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

dental biomaterials

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

AIM: “To discover truth”
Clinical Scientists

AIM: “To provide best care”
Experience challenges
See opportunities
Encounter problems/“complications”

AIM: “To make a profit”
Likelihood of new product:
Predictable performance
Cost – purchase - distribution
Market penetration - competition

Reflective practitioners (on behalf of their patients)

Basic Scientists

Researchers

‘Advisory boards” “Consultants”

Marketing dep.

Manufacturers

Scientific dep.

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

A consequence of the “substantial equivalence” principle
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

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

* and PATENT

Investment costs for advancing a new product

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

Amongst (the few) RCTs, a distinct minority are aimed at product development

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

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

(Scandinavian solution v.z. North America solution)

Materials for restoring lost oral tissues - unwanted clinical performance

- 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

Standardisation initiatives in dentistry

• 1960: 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

1920 1930 1940 1950 1960 1970

Standardisation initiatives in dentistry

US. National Bureau of Standards pub. #571
A listing of the currently available standards throughout the world shows the following

1980 - 1990:
Focus on clinical aspects
• 1974: Acceptance programs for dental materials and devices

• 1977: Guidelines for reporting clinical trials

• 1977: ADA specification #27 for direct filling resins

• 1977: 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

1980's & 1990's: Guidance documents for conducting good clinical 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


Standardisation initiatives in dentistry

1980 - 1990:
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

• 1977: 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

1980's & 1990's: Global standardisation work on biomaterials (including dental)

ISO/TC106 Dentistry


Global Harmonization Task Force GHTF 1992-2012

→ International Medical Device Regulators Forum (IMDRF)

ISO/TC1194 Biological evaluation of medical devices
ISO/TC214 Quality management and corresponding management and general aspects for medical devices

ISO TC106 Products

Australia DMRL ...DSC

Global Medical Device Nomenclature. GMDN Cat.03

ASTM, ANSI, BSI, DIN, AFNOR, NIOM ...

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


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

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.

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

My top-3 review papers on today’s theme

Thank you for your kind attention