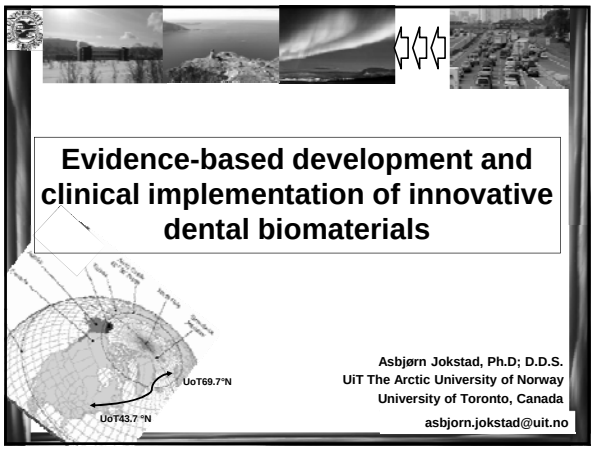


Evidence-based development and clinical implementation of innovative dental biomaterials

Asbjørn Jokstad, Ph.D; D.D.S.
UiT The Arctic University of Norway
University of Toronto, Canada
asbjorn.jokstad@uit.no

Disclosure

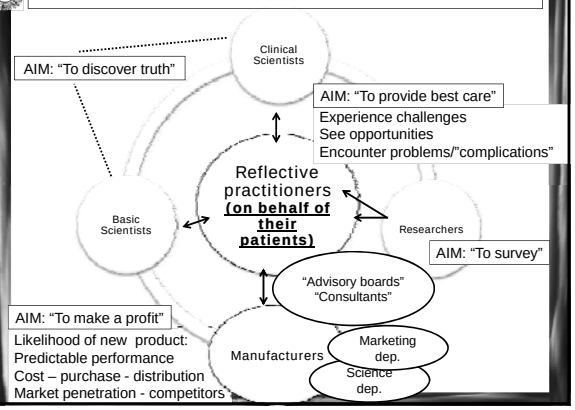
No financial relationships exists between the presenter and

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

Stakeholders in advancing innovations

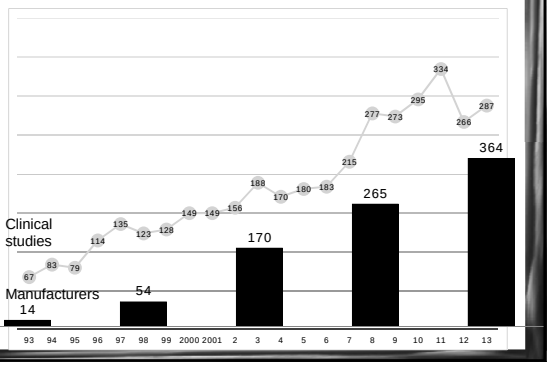


Differentiate between two categories of innovative products and devices

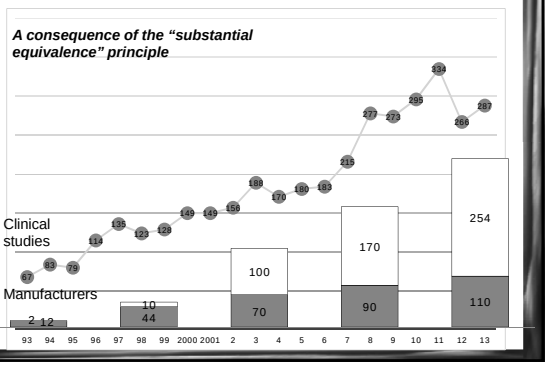
1. Comparable to a material or device already on the market
   - Identify an existing product of a competitor that sells well (or may) and "improve" its performance while not infringing on a patent (or, alternatively acquire the manufacturer)
   - Relatively easy regulatory process
   - Challenge is 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

Growth of manufacturers of dental implants *v.z.* clinical documentation of effectiveness



Growth of manufacturers of dental implants *v.z.* clinical documentation of effectiveness



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

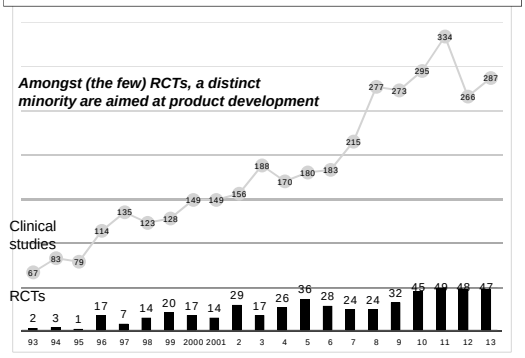
Have promising...	*NEED*
• Theory*...	Some seed $ to continue...
• results from initial experiment(s)*...	Seed $ to continue...
• results from basic research*....	More seed $ to continue...
• results from animal study(/-ies)*....	Much more seed $ to continue...
• results from a Phase 1 trial (screen 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

Total number of clinical studies versus proportion of Randomized Controlled Trials



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

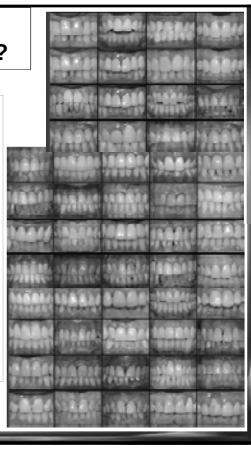
Once a new product is released, what are the incentives to the industry for funding further clinical studies; clinical studies with stringent protocols?

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?

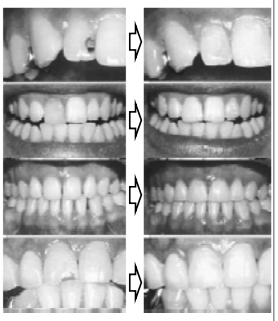
A good idea for a new product that should sell?

- 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

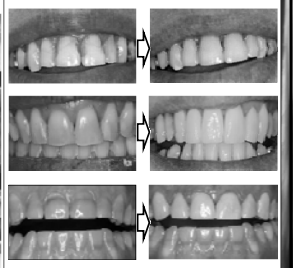


A strong drive for esthetics

Composite polymers

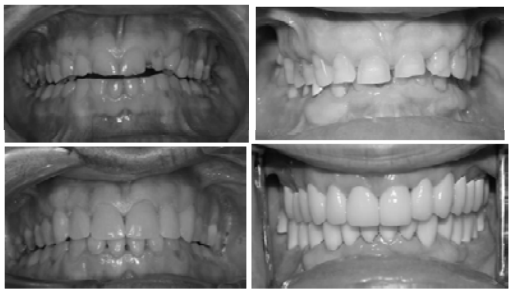


Ceramics



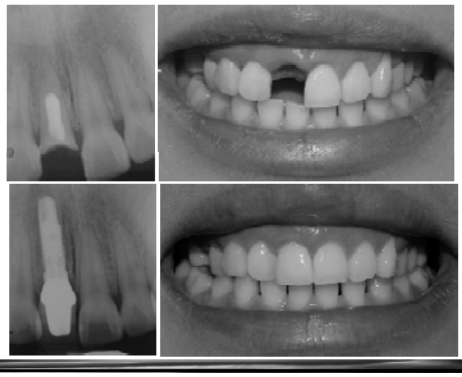
+ new hybrids of Ceramic:Polymer
Chairside handling
CAM additive/subtractive methods

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

Degradation
- Material
- Interface

Wear

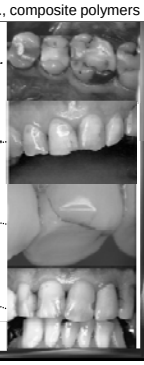
Fracture

Surface roughness

Inadequate interface

(Discoloration
- Bulk
- Marginal)

E.g., composite polymers



Can these adverse outcomes be predicted?

Standardisation initiatives in dentistry

1920 1930 1940 1950

ADA

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

1900

Mid-50ies, first attempts to develop standards

Standardisation initiatives in dentistry

1920 1930 1940 1950 196

ADA

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

Standardisation initiatives in dentistry

ISO TC106 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

Standardisation initiatives in dentistry

ISO TC 106 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

---

Standardisation initiatives in dentistry

ISO TC 106 Dentistry

1980: Paffenbarger, Rupp & Malmstedt.
US. 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)	Uses ISO Standards
International Organization for Standardization (ISO)	24
American Dental Association (ADA)	65
Dental Specifications of Various States of the U.S.A.	10
American National Standards Institute (ANSI)	31
Defense Medical Materiel Board (DMMB) (U.S.A.)	334*
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 (JISQ)	63
Polish Committee of Standardization and Measures (PKNIM)	45
South African Bureau of Standards (SABS)	21
Swedish Planning and Rationalization Institute (Spri)	61

1920 1930 19

ADA

Laboratory tests only
-
What about standards for clinical research?

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,r1991,r1994, r2001: Evaluation of dentin and enamel adhesive materials;1989, r1996, r2001: Composite resins for posterior restorations; 1998: Dentin hypersensitivity; 1998: Whitening products

ADA

Global standardisation work on biomaterials (including dental)

ISO TC106 Dentistry

ISOTC194 Biological evaluation of medical devices

ISOTC210 Quality management and corresponding general aspects for medical devices

Global Harmonization Task Force GHTF 1992-2012

→ International Medical Device Regulators Forum (IMDRF)

1920 1930 1940 1950 1960 1970 1980 1990 2000

ADA

EUCOMED

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

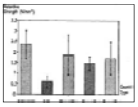
ISO/TC106 Dentistry
SC1 Filling and restorative materials: 14 workgroups
SC2 Prosthodontic materials: 20 workgroups
SC3 Terminology: 4 workgroups
SC4 Dental instruments: 10 workgroups
SC6 Dental equipment: 8 workgroups
SC7 Oral hygiene products: 4 workgroups
SC8 Dental implants: 5 workgroups

SC9 CADCAM: 4 workgroups

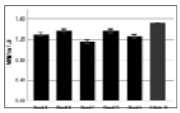
Test validity
- Reproducible
- Known parameters
- Low C.V. (#samples)
- Calibrated devices

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



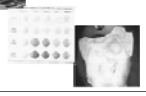
Dynamic tests ?
Compressive modulus
Tensile modulus
Bending modulus
Resilience
Fatigue
Fracture toughness



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. Siegward D. Heintze, Head of Preclinical Research, Ivoclar Vivadent. Dent Mater 2013.**

My top-3 review papers on today's theme

Thank you for your kind attention