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

AIM: “To discover truth”
Basic Scientists
AIM: “To provide best care”
Clinical Scientists
Experience challenges
See opportunities
Encounter problems/“complications”
AIM: “To survey”
Researchers
“Advisory boards” “Consultants”
AIM: “To make a profit”
Manufacturers
Marketing dep.
Stakeholders in advancing innovations

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>
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<tr>
<td>results from animal study(s)*...</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>
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<tr>
<td>results from a Phase 3 trial (confirm safety and efficacy)*...</td>
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</tbody>
</table>

* 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

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

(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)

Can these adverse outcomes be predicted?

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

1920-1950s, first attempts to develop standards

Mid-50ies, first attempts to develop standards


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

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

1980 – “USPHS system (3)”

1981

1982: Recommendations for clinical research protocols for dental materials

1982: Principal requirements for controlled clinical trials of caries preventive agents and procedures

1985: Accepted protocol for clinical research programs

1986: Acceptance programs for controlled clinical trials

1987: Recommended format for protocol for clinical research programs

1990: Good manufacturing practices, including quality assurance for dental materials

1991: Cvar & Ryge, “Ryge system” (Ordinal scale (3))

1992: Recommended standard practices for clinical evaluation of dental materials and devices

1993: Guidelines for reporting clinical trials

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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 Prosthetic 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

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


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

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My top-3 review papers on today’s theme

Thanks you for your kind attention