Biomaterials Enhanced Simulation Test: as alternative towards true 1R implementation

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Surgeons’ verdict:

“There is little or no scientific evidence that newer prostheses are better. The success of implants is guided by quality of biomaterials.”
Market key drivers

- Increased **lengths of hospital stay** and **risk of complications**, supply, etc.
- New **technological advancements** coming (flowable allografts, bone glues)
- **Demographic** factors (increased arthritis, osteoporosis, elderly population, obesity, etc.).
- Patients demanding **alternatives** to TJA to extend their physically-active lives by postponing major surgeries.
- Significant need remain for **soft tissue reinforcement grafts** in sports medicine applications (traumas → faster recovery)
- To develop **alternates** to the “gold standards” under healthcare financial constraints
- Products assessment and validation still in its infancy
- More pressure to develop and market **better biomaterials** and **ATMP solutions**
- Only possible with **new validated** solutions (viscosupplementation, allografts, syntgrafts) → require efforts in their analysis
- **Higher requirements** for these solutions vs. general cases. Need for difficult and ‘uncommon’ joints repair (fingers, rotator cuff, Achilles tendon, knee ligament, cartilage)

**World-wide growing biomaterials market:**

$62,060 millions (2015) → $130,570 millions in 2020 (CAGR 16%)
What are the problems

• Biomaterials need a very high confidence, but no one waits for 10 years follow-up results → lost time and momentum, legal actions risks, obsolete medical technology

• Biomaterials evaluation limited to too oversimplified tests and too expensive in vivo tests (“successful in vivo” → 80-95% fail in clinical trials*) → billions €€€ spent; animals killed for none

• New regulatory issues require a scientifically based evidence → tougher risks and quality management, new special NB for Class IIa/III, no “grandfathering”!

• Changes in the conformity assessment ongoing → the transition clock is down counting for implants and MD producers

True stories:
DePuy → losses ~$2.5B in 2013 to cover hip implants failure caused injuries.
Zimmer → NextGen (2010) and Persona (2015) knee implants withdrawn from the market

* FICAM / EVCAM data, 2014
The need for good-quality evidence is vital for any medical technology or therapy development.

There is a continuous lack of a level of evidence (LoE) established in many studies: publications are often heterogeneous or incomplete, making it difficult for clinicians to evaluate the actual LoE of results and recommendations.

- For example, orthopaedic registers differ in methods of data analysis, have unavoidable errors and variations in reporting, limits the interpretation, makes comparisons difficult.
- In one national hip register, error of 50-55% was estimated (wrong bed, age, gender, missing and incomplete information, etc.)

How to improve the evidence level?
Where is the evidence?

Clinical evidence

But where is *in vitro* LoE?
- ISO standards..
- OECD regulations..
- EU directives..
- FDA guidelines..
- In-house practices..
- “my own experience”..
- “someone said”..

Where’s the key?

Proper **quantification, scientific validation and documentation** of *in vitro* evidence are prerequisites for successful breakthroughs in 3R and true 1R implementation for medical devices, ATMP and pharma products.
LoE problem example

Orthopaedic case

Target: THA

Material: porous/coated Ti alloy

Usual requirements evaluated in separate tests:

- Mechanical
- Biofilm resistance
- Chemical
- Wear
- Biocompatibility

But what do these tests answer about:

- Osteogenesis
- Infection risk
- “Race for space”
- Osteolysis risk
- Stimulus
- Cells metabolism
- Stress transfer
- Microfluidics
- Local conditions
- Nutrients supply
Does theory tell true: viscoelasticity of bone

[Diagram showing various data points and lines relating to viscoelastic properties of bone, with labels for theory and real life areas.]
Viscoelastic fate of bone

How to assess this in vitro?

Extreme gym

Running

Walking

“Lazing in the sunny afternoon”

Number of daily loading cycles

Microstrain

10,000

1000

100

10

1

0.1
Biomaterials testing objectives

Biomaterials must be evaluated in the closest host-like \textit{in vitro} environments, with relevant control of chemical, biological, cytological etc. reactions.

based on:

• **Conditions closest to real life applications**, scientifically \textit{designed} and \textit{optimized}, aiming on predictive outputs (2012/0266/COD)

• Combination of critical \textit{key parameters in minimal tests}, reducing number of specimens, enabling \textit{high-throughput} screening

• **Minimization** animal \textit{in vivo} (2010/63/EC) and clinical tests (2001/20/EC, 2005/28/EC), including “live biomaterials” (ATMP as of 2001/83/EC, 2007/47/EC)

• **Shortening time to market** – eliminating unfeasible solutions at early stages, simulating “worst cases” (2003/94/EC) – a part of quality management and risk minimization actions (2012/0266/COD)
How this can be done

Introducing **BEST**: the **B**iomaterials **E**nhanced **S**imulation **T**est

US and EP patents applied
BEST protocols for biomaterials

Application-driven basic conditions

Biomechanical basic patterns

Media (pH, T, P, rate, compositions, etc.)

Proteins, enzymes, factors

Bacteria, toxins, virions

Pharma (drugs, etc.)

Cells and cells combinations

User-defined

Patient conditions

User-selected combinations

Increasing clinical relevancy

ASTM

ISO

BEST

Application-driven basic conditions

Biomechanical basic patterns

Cells and cells combinations

Proteins, enzymes, factors

Bacteria, toxins, virions

Pharma (drugs, etc.)

User-defined
Evaluation for orthopaedic cases

Different simulation cases to estimate tissue formation probability

**Bone probability:** 93%

**Bone probability:** 45%

Predictive ability with meta-models:

Towards 1R: elimination of animal tests
Benefits with a smart biomaterials evaluation

- **Consistent results**: no fragmented and separate tests → reduced risk of improper measurements – fitted to regulatory requirements
- **Synergetic effects** of different parameters revealed → otherwise impossible to obtain
- **Correct effect** of specimen size and boundary conditions → clinically relevant answers
- **More realistic in vitro conditions** than others → solid evidence – better insurance against claims – less probability of adverse effects
- **Shorter time** for getting the results → higher throughput
- Substantial **costs reduction** → faster and combined experiments
- **Better environmental control**, supported by validated models
- Ability to experiment with **user-specific** and **multi-purpose ‘ghost’ protocols**
BEST one can get for a biomaterial:

- **Varieties of biomaterials tested on:**
  - set of biomechanical-fluidic properties in pseudo-static and dynamics
  - static and dynamic permeability / permittivity for porous biomaterials
  - control of (bio)degradation dynamics / kinetics for/with predictive models
  - consistent comparison between different biomaterials (LD/LO)
  - patient surgery protocol mimicking; customized protocols
  - optionally co-cultures (with pathogens), toxi- and pharma-tests
  - optimization of conditions for fast throughput and lower costs
  - data for risk reduction (3E) and quality assessment
  - data for 3R and true 1R implementation ("not tested on animals")
  - independent expertise of competing MD materials cases – evidence for legal cases
  - extra security for [unannounced] SNB audits

- **BEST is working now for biomaterials in:**
  - dental, macrofacial, cranial, gynaecology, ophthalmology, orthopaedic, plastic surgery, veterinary, ATMP (orthobiology)
What need we BEST for?

Example from new MD Directive (2012/0266/COD):

- prove **MD similarity** for Class III (49 §2.a)
- scientifically **justify equivalency** (XIII.4.a)
- demonstrate earlier **residual risks/effects** (26 §1.a/b)
- verify and validate by tests: **is the MD enough “suited”** (II.6.1)
- enforce **3E for risks management**: “Estimate, Evaluate, Eliminate” (I.1,2.b)
- **demonstrate the compatibility** between materials, tissues and body fluids incorporating processing, modelling, biomechanical properties (I.7)
- prove the tests above **before, during and after manufacturing** (VIII.3.2.e)
- prove elimination/reduction **risk of simultaneous bacterial adhesion** (I.8.1)
- prepare enough information for earlier clinical trials (50 §5)
SUMMARY

• A lot of issues still to be resolved for better biomaterials!
• New solutions vs. costs, community demands, quality/risk control
• Infections are on the critical level now → “race for space” knowledge and non-antibiotic cure options are insufficient
• Regulatory pressures demand higher responsibility from MD manufacturers – but who is paying the bill?
• Market requires more efficiency – but financial pressures obstruct: these are not options for patients → suffering, costs, legal, insurance…
• Biomaterials in vitro evaluation/screening can be improved with combined scientifically based tests and models with multi-purpose protocols → BEST can secure patient safety of a medical device by certifying biomaterial in hostile-like conditions
• Multidisciplinary joint effort is needed from all stakeholders!
THANK YOU!

Let’s make **NEW GEN**eration of biomaterials the BEST one!