Cell-based medicinal products for clinical trials - Advice on data requirements

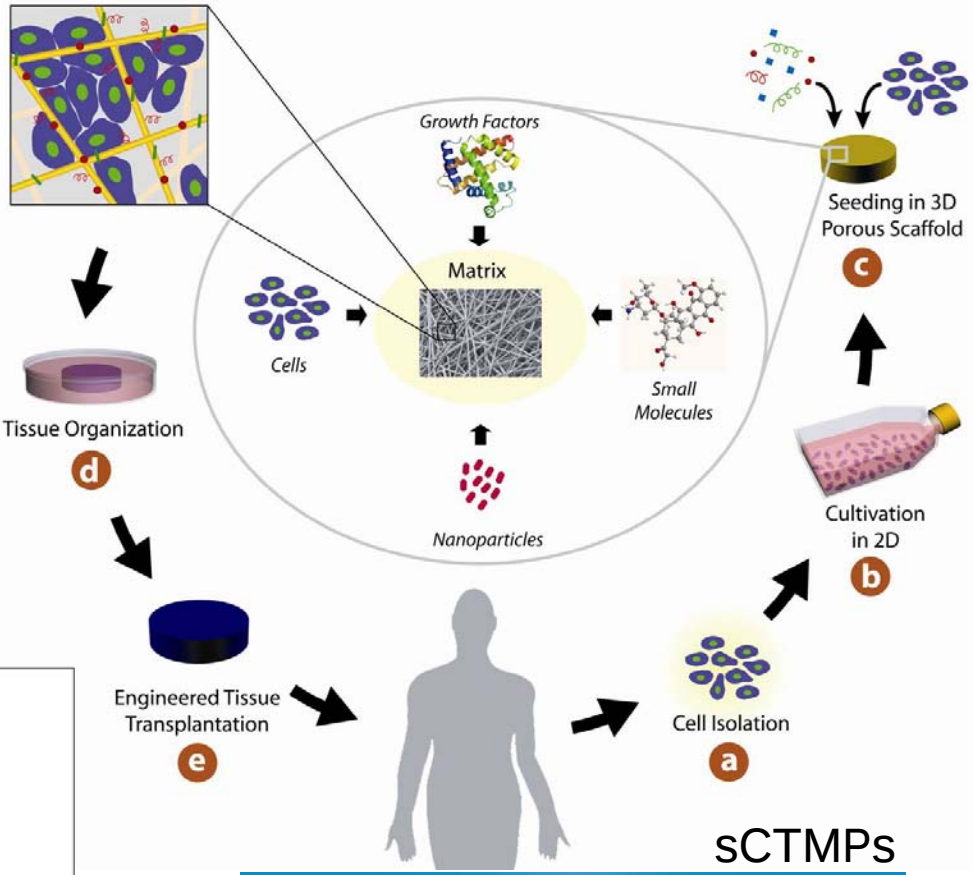
PDA/IMB meeting Dublin 11.7.2012

Disclaimer: The views expressed in this presentation are those of the speaker and do not represent official opinion of EMA or any of its´ committees. The views are based on EU legislation and guidelines.

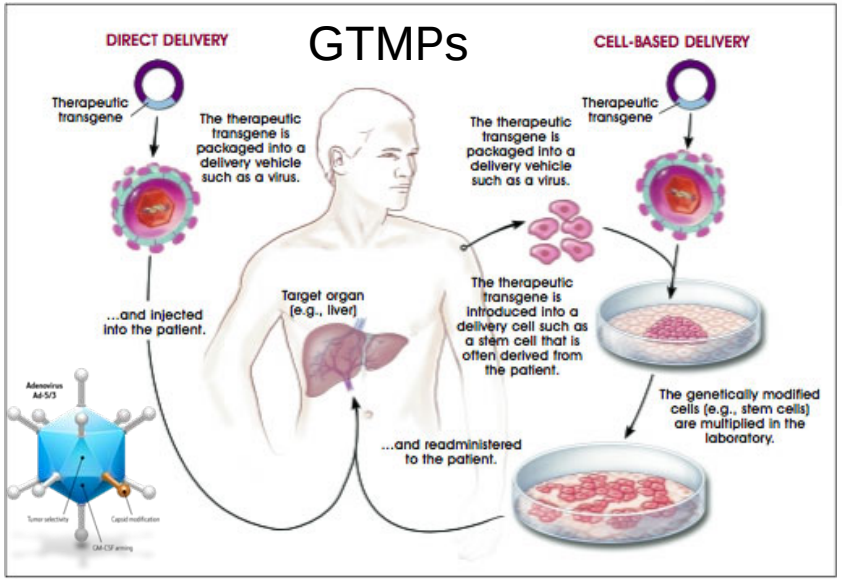
Topics for discussion

- latest experiences of CBMPs in clinical trials
- GMP/GCP requirements for clinical trials
- quality and non-clinical issues to be considered before conduct of clinical trials
- factors of successful clinical development
- available guidance for cell-based medicinal products
- risk-based approach also part of clinical development

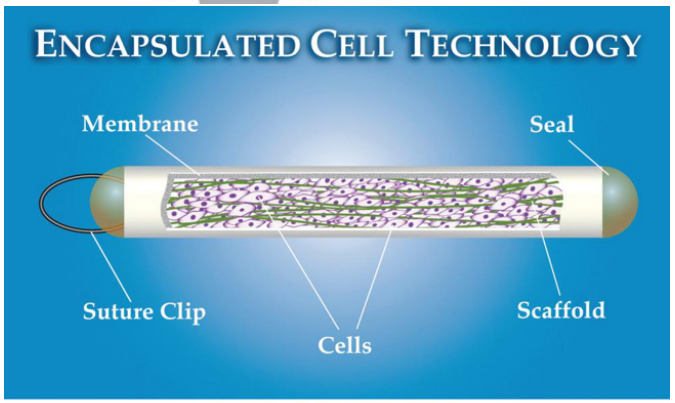
TEPs



GTMPs



sCTMPs



MA experience of ATMPs

- Chondrocyte-containing product for treatment of cartilage defects (Carticel, Genzyme US 1996)
- Tissue-engineered skin as the first approved combination product (Apligraf, US 1998)
- Provenge first approved cancer immunotherapy product (US 2010)
- Hemacord for HSC transplantation (US 2011), LaViV fibroblasts for wrinkles (US 2011)
- ChondroCelect first CBMP to gain a MA licence in EU (2009)
- 3 CBMPs evaluated thus far in EU, four ongoing, two initiating 2012
- appr. 20-30 CBMPs on national markets in EU, which should apply for centralised MAA by the end of 2012?
- over 300 companies worldwide developing CBMPs

Novel ATMPs in clinical trials / EU

IMPs	2005	2006	2007	2008	2009	2010	2011*
GTMP	9	23	35	59	75	99	**119**
sCTMP	8	47	84	123	162	239	**288**
TEP	5	12	28	48	74	80	**90**

Main indications:

- Cancer immunotherapy (sCTMP and GTMP)
- cardio-vascular
- TEPs for repair of skin/eye/liver/bone/cartilage
- vaccines (GTMPs for HIV, HPV, HCV etc.)

•Cumulative number of new applications (report is suggestive and should not be considered exhaustive)

-CBMPs are potentially important for health care; many products are for indications, where limited or no treatment options are available

Clinical trials

- approval of clinical trials within the remit of national authorities

- legal framework in Dir. 2001/20/EC (under revision)

- voluntary harmonisation procedure (VHP) possible for multicenter studies (one evaluation team, other agencies comment the evaluation report and accept the final outcome) (CTFG, see http://www.hma.eu/78.pdf)

-no harmonised guidance for IMPs or conduct of clinical trials for cell-based medicinal products (CBMPs); however, CBMP guidance includes also requirements for clinical studies which will form part of a MAA and those requirements should be consulted

GMP requirements for clinical trials

- 2001/20/EC: each batch of investigational medicinal products should be manufactured and checked in compliance with the requirements of Commission Directive 91/356/EEC laying down the principles and guidelines of good manufacturing practice for medicinal products for human use

- GMP Annex 13 for IMPs (2010)

GMP related issues

- manufacture and release of the IMPs under control of a qualified person (QP)
- requirements for quality management, personel, premises and equipment, documentation, production, quality control, batch release, labelling, shipping, handling of complaints, recalls and returns
- production processes for IMPs are not expected to be validated to the extent necessary for routine production but premises and equipment are expected to be qualified
- aseptic and sterilising processes, viral safety and removal of impurities should be of same standard as defined in guidance

GCP requirements

- protection of clinical trial subjects
- informed concent from subjects, special provisions when minors or incapacitated adults are part of the study
- approval by ethical committee
- manufacture of the medicinal product authorised by national competent authorities (NCA)
- protocol and conduct of the trial authorised by NCA
- follow-up and reporting of adverse event (AE + SAE)
- reporting of the results to NCA(s)

Quality issues for consideration

- manufacturing process should be able to produce consistent, good quality product
  → characterisation of the product and definition of specifications and IPCs important for consistency evaluation

- product characterisation should provide information on critical parameters of the cells/product and tools for IPC/release and stability testing, setting limits for composition, dose and level of impurities

- if the product or its´ manufacturing process are changed during or after the pivotal clinical studies, comparability of the product before and after the change(s) has to be demonstrated

Critical parameters of cells/GTMPs?

Critical parameters of most MPs are related to molecular integrity;

Critical parameters of cells and GTMPs

- should safeguard both structural and functional integrity of the cells / GTMPs

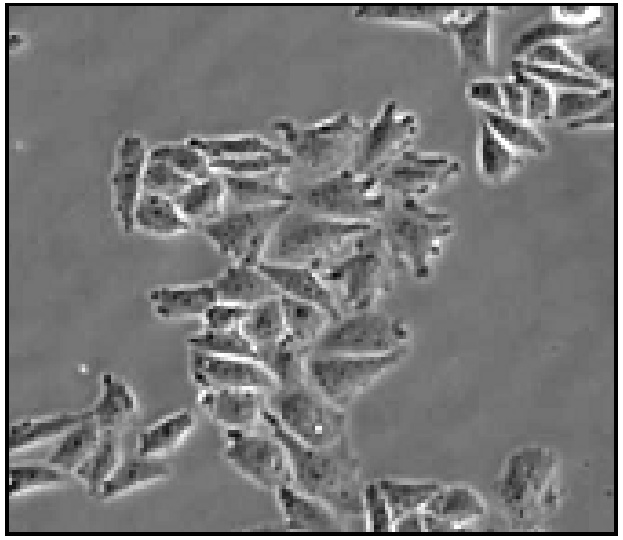
-should be able to reflect changes in complexed, dynamic and viable entities

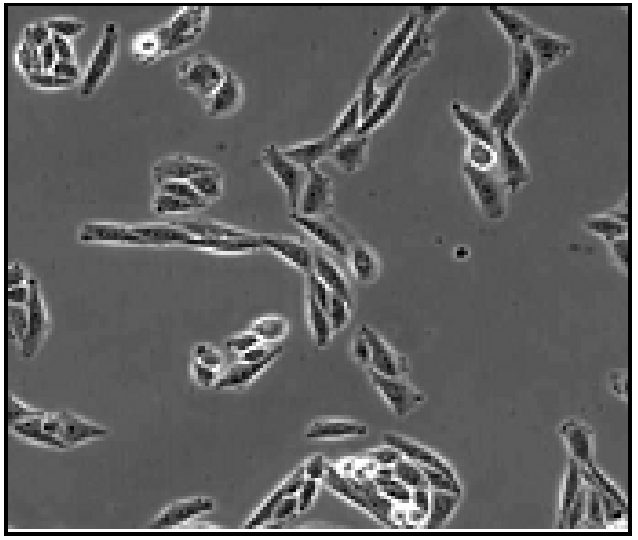
Main quality aspects to be considered

- starting materials
- identity
- purity / impurities, sterility
- potency
- karyology / tumourigenicity
- biocompatibility
- consistency / IPCs, aseptic process validation
- stability

→ requirements dependent on the phase of development; i.e. in phase I/II safety aspects in scope, for phase III requirements are more stringent

Comparability?





CHO cells, plated under different conditions, exhibit different cellular morphology.
(Bucher Biotech)

Cells do change when culture conditions are changed!

Risk mitigation by quality management

- Appropriately defined product (characterisation)
- Good quality starting materials
- Aseptic manufacturing process
- Consistency of the process and of the product
- Feasible quality control system (IPCs, release, stability and comparability testing)
- Suitable, qualified analytical tools

Safety

- safety should be built within the product
  - risk mitigation through proper quality management
  - evaluation of remaining risks through NC and C studies
- non-clinical studies should
  - provide information on toxicological effects predictive of the human response; choice of animal models of outmost importance
  - support selection of a safe dose
  - support the choice for route of administration and follow-up of patients
  - demonstrate safety and suitability of all components of the product
- clinical studies should
  - provide pivotal evidence of safety in target population
  - identify possible risks to be covered by proper PM safety follow-up (risk-management plan)

Pro´s and con´s of the non-clinical development

- conventional pharmacological and toxicological testing may not always be appropriate, instead parameters such as viability, longevity, distribution,growth, differentiation and migration should be investigated

- for some pharmacological and toxicological aspects, data can be gained only by animal studies (biodistribution, ectopic engraftment, graft alignment to the surrounding tissue etc.)

- Relevant animal models?

→appropriate disease models rarely exist

→immunocompromised animals may have limited value

→ structural and functional similarity of the target organ / tissue/ cells between animals and humans?

→ Homologous models?

→ Weight of information gained through NC studies (PoC, toxicology, pharmacokinetics)? In vivo / in vitro?

Efficacy

- proof of efficacy through exploratory and pivotal clinical studies
- for CBMPs special limitations and challenges have to be carefully considered before phase III
- data should establish a link from the quality of the product to the clinical outcome (need to analyse the root cause of treatment failures); especially important for CBMPs
- proof of efficacy for ATMPs can be partly addressed also post marketing (article 14), but even in this case positive B/R profile at the time of MA is a prerequisite for further commitments

Points to consider in clinical development

- Properly defined and controlled product, consistent production?
- If changes made during development, is the product comparable?
- Study design (end-points, patient group, comparator, blinding etc.)
- Validity of surrogate markers, if used
- Duration and follow-up of patients
- Concomitant treatments (surgical and medical)
- Training of the health care personnel

Risk-based approach for all ATMPs

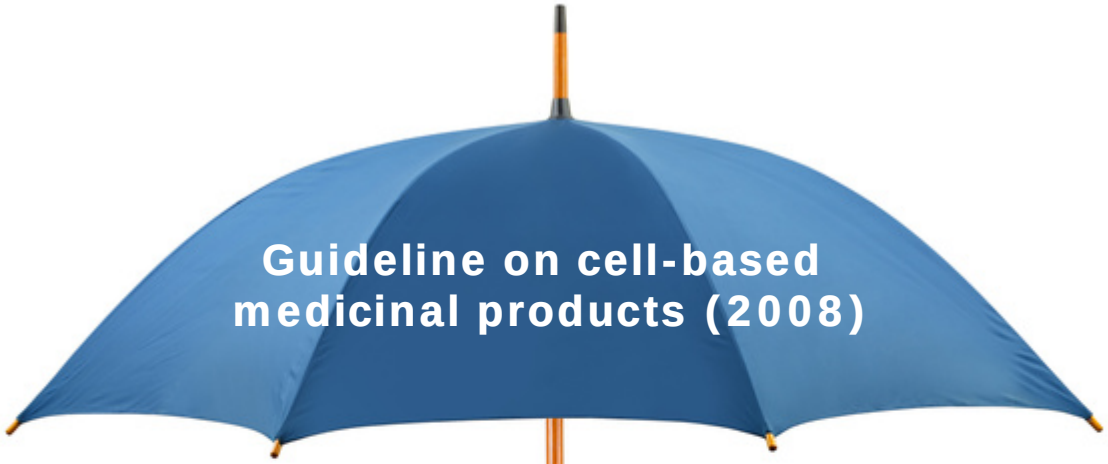
- A risk-based approach can be applied for all CBMPs (GL on cell-based products, CHMP/CPWP/410869/06)
- the risk-based approach for all ATMPs included into the legislation (revised Annex I, Part IV, Dir. 2001/83/EC)
- The risk analysis should cover the whole development and should be used to determine the amount of data needed in the MAA
- further guidance under development (CHMP/CPWP/708420/09)

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

Available guidance for CBMPs



Potency testing of cell-based immunotherapy MPs for treatment of cancer (2007)

Reflection paper on stem-cell based MPs (2011)

Reflection paper on Chondrocyte containing MPs for cartilage repair (2009)

Guideline on Risk-based approach for ATMPs

Guideline on Xenogeneic CBMPs (2009)

Guideline on MPs containing genetically modified cells (2012)

Other applicable EU guidance

GMP Guideline Annex 13

Guideline on Safety and Efficacy Follow-up – Risk Management of ATMPs

Available disease specific guidance

Ph.Eur. monographs

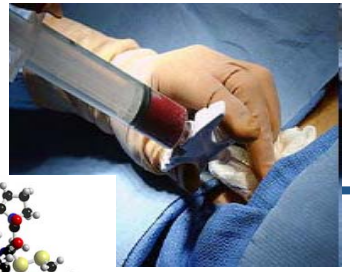
EMA / ICH guidelines Q, S, E

traceability guidance

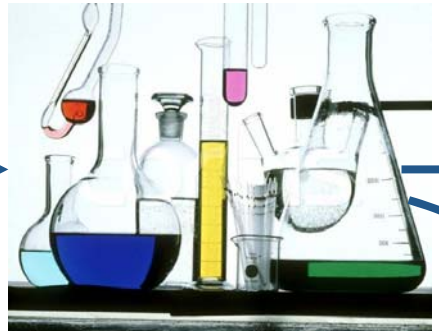
GCP guidance

http://www.ema.europa.eu/htms/human/humanguidelines/biologicals.htm

”Retrospective” product development

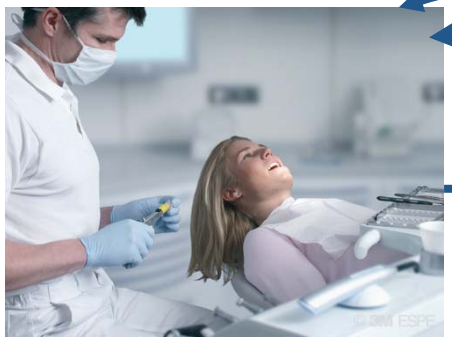


Idea/molecule



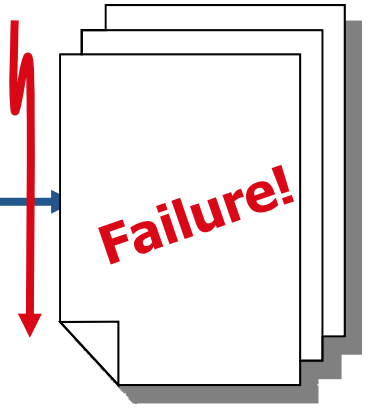
R&D
Pilot production

Preclinical testing



Clinical studies
Phase I-III

Characterisation, analytical testing,
upscale of production



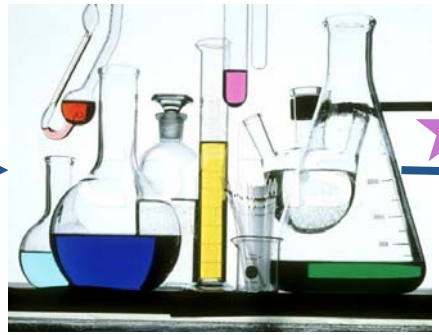
MAA

★=scientific advice

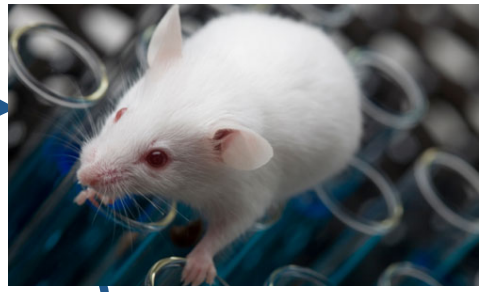
x years

Prospective product development for ATMPs

Idea/molecule

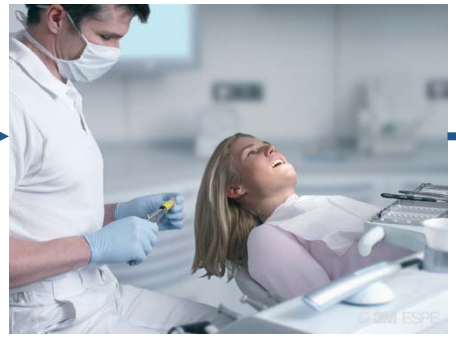


R&D
Pilot production



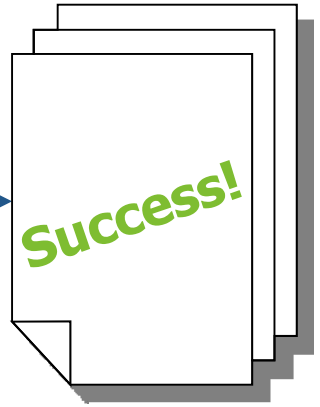
Preclinical testing

Characterisation,
analytical testing



Clinical studies
Phase I-III

Commercial production



MAA

★ = scientific advice ★ = guidance

☺ Thank you!