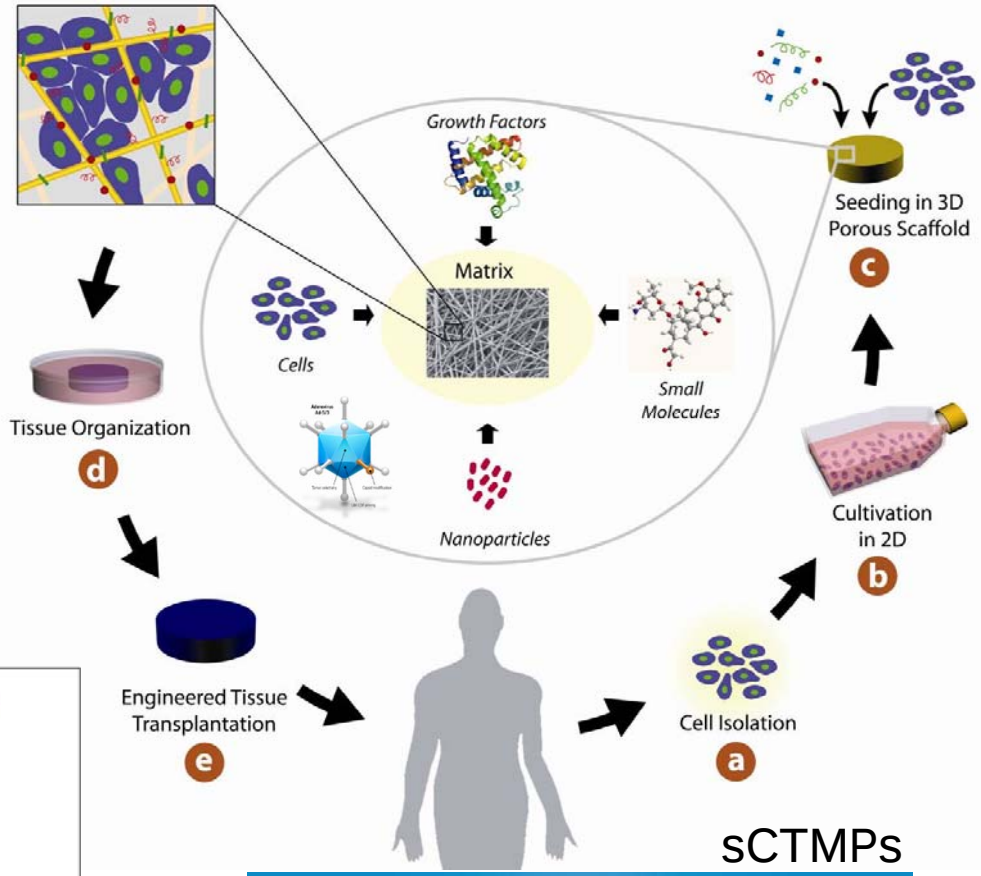
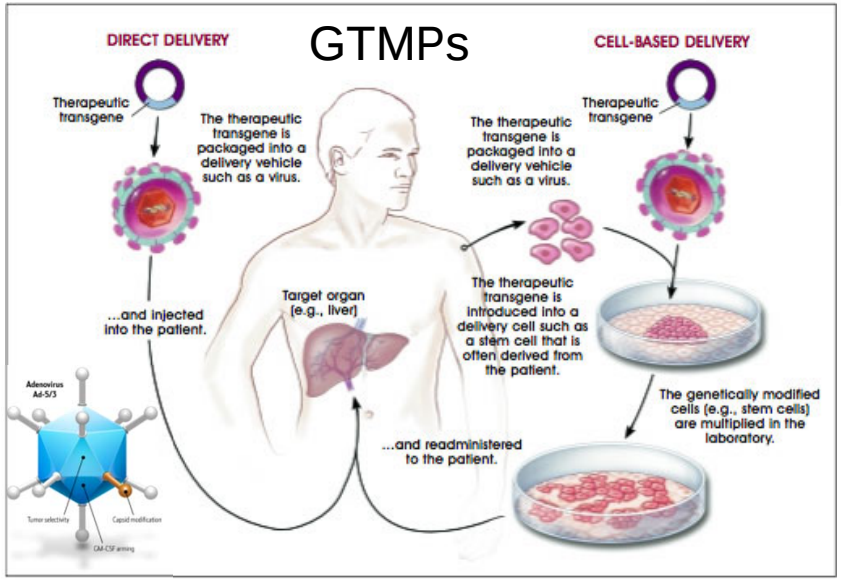
Risk-based approach applied to Advanced Therapy Medicinal Products

Lääkealan turvallisuus- ja kehittämiskeskuksen (Fimea) keskustelutilaisuus kehittyneen terapian valmisteista (ATMP) 4.2.2015

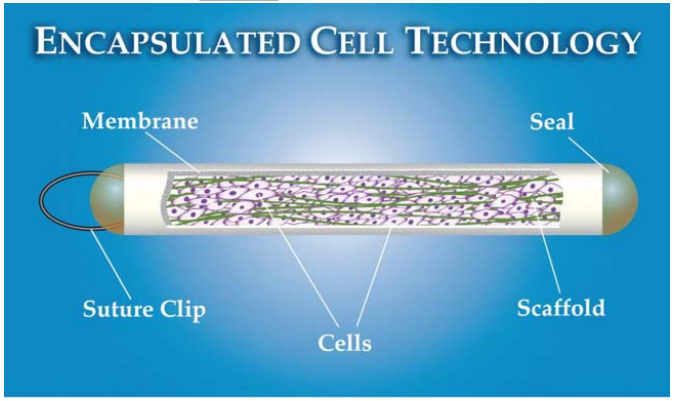
TEPs



GTMPs



sCTMPs



MAA, Classifications, Certifications, SA, PIP

ATMPs

Period: 2009 - 2014
Date of analysis: 23/01/2014
Update: 23/06/2014
update: 20/01/2015

	2009	2010	2011	2012	2013	2014	Total	
MAA's	3	1	2	3	2	4	15	15 Rapp appointments, 13 MAA's submitted
Classification	22	19	12	17	20	28	123	submitted classifications
Certification	1	0	0	1	3	1	6	submitted certifications
SA	17	19	21	19	23	33	132	number of SA procedures
PIP	3	4	4	8	5	6	30	number of PIPs

Data provided by Patrick Celis - CAT secretariat / EMA,
courtesy of Margarida Menezes-Ferreira / CAT

ATMPs on the market and the future

5 ATMPs approved so far, 4 other under review,
> 3 expected to start in next 12 mo

- **ChondroCelect** - TEP / Approved on 5 October 2009
- **Glybera** - GTMP / Approved on 25 October 2012
- **MACI** – TEP, combined ATMP / Approved on 27 June 2013
- **Provenge** – CBMP / Approved on 6 September 2013
- **Holoclar** – CBMP / Pending EC Approval on 6 December2014
  1st stem cell approved
  moderate to severe limbal stem-cell deficiency due to ocular burns
  CONDITIONAL

✓ 4 applications withdrawn prior to approval

❖ **4 new approval procedures on going:** 2 GTMP, 2 CBMP
- ophtalmology, haematology, oncology, metabolic disorders

Slide gently provided by Lisbeth Barkholt (MPA, SE / EMA) – adapted,
Courtecy of Margarida Menezes-Ferreira / CAT

Paralysed man Darek Fidyka walks again after pioneering surgery

Medical team regrow cells of patient's severed spine in breakthrough that offers hope to millions with disability

Ben Quinn and agencies
The Guardian, Tuesday 21 October 2014

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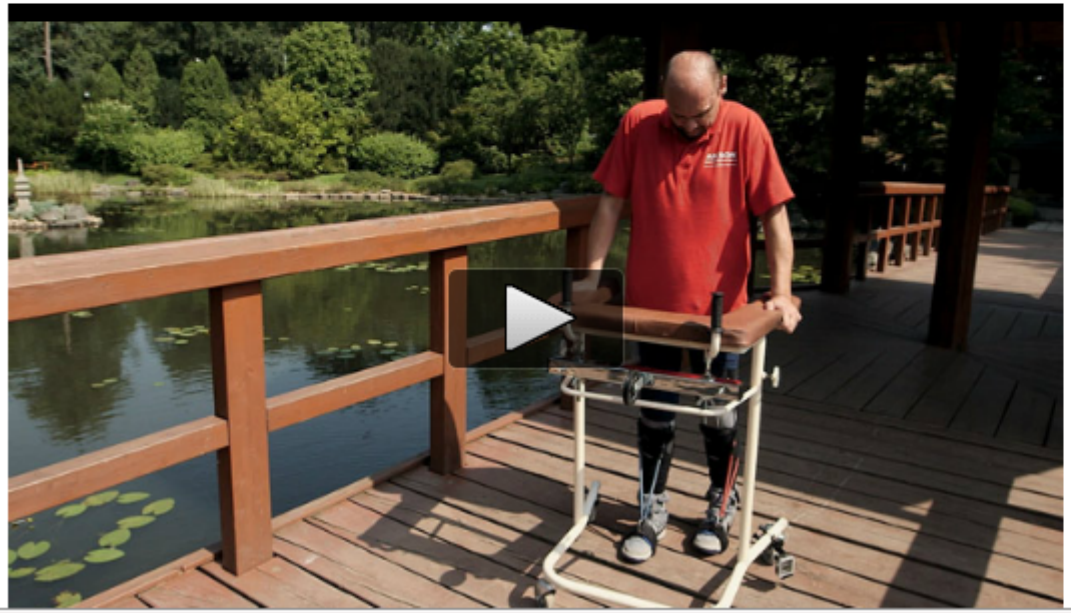

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Stem cell treatment causes nasal growth in woman's back

› 09:00 08 July 2014 by Clare Wilson
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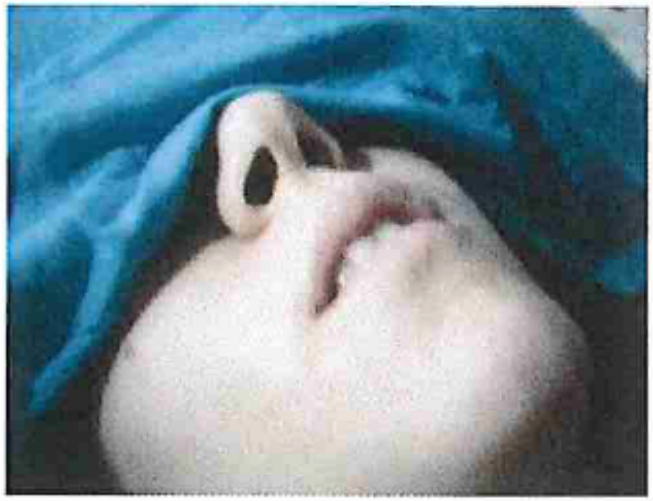
A woman in the US has developed a tumour-like growth eight years after a stem cell treatment to cure her paralysis failed. There have been a handful of cases of stem cell treatments causing growths but this appears to be the first in which the treatment was given at a Western hospital as part of an approved clinical trial.

At a hospital in Portugal, the unnamed woman, a US citizen, had tissue containing olfactory stem cells taken from her nose and implanted in her spine. The hope was that these cells would develop into neural cells and help repair the nerve damage to the woman's spine. The treatment did not work – far from it. Last year the woman, then 28, underwent surgery because of worsening pain at the implant site.

The surgeons removed a 3-centimetre-long growth, which was found to be mainly nasal tissue, as well as bits of bone and tiny nerve branches that had not connected with the spinal nerves.

The growth wasn't cancerous, but it was secreting a "thick copious mucus-like material", which is probably why it was pressing painfully on her spine, says Brian Dlouhy at the University of Iowa Hospitals and Clinics in Iowa City, the neurosurgeon who removed the growth. The results of the surgery have now been published.



Cells taken from the nose may have great potential *(Image: Getty Images/WIN-Initiative)*

Risks vs. limitations of ATMPs

- infections (microbial contamination of starting materials or during processing)
- tumourigenicity (cell transformation, integration to genome)
- dedifferentation / loss of function of the cells
- immunogenicity, rejection
- ectopic engraftment of cells to non-target tissues
- shedding (germ line, environment)
- small sample sizes, short shelf-lives, availability of proper animal models, applicability of analytical methods etc.

→ Risk-based approach for all ATMPs

Risk-based approach

- A risk-based approach can be applied for all CBMPs (GL on cell-based products, CHMP/CPWP/410869/06)
- the risk-based approach for all ATMPs included into the legislation (revised Annex I, Part IV, Dir. 2001/83/EC)
- The risk analysis should cover the whole development and should be used to determine the amount of data needed in the MAA
- initial risk evaluation to be included in module 2 of the MAA
- GL on risk-based approach adopted by CAT and CHMP in February 2013
- GL drafted by CPWP and GTWP; Dr. E.Flory and Dr. Mathias Renner rapporteurs of the GL

GL-Structure on RBA

Executive summary

1. Introduction (background)
2. Scope
3. Legal basis
4. Methodology of the risk-based approach
    - Definition of Risks and Risk factors
    - Definition of Risk profiling
    - Fictious examples to illustrate the risk-based approach
5. Consequences for MAA dossier
6. References and glossary

Risk

- Definition “Unfavourable effect that can be attributed to the ATMP and is of concern to the patient and/or to third parties”

- Risks include risks to the patient, other populations (e.g. caregivers) and off-spring.

- Risk identification should start as early as product development

Risk factors

- Definition “qualitative or quantitative characteristics that contribute to a specific risk following administration of an ATMP”.

- Aspects that should be taken into account when identifying risk factors include, but are not limited to the nature of the product, non-cellular components, biodistribution, manufacturing issues and clinical aspects.

Examples of potential risk factors

- Origin of cells (autologous vs allogeneic)
- Ability to proliferate and differentiate
- Ability to initiate an immune response (as target or effector) / vector immunogenicity
- Level of cell / GTP manipulation (in vitro / ex vivo expansion/activation, genetic manipulation)
- Aspects of manufacturing process including non-cellular components
- Mode of administration (ex vivo perfusion, local, systemic)
- Duration of exposure (short to permanent)
- Integration potential of the vector
- Potential for biodistribution to non-target sites etc.

Conclusions on the risk factor – risk relationships

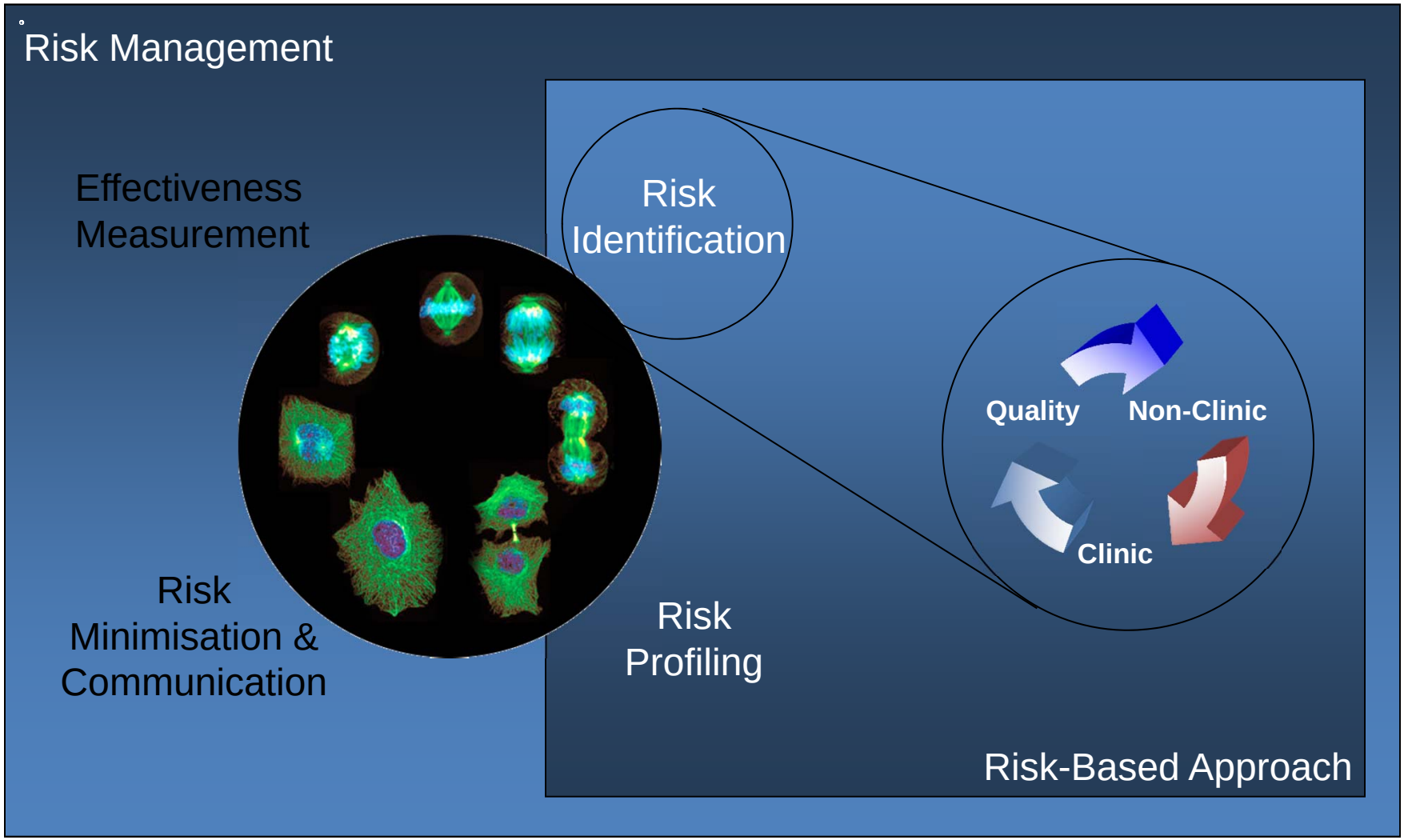
- RBA may be presented in form of a matrix table as outlined in the example tables and as narrative text addressing risks and risk factors identified to be of relevance for the use of the respective ATMP.

- Risk factor-risk combinations for which a reasonable relationship has been identified should be further detailed

- Studies that have been performed to address the impact of the identified risks and risk factors should be provided. If studies are omitted, a scientifically sound justification is needed

- A conclusion whether the provided scientific data (quality, non-clinical and clinical) and published information addressing the individual risk factor-risk combinations are considered adequate and sufficient to support MAA (and possible risk mitigation actions)

Risk Risk factor	Tumour formation	Unwanted immunogenicity	Treatment failure	Disease transmission	Unwanted tissue formation	Toxicity
Cell starting material						
Culture conditions	Risk for cell transformation due to culture conditions. Limit to population doubling, CTD 3.2.S.2.4. & 5, literature data for similar products and cell senescence studies. CTD 3.2.S.2.5 -Process validation and/or evaluation & 3.2.S.4.2. - Analytical procedures.	Potential for immune reaction in patient. Removal of animal-derived materials and antibiotics. CTD - 3.2.S.2.3 - Control of materials, 3.2.S.3.2 - Impurities.	Influence of cell culture (i.e. time, population doublings) on chondrocyte senescence / dedifferentiation may result in treatment failure. Control of population doublings. CTD 3.2.S.2.3 - Control of materials, 3.2.S.3 - Characterisation, cartilage formation model in vivo. CTD 4.2.2.3 - Pharmacokinetics - Distribution	Potential for mycoplasma contamination. Microbiological control. - CTD 3.2.A.2 - Adventitious Agents Safety Evaluation		
Relevance of the animal model	Age, dosing, immuno-competence and duration of animal study not appropriate for detection of tumour formation. Tumourigenicity Study CTD 4.2.3.4 - Toxicology - Carcinogenicity		Available animal model is not reflecting human disease. See proof of concept. - CTD 4.2.1 - Pharmacology and discussion in CTD 2.4 - Non -clinical overview			
Patient-related		Risk for unwanted immunogenicity due to patient history (Allergy to components of product). Patient selection criteria (Contraindication), pre-treatment testing for allergies. CTD 5.3 - Clinical study reports	Risk for treatment failure due to patient history (age, suboptimal microenvironment) and insufficient dose finding data. Determination of age optimum and dose limits based on in vivo and/or in vitro testing CTD 5.3 - Clinical study reports		Risk for unwanted tissue formation due to microenvironment (lack of maturation in situ, scar tissue formation) CTD 2.5.- Clinical overview	
Disease-related			Risk for cell failure to differentiate due to chronic inflammation and other factors. Stratification based on patient history and pre-treatment testing. Reports of efficacy and safety studies and Post-marketing studies. CTD 5.3.5 - Reports of efficacy and safety studies, 5.3.6 - Reports of post-marketing experience and 5.3.7 - Case report forms and individual patient listings			



Picture provided by Dr. Egbert Flory, PEI

Risk-based approach

- Is not a traditional Risk analysis such as used for Medical devices or quality control of MPs.
- Does not provide a rigid classification system of different risks of a product as whole (e.g. High-risk product vs. low-risk product)
- Should be distinguished from Benefit/Risk Assessment, Environment Assessment and Risk Management in the context of MAA evaluation
- Is intended to provide flexibility to regulation of ATMPs

Thank you for your attention!

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000405.jsp&mid=WC0b01ac058002958a