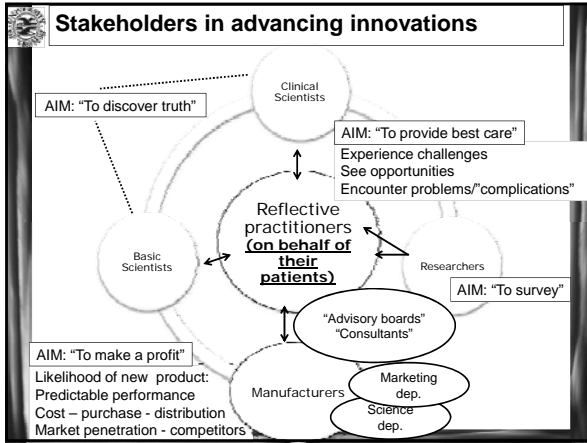


## Evidence-based development and clinical implementation of innovative dental biomaterials

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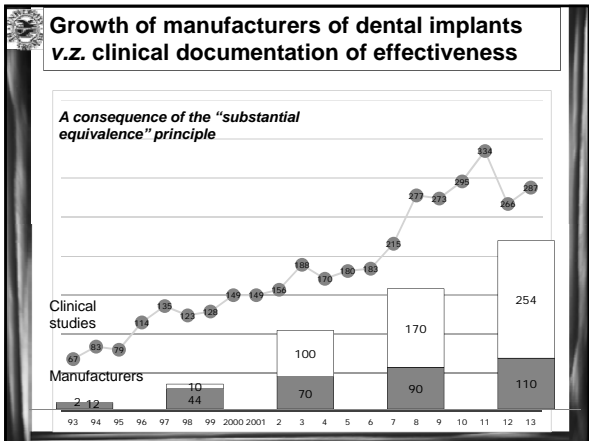
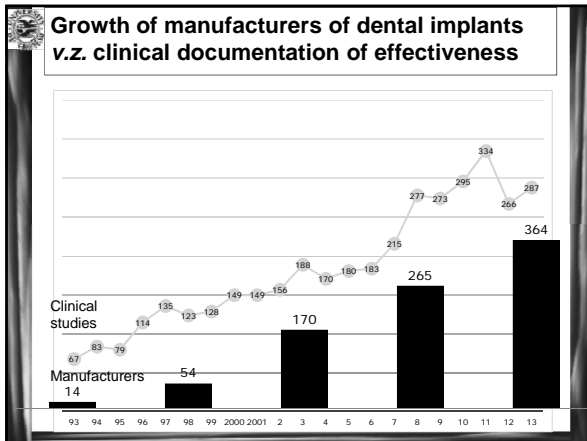
### Disclosure

No financial relationships exists between the presenter and any company that manufactures or distributes a product discussed in the presentation,  
Or,  
any company whose product competes, or may compete, with a product discussed in this presentation



- ### Differentiate between two categories of innovative products and devices
- Comparable to a material or device already on the market
    - Identify an existing product of a competitor that sells well (or may) and "improve" its performance while not infringing on a patent (or, alternatively acquire the manufacturer)
    - Relatively easy regulatory process
    - Challenge is to persuade the regulatory body to apply a *least burdensome approach*. (FDA (USA): "involve the most appropriate investment of time, effort, and resources on the part of industry and regulatory body")

**Hence: no requirement for clinical testing – enough to demonstrate substantial equivalence**



### Differentiate between two categories of innovative products and devices

1. Comparable to a material or device already on the market: document *substantial equivalence* & adherence to *good quality system regulation (QSR)* (e.g., in USA: 510k clearance)
2. Completely new formulations or material classes or new combinations of existing biomaterials

- Complex regulatory process
- Unpredictable outcome of development, examples from dentistry:
  - » "Consolidated silver"; "Gallium alloy"; "Hydroxyapatite cement"; "Calcium-Aluminate-cement" (*Doxadent*); Portland cement / MTA-variants...

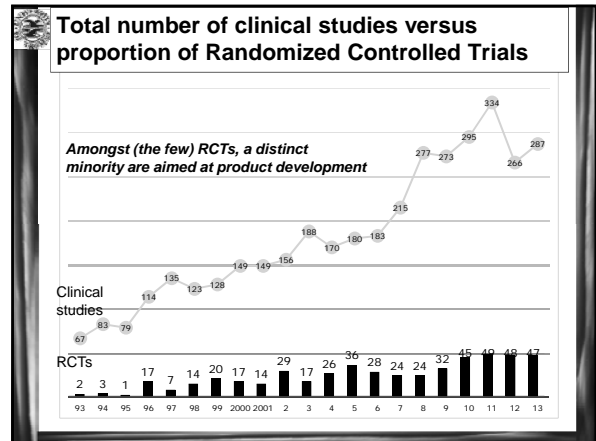
### Investment costs for advancing a new product

Have promising...	NEED
Theory* ...	Some seed \$ to continue...
results from initial experiment(s)* ...	Seed \$ to continue...
results from basic research* ....	More seed \$ to continue...
results from animal study(/-ies)* ....	Much more seed \$ to continue...
results from a Phase 1 trial (screen for safety)* ...	What do you think? .....
results from a Phase 2 trial (establish efficacy)* ....	
results from a Phase 3 trial (confirm safety and efficacy)* ...	

\* and PATENT

### Development phases of a completely new biomaterial or device

1. A justified idea for a new product
2. Arduous *in vitro* investigations to establish safety and efficacy → verify proof of concept → document utility of new product *in vivo*
3. Demonstrate clinically that the new product is better or comparable with existing – the gold standard is to undertake a RCT (randomized clinical trial) with:
  1. adequate statistical power
  2. high internal and external study validity
  3. appropriate observation period
  4. relevant primary outcome(s)
  5. meaningful statistical interpretation and presentation
4. Relative few RCTs are ever published - even fewer that fulfill all 5 criteria - for various reasons



### Investment costs for advancing a new product

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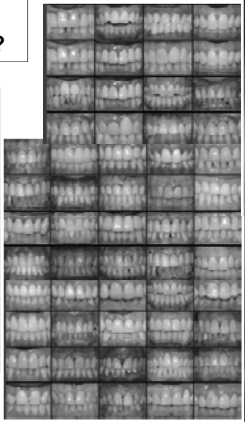
Once a new product is released, what are the incentives to the industry for funding further clinical studies; clinical studies with stringent protocols?

### How can innovative products be compared with already existing ones?

1. Few clinical studies provide strong evidence for endorsement of specific products
2. Clinicians, regulators & industrial competitors base more or less grounded decisions on syntheses of data from:
  1. biocompatibility assessments
  2. mechanical-physical properties tests
  3. occasional animal experiments
  4. sometimes preliminary clinical investigations
3. Extrapolation of evidence obtained *in vitro* to predict *in vivo* performance intraorally is a classic dilemma in dental materials research
4. Which preclinical tests are currently available and what are strengths and weaknesses in terms of correlation to reported clinical behaviour and performance?

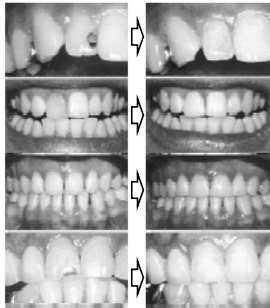
### A good idea for a new product that should sell?

- The drive for **esthetics** is stronger than ever before!
- An **aging** population is willing to maintain (worn) teeth
- New classes of biomaterials
- New **combinations of biomaterials** for replacing / restoring soft and hard oral tissues

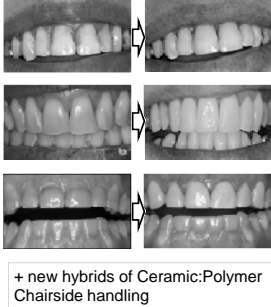


### A strong drive for esthetics

#### Composite polymers



#### Ceramics




+ new hybrids of Ceramic:Polymer  
Chairside handling  
CAM additive/subtractive methods

### An aging population is willing to maintain (worn) teeth



(Scandinavian solution v.z. North America solution)

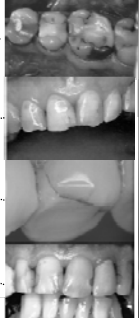
### Combination of new biomaterials to improve esthetics – hard and soft tissues



### Materials for restoring lost oral tissues- unwanted clinical performance

E.g., composite polymers

- Degradation
- Material Interface
- Wear
- Fracture
- Surface roughness
- Inadequate interface
- (Discoloration Bulk Marginal)




Can these adverse outcomes be predicted?

### Standardisation initiatives in dentistry

#### American Dental Association

- 1919: Surgeon General request on assessment of amalgam from National Bureau of Standards
- 1926 First ADA specification on dental amalgam (ADA specification #1)
- 1942: Bureau of Standards, Research commission
- 1955: Clinical testing of dental caries preventives. Report of a conference to develop uniform standards and procedures

1920 1930 1940 1950



1900 **fdi**

Mid-50ies, first attempts to develop standards

### Standardisation initiatives in dentistry

1920 1930 1940 1950 1960

**ADA**

Sweeney WT. Dental research at the National Bureau of Standards 1919-1969. History of Dental Research Section. 1969.

**fdi**

ISO TC106 Dentistry

### Standardisation initiatives in dentistry

1920 1930 1940 1950 1960 1970

**ADA**

FDI: "CLINICAL & BIOLOGICAL STANDARDS": Commission on Dental Materials, Instruments, Equipment and Therapeutics 1964-1979, 15 members, 5 from industry  
 1967: Principal requirements for controlled clinical trials  
 1974: Acceptance programs for dental materials and devices  
 1977: Recommended format for protocol for clinical research programs

ISO TC 106 Dentistry [1959] "PHYSICAL & TECHNICAL MATERIAL STANDARDS"  
 1. Filling & restorative materials  
 2. Prosthodontic materials  
 3. Dental instruments  
 4. Dental equipment

**fdi**

ISO TC 106 Dentistry

### Standardisation initiatives in dentistry

1920 1930 1940 1950 1960 1970

**ADA**

ASTM / ANSI  
 BSI ...DIN...AFNOR ... NIOM  
 Australia DMRL ...

**ADA / USA - 70ies**  
**Focus on clinical aspects**

- 1971: Cvar & Ryge, "Ryge system" (Ordinal scale (3))
- 1972: Recommended standard practices for clinical evaluation of dental materials and devices
- 1973: Guidelines for reporting clinical trials
- 1977: ADA specification #27 for direct filling resins
- California Dental Association, 1977 - "CDA system (4/5)"
- 1978: Clinical evaluation of dental materials. USPHS Publ 1980 - "USPHS system (3)"
- 1979: ANSI/ADA document no 41 for recommended standard practices for biological evaluation of dental materials

**fdi**

ISO TC 106 Dentistry

### Standardisation initiatives in dentistry

1920 1930 1940 1950 1960 1970

**ADA**

Laboratory tests only  
 - What about standards for clinical research?

1980: Paffenbarger, Rupp & Malmstedt. U.S. National Bureau of Standards pub. #571

A listing of the current specifications for dental materials throughout the world shows the following:

Organization	Number of Specifications
Federation Dentaire Internationale (FDI)	Use ISO Standards
International Organization for Standardization (ISO)	26
American Dental Association (ADA)	65
Dental Specifications of Various States of the U.S.A.	10
American National Standards Institute (ANSI)	34
Denture Medical Approval Board (DMAB) (U.S.A.)	234*
Standards Association of Australia (SAA)	54
British Standards Institution (BSI)	30
Canadian Standards Association (CSA)	9
Czechoslovakian Society for Standardization and Measuring (CSN)	7
French Standards Association (AFNOR)	29
German Standards Institute (DIN)	66
Hungarian Office of Standardization (MSZH)	27
Indian Standards Institution (ISI)	135
Standards Institution of Israel (SII)	3
Japanese Standards Association (JIS)	63
Polish Committee of Standardization and Measures (PKND)	45
South African Bureau of Standards (SABS)	21
Swedish Planning and Standardization Institute (SPT)	61

**1980'ies & 1990'ies: Guidance documents for conducting good clinical dental research**

- 1980: Recommended standard practices for biological evaluation of dental materials
- 1982: Principal requirements for controlled clinical trials of caries preventive agents and procedures
- 1982: Recommendations for clinical research protocols for dental materials
- 1990: Good manufacturing practices, including quality assurance for dental materials
- ISO/TC106/FDI joint WG - toothpaste [since 1985]
- ISO/TC106/FDI joint WG - biological testing [since 1986] → ISO 7405
- ISO/TC194 Biological evaluation of medical ~~and dental materials~~ **and** devices [since 1988] ISO 10993 Parts 1 – 20
- 1981: Expansion of the ADA acceptance program: Composite resin materials for occlusal class I and II restorations; 1986, 1991, 1994, 2001: Evaluation of dentin and enamel adhesive materials; 1989, 1996, 2001: Composite resins for posterior restorations; 1998: Dentin hypersensitivity; 1998: Whitening products

**fdi**

**ISO**

**ADA**

**fdi**

ISO TC106 Dentistry

### Global standardisation work on biomaterials (including dental)

1920 1930 1940 1950 1960 1970 1980 1990 2000

**ADA**

Global Harmonization Task Force GHTF 1992-2012  
 → International Medical Device Regulators Forum (IMDRF)

ISOTC194 Biological evaluation of medical devices  
 ISOTC210 Quality management and corresponding general aspects for medical devices

EUROCOM EC Directive 93/42

Global Medical Device Nomenclature GMDN Cat.03

TC55 Dentistry

ASTM, ANSI, BSI, DIN, AFNOR, NIOM ...  
 Australia DMRL ...DSC  
 CEN (Comite Europeen de Normalisation)

Good Clinical Practice 75/318/EEC -ICH GCP

### Guidance documents since 2000 on:

1. Conduct of good clinical dental research
2. Valid tests for preclinical testing

2007: Hickel ea. Recommendations for conducting controlled clinical studies of dental restorative materials & criteria for evaluation of direct and indirect restorations including onlays and partial crowns. FDI Commission Project 2-98

2010: Hickel ea. Clinical criteria for the evaluation of direct and indirect restorations. Update and clinical examples

2001-2008. Acceptance program guidelines for resin-based composites for posterior restorations & for dentin and enamel adhesive materials

**ISO/TC194 ISO 14155:2011 Clinical investigation of medical devices for human subjects - Good clinical practice**

**ISO/TC106 Dentistry**

- SC1 Filling and restorative materials: 14 workgroups
- SC2 Prosthodontic materials: 20 workgroups
- SC3 Terminology: 4 workgroups
- SC4 Dental instruments: 10 workgroups
- SC6 Dental equipment: 8 workgroups
- SC7 Oral hygiene products: 4 workgroups
- SC8 Dental implants: 5 workgroups
- SC9 CAD/CAM: 4 workgroups

**Test validity**

- Reproducible
- Known parameters
- Low C.V. (#samples)
- Calibrated devices

### Which laboratory tests predict clinical performance of restorative materials? 1/2

**Static stresses ?**

- Compressive (crushing) strength, e.g., 1h. & 24 h.
- Tensile strength, e.g., 5 min.
- Transverse strength, e.g., 1h. & 24 h.
- (Flexure/bending/modulus of rupture)
- Modulus of elasticity (Young's Modulus)
- Shear modulus

**Dynamic tests ?**

- Compressive modulus
- Tensile modulus
- Bending modulus
- Resilience
- Fatigue
- Fracture toughness

### Which laboratory tests predict clinical performance of restorative materials? 2/2

**Other defined tests**

- Flow (Creep), 3-24 h.
- Dimensional change, e.g., 5 min. -24 h.
- Polymerization- /Setting-...contraction/expansion
- Hardness
- Thermal expansion coefficient
- Water solubility / - sorption

**Other undefined tests**

- Abrasion resistance (Wear)
- Adhesion
- Color stability
- Surface roughness
- Marginal leakage

*"Neither dentists nor laboratory researchers have a clue as to what these tests say on possible clinical outcome in terms of predictability and longevity" Dr. Stegward D. Heintze, Head of Preclinical Research, Ivoclar Vivadent. Dent Mater 2013.*

### My top-3 review papers on today's theme

1. **Correlation of clinical performance with 'in vitro tests' of restorative dental materials that use polymer-based matrices**  
 Stephen C. Bayne\*

2. **The slippery slope - Critical perspectives on in vitro research methodologies**  
 J. Robert Kelly\*\*, Paula Barrett\*, Jennifer Kraggsangman\*\*, Alison Duffin Jones\*

3. **Clinical relevance of tests on bond strength, microleakage and marginal adaptation**  
 Hargrett-El Marfaty\*\*

# Thank you for your kind attention