EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Introduction and Regulatory update

Workshop on Scientific and Regulatory Challenges of Genetically Modified Cell-based Cancer Immunotherapy Products, 15.11.2016 London

Paula Salmikangas
CAT Chair

CANCERS SURVIVAL RATES UP

Fewer men & women die

CANCER SURVIVAL RATES		
Percentage alive after five years		
2007	BEST (MEN)	2016
96.2%	Testicular	96.8%
81.1%	Skin	87.1%
80.2%	Hodgkin's lymphoma	84.5%
77%	Prostate	83.6%
54.7%	Non Hodgkin's lymphoma	66.1%
2007	BEST (WOMEN)	2016
89.6%	Skin	92.6%
No data	Thyroid	89.5%
82%	Breast	86.3%
81.3%	Hodgkin's lymphoma	86%
75.5%	Womb	77.8%
2007	WORST (MEN)	2016
3.1%	Pancreas	6.2%
8.7%	Lung	15.5%
12.7%	Liver	17.6%
16.4%	Gullet	21.1%
13.8%	Stomach	21.7%
2007	WORST (WOMEN)	2016
3.1%	Pancreas	6.2%
8.7%	Lung	15.5%
12.7%	Gullet	17.6%
16.4%	Stomach	21.1%
13.8%	Brain	21.7%

By PAT HAGAN

MORE Brits than ever are surviving cancer, it was revealed yesterday.

The cut in the death toll follows a marked improvement in treatment over nine years.

Almost 84 per cent of men with prostate cancer are still alive five years after being diagnosed, latest figures from the Office for National Statistics show.

That compares with just 77 per cent in 2007. Meanwhile testicular cancer survival rates have hit 96.8 per cent.

Among women with breast cancer 86.3 per cent survive. The figure nine years ago was 82 per cent.

Skin cancer is also proving less fatal for both sexes. More than nine in ten women survive it.

The figure for fellas is 87.1 per cent, up from 81.1 per cent.

The data experts also predict for the first time the number of patients who can expect to survive a decade.

Among men diagnosed with bowel cancer last year, 56 per cent will still be alive in 2025. In the same period almost two thirds of women with cervical cancer will not have died from it.

Dr Rebecca Smittenaar, of Cancer Research UK, said overall cancer survival had doubled in 40 years.

She explained: "Research has led to better treatments, new drugs, more accurate tests, earlier diagnosis and screening programmes."

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Cancer Statistics for the UK

Cases

New cases of cancer, 2013, UK

Deaths

Deaths from cancer, 2014, UK

Survival

Survive cancer for 10 or more years, 2010-11, England and Wales

Prevention

Preventable cases of cancer, UK

How is the oncology sector changing?

- currently mAbs and protein kinase inhibitors
- immuno-oncology treatments – particularly the PD-1/PD-L1 inhibitors – have dominated current headlines; BMS´s Opdivo (Nivolumab) and Merck's Keytruda (Pembrolizumab) — worth $33 billion by 2022?
- Genetic basis of cancer better understood → companion diagnostics, biomarkers
- Progress also in chemotherapy, radiation and surgery
- Cell-based immunotherapies (CAR-Ts, TCR- and NK cell –based therapies)

→ Personalised Medicine

	Medicine	Active substance	Indication(s)	Company	Global sales $
1.	Rituxan	Rituximab, monoclonal Ab	Non-Hodgkins Lymphoma, chronic lymphocytic leukemia	Roche	7.5 billion
2.	Avastin	bevacizumab monclonal Ab	Breast, colorectal, lung, kidney, ovarian cancers	Roche	6.7 billion
3.	Herceptin	Trastuzumab monoclonal Ab	HER2+ breast cancer	Roche	6.5 billion
4.	Imbruvica	Ibrutinib capsules, Protein kinase inhibitor	Mantel cell lymphoma, chronic lymphocetic leukemia	Johnson & Johnson/Pharm acyclics	5.3 billion
5.	Gleevec	Imatinib Protein kinase inhibitor	Chronic myeloid leukemia, gostrointestinal stromal tumors	Novartis	4.7 billion
6.	Revlimid	Lenalidomide Thalidomide analogue, immunomodulator	Multiple myeloma	Celgene	4.2 billion
7.	Velcade	Bortezomib Proteasome inhibitor	Multiple myeloma, mantle cell lymphoma	Johnson & Johnson/Takeda	2.6 billion
8.	Alimta	Pemetrexed Enzyme inhibitor	Non-small cell lung cancer	Eli Lilly	2.5 billion
9.	Erbitux	Cetuximab, monoclonal Ab	Colorectal, head and neck cancers	BMS/Merck Serono	1.9 billion
10	Gardasil	Human Papillomavirus Recombinant Vaccine,	Cervical cancer	Merck & Co.	1.8 billion

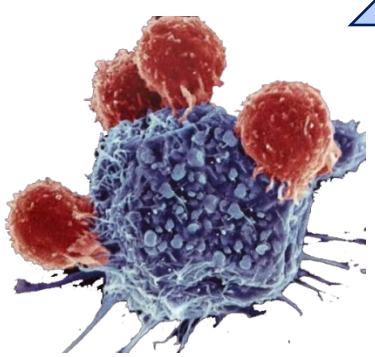
Genetically modified, cell-based cancer immunotherapies

GOAL to modify immune cells to attack and clear tumor cells

APPROACH CAR-T –cells, TCRs, NKs / TANKs, TRUCKS,….

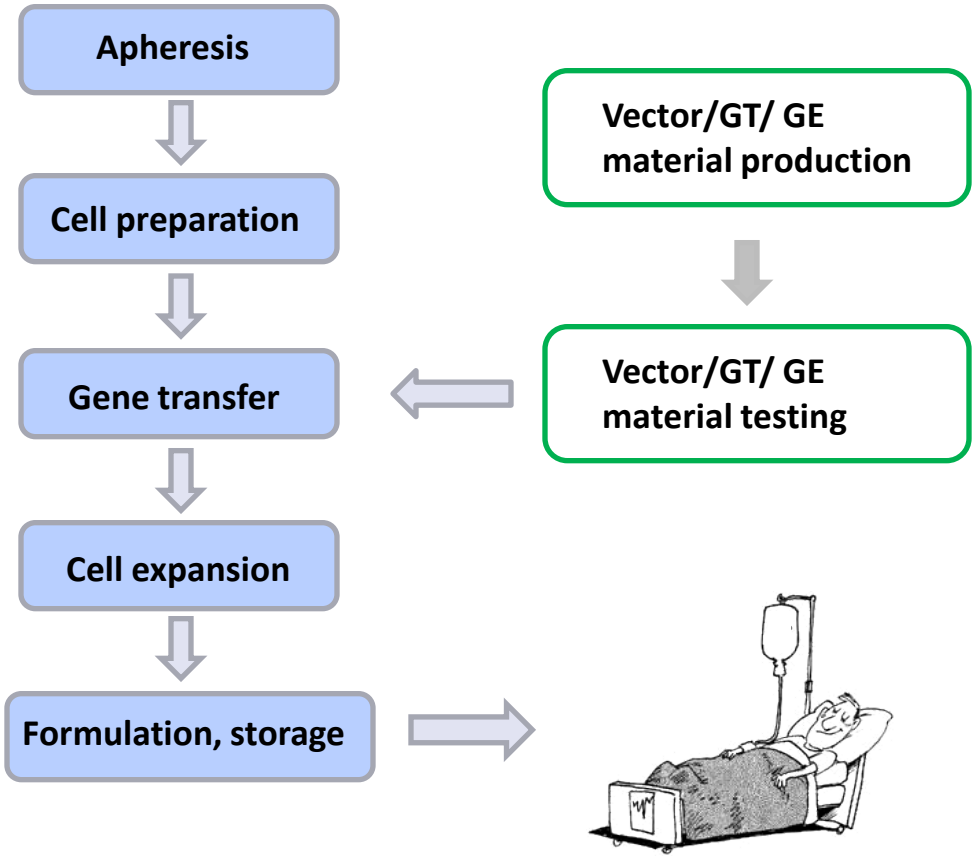
MEANS cell modification using viral vectors, gene editing

STATUS several products in clinical studies, but science evolves fast due to new technologies



FUTURE more and more complex products, multiple modifications, off the shelf/allogeneic products safety switches, inductors, in vivo GE?

Cell-based cancer immunotherapies (GTMPs!)



Quality, Safety and Efficacy are interlinked!

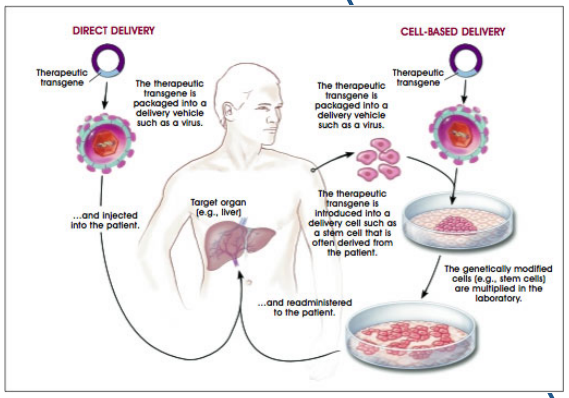
Advanced Therapy Medicinal Products (ATMPs)

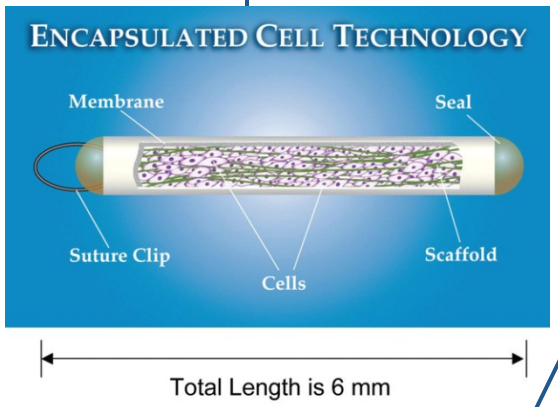
Gene Therapy Medicinal Products

Somatic Cell Therapy Medicinal Products

Tissue Engineering Products

Genetically modified cells

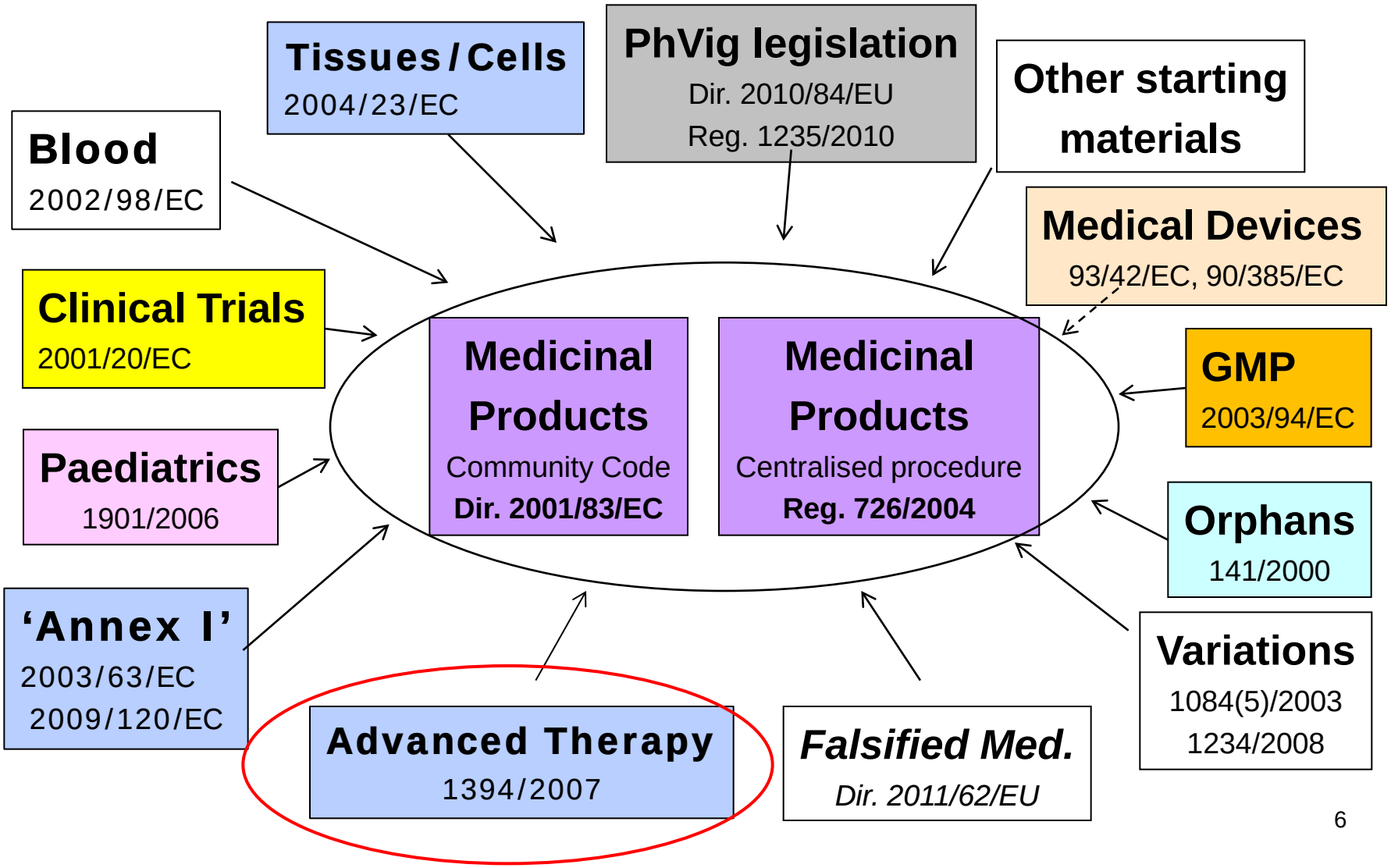





Severe burn victim before and 6 months after treatment with Dermagraft.

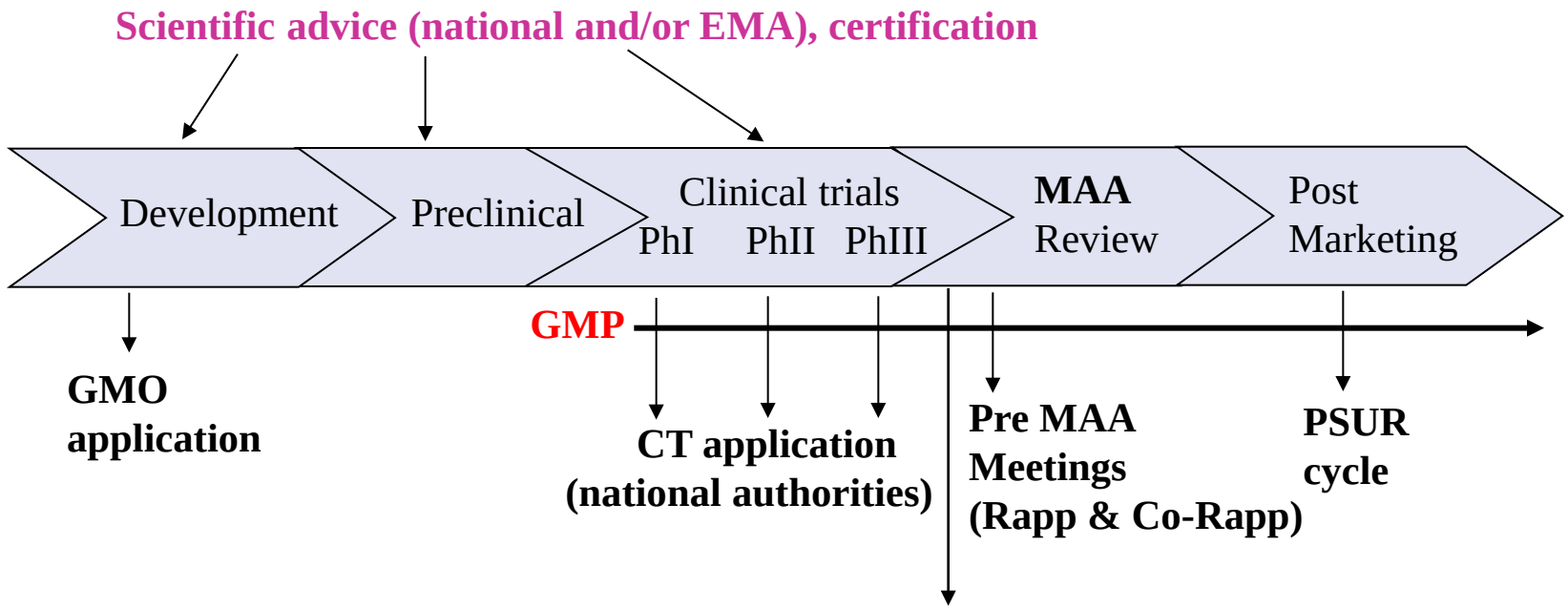
medical device + ATMP → combined ATMP

The EU legal / regulatory framework

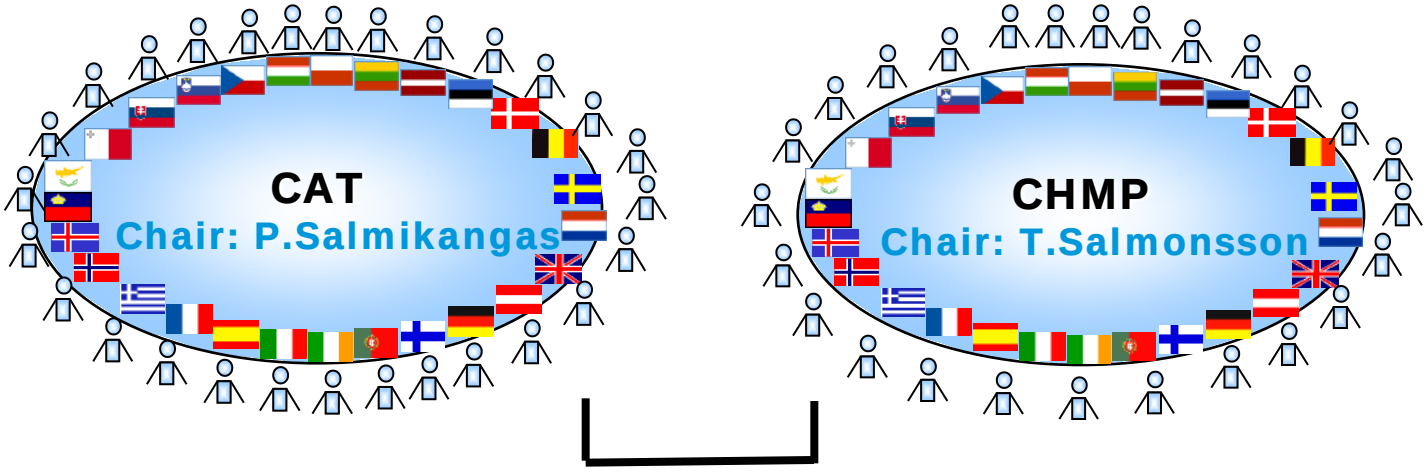


→ A new class of medicinal products with a dedicated regulation

Centralized Marketing Authorisation obligatory for ATMPs

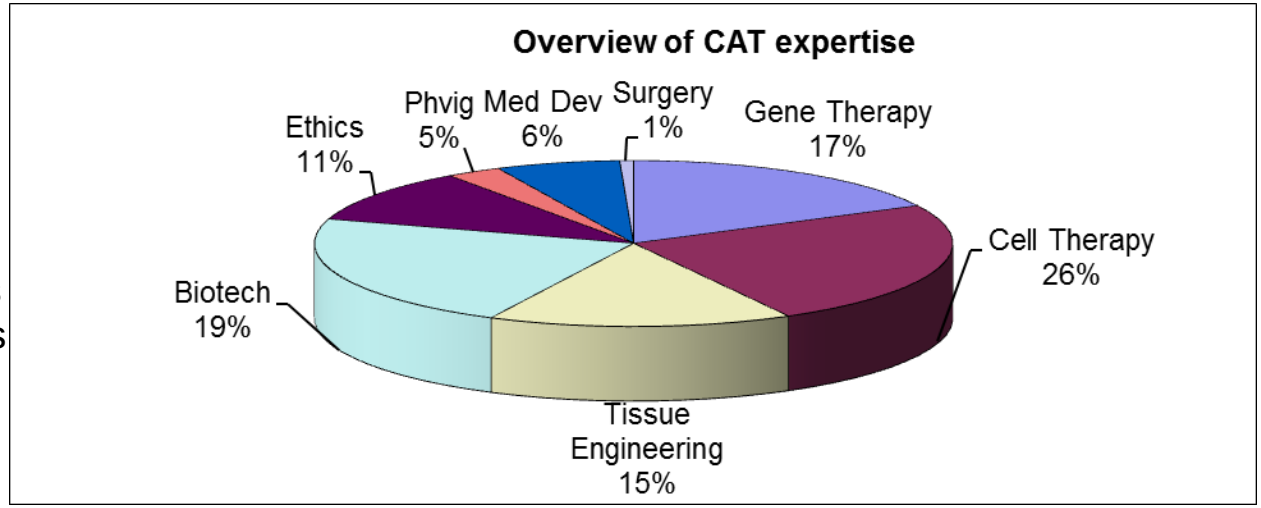


EMA Committees for ATMPs



- 18 quality experts
- 12 non-clinical experts
- 21 clinical experts (including 4 members representing physicians)
- 1 inspector
- 4 patient representatives
- 8 other (scientists, heads of departments etc.)

Total **68** experts



Marketing authorization applications / CAT 2009-2016 (September)

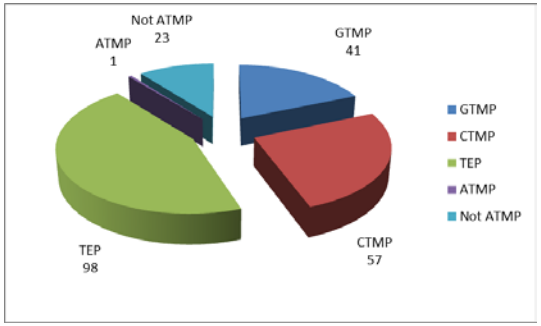
	2009	2010	2011	2012	2013	2014	2015	2016	Total	Approved
Submitted	3	1	2	3	2	2	1	1	**15**	**8**
GTMP	2	1				2	1	1	6	2
SCTMP				1					1	1
TEP	1		2	2	1	1			7	3
Variations	0	0	1	1	9	4	3	4	22	

Approved:
- **ChondroCelect** for cartilage repair, 2009 *(withdrawn 06/2016)
- **MACI** for cartilage repair, 2012 *(closure of EU manufacturing site 09/2014)
- **Glybera** for treatment of LPL deficiency, 2013
- **Provenge** for treatment of advanced prostate cancer, 2013 *(withdrawn 05/2015)
- **Holoclar** for treatment of limbal stem cell deficiency, 2015
- **Imlygic** for treatment of advanced melanoma, 2015
- **Strimvelis** for treament of ADA-SCID, 2016
- **Zalmoxis** for treatment of high-risk haematological malignancies (adjunctive to HSCT)

✓ 2 ATMPs under evaluation, several new ones expected 2017

Other CAT procedures (October 2016)

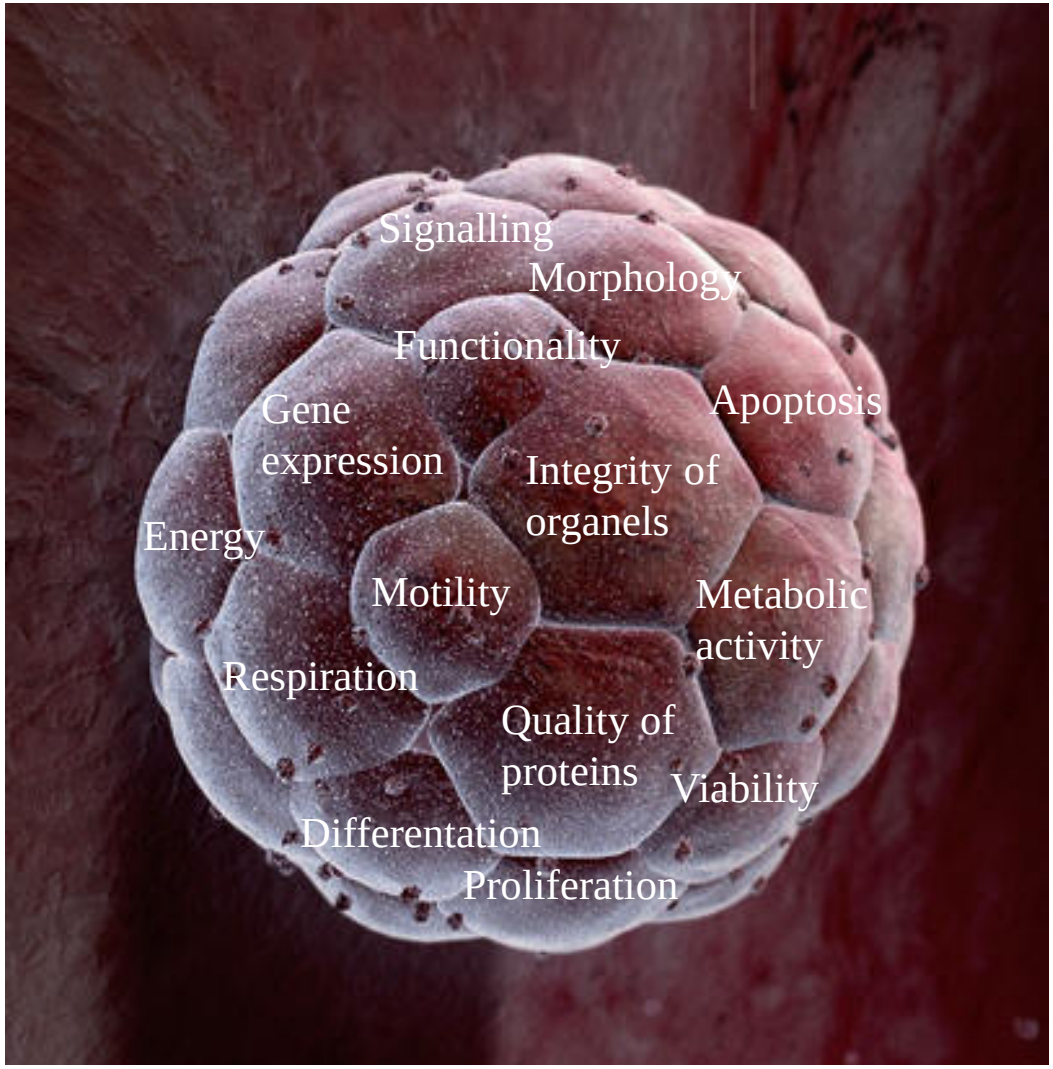
Classifications 2009-2016



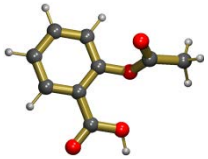
Scientific recommendation on advanced therapy classification									
	2009	2010	2011	2012	2013	2014	2015	2016	Total
Submitted	22	19	12	22	20	28	61	53	237
Adopted	12	27	12	16	23	29	31	79	229

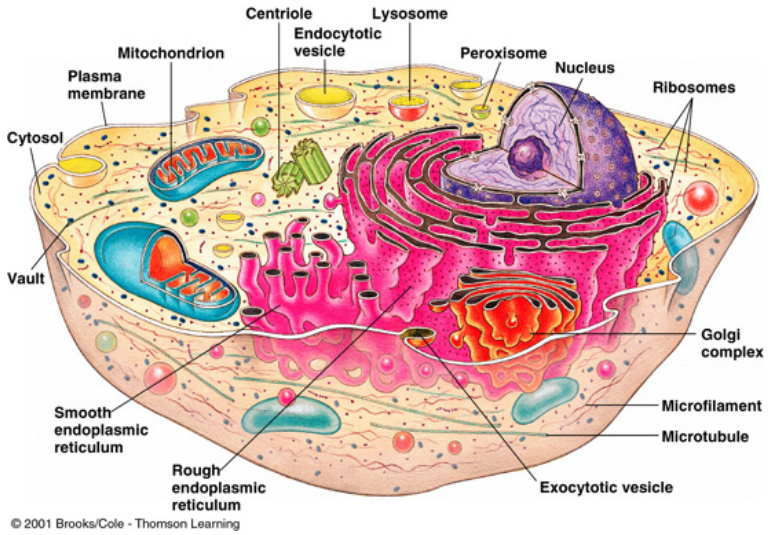
- **211** scientific advice procedures for ATMPs
- **47** PIPs
- **18** ATMP applications for PRIME, **6 granted**
- Over **300** ATMPs have been studied in clinical trials during 2011-2015 (~200 CTs during 2004-2010)

Cells as pharmaceuticals?



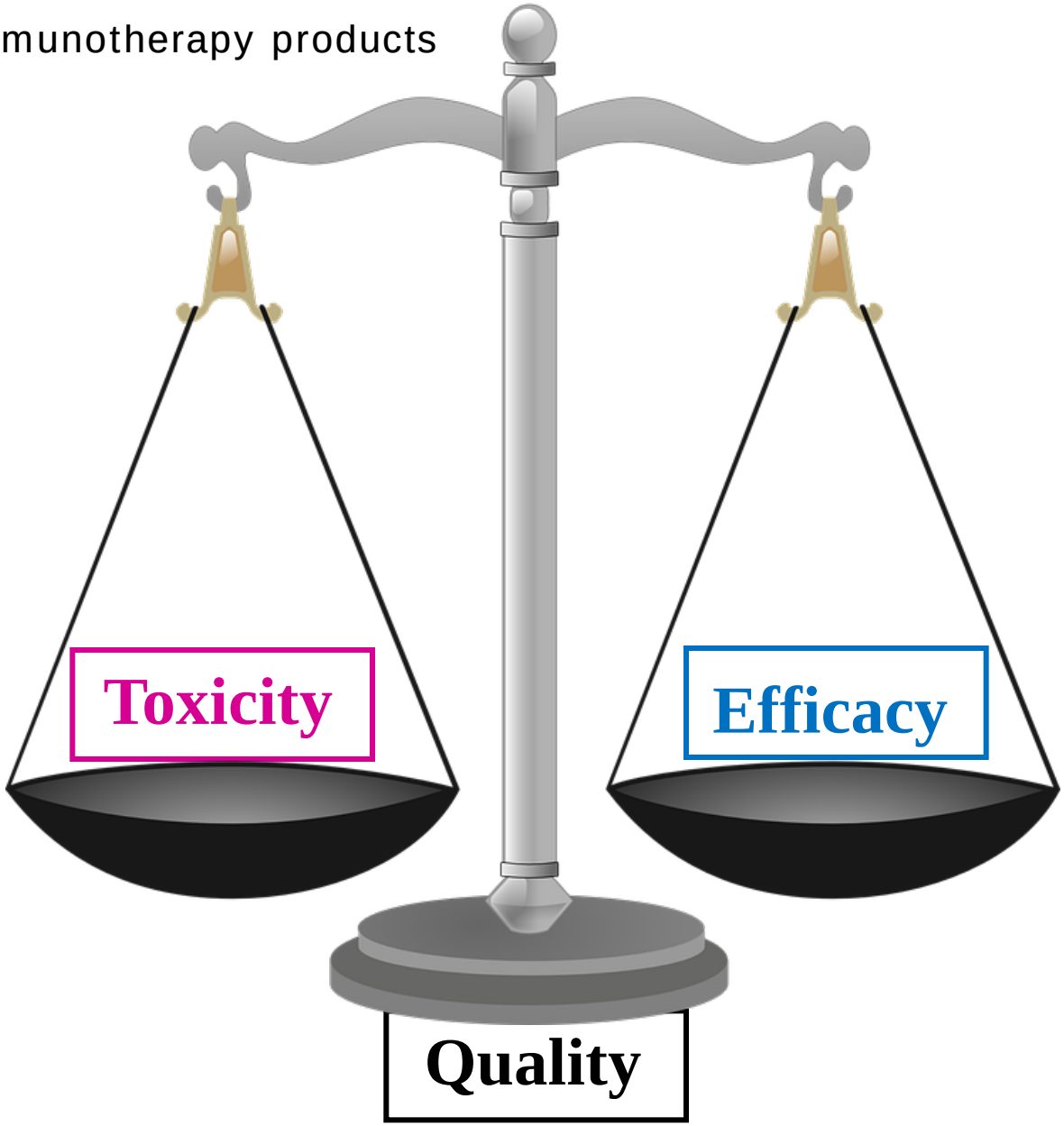
Aspirin



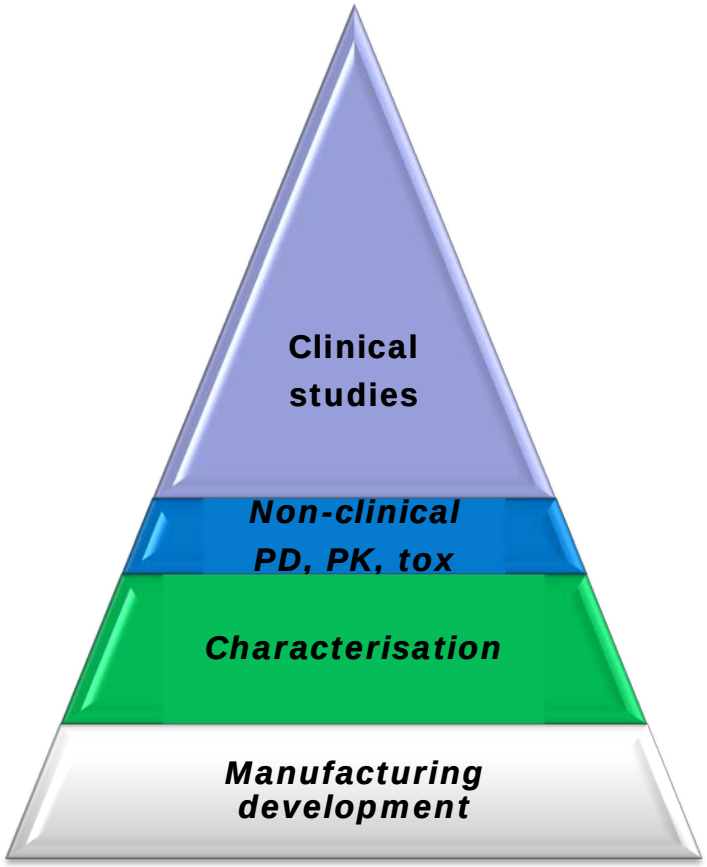


Eucaryotic cell

Cancer immunotherapy products

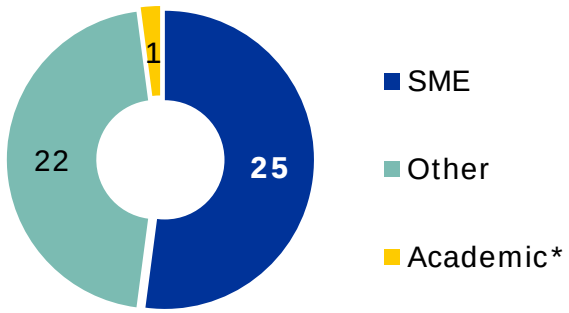


Way of building the evidence – applicable for innovative products?



- Conditional MA
- Adaptive Pathways
- PRIME
- Registries
- Real World Data
- HTA and reimbursement

Applicants type and products submitted (September)



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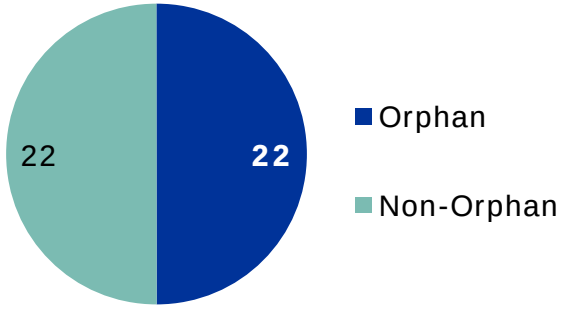

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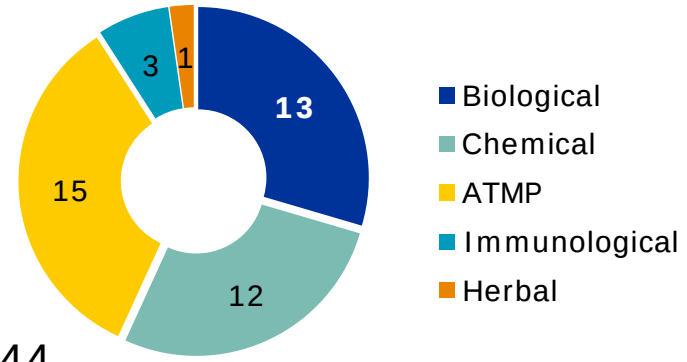
Strong presence of ATMPs in applications and products granted (up to September 6 out of 10 granted)



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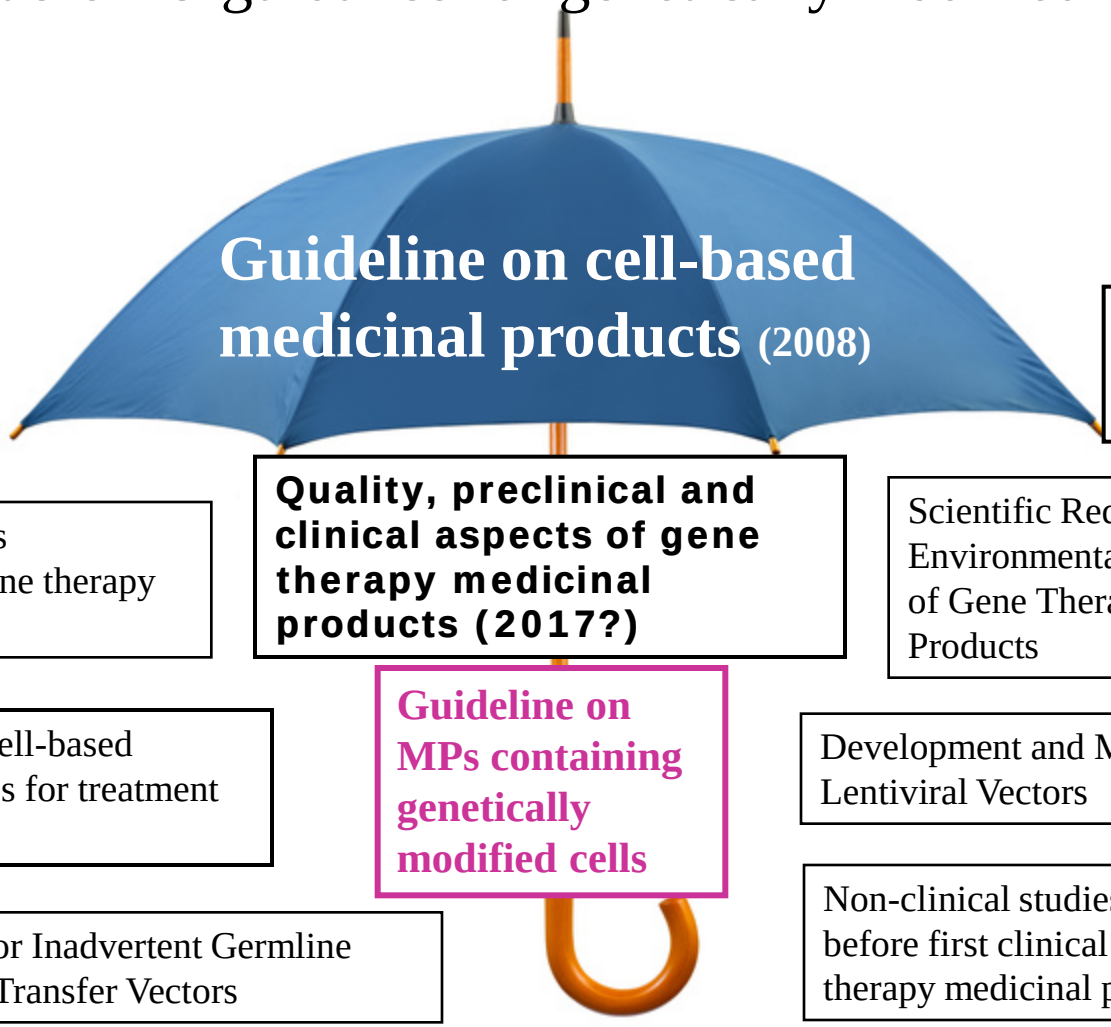
Regulatory and scientific management department

Risk-based approach

- Propectively planned strategy to justify the need for data in the MAA, **proportionate requirements based on risks**
- Does not provide a rigid classification system of different risks of a product as whole (e.g. high-risk product vs. low-risk product)
- Is intended to provide flexibility to regulation of ATMPs
- Should help developers to overcome challenges due to the specific nature of the ATMPs
- How to do the risk/risk factor profiling?

  → GL on risk-based approach (EMA/CAT/CPWP/686637/2011)
  → Q/A document on RBA under preparation
  → scientific advice

Available EU guidance for genetically modified cells



Guideline on the Risk-based approach (2013)

Reflection paper on stem-cell based MPs

Follow-up of patients administered with gene therapy medicinal products

Scientific Requirements for the Environmental Risk Assessment of Gene Therapy Medicinal Products

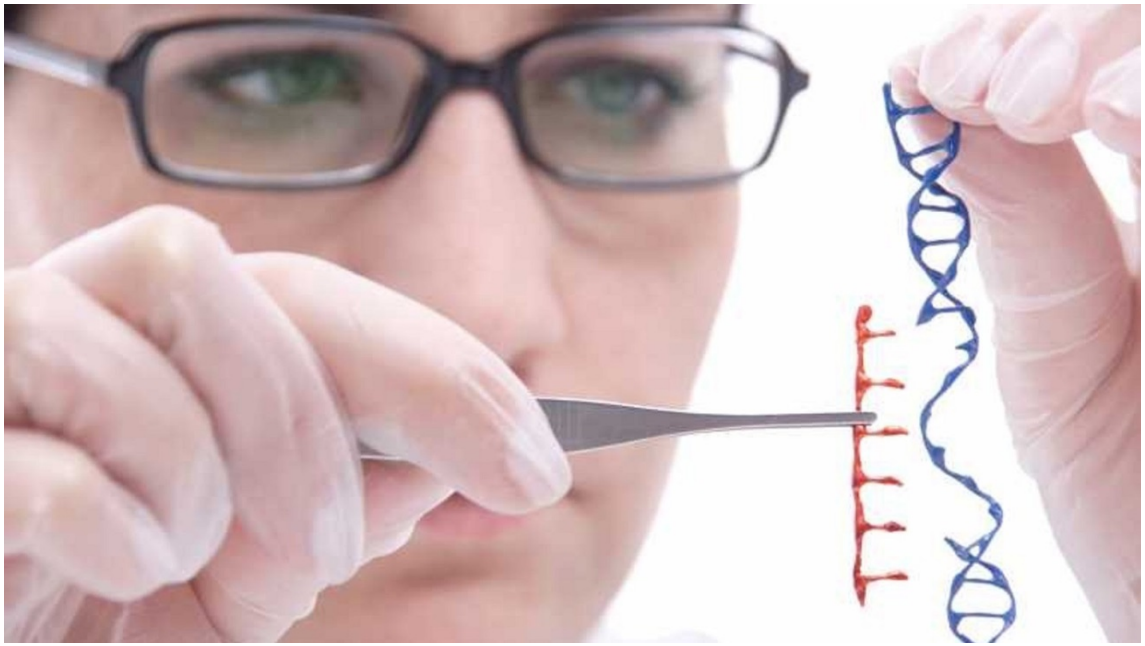
Potency testing of cell-based immunotherapy MPs for treatment of cancer (2007)

Development and Manufacture of Lentiviral Vectors

Non-Clinical testing for Inadvertent Germline transmission of Gene Transfer Vectors

Non-clinical studies required before first clinical use of gene therapy medicinal products

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



Thank you for your attention!