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Leveraging Regulatory Controls for Product Development

Points to Cover

- ✓ Creating the right Culture
- ✓ Design Controls and V&Vs
- ✓ Pre-Clinical Testing
- ✓ Clinical Testing
- ✓ Conclusion

Creating the right culture

What to look for in hiring regulatory expertise?

GUNS CARRY
CHUCK NORRIS
FOR PROTECTION

Design Controls & V&Vs

The Product Development Lifecycle

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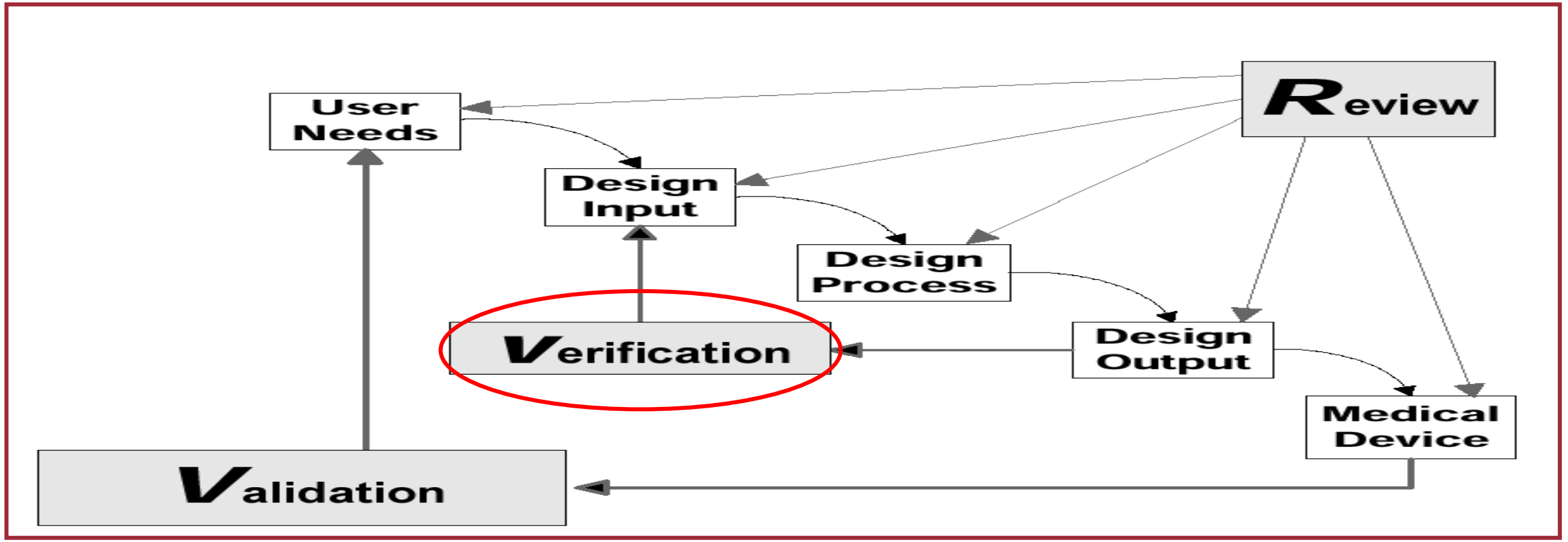
FDA Guidance: Design Verification & Validation (V&Vs)

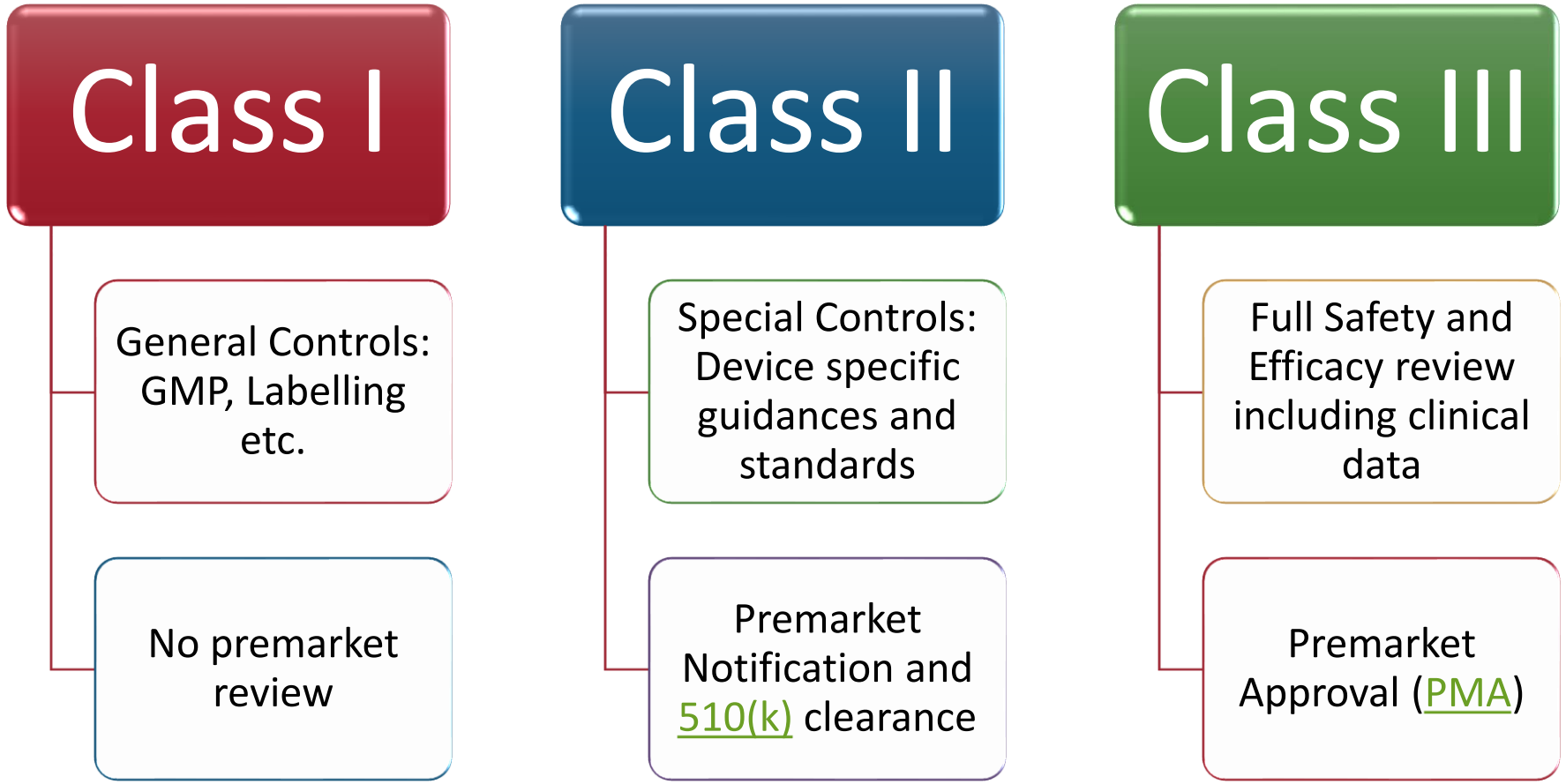


Guidance Doc on Design Controls: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070642.pdf
Presentation on Design Controls: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/UCM466494.pdf

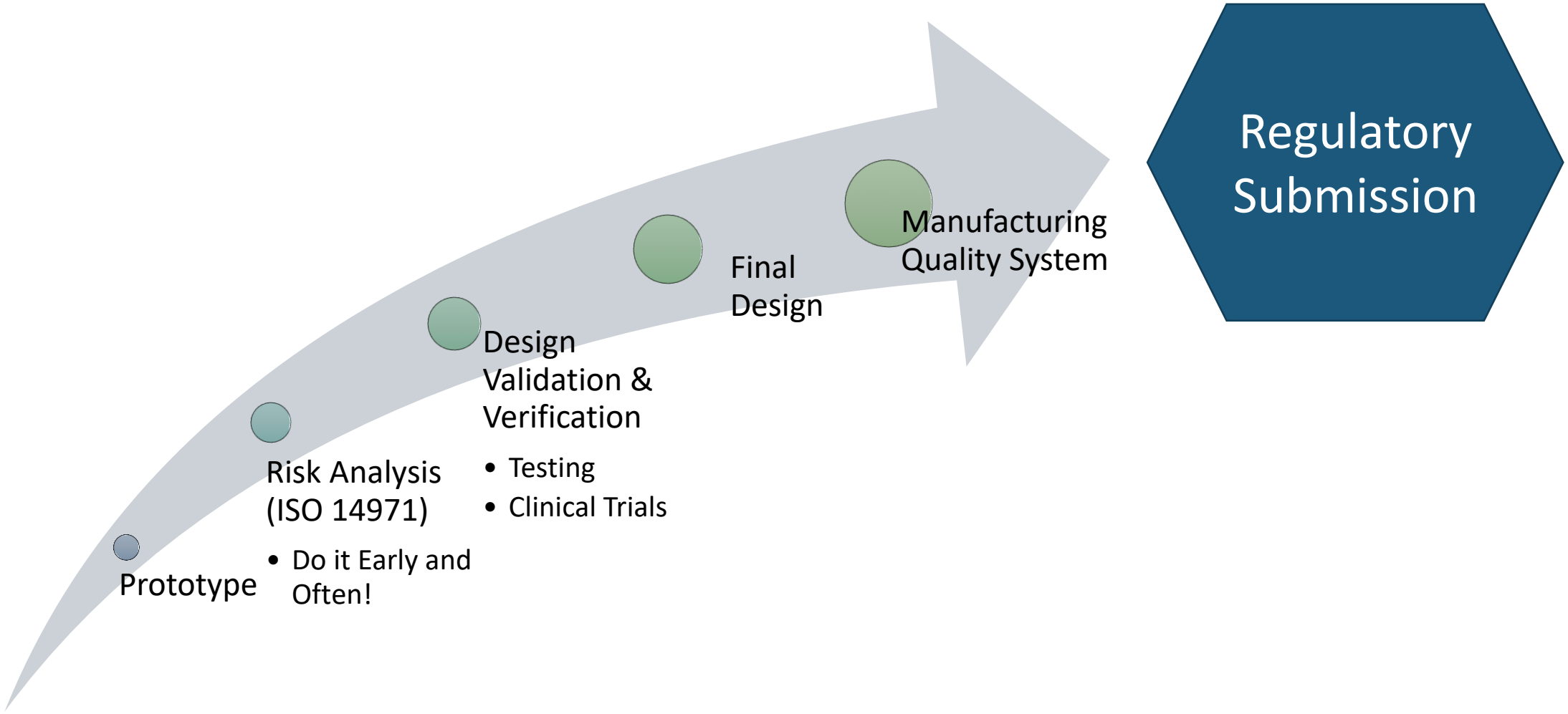
Design Controls

FDA 21CFR 820: ttps://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820

US Classification & Regulation



Device Development



Pre-Clinical Testing

Safety Evaluation Outline

Device Definition

- Intended use
- Indications for use
- Instructions for use
- Principles of operation
- Extent of use
- Device categorisation

Physical Characterisation

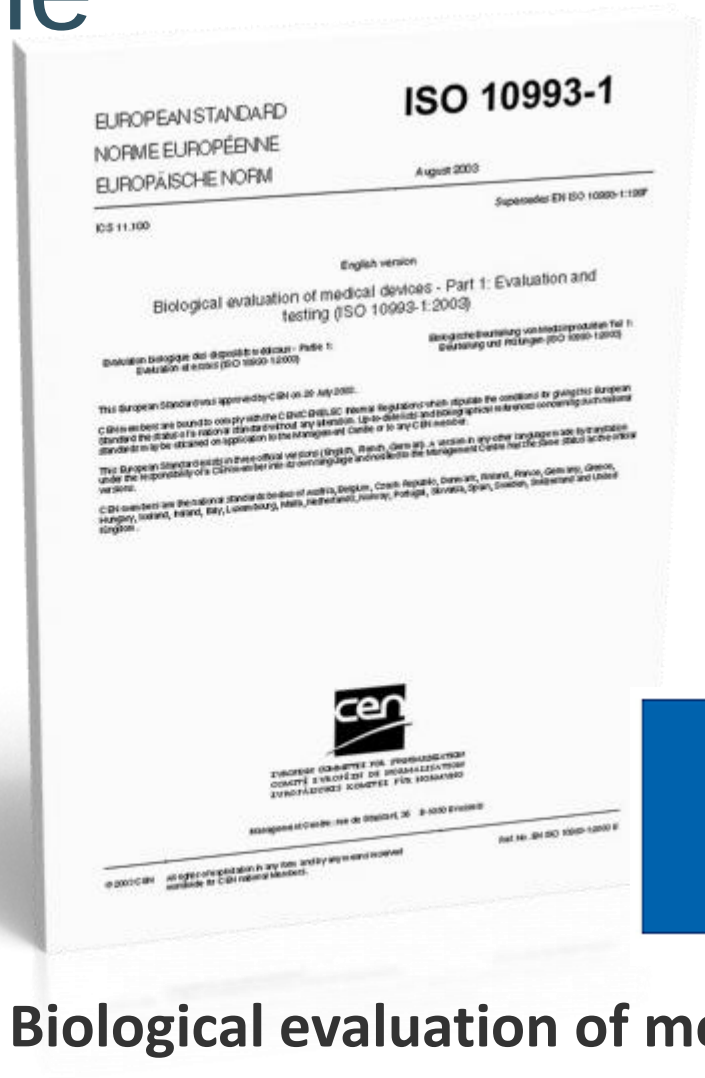
Chemical Characterisation

Toxicological Risk Assessment

Biological Data

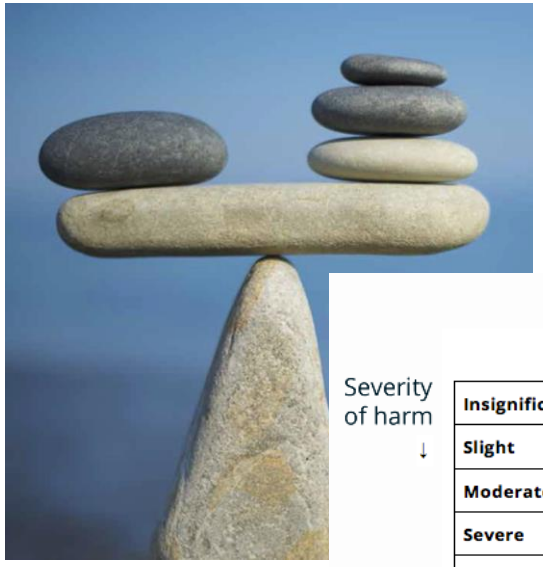
Interpretation of Biological Data

Overall Biological Risk Assessment & Evaluation



Biological evaluation of medical devices

Toxicological Risk Assessment



Likelihood →

Severity of harm ↓	Unlikely	Plausible	Likely	Very Likely
Insignificant	Trivial	Trivial	Low	Low
Slight	Trivial	Low	Low	Medium
Moderate	Low	Low	Medium	High
Severe	Medium	Medium	High	Very High
Very Severe	Medium	High	Very High	Very High

Chemical Characterisation
Toxicological Risk Assessment

Contract Research Organisation

Safety Evaluation

- ✓ Don’t just “test” for it
- ✓ Use all the existing data, to reduce testing

Risk Management

- ✓ Evaluation and Testing is done in a “risk management process.”
- ✓ Very specialised skill
- ✓ Ongoing, non-static

Clinical Evidence

What is Clinical Evidence?

The Literature Search

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Databases searched

e.g. PubMed, Google Scholar, emBase, Cochrane etc.

Search Terms

"Stent" AND "abdominal aortic aneurysm"

Search filters: Review articles, published in the last 10 years

Date of search

Inclusion Criteria

Application: abdominal aortic aneurysm stent

Study size: e.g. multiple patients, case reports.

Study population: human only or animal studies?

Follow-up period

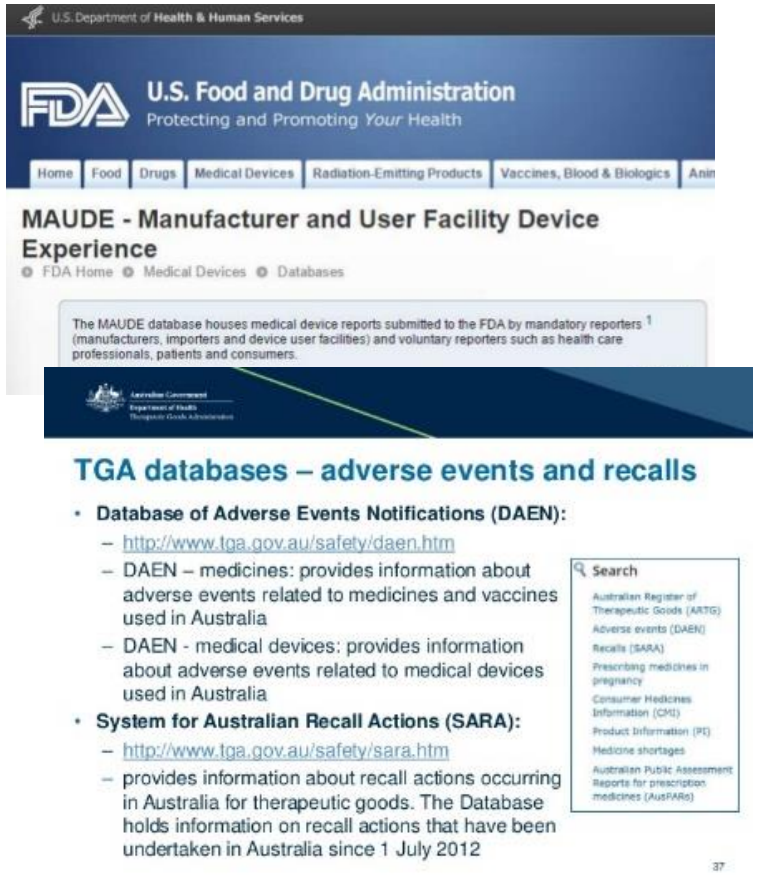
Exclusion Criteria

Stents for different intended purpose or extended claims, e.g. thoracic aortic aneurysm, cerebral aneurysm.

Applications contraindicated in the device IFU. ….

Post-Market Data

Adverse event databases



In-house complaints data

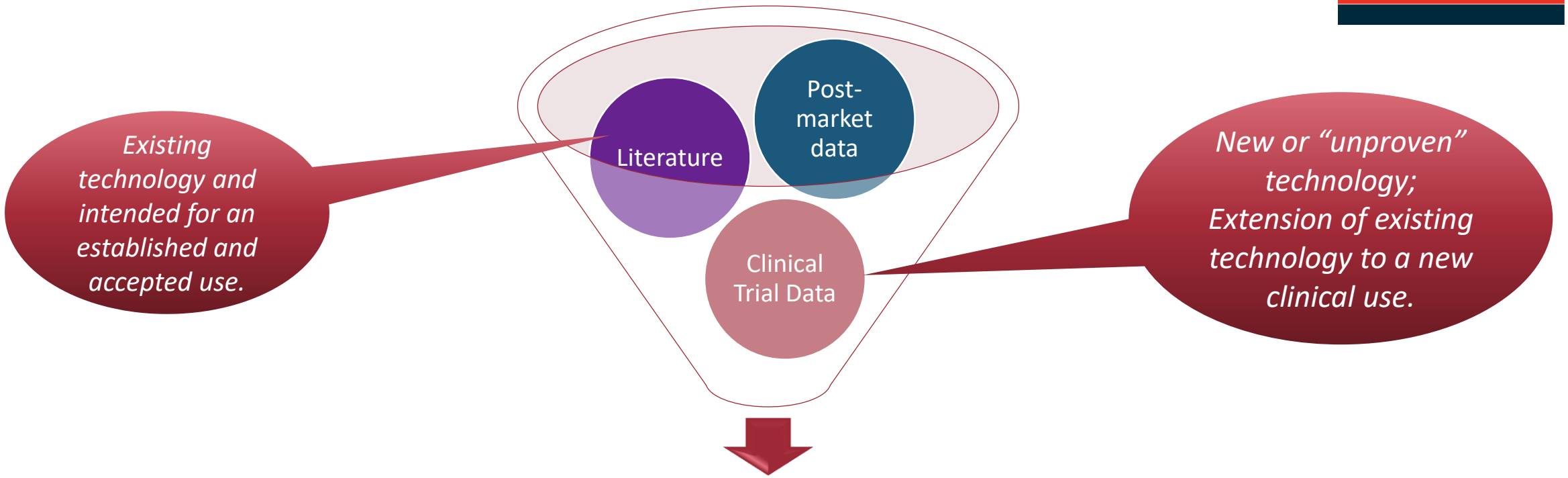
Reports of clinical experience

MAnufacturer and **U**ser Facility **D**evice **E**xperience Database - (MAUDE)

80,000 to 120,000 reports EACH YEAR

www.fda.gov/cdrh/maude

Objective Analysis of Data



Data on hazards and risks

- *E.g. infection, rupture, leak, thrombosis, etc.*
- *Some of this may be pre-clinical*

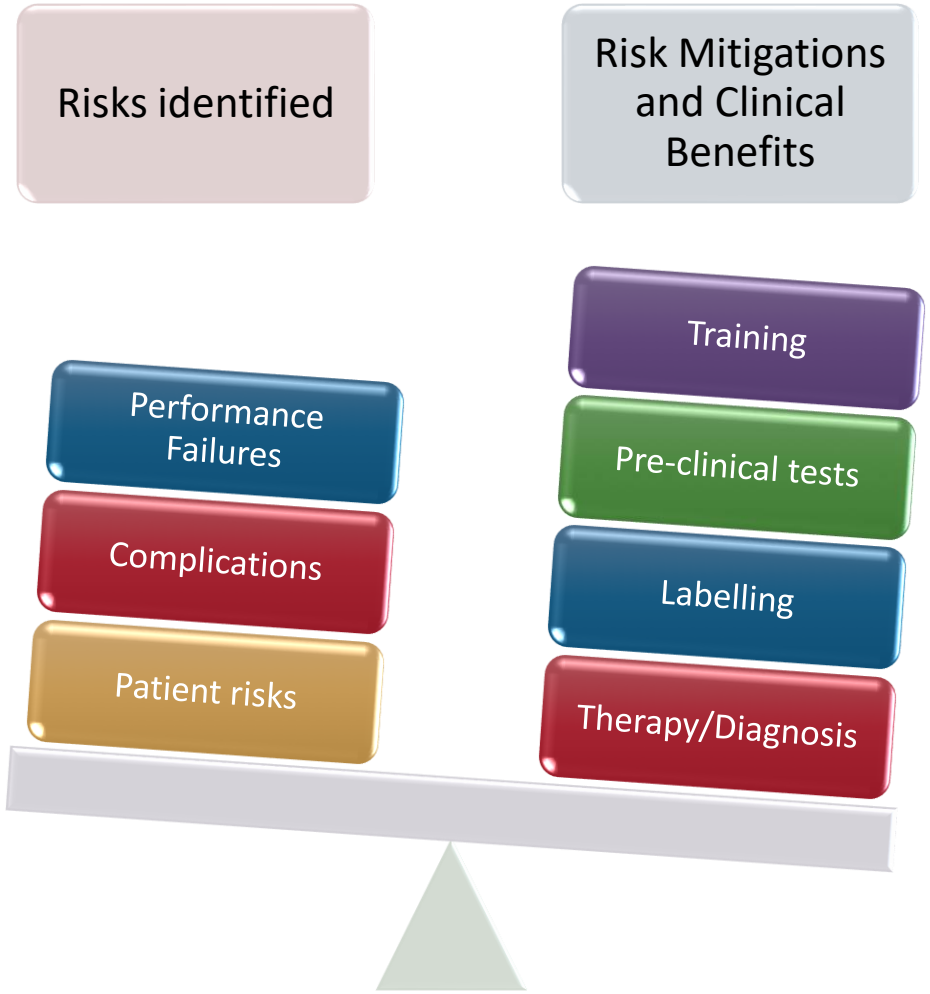
Data on performance in clinical use

- *E.g. clinical outcomes, stent deployment, removal of delivery system, etc.*

Favourable / unfavourable scientific data

- *Level of Evidence*
- *E.g. review of randomized controlled trial studies versus single case report.*

Balance and a favourable risk : benefit ratio

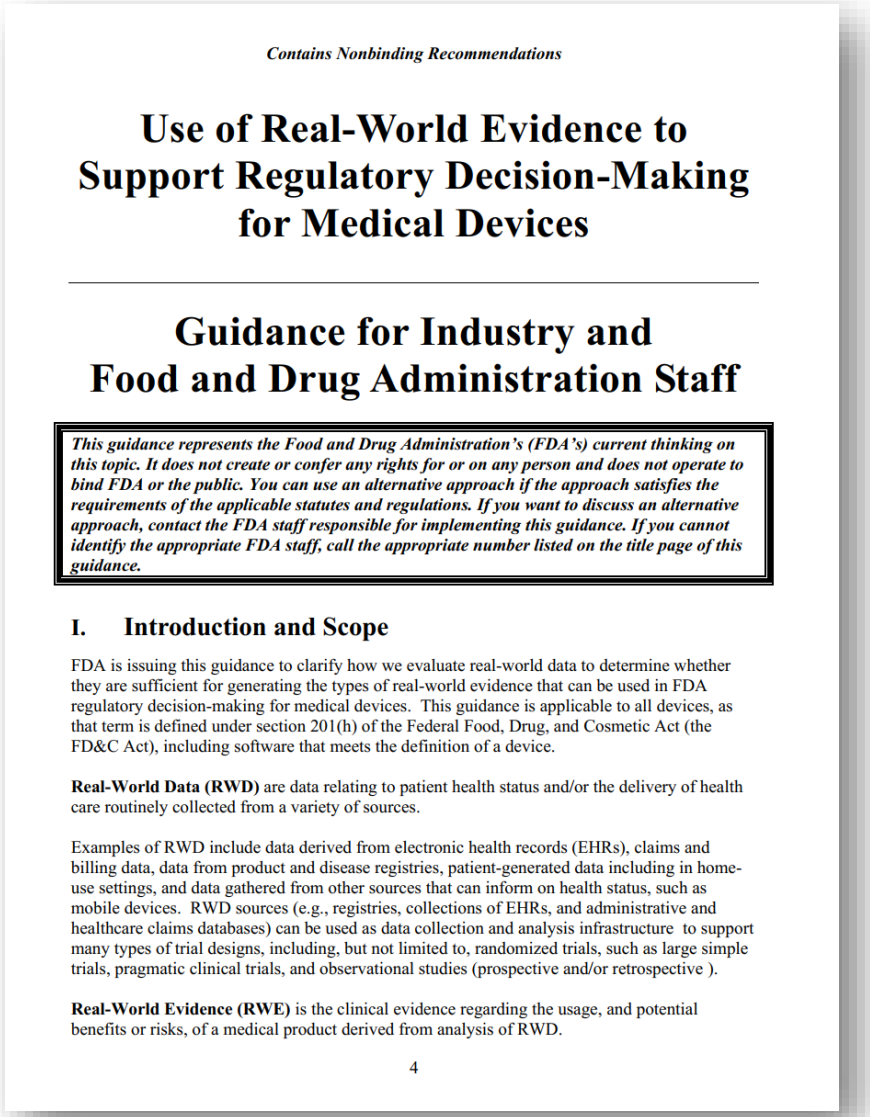


Who needs clinical a trial?

Submission Type	Requirement
Premarket approval (PMA)	Always requires direct clinical trial data (may be submitted in modules –with preclinical data under review pending completion of clinical trials)
Humanitarian device exemption	Possibly – but only to support safety
510(k)	Clinical data in ~15% of cases
De novo 510(k)	Almost always

So which 15%?

- New clinical indications not present in predicates
- Substantially new technology
- All de novo submissions
- If in doubt – preconsult
  - Pre-Submissions and Meetings with FDA Staff



Contains Nonbinding Recommendations

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction and Scope

FDA is issuing this guidance to clarify how we evaluate real-world data to determine whether they are sufficient for generating the types of real-world evidence that can be used in FDA regulatory decision-making for medical devices. This guidance is applicable to all devices, as that term is defined under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), including software that meets the definition of a device.

Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

Examples of RWD include data derived from electronic health records (EHRs), claims and billing data, data from product and disease registries, patient-generated data including in home-use settings, and data gathered from other sources that can inform on health status, such as mobile devices. RWD sources (e.g., registries, collections of EHRs, and administrative and healthcare claims databases) can be used as data collection and analysis infrastructure to support many types of trial designs, including, but not limited to, randomized trials, such as large simple trials, pragmatic clinical trials, and observational studies (prospective and/or retrospective).

Real-World Evidence (RWE) is the clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of RWD.

4

Alternatives to Clinical Trials?

Registries

Collections of electronic health records

Healthcare claims databases

…

Who Does the Clinical Evaluation? Individual or Team?

- **Qualifications**
  - *Degree + 5 years experience*

    OR
  - *10 years experience alone*

- **Knowledge**
  - the Device and its application **Specialist Clinical Expertise**
  - Research methods, (including statistics)
  - Regulatory Requirements
  - Medical Writing (including practices of systematic review)

MEDDEV 2.7.1/4 Section 6.4

Conclusion

Key Points

- Regulatory requirements are the result of a consensus of best practices
- The conservative check-the-box approach can hamper innovation
- Risk Based Management of the development process can create significant savings
- Maintain a global perspective

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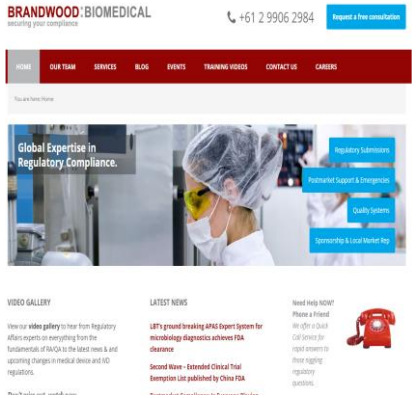

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