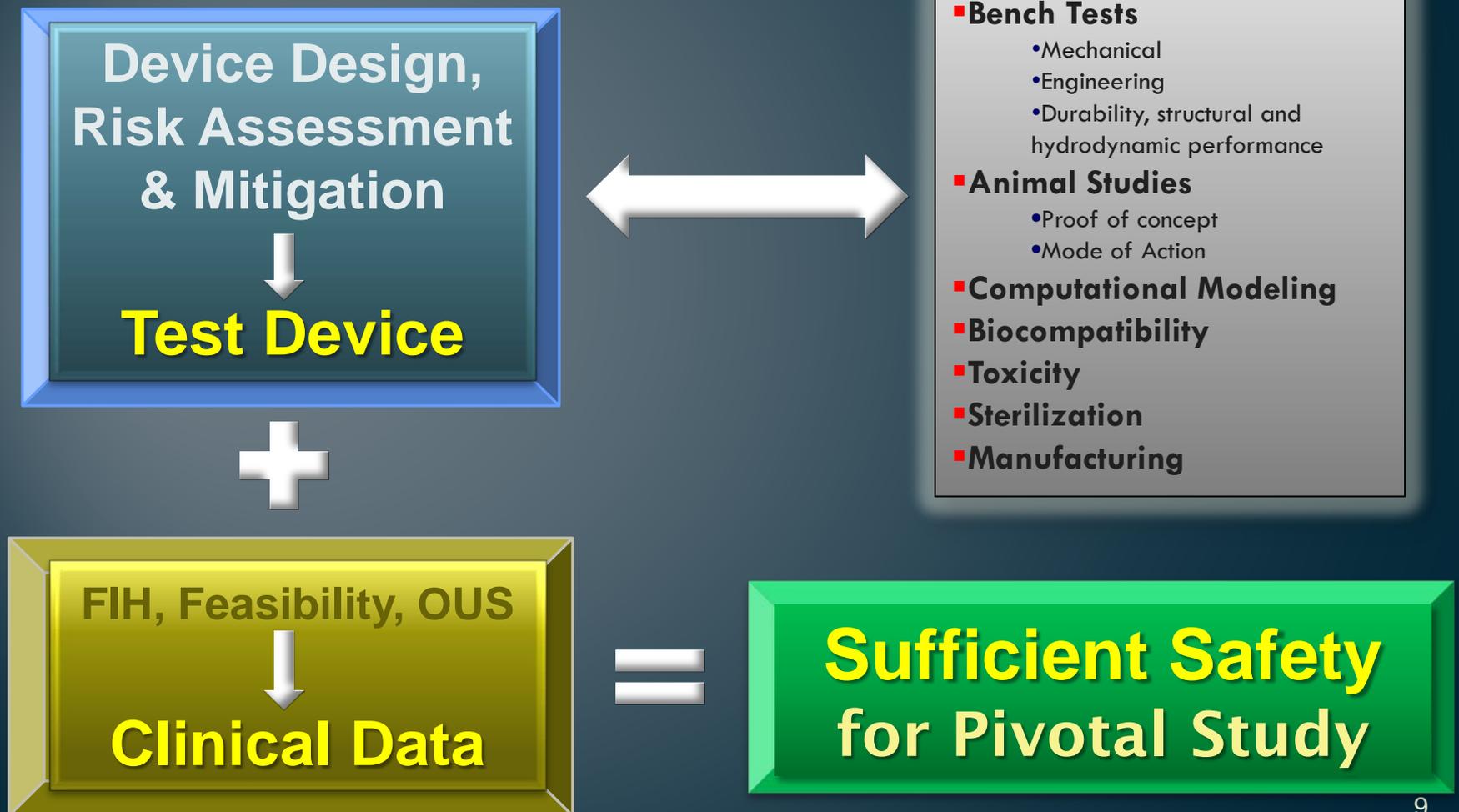
Significant Risk Device: PMA/HDE Approval Process



Approval Thresholds: Valid Scientific Evidence of Safety and Effectiveness (PMA) or Probable Benefit (HDE)

Device Design and Safety

Pre-Clinical Assessment and Feasibility Trials



The Pivotal Clinical Trial

Acquisition of Valid Scientific Evidence

DESIGN

Population/Subsets
Intended Use
Conditions of use
Controls/Randomization
Key Outcomes, AEs
Objective Endpoints

Protocol Driven
Inclusion/Exclusion
Informed Consent
Site Selection &
Monitoring
Data Integrity
Core Labs
DSMB & CEC

Pre-specified SAP
- Hypotheses
- Methodology
Defined Analysis
Population
Minimize Bias &
Missing Data

CONDUCT

ANALYSIS

Purpose and Goals:

- Provide unbiased **data**
- Generate **interpretable results**
- Allow **adequate clinical assessment** of a Device for its proposed intended use and conditions of use

Goals of The Pivotal IDE Trial: Adequate Clinical Assessment

Class III Medical Devices

PMA - Reasonable assurance that the device is
safe and effective
for the proposed intended use

Significant Risk Humanitarian Use Devices

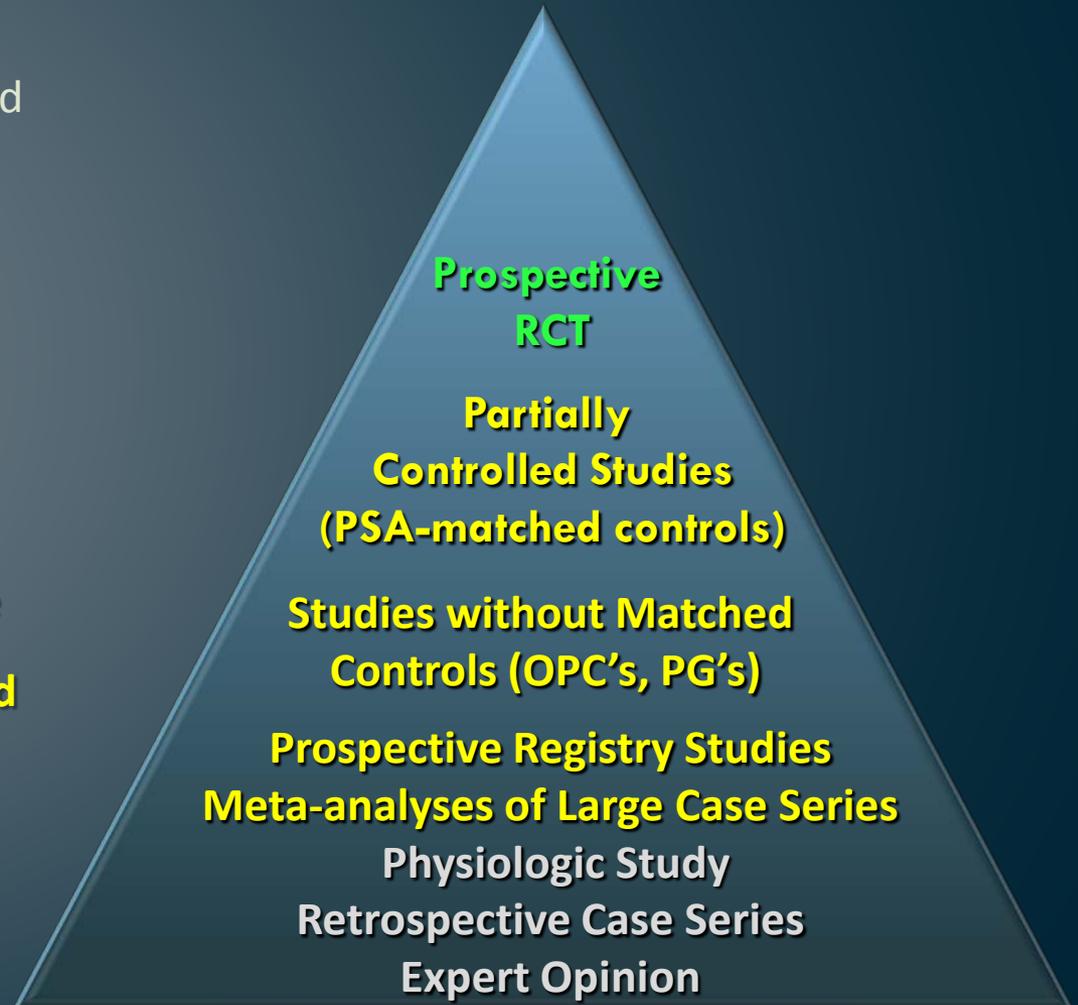
HDE - Reasonable assurance that the device is
safe and provides probable benefit
for the proposed intended use

What is Valid Scientific Evidence

“Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. **The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use.**”

CFR 860.7(c)2

Evidence Hierarchy



What is Safety

“There is reasonable assurance that a device is safe when it can be determined based on valid scientific evidence that **the probable benefits** to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, **outweigh the probable risks.**”

Safety: Benefits Outweigh the Risks

Benefits

Clinically Meaningful

- Type, Magnitude & Probability
- Reproducible & generalizable
- Durable over relevant duration

Patient Factors

- Tolerance to Disease/Symptoms
- Disease severity/Chronicity

Available Rx options

Risks

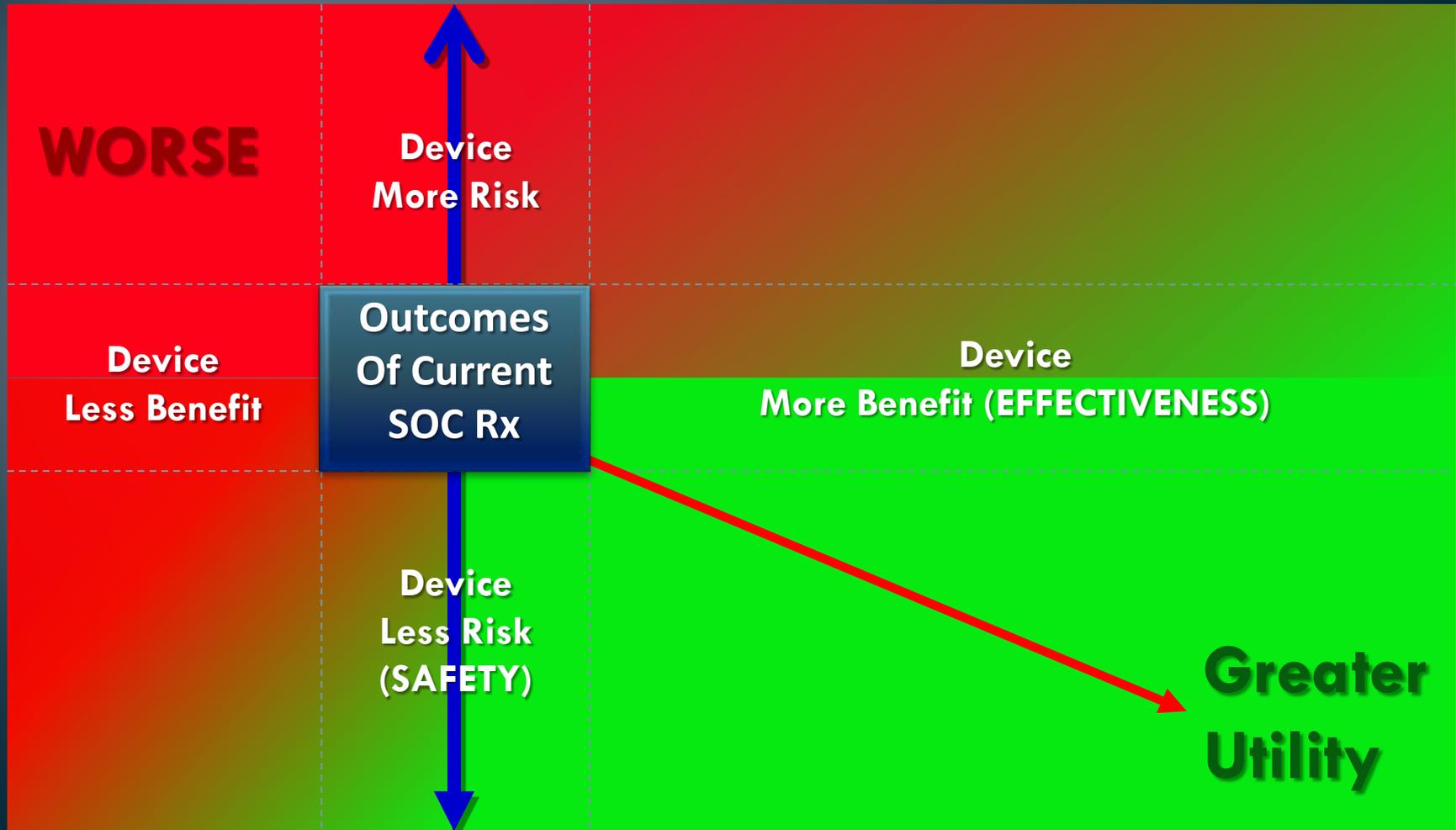
Harmful events

- Type
- Number & Severity
- Probability
- Duration
- Mitigation

What is Probable Benefit

“...an explanation of why the **probable benefit to health from the use of the device outweighs the risk of injury or illness** from its use, taking into account the **probable risks and benefits of currently available devices or alternative forms of treatment**. Such explanation shall include a description, explanation, or theory of the underlying disease process or condition, and **known or postulated mechanism(s) of action of the device in relation to the disease process or condition**”

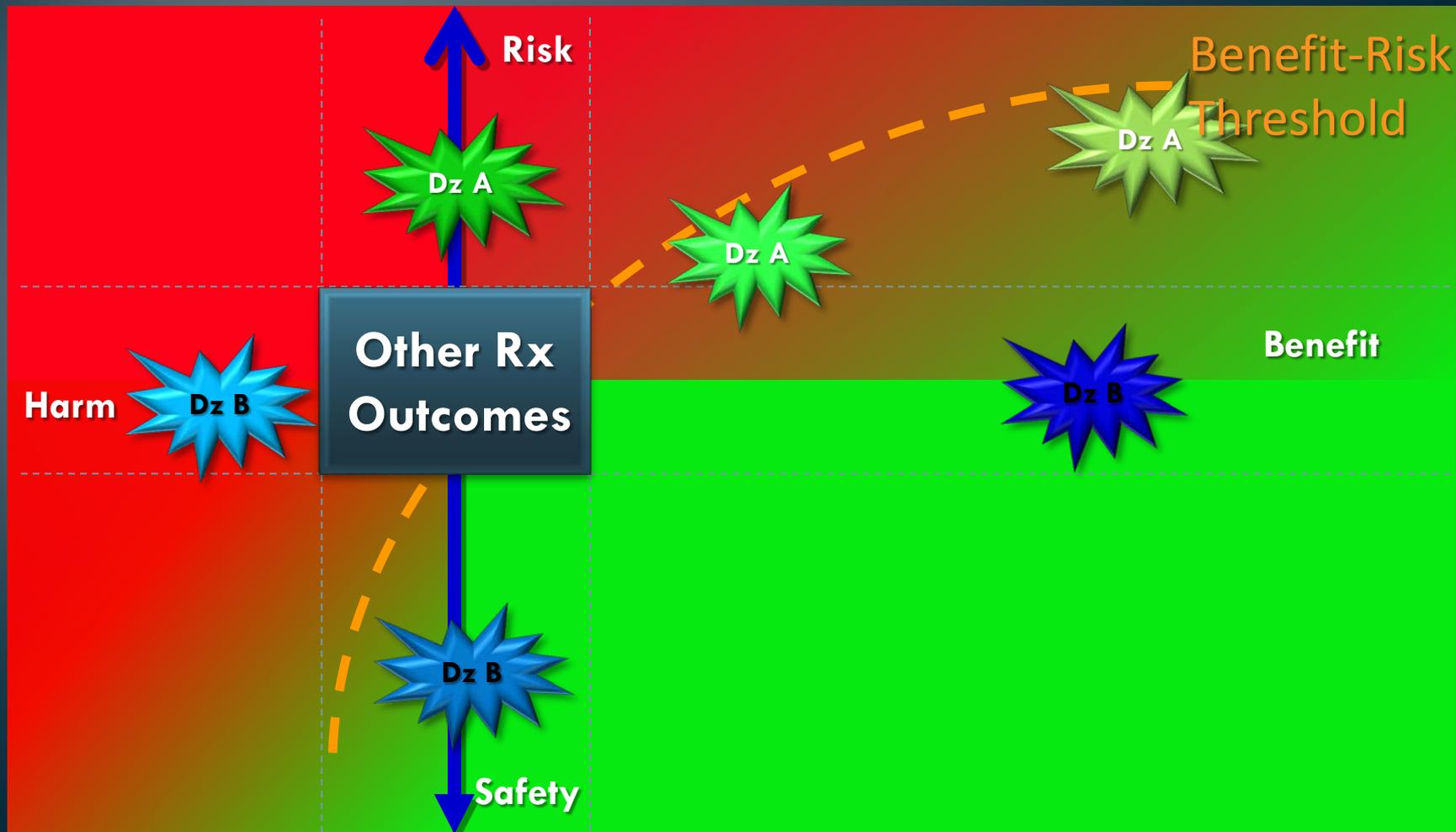
Overall Benefit –Risk Analysis



Benefit Risk Profile Considerations

Dz A – Severe disease , no other Rx options

Dz B – Severe disease , other proven Rx options available



Thank You!

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