
Evaluation and regulatory policy
tissue-engineered technologies in
healthcare systems
HTAi Rome, June 2005

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Evaluation and regulatory policy: tissue-engineered technologies in healthcare systems

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Questions

- What forms of evaluation are used and needed for hybrid, combination technologies such as ‘human-derived therapeutic products’?
- How do TE technologies affect evaluative regulatory policy and healthcare practice ?

Regulatory evaluation

- Evaluation of ‘risks’ & ‘benefits’ clinically and societally complex, new hazards non-predictable
- Regulatory policy includes representations of (‘evaluation’ of) social values & ethics
- Rules of evidence/evaluation contested, negotiable, uncertain and changeable

Domains of regulatory evaluation

- Safety & quality *(technology)*
- Efficacy/effectiveness *(system)*
- Other values – 'social shaping'/ acceptability *(system, society)*

Device
Pharmaceutical
Biologic
TE?

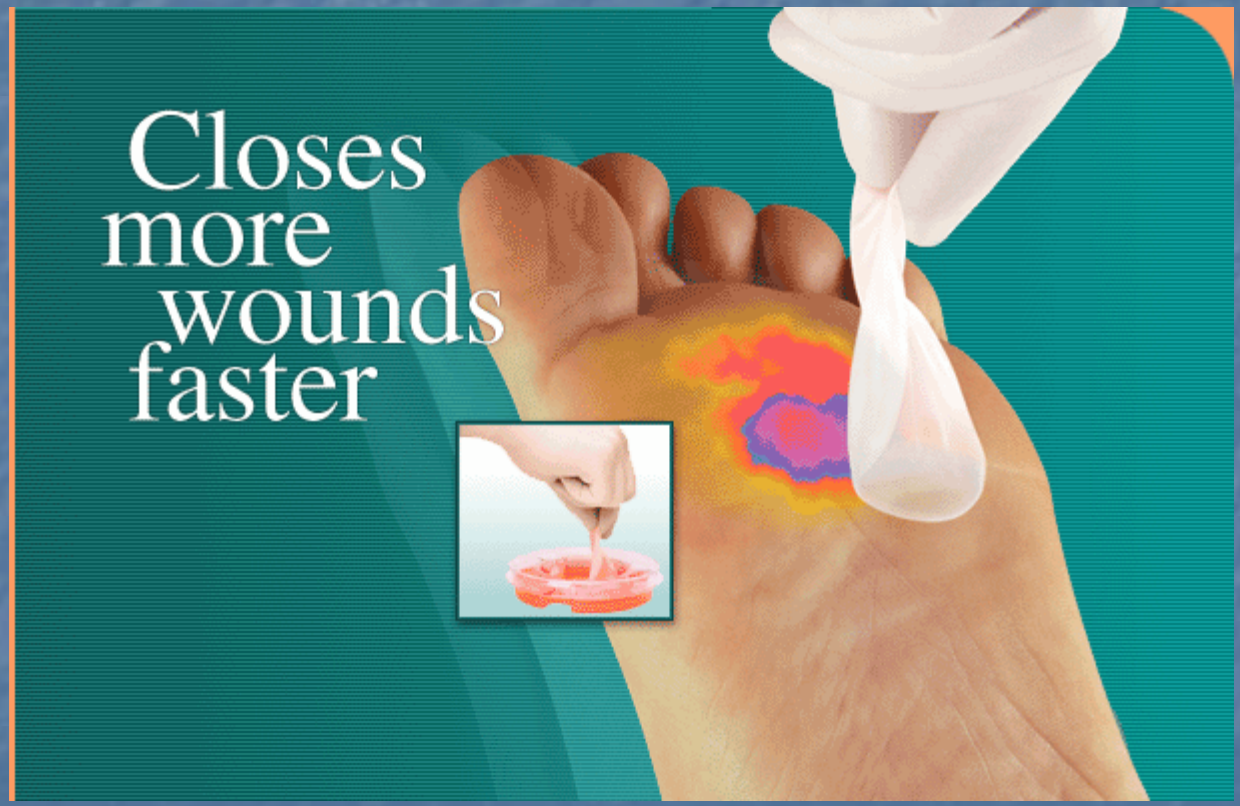
One definition of TE technology

"The use of living cells, together with either natural or synthetic extracellular components, in the development of implantable parts or devices for the restoration or replacement of function"

Combining TE materials

- Viable human cells or tissue e.g. chondrocytes
- Growth factors
- Cell culture materials – human serum, bovine and/or murine cells
- Manufactured biomaterials e.g. polymer scaffolds
- *Single OR multiple recipient products*

Skin system: Apligraf®



Apligraf® skin system - safety

- **Composition**
  'APLIGRAF is supplied as a living, bi-layered skin substitute.† Like human skin, APLIGRAF consists of living cells and structural proteins. The lower dermal layer combines bovine type 1 collagen and human fibroblasts (dermal cells), which produce additional matrix proteins.....'

- **Safety testing**
  The mother's blood and donor's cells are thoroughly screened and found negative for pathogens and other contaminants. The working cell banks are then further screened to help ensure product safety.

- *The persistence of Apligraf cells on the wound and the safety of this device in venous ulcer patients beyond 1 year and in diabetic foot ulcer patients beyond six months has not been evaluated.*

Source: Organogenesis Inc. website 2003

Cost effectiveness

- ‘Apligraf plus ‘good wound care’ treatment result in 12% reduction in cost over one year vs. gwc only’*
- TE for wounds: ‘still weak scientific basis for the cost-effectiveness of TE treatments for skin ulcers, Apligraf seems to have proven effectiveness’.** (MEDLINE, Cochrane Library, NHS Centre for Reviews and Dissemination, German Agency for HTA).

**Redekop et al in Pharmacoeconomics 2003 (Inst. For Med, Technol Assessment, Rotterdam)*

*** Bührlen & Hüsing, Fraunhofer Institute for EC JRC-IPTS, 2003*

HTA effectiveness (+safety?) – Cochrane review

- *Headline:* 'bilayer artificial skin, used in conjunction with compression bandaging, increases the chance of healing a venous ulcer compared with compression and a simple dressing'. (2 RCTs)
- *Noted-in-passing:* 'The most serious concern with allogeneic skin is the possibility of transmission of infection, particularly of the human immunodeficiency virus (HIV) or hepatitis. Even with rigorous screening it is still possible that skin could be harvested from an HIV-infected but seronegative donor'.

(Jones and Nelson, Skin grafting for venous leg ulcers, Cochrane Library 2000)

Challenges to evaluation: device or pharmaceutical or TE?

'..In the US Apligraf was seen as a device...the only issue was to prove the product was not contaminated ..unlike medicinal products *there was no need to demonstrate safety, no toxicology testing or evidence of efficacy* was needed...In April 2001 there was the BSE scare and Germany put pressure on the EMEA to see Apligraf as a medicinal product...the product is very complex..... *company had to define and devise tests for the product and then test it*'

(M-EU6, 2003)

device or pharmaceutical or TE.....or xenotransplant?

- ‘hTEPs containing not intentionally small quantities or traces of material of animal origin (used during the manufacturing process) which do not perform any function *in the finished product* are not, for the purpose of this regulation, regarded as xenogenic products.’

(EuropaBio et al 2004)

Challenges to evaluation – safety and effectiveness

'....(question) whether RCTs are, in fact, always the "gold standard" of evidence. This appears to be an appropriate time to explore the extent to which surface characterization measurements, bench-top experiments, gene expression measurements, and/or simulation can be effectively extrapolated to confidently assess safety and effectiveness'.

(MTLF, 2002)

Challenges to evaluation - safety of TE technologies

Requirements for:

- New assays
- Nontraditonal animal models – eg transgenic animals, larger - but statistical problems
- Testability problems (short shelflife)
- New endpoints eg genotoxicity, immunogenicity

(Regulator/industry forum 2003)

Challenges to evaluation – social shaping/acceptability

"Currently, consent is not obtained when biological products (including allografts and xenografts) are applied to patients belonging to diverse religious and cultural backgrounds. Furthermore, the awareness of the healthcare professionals about the constituents of biological products has never been evaluated nor whether they have the necessary knowledge to obtain informed consent from patients being treated with such material".

Enoch S, Shaaban H and Dunn KW. Informed consent should be obtained from patients to use products (skin substitutes) and dressings containing biological material *J Med Ethics* 2005;31:2-6.

contd..... Enoch *et al* survey results for specialist healthcare professionals (n=100, multi-sites, UK):

Product includes 'pig' or 'cow' biol.material	**Applica-tion**	**% "don't know"**
Apligraf	burns, ulcers	68%
Biobrane	biol. dressing	57%
Integra	burns	30%
Alloderm	burns	74%

Conclusions

- Tissue *sourcing* evaluable for safety and social shaping/acceptability, not HTA
- ‘Social shaping’, acceptability, ‘consent’
- More social values assessment – complexity of healthcare delivery
- Trials as a route to ‘approval’
- Separability of evaluation domains? - pressure of material technology regulatory framing, social meanings