Medical Device Product Development Process

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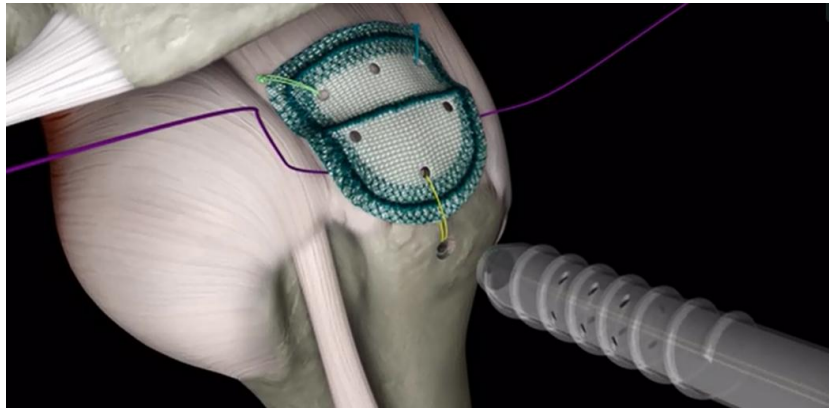


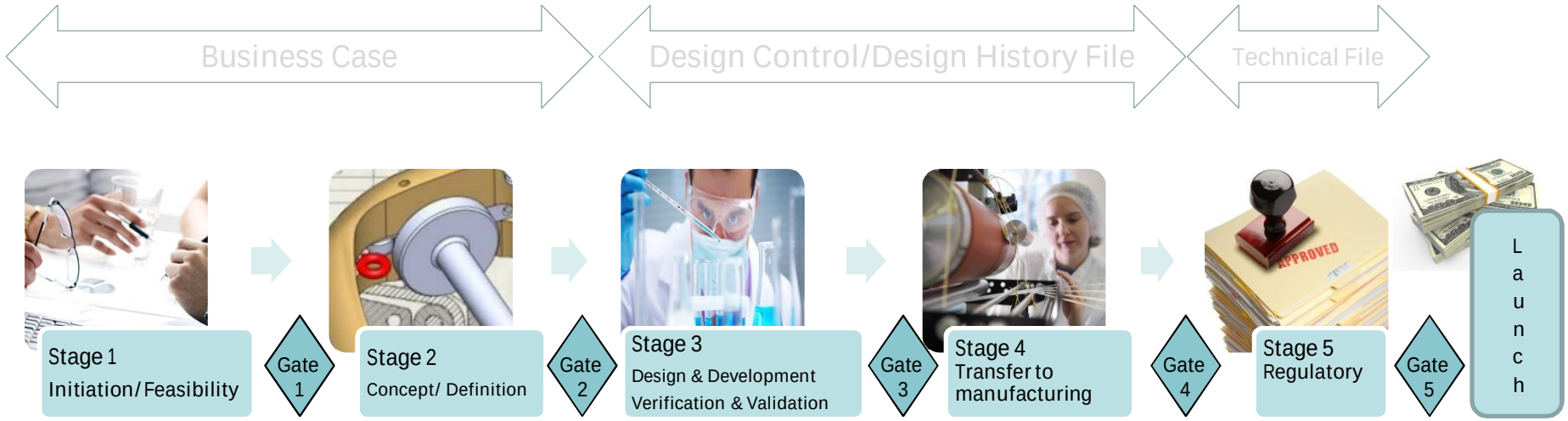
“Nothing is accomplished in the real world unless it is adopted by industry.
Academic scientists do not manufacture devices.
A paper in Science cannot save lives.
How to repay the taxpayers supporting academic research?”

Buddy Ratner
Biomaterials Scientist & Entrepreneur

New Product Development

- **Doing projects right**
  - Project planning
  - Project Management
  - Stage-Gate
- **Doing the right projects**
  - Business Cases
  - Valuation
  - Portfolio Management

Development Process – Stage-Gate



- Development process broken into key phases
- Project reviewed by management team at end of each phase – Gate Review
- Project must successfully pass through Gate before it can proceed to next phase
- Stops projects running out of control
- Focuses team on what information/results are required

Development Process

Stage	Description/Activities	
0: Idea creation/gathering	• Brainstorming • Internal R&D • Technology scouting	• Literature review • Companies/Universities
1: Initiation/Feasibility	• Initial proposal & business case	• Initial proof-of-concept and prototypes
2: Concept/Definition	• Full business case & project plan • Research Customer Requirements • Market evaluation • IP Review	• Initial regulatory plan • Manufacturing plan • Further develop/test prototypes
3: Design & Development	• Define design inputs • Verification & Validation Plan • Further testing/development • Risk assessment • Develop/review manufacturing process	• Develop/test final prototype • Design packaging/labelling • Update market, IP, regulatory reviews etc.
4: Transfer to Manufacturing	• Establish and validate process • Approve suppliers	• Document procedure • Train operators
5: Regulatory	• Prepare Technical File • Regulatory submission	• Obtain regulatory approval
6: Post Launch	• Surgeon training • Product/Process improvements	• Complaints • Post-market surveillance

Stage 0: Where do ideas come from?

- Market pull
  - Identify an unmet clinical need and then find technologies to address it
- Technology Push
  - Invent a new material, technology and then identify clinical needs it might satisfy

- Clinical Needs – literature, talking to surgeons, market research, observing surgery, clinical conferences, feedback from sales reps etc.
- New Technologies – literature, brainstorming, internal R&D, technology scouting, approaches from universities/companies etc.

Stages 1/2: Making the Case…

- Most companies will develop a “Business Case” before investing significantly in a new project.
  - Justifies the resources/funding needed to bring a new product to market.
  - Enables projects to be prioritised
    - Portfolio Management

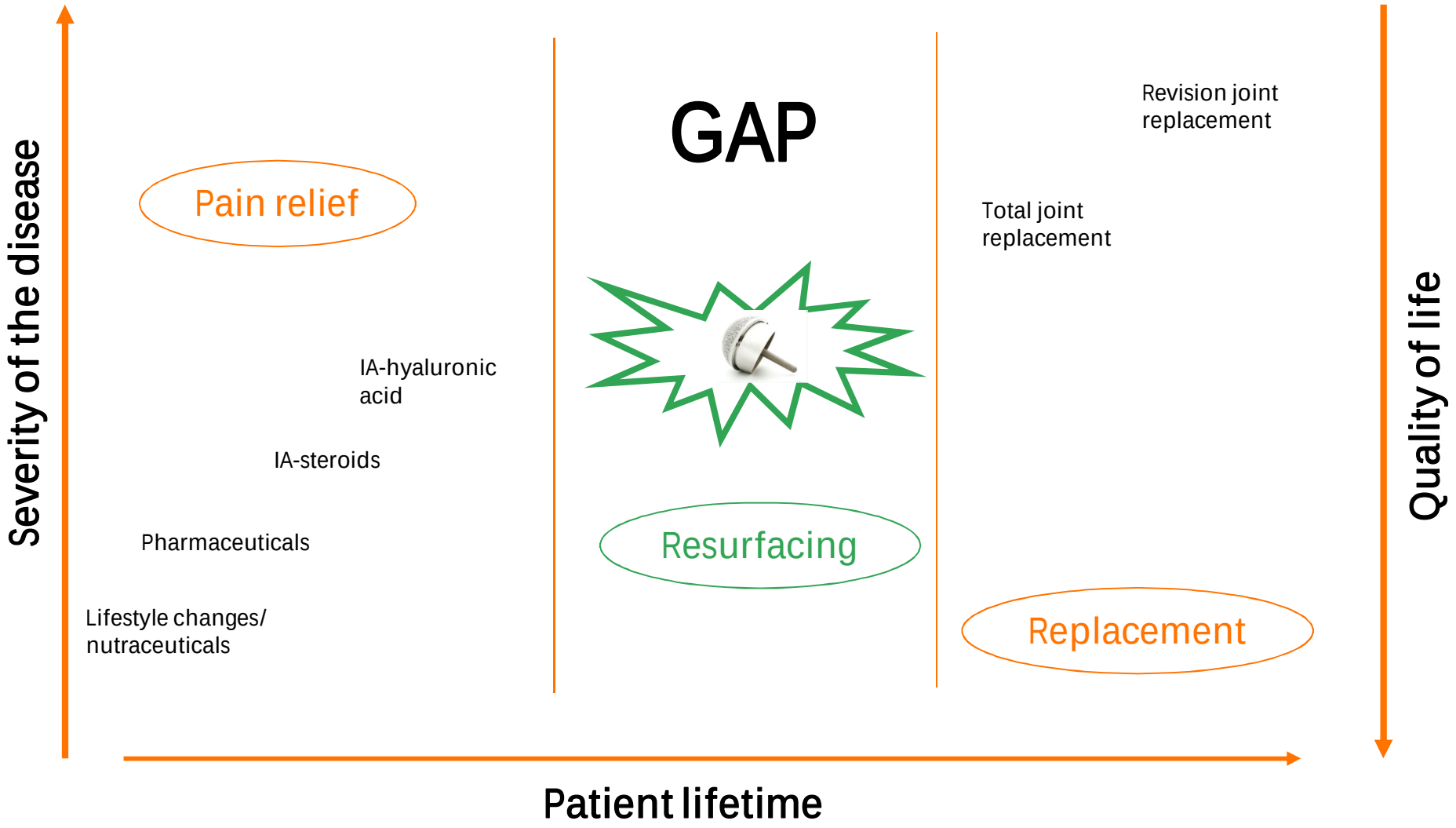
Typical Business Case Content
(or what you need to think about before you start to commercialise a medical device)

- Product attributes/technical specification
- Value proposition
- Strategic fit
- Market (size, growth, penetration)
- Sales channels
- Competition
- Intellectual Property position (patent protection, freedom to sell)
- Development plan/costs
- Manufacturing plan & costs
- Regulatory route
- Clinical trials
- Reimbursement
- Health economic analysis
- Risk analysis
- Value/financials

Value Proposition Case Study: HIP Resurfacing System

•For the young, active patient with advanced hip disease, hip resurfacing can be an alternate treatment to total hip replacement. The procedure often permits a return to normal life activities and more bone stock is preserved than with a total hip replacement.

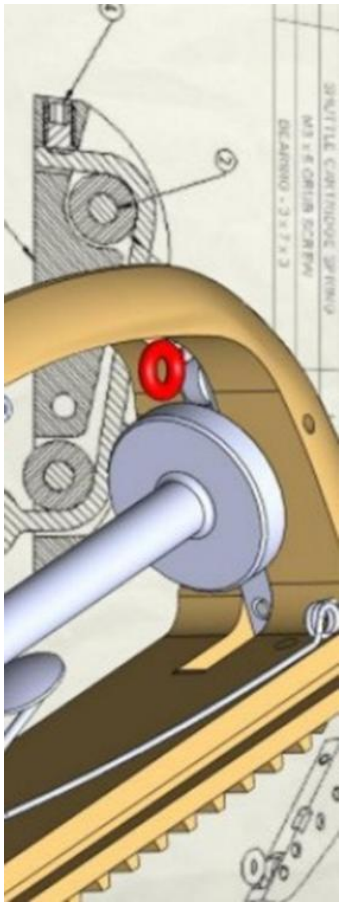
Patient Journey – Treatment for Osteoarthritis



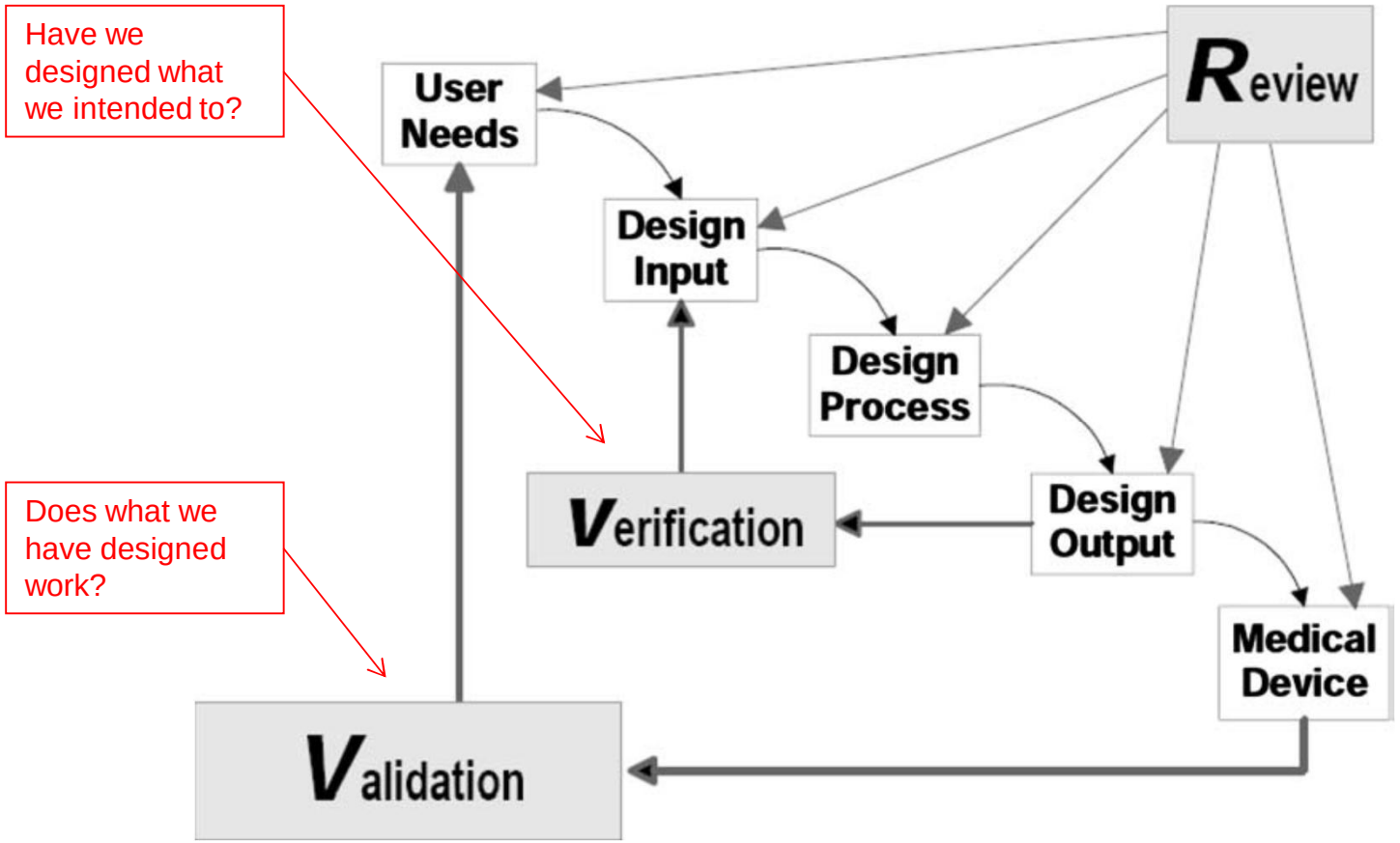
Stage 3: Developing and Testing

- Establish customer needs and define design inputs
- Develop device to meet design input requirements
- Test and record outputs of design.
- “Verification and Validation”
- Development process recorded in **Design History File**

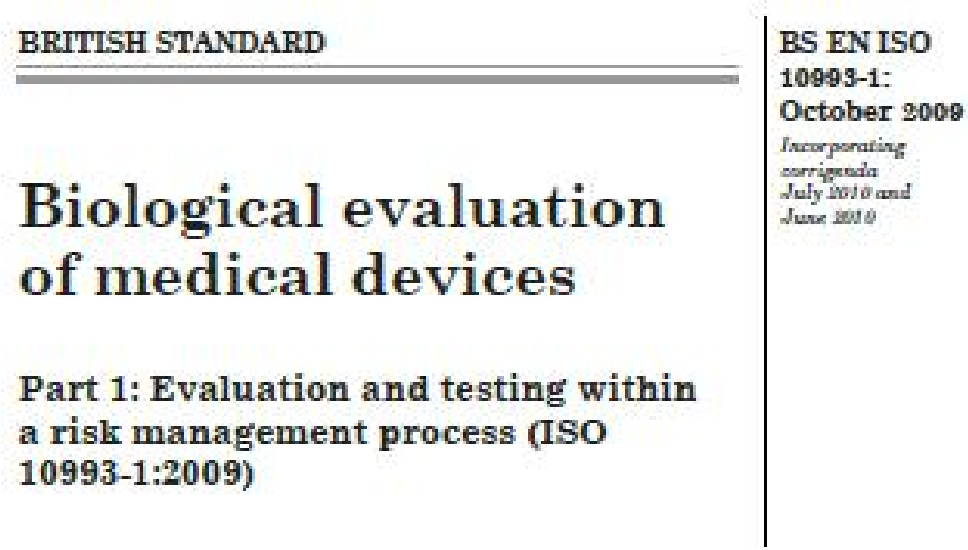
- Need to demonstrate safety and efficacy – supporting data needed for any marketing claims
- Time and cost of this stage often dominated by *in vivo* and clinical testing



FDA Waterfall Diagram



Case Study: Biological Safety Testing



BRITISH STANDARD

Biological evaluation of medical devices

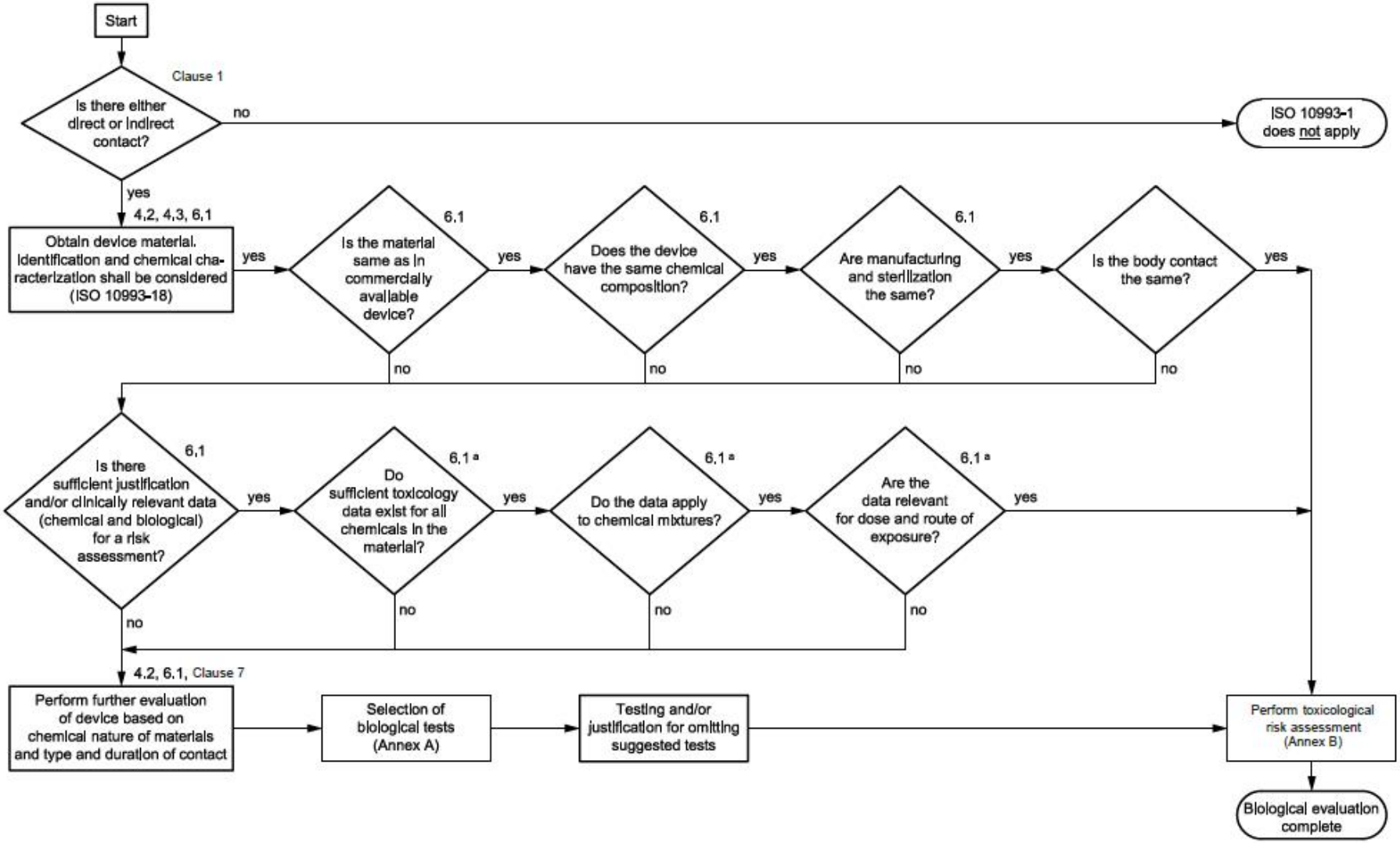
Part 1: Evaluation and testing within a risk management process (ISO 10993-1:2009)

BS EN ISO 10993-1: October 2009

Incorporating corrigenda July 2010 and June 2010

- ISO10993
  - provides a framework for biological safety testing
  - 20 parts covering characterisation, in-vitro and in-vivo testing
  - Part of a wider risk management process

ISO10993-1

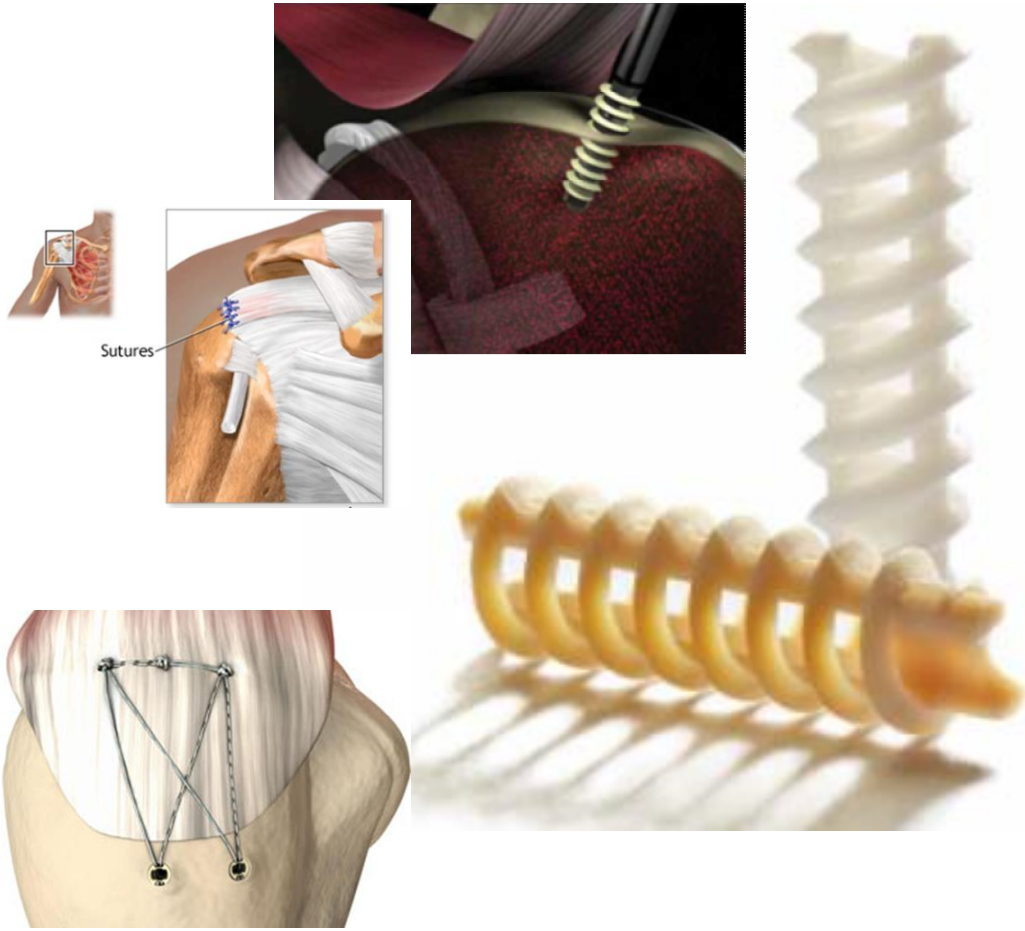

Start
Clause 1
Is there either direct or indirect contact?
no
ISO 10993-1 does not apply
yes
4.2, 4.3, 6.1
Obtain device material. Identification and chemical characterization shall be considered (ISO 10993-18)
yes
6.1
Is the material same as in commercially available device?
yes
6.1
Does the device have the same chemical composition?
yes
6.1
Are manufacturing and sterilization the same?
yes
Is the body contact the same?
yes
no
no
no
no
6.1
Is there sufficient justification and/or clinically relevant data (chemical and biological) for a risk assessment?
yes
6.1 a
Do sufficient toxicology data exist for all chemicals in the material?
yes
6.1 a
Do the data apply to chemical mixtures?
yes
6.1 a
Are the data relevant for dose and route of exposure?
yes
no
no
no
no
4.2, 6.1, Clause 7
Perform further evaluation of device based on chemical nature of materials and type and duration of contact
Selection of biological tests (Annex A)
Testing and/or justification for omitting suggested tests
Perform toxicological risk assessment (Annex B)
Biological evaluation complete

Medical device categorization by			Biological effect							
nature of body contact (see 5.2)		contact duration (see 5.3) A – limited (⩽ 24 h) B – prolonged (> 24 h to 30 d) C – permanent (> 30 d)	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Systemic toxicity (acute)	Subchronic toxicity (subacute toxicity)	Genotoxicity	Implantation	Haemocompatibility
Category	Contact									
Surface device		A	X [a]	X	X					
		B	X	X	X					
		C	X	X	X					
	Mucosal membrane	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
	Breached or compromised surface	A	X	X	X					
		B	X	X	X					
		C	X	X	X		X	X		
External communicating device	Blood path, indirect	A	X	X	X	X				X
		B	X	X	X	X				X
		C	X	X		X	X	X		X
	Tissue/bone/dentin	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Circulating blood	A	X	X	X	X				X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X
Implant device	Tissue/bone	A	X	X	X					
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Blood	A	X	X	X	X	X		X	X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X

[a] The crosses indicate data endpoints that can be necessary for a biological safety evaluation, based on a risk analysis. Where existing data are adequate, additional testing is not required.

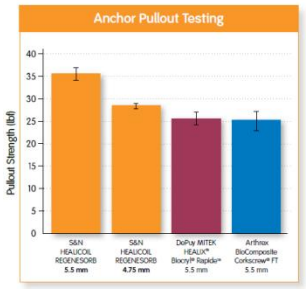
Case Study: Suture Anchor - Safety

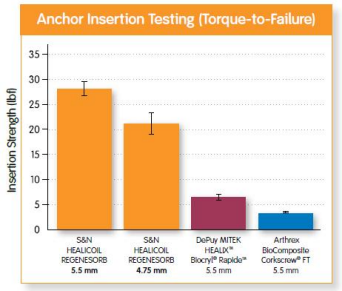
- Suture anchor for repair of the rotator cuff (shoulder)
- Available in PEEK or in a novel bioresorbable composite material
- For purposes of ISO10993:
  - what category is the device?
  - what is the contact type?
  - What biological safety testing is required (PEEK and biocomposite)?

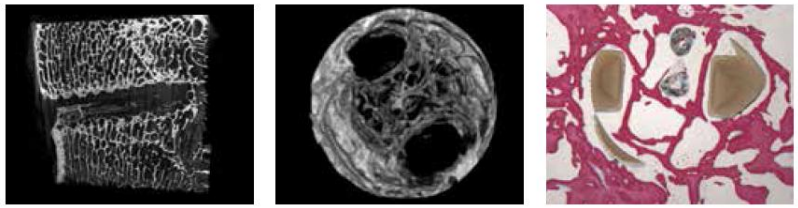


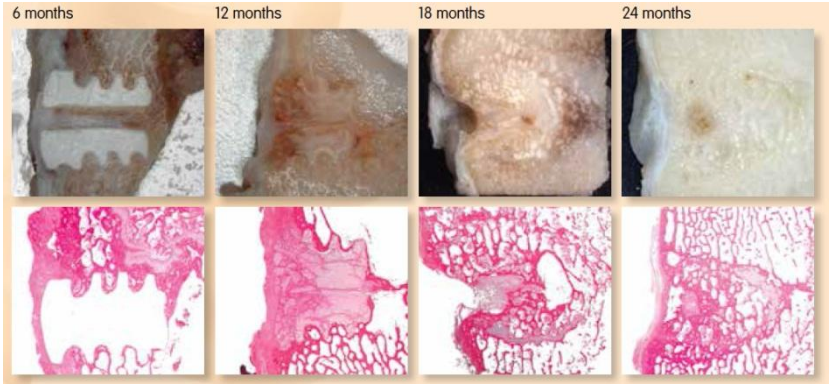
Case Study: Suture Anchor - Efficacy

- What might we want to claim?
- Strength – Insertion and Pullout
- Bone Ingrowth
- Bioresorption and replacement by bone







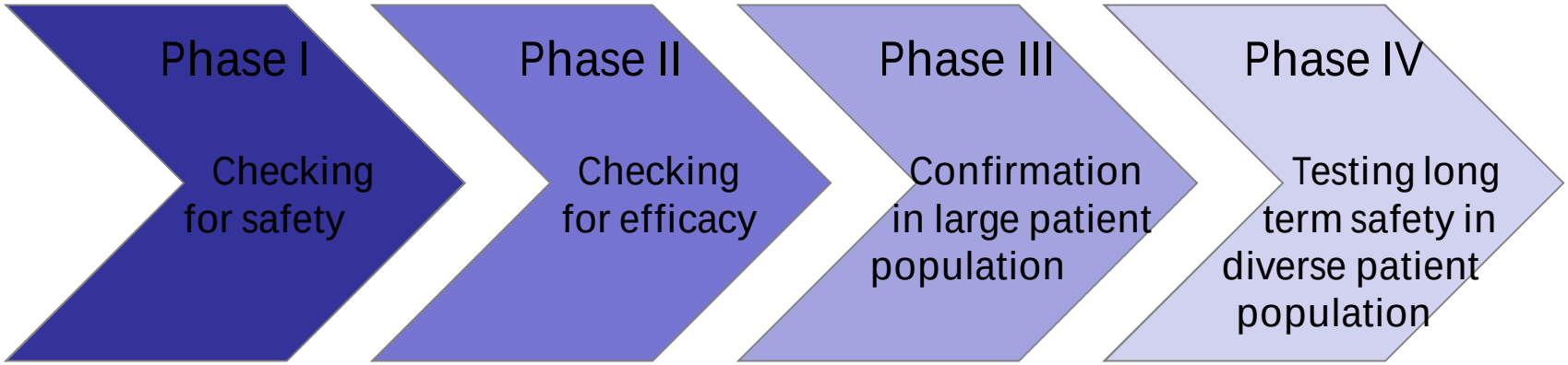


Need to consider choice, relevance and justification
of animal model as well as any mechanical/in-vitro testing.

Clinical Trials

- Likely to be needed for any new/innovative product.
- Can be the most costly part of the development process.
- Need to consider:
  - Acceptance of outcome measures
  - Variability of patient population
  - Follow-up time needed
  - Sample size
  - Cost

Stages of Clinical Development



Sample: 10-20 healthy volunteers

Risk: Unexpected side effects

Sample: about 200 patients

Risk: Many projects fail in Phase II due to product not being as effective as expected

Sample: more than 1,000 people

Risk: Chance of detecting rare side effects increases with number of people involved

Sample: real life patients – post-marketing studies

Risk: Previously untested groups may show adverse reactions

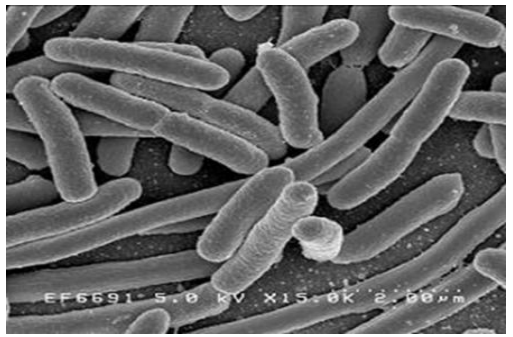
Case Study: Angiogenic Suture

- Suture for rotator cuff tears.
- Contains small molecule active to stimulate repair.
- Drug-device combination.

- Regulatory bodies required a clinical trial.
- Primary objective to obtain safety data on the active suture and the assess preliminary effectiveness of active suture vs. control in patients undergoing rotator cuff repair.
- 80 patients.
- Primary outcome: rotator cuff integrity 6 months post-op.
- Secondary outcomes include: RC integrity at 1, 3, 6, 12 & 52 weeks, change in cuff/shoulder assessments, rehabilitation time etc

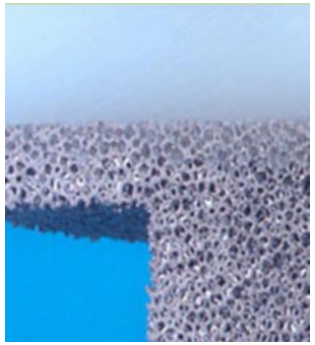
Case Study – Anti-microbial hip implant

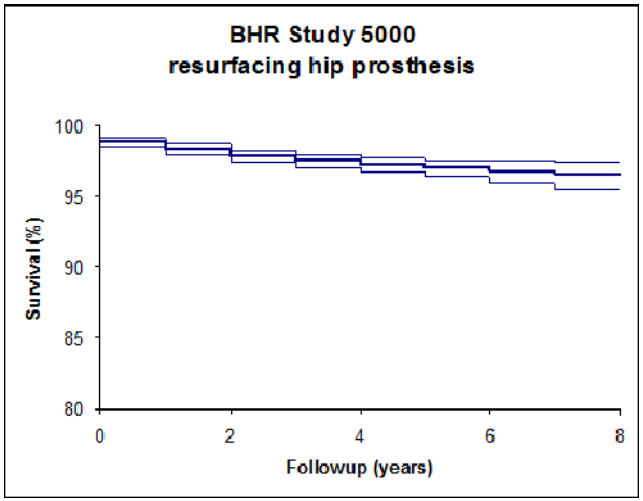
- Infection rates 1-2%
- Low incidence but devastating when it happens
- Incorporate antibiotics/antimicrobial surface
- Potential “combination” product (drug-device)
- How many patients do you need in your clinical trial to show a reduction?



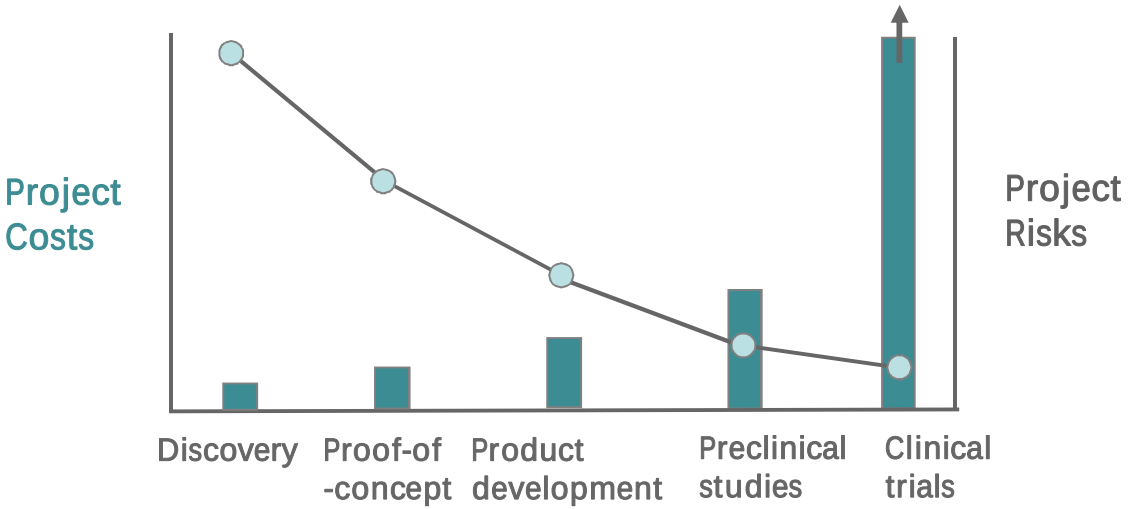
Case Study – Advanced In-Growth Surfaces

- Improved in-growth surfaces to improve cementless fixation of implants
- Advanced porous surfaces
- Active Surfaces e.g. BMP, bisphosphonate – “Combination”
- How long/how many patients for clinical trial?





Project Costs



Research
- Personnel
- Facilities
- Materials
- IP fees

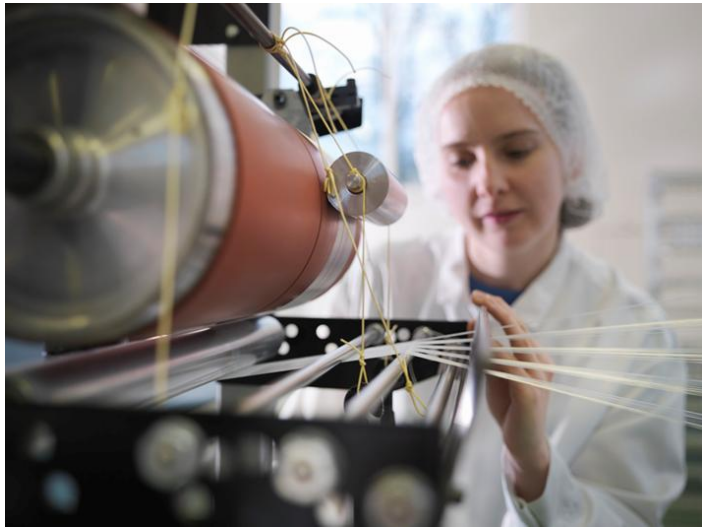
Development
- Prototype mftr
- Preclinicals
- Clinical studies
- Regulatory fees

Manufacturing
- CAPEX
- Tooling
- Materials
- Packaging

Commercialization
- Distribution
- Launch costs
- Training / education
- Sales commissions

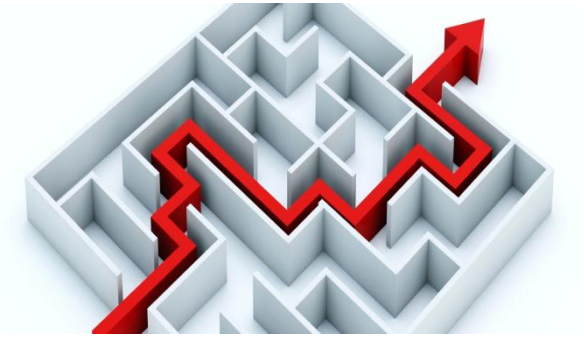
Stage 4: Getting ready to manufacture

- Design for manufacturing should start early in the process – how will the product be made?
- Process needs to be robust, efficient and cost effective
- Establish and validate process, including suppliers
- Document procedures and train operators



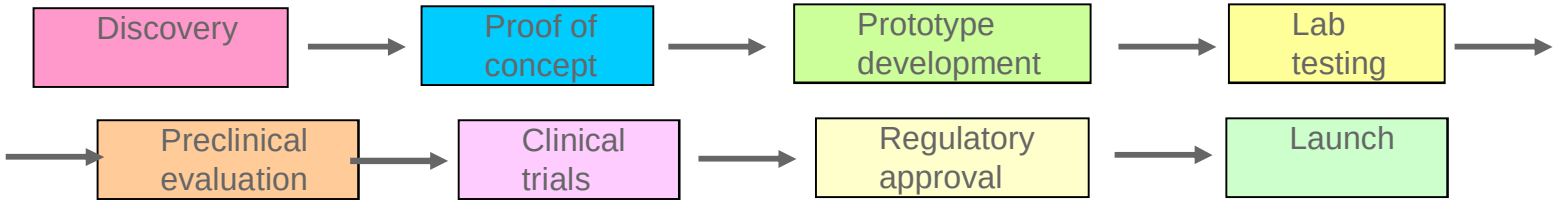
State 5:Regulatory Approval

- Probably the biggest driver in determining development route
- US FDA – 510(k) vs. PMA
- Europe – CE mark

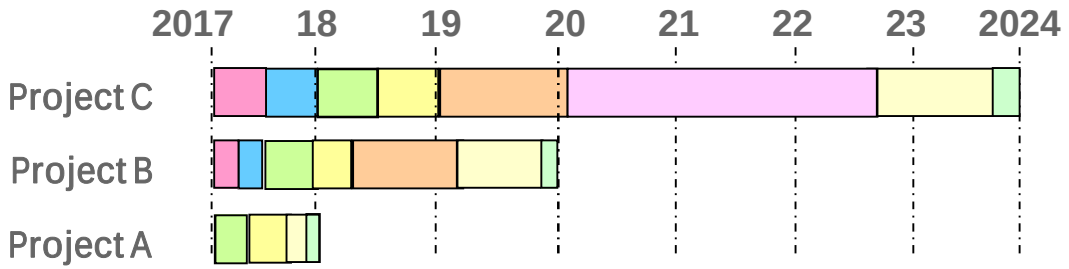


- Focus on Safety, Efficacy and Quality
- Is the product safe? Do benefits outweigh risks?
- Does the product do what it claims?
- Are adequate manufacturing controls in place?
- What testing is required?
- Are clinical trials necessary?

Project Timelines



Examples



Project A
- Instrument modification
- Demonstrate fit for purpose
- Minimal regulatory requirements (class 1)

Project B
- Next generation product development
- Demonstrate safety / efficacy in preclinical studies
- Short regulatory route (class 2 - 510k)

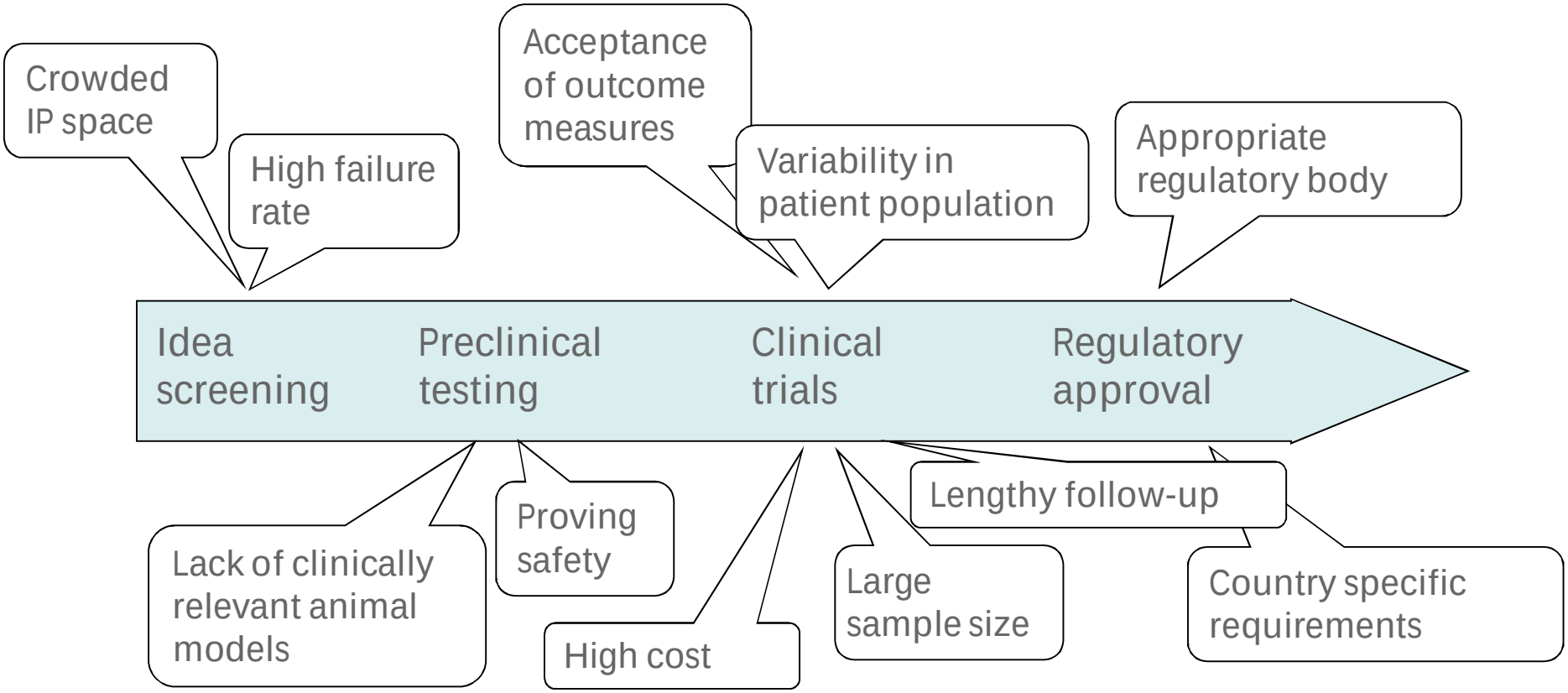
Project C
- Technically challenging, new product concept
- Requires preclinical evaluation and clinical trials
- Long regulatory route (class 3 - PMA)

- Project timelines vary widely
- Not all steps necessary in each case
- Determined by regulatory pathways (can be complex and uncertain!)
- Consider requirements to show safety & efficacy

Stage 6: Post Launch

- Surgeon training
- Product/Process improvements
- Complaints
- Post-market surveillance

Challenges in product development



…or how things get lost in translation

Thank you for listening!