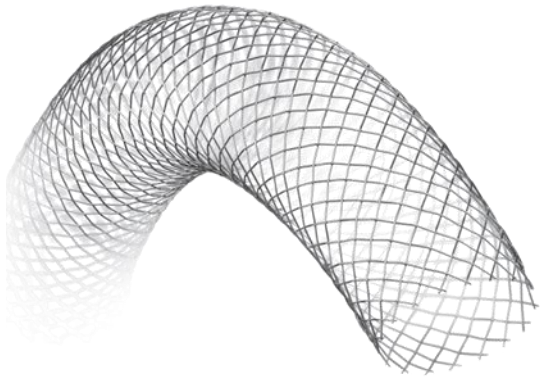


Utility of standards for a manufacturer

PERU Workshop on Medical Device Regulation and Standards: Policy and Technical Aspects

Brian Berg, Senior Research Fellow, Boston Scientific
brian.berg@bsci.com

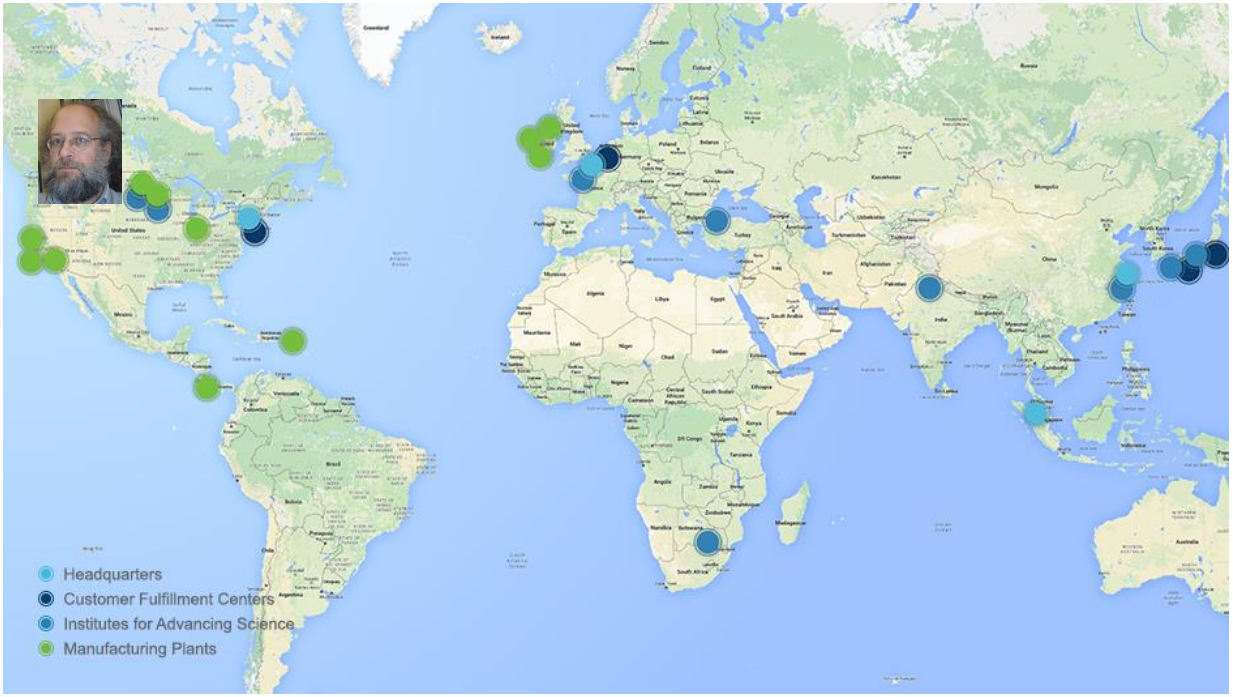
24 January, 2017

History of Boston Scientific

1979: Peripheral Angioplasty Balloons

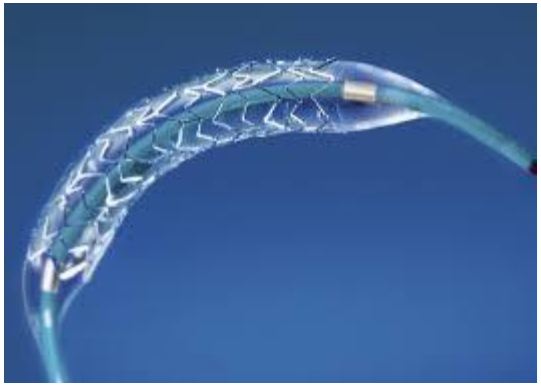
John Abele, 1979

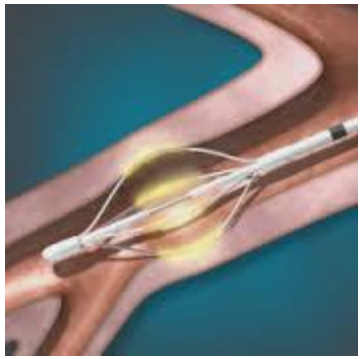
2017: ~13,000 products serving 22 million patients per year. A world-wide company of 23,000+ employees with annual sales of ~8 billion dollars.



http://www.bostonscientific.com/en-US/about-us/history

Boston Scientific Businesses





2015 OPERATIONAL SALES BY PRODUCT CATEGORY

(Dollars in millions)

		2015
CARDIOVASCULAR	Interventional Cardiology	$2,242
	Peripheral Interventions	975
RHYTHM MANAGEMENT	Cardiac Rhythm Management	1,934
	Electrophysiology	248
MEDSURG	Endoscopy	1,422
	Urology and Pelvic Health	735
	Neuromodulation	512
		$8,068

Standards used extensively in Product Development

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Strategy, Market Changes

Exploratory, **Acquisitions**

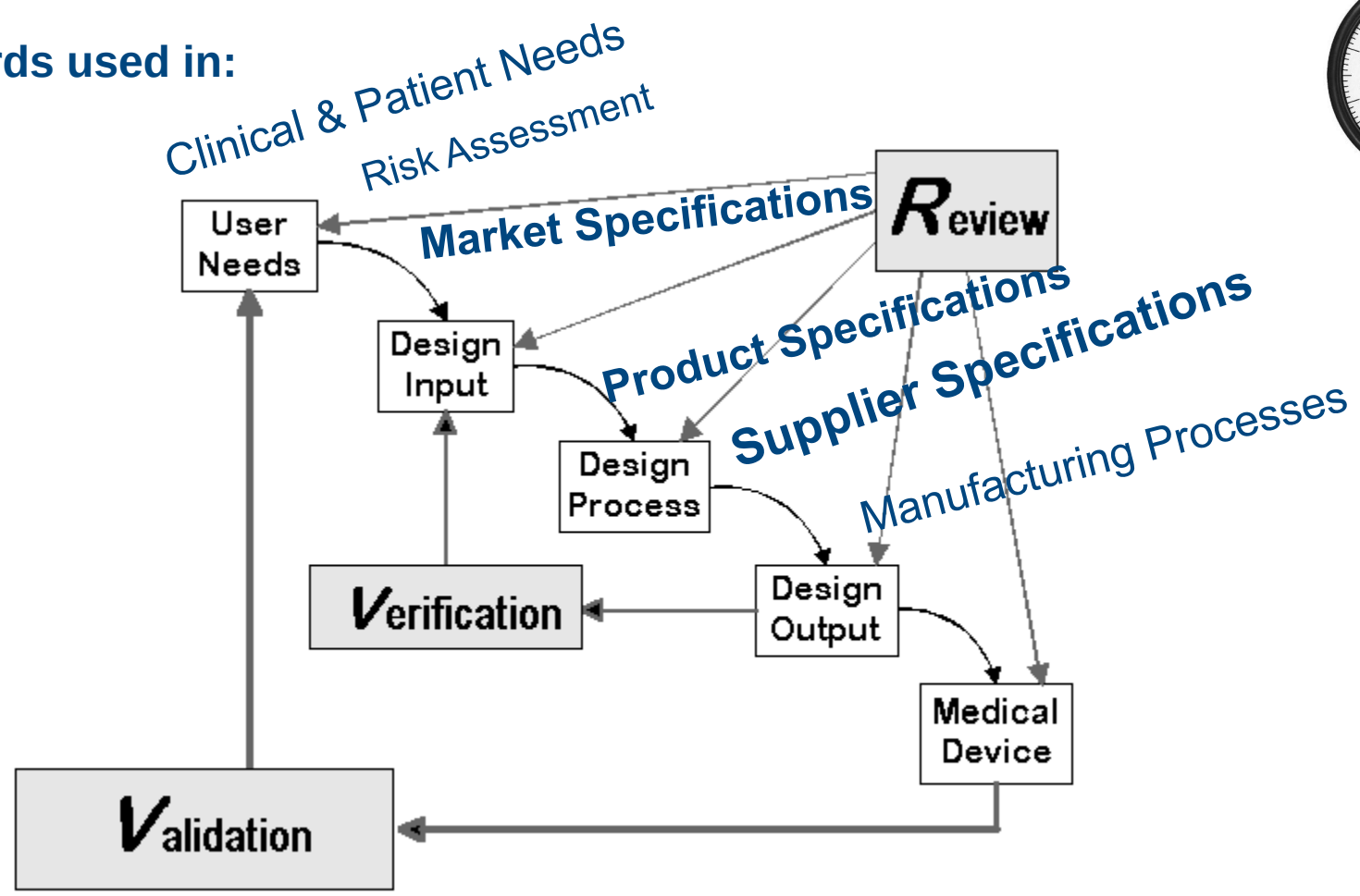
Product Development

Clinical

Manufacturing & Sustaining

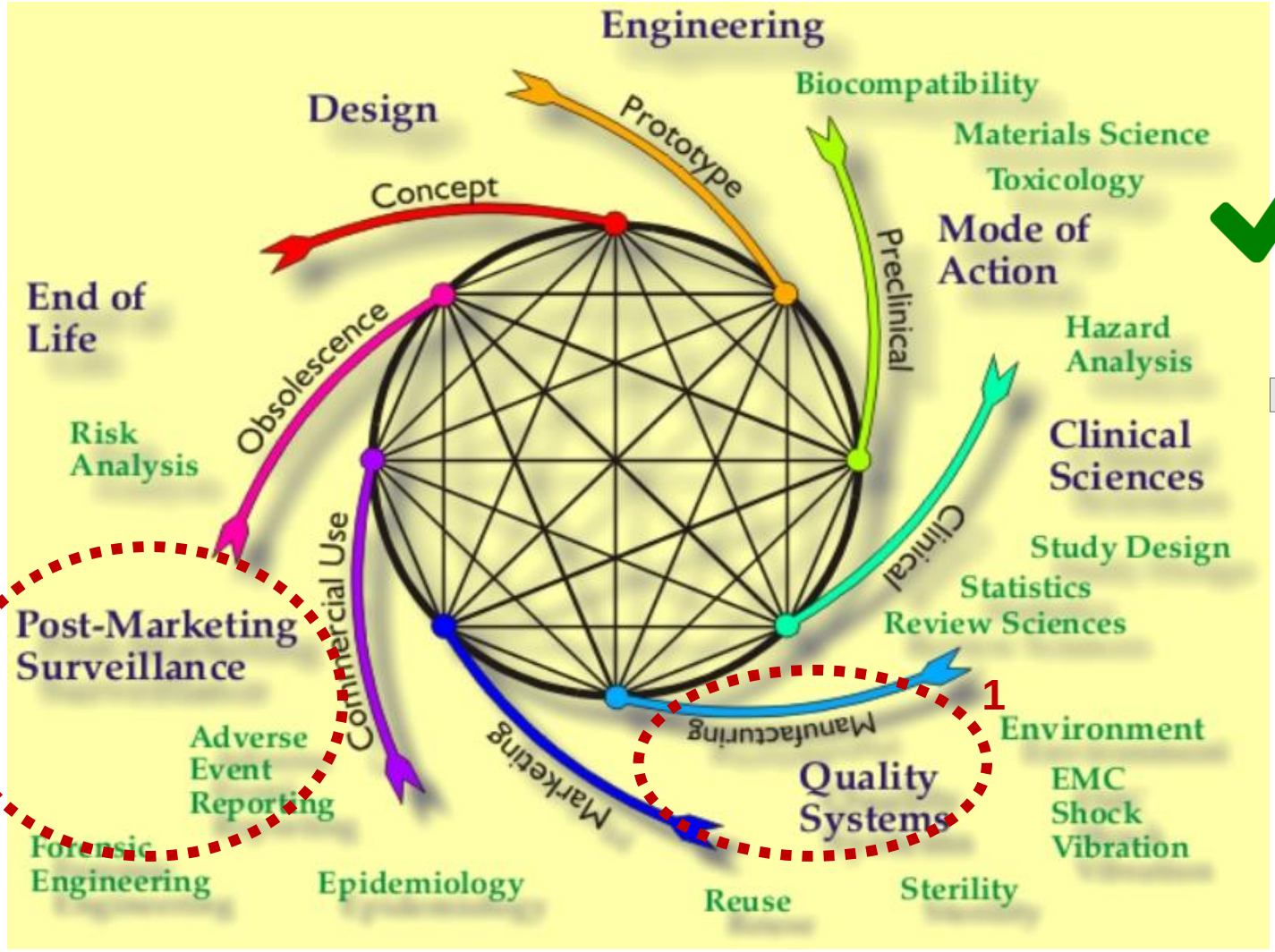
Standards are consensus tools for Suitable & Capable Testing; such tests are the foundation for assessing good products throughout the product life-cycle.

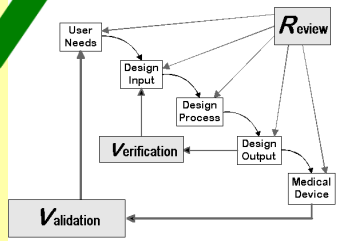
Standards used in:



http://www.fda.gov/RegulatoryInformation/Guidances/ucm070627.htm

Standards are consensus tools for Suitable & Capable Testing; such tests are the foundation for assessing good products throughout the product life-cycle.





http://www.fda.gov/ohrms/dockets/ac/01/slides/3799s1_11_Feigal/sld004.htm

Standards are developed by the individuals who show up and follow a consensus process.

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Regulators, Device Manufacturers, Material Suppliers, Test Labs, Test Equipment Suppliers, Consultants, Academics, Physicians

FDA U.S Food and Drug Administration

MTS

INSTRON

GORE

Medtronic

FORT WAYNE METALS RESEARCH PRODUCTS CORP.

G.RAU INNOVATIVE METALLE

echobio

Boston Scientific

saes group

BDC LABORATORIES

COOK

Edwards Lifesciences

ASTM standards are develop by consensus.
All dissenting parties receive due process.

Tests have to be suitable and capable

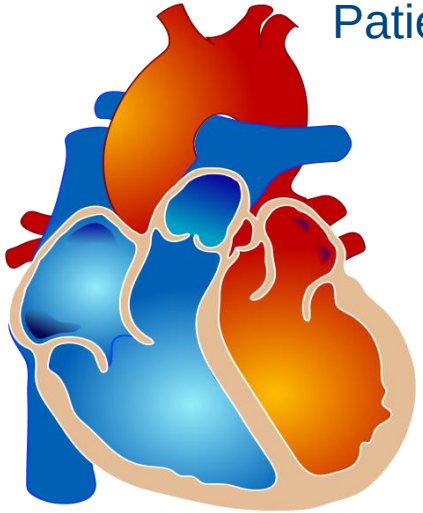
21 CFR 820.72 Inspection, measuring, and test equipment.
(a) Control of inspection, measuring, and test equipment. Each manufacturer shall ensure that all inspection, measuring, and test equipment, including mechanical, automated, or electronic inspection and test equipment, is **suitable** for its intended purposes and is **capable** of producing valid results. ……

Suitable Testing – For new products or new applications the ***suitability*** can be especially hard to assess.

21 CFR 820.72 Inspection, measuring, and test equipment.
(a) Control of inspection, measuring, and test equipment. Each manufacturer shall ensure that all inspection, measuring, and test equipment, including mechanical, automated, or electronic inspection and test equipment, is **suitable** for its intended purposes and is capable of producing valid results. ……

Patient

Physician

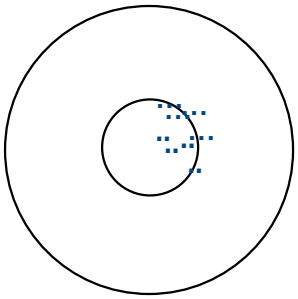


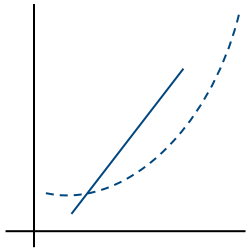
Patient Anatomy

Patient Activity

Capable Testing – Capability assessment takes work but there are Standard Practices.

- E29 Practice for Using Significant Digits in Test Data to Determine Conformance with Specifications
- E177 Practice for Use of the Terms Precision and Bias in ASTM Test Methods
- E691 Practice for Conducting an Interlaboratory Study to Determine the Precision of a Test Method
- E2554 Practice for Estimating and Monitoring the Uncertainty of Test Results of a Test Method Using Control Chart Techniques
- …..



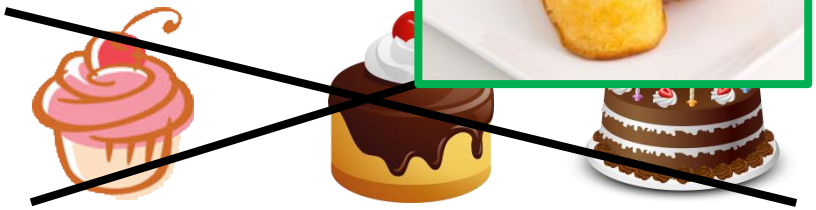


Precision, Accuracy, Range, Linearity

Operator Variability

Machine & Setup Variability

Surrogate Part:



Standards are a consensus document that are capable and likely suitable, albeit with caveats.

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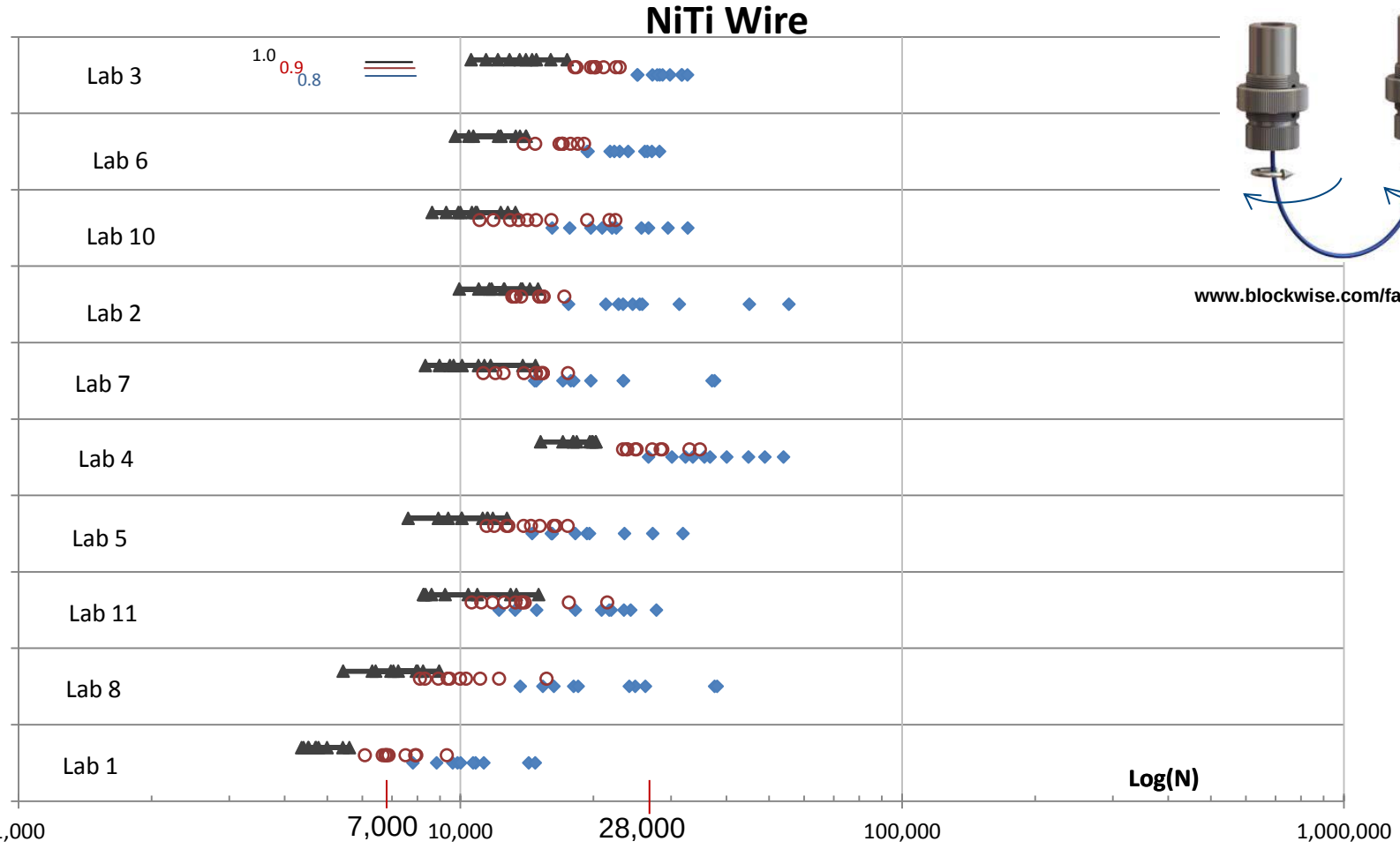
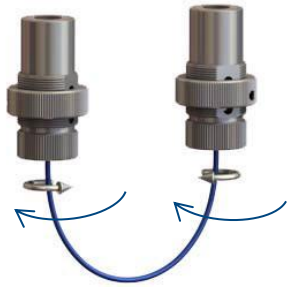
Example – Inter-Laboratory Study (ILS)

E2948-14, Test Method for Conducting Rotating Bending Fatigue Tests of Solid Round Fine Wire





www.blockwise.com/fatiguetester

Use Standards to purchase materials, plan testing, and interpret testing.

- Recognized by requester and supplier.
  - Clear & Concise Communication
  - Readily available

Test Methods*

Designation: E2948 – 16a

Standard Test Method for
Conducting Rotating Bending Fatigue Tests of Solid Round
Fine Wire[1]

Guides

Designation: F2942 – 13

Standard Guide for
in vitro Axial, Bending, and Torsional Durability Testing of
Vascular Stents[1]

Material Specifications

Designation:

Standard Specification for
Wrought 18Chromium-14Nickel-2.5Molybdenum Stainless
Steel Bar and Wire for Surgical Implants (UNS S31673)[1]

Practices

Designation: E1

Standard Practice for
Calculating Sample Size to Estimate, With Specified
Precision, the Average for a Characteristic of a Lot or
Process[1]

Terminology

Designation:

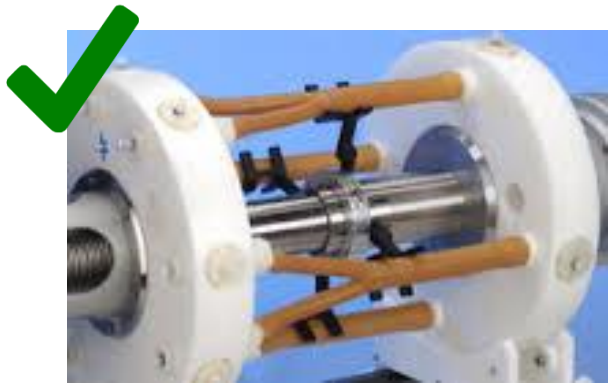
Standard Terminology
Relating to Quality and Statistics[1]

Challenges with Standards – **Standards covering new situations take time to develop.**

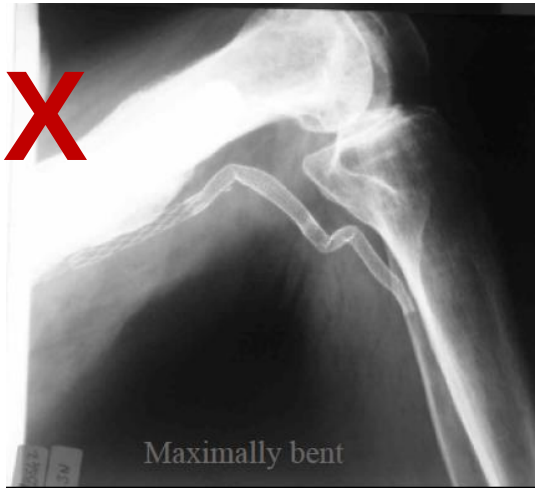
Example - Superficial Femoral Artery Stent Fatigue Testing

~2004

Cardiac Cycle Induced Load Test



Bending Induced Fatigue



Emilio Calabrese, MD

~2013

Designation: F2942 – 13

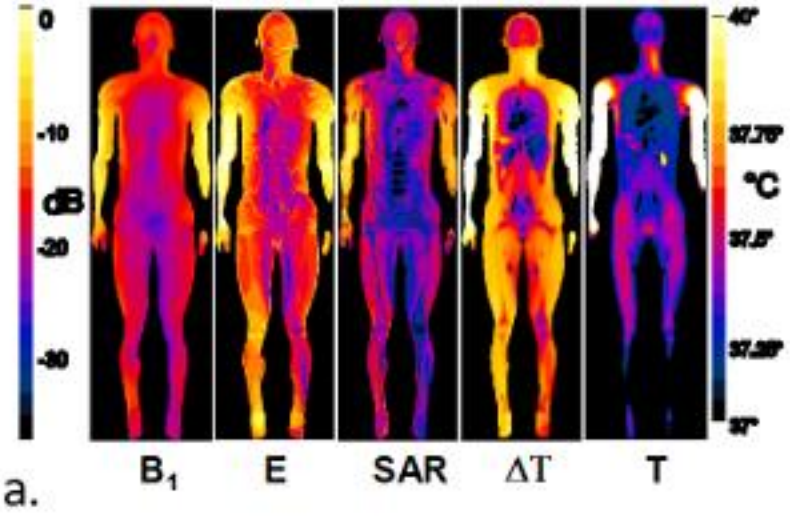
Standard Guide for *in vitro* Axial, Bending, and Torsional Durability Testing of Vascular Stents[1]

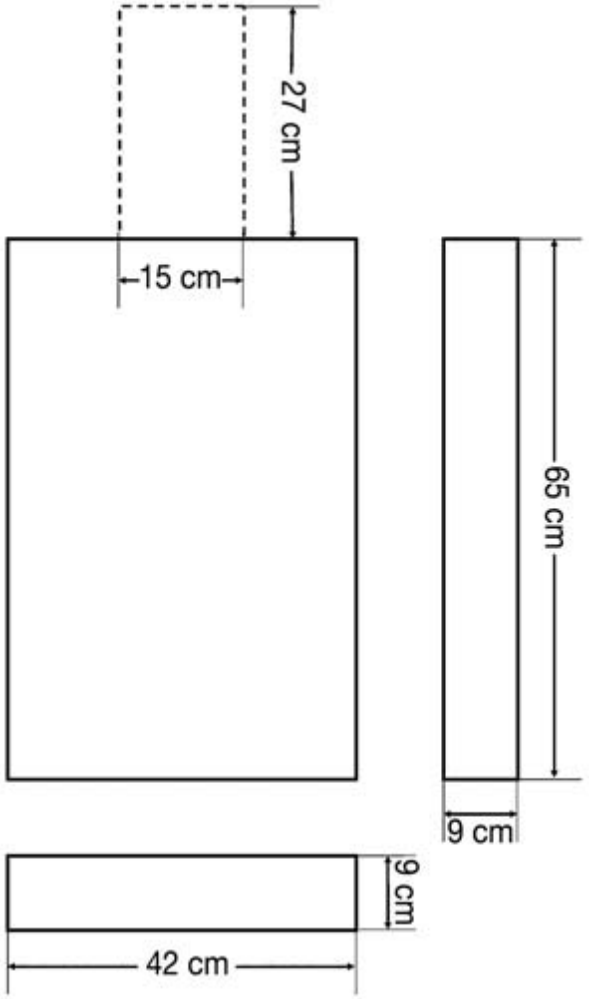
Challenges with Standards - **Standards are imperfect, but with effort get better.**

The map is not the territory.
Alfred Korzybski

Designation: F2182 – 11a

Standard Test Method for Measurement of Radio Frequency Induced Heating On or Near Passive Implants During Magnetic Resonance Imaging[1]





www.cmrr.umn.edu/research2016/novel-3.php

Challenges with Standards (or any test) - **Test results may be interpreted poorly**

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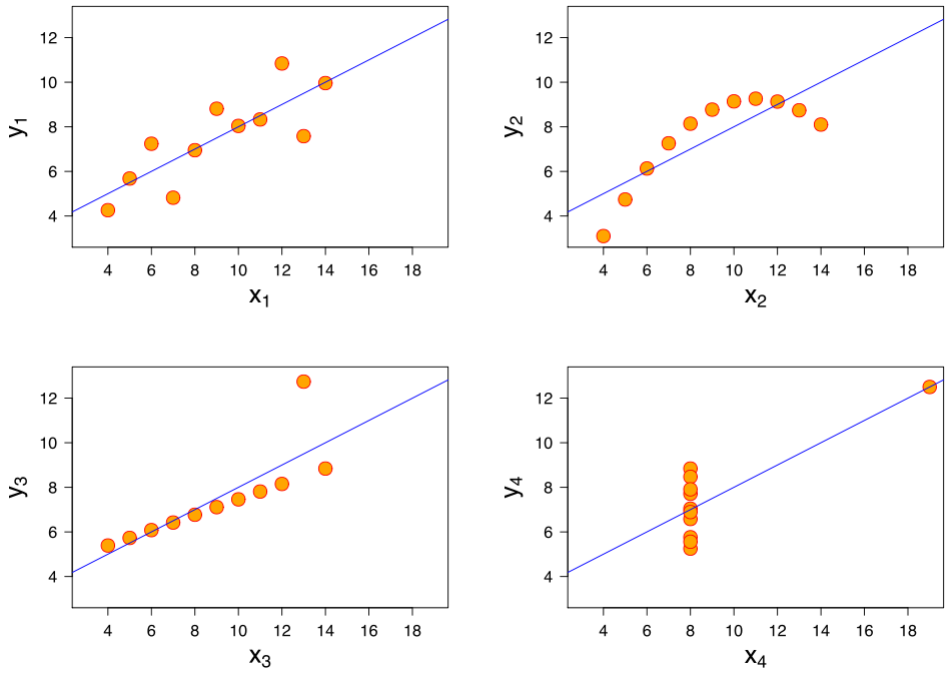
Show the data!

Anscombe's quartet – Same Statistics, Distinct Stories

Property	Value
Mean of x	9
Sample variance of x	11
Mean of y	7.5
Sample variance of y	4.125
Correlation between x and y	0.816
Linear regression line	y = 3.00 + 0.500x



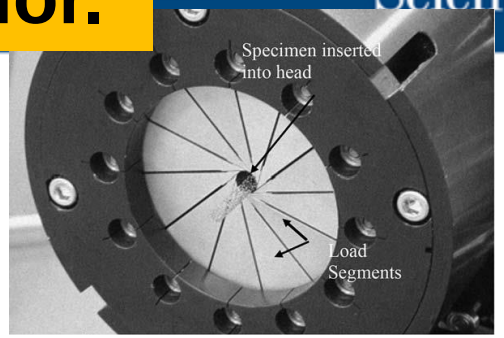
https://en.wikipedia.org/wiki/Anscombe's_quartet

Challenges with Standards - **Test results may be interpreted poorly**

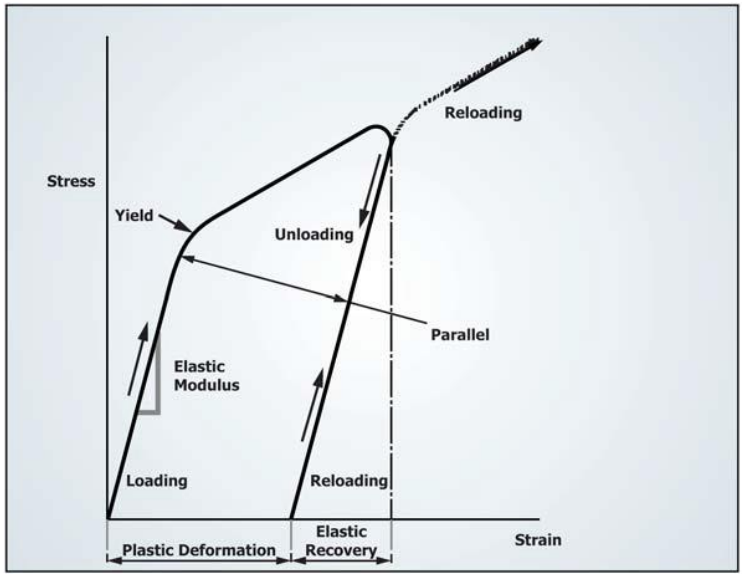
Test to see behavior.

Designation: F3067 – 14

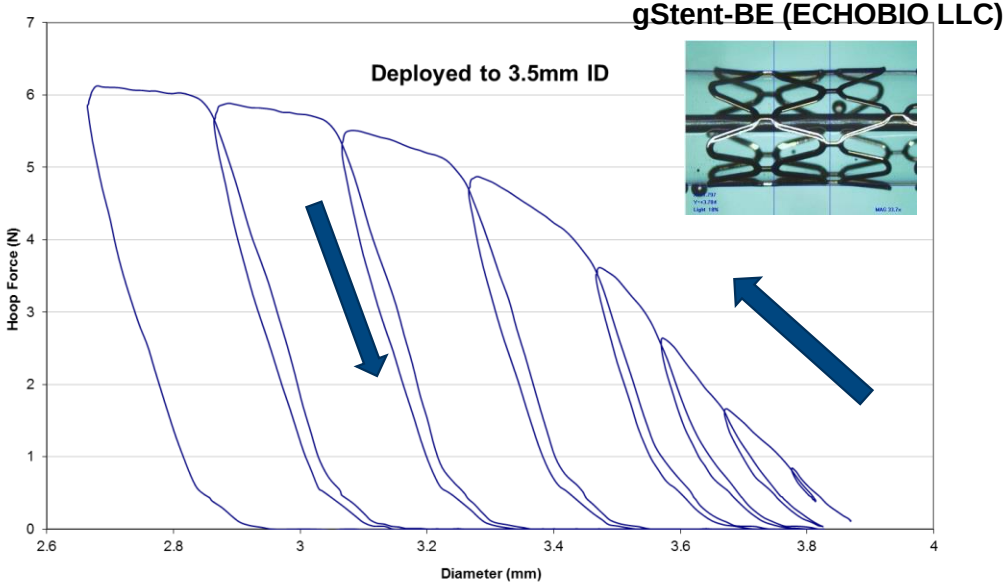
Guide for
Radial Loading of Balloon Expandable and Self Expanding Vascular Stents[1]



Tensile Test Conceptual Model is Elastic then Plastic



Plastic <u>Unloading</u> after any loading - Reality doesn't match model.



Comments from Managers, Engineers, Technicians regarding Standards:

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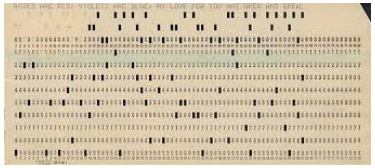
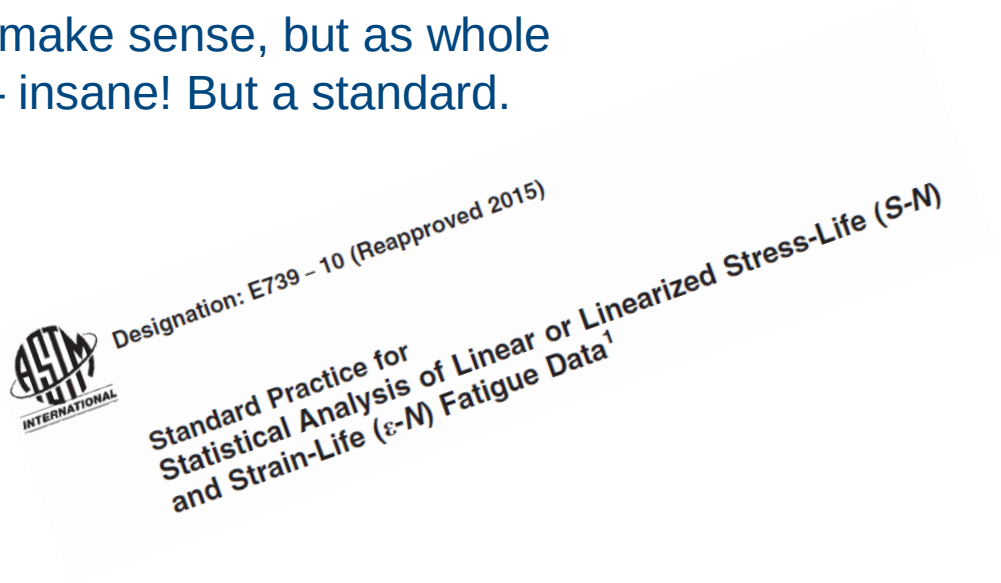
Don't or Do Updates



- Whenever a standard changes, we have to see if it effects any tests we do and update as appropriate.

- Some standards recommend obsolete methods because they are not using the latest equipment or software.
- But the latest equipment may be too expensive or does not provide more actionable information.

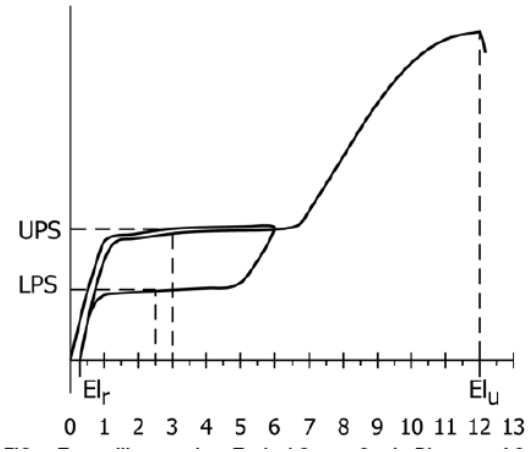
- Individual choices in standards may make sense, but as whole not so much. Think French poodle – insane! But a standard.



Comments from Managers, Engineers, Technicians regarding Standards:

Be flexible or Be very prescriptive; Explain!

- Flexibility in how to run a test is desirable to customize it for our particular application.
- Standards are so flexible that simply citing the standard does not guarantee similar results.
- Automatic software running & interpreting tests may build in new test result biases. The tensile modulus is especially sensitive to calculation details.
- Non-mandatory appendices with explanations of why specifics were chosen is very helpful to know when to deviate from the standard. Why soak “2 hours”, could 30 minutes be enough?



37 or 23°C?

Comments from Managers, Engineers, Technicians regarding Standards:

Standards aid understanding and allow comparisons, but may not be applicable.

- Standards help provide common language*, common meaning. They allow us to communicate results quickly and clearly. The explicate details in the standard provide a way to learn, clarity on how to do, and how to interpret.
- Tests require idealization. Individuals & physicians vary and idealization may miss their uniqueness.

Regulatory Requirements and "My mom could be the patient" testing

- We leverage standards when we can to speed up our development process and to meet regulatory requirements.
- We develop and run additional tests to assure ourselves device is safe assuming our mom will be the patient.

Conclusion

Standards are consensus documents that can aid in demonstrating compliance with regulatory requirements, meeting patient and clinical needs.

Standards are living documents, imperfect, but hopefully as good as our knowledge at any one time and evolving as our understanding evolves.

There are two ways to slide easily through life: to believe everything or to doubt everything; both ways save us from thinking.

Alfred Korzybski