



The European Conference  
on Rare Diseases ●●●●

Lisbon  
November 27 - 28th 2007

# European Conference on Rare Diseases

## Lisbon 2007

## Agenda

### Gene / cell therapy : emergence

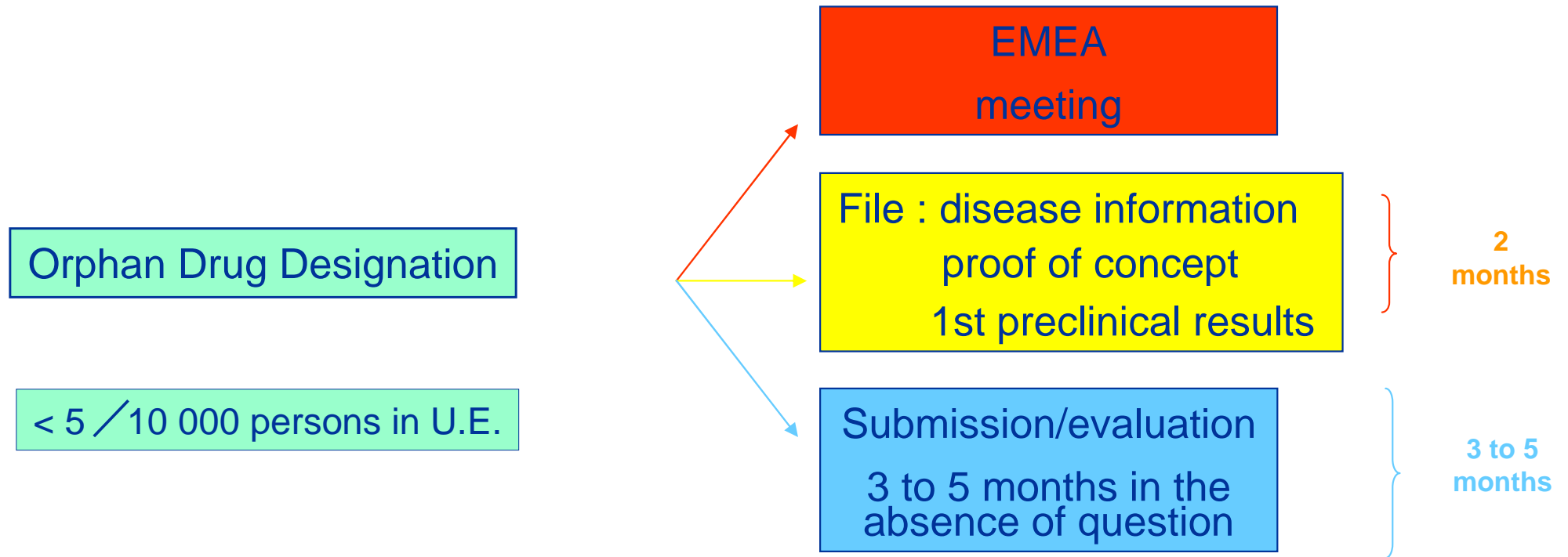
- Orphan drug designation
  - On-going clinical trials
  - 1st MAA on going
- 
- Regulations on advanced therapies: update
  - Development and marketing on advanced therapies: Key issues , bottleneck, reflexions to be addressed

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### Gene / cell therapy : emergence

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As soon as a proof of concept



COMP Opinion → EC designation

**Total duration = 5 to 7 months**

**In parallel of the development process**

- Advantages :** *Priority product for the agencies*  
*10 years of exclusivity in the all E.U.*  
*Protocol assistance from EMEA*  
*Direct assess to the centralised Procedure for Marketing*  
*Fees reduction for centralised application (min 50% → 90%???)*



# Accepted Orphan designations for advanced therapies (TG/ TC)

## Designated Advanced Therapies (Cell, Tissue, Gene) 1/3

26/10/2007

NPN	type	form	route	disease	prev	sponsor	ctry	designation date	proposed name
Cytochrome P450 isoform 2B1 gene transfected human embryonic kidney 293 cells encapsulated in polymeric cellulose sulphate	CT	Implant	LOC	Treatment of pancreatic cancer in combination with ifosfamide	1	FSG BTnologie Austrianova GmbH	AUT	30/06/03	
herpes simplex 1 virus-thymidine kinase and truncated low affinity nerve growth factor receptor transfected donor lymphocytes	CT	Suspension	IV	Adjunctive treatment in hematopoietic cell transplantation	0,2	MolMed SpA	ITA	20/10/03	HSV-TK/LNGFR MG T-Lymphocytes
HLA-A2 restricted CD8 <sup>+</sup> cell line expressing MART-1 T-cell receptor	CT	Solution	ITM	Treatment of MART-1 positive malignant melanoma in HLA-A2 positive patients	3,6	CellC ApS	DNK	21/06/04	C-Cure 709
human autologous mesenchymal adult stem cells extracted from adipose tissue	CT	Suspension	LOC	Treatment of anal fistula	1,8	Cellerix SL-CSIC	ESP	26/08/05	
human heterologous liver cells	CT	Injection	IV	Treatment of acute liver failure	3,36	Cytonet GmbH & Co. KG	DEU	11/04/06	
Autologous CD34+ cells transfected with retroviral vector containing the human gp91 (phox) gene	CT	NA	NA	Treatment of chronic granulomatous disease	NA	Vision 7 GmbH	DEU	28/08/06	Oxisin
allogenic (human) tumor cells, transfected with MIDGE vectors for the expression of IL-7, GM-CSF, CD80 and CD154, in combination with dSLIM immunomodulators	CT	Suspension	ITD	Treatment of renal cell carcinoma	3,5	Mologen AG	DEU	23/10/06	
L-asparaginase encapsulated in red blood cells	CT	Cell suspension	IV	Treatment of acute lymphoblastic leukaemia	0,5	Erytech Pharma S.A.	FRA	27/10/06	GRASPA
ex-vivo cultured adult human mesenchymal stem cells	CT	NA	IV	Treatment of acute graft-versus-host disease	1	Quintiles Ltd	GBR	20/02/07	Prochymal



# Accepted Orphan designations for advanced therapies (TG/ TC)

## Designated Advanced Therapies (Cell, Tissue, Gene) 2/3

26/10/2007

NPN	type	form	route	disease	prev	sponsor	ctry	designation date	proposed name
autologous dendritic cells loaded with autologous brain tumour cell lysate	CT	Solution	ID	Treatment of glioma	1	Dorian Regulatory Affairs BV	NLD	15/02/07	
autologous CD34+ cells transfected with lentiviral vector containing the human ARSA cDNA	CT	NA	NA	Treatment of metachromatic leukodystrophy	NA	Fondazione Telethon	ITA	13/04/07	
human heterologous liver cells	CT	Infusion	Intraportal	Treatment of ornithine-transcarbamylase deficiency	0,1	Cytonet GmbH & Co KG	DEU	14/09/07	
retroviral gamma-c CANA containing vector	GT	Suspension	EXVO	Treatment of Severe Combined Immunodeficiency (SCID)-XI Disease	0,003	Genopoietic S.A.S.	FRA	30/05/01	ImmuGene
adenovirus-mediated herpes simplex virus-thymidine kinase gene	GT	Solution	ITM	Treatment of high-grade glioma with subsequent use of ganciclovir sodium	0,7	Ark Therapeutics Ltd	GBR	06/02/02	Cerepro
recombinant adenovirus carrying a gene coding for the human interferon gamma	GT	Suspension	ITM	Treatment of cutaneous T-cell lymphoma	0,63	Transgene S.A.	FRA	09/07/03	Ad-IFN $\gamma$
herpes simplex virus lacking infected cell protein 34.5	GT	Solution	ITM	Treatment of glioma	0,8	Crusade Laboratories Ltd	GBR	09/07/03	
adeno-associated viral vector expressing lipoprotein lipase	GT	Emulsion	IM	Treatment of lipoprotein lipase deficiency	0,02	Dr. Aart Brouwer	NLD	08/03/04	AMT-010
vascular endothelial growth factor-D gene in an adenoviral vector for use with a collagen collar	GT	Solution	LOC	Prevention of stenosis in synthetic grafts used in haemodialysis	0,4	ARK Therapeutics Ltd	GBR	08/06/04	Trinam
adeno-associated viral (AAV) vector containing the human gamma-sarcoglycan gene	GT			Treatment of gamma sarcoglycanopathies	0,2	Généthon	FRA	21/10/04	



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NPN	type	form	route	disease	prev	sponsor	ctry	designation date	proposed name
adeno-associated viral vector containing modified U7 sn RNA gene	GT	NA	NA	Treatment of Duchenne muscular dystrophy	0,5	Genethon	FRA	27/07/05	
autologous CD34+ cells transfected with retroviral vector containing adenosine deaminase gene	GT	Suspension	IV	Treatment of ADA-deficient SCID	NA	Fondazione Telethon	ITA	26/08/05	
lentiviral vector containing the human Wiskott Aldrich syndrome gene	GT	NA	NA	Treatment of wiskott aldrich syndrome	0,01	Genethon	FRA	24/01/06	Protein gene
adeno associated viral vector containing the human calpain 3 gene	GT			Treatment of calpainopathy	0,1	Genethon	FRA	06/04/06	
adenoviral vector containing human p53 gene	GT	Suspension	ITM	Treatment of Li Fraumeni Syndrome	0,05	Gendux AB	SWE	23/10/06	Advexin
recombinant adeno-associated viral vector expressing human alpha-1 antitrypsin gene	GT	Solution	IM	congenital alpha-1 antitrypsin deficiency	2,5	The Matthews Consultancy Ltd	GBR	20/03/07	
recombinant modified vaccinia virus Ankara expressing human 5T4	GT	Lyophilisate	IM	Treatment of renal cell carcinoma	3,6	Oxford Biomedica Ltd	GBR	26/01/07	TroVax
recombinant adeno-associated viral vector expressing human alpha-1 antitrypsin gene	GT	Solution	IM	Treatment of Pompe Disease	2,7	The Matthews Consultancy Ltd	GBR	09/07/07	
bilayer engineered skin composed of keratinocytes from the patient (autologous) and fibroblasts from a donor (allogeneic) embedded in a plasma matrix	TT		TOP	Treatment of epidermolysis bullosa	0,4	Cellerix SL	ESP	28/05/06	

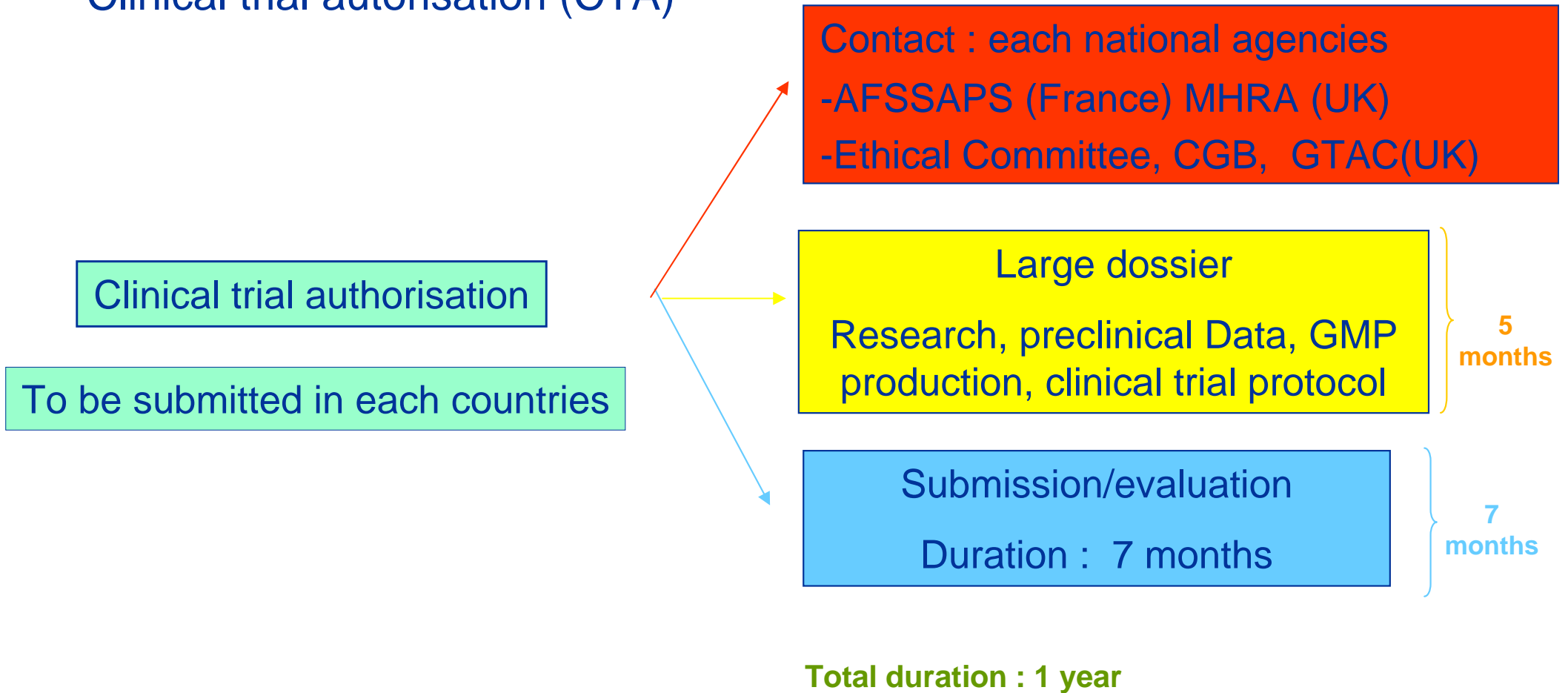
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# Regulatory strategy : CTA

## Clinical trial autorisation (CTA)



***Mandatory to begin clinical trial***



# Advanced therapies : on-going CT TG/TC

## GENE THERAPY CLINICAL TRIALS

Phase III ( <i>updated 11/2007</i> )	22 « open » (out of 32) Monogenic diseases : 0
Phase II/III ( <i>updated 11/2007</i> )	6 « open » (out of 13) Monogenic diseases : 0
Phase II TG ( <i>updated 11/2007</i> )	95 « open » (out of 169) Monogenic diseases : 1
Phase I/II ( <i>updated 11/2007</i> )	131 « open » (out of 258) Monogenic diseases : 12
Phase I ( <i>updated 11/2007</i> )	473 « open » (out of 801) Monogenic diseases : 31
<b>Total of « open »</b>	<b>727</b>

# Regulatory Strategy : PLA

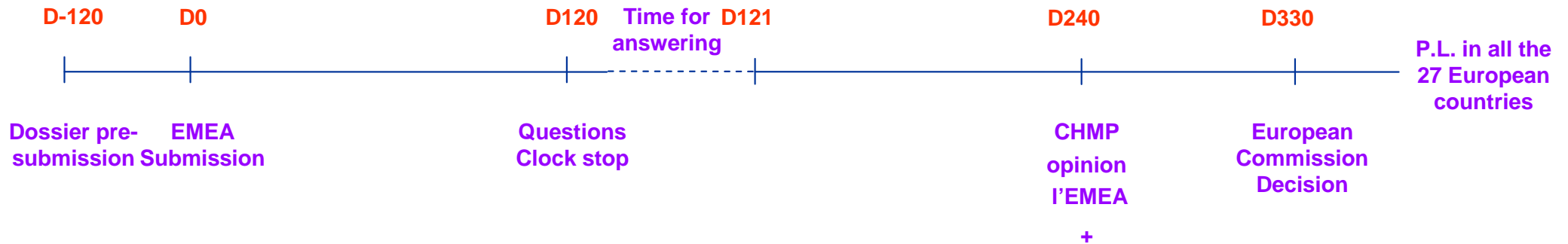
## Product License Authorization (PLA)

Product License (P.L.) authorization

Interlocutor :  
European Agency  
(EMA)

Complete file  
Research, all pré-clinical, all  
clinical efficacy and safety data  
GMP production

### Centralised procedure for biotech products



**Compassionate Use :**  
**Autorisation under exceptional circumstances**

## Agenda

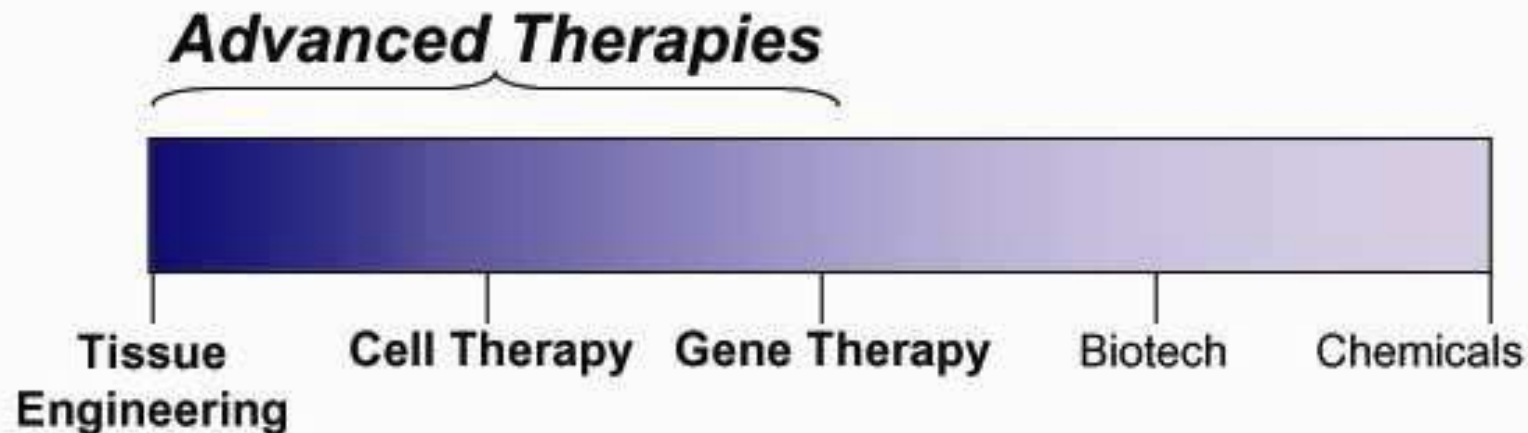
### Gene / cell therapy : emergence & questions

- Orphan drug designation
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- **Regulations on advanced therapies: update**
  - Development and marketing on advanced therapies :  
Key issues , bottleneck, reflexions to be addressed

# Regulations on advanced therapies : What do we mean?

Medicinal products based on

- Genes
- Cells
- Tissues





# Regulations on advanced therapies : Why do we need legislation?

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## Different approaches across EU :

Hinder patient's access to treatments

Lead to a market segmentation

Undermine Industry development

→ Public consultations (2002, 2004, 2005):

All stakeholders want clear EU Rules

→ need for a specific, harmonised and coherent  
EU regulatory framework



# Regulations on advanced therapies : CAT: evaluation procedure

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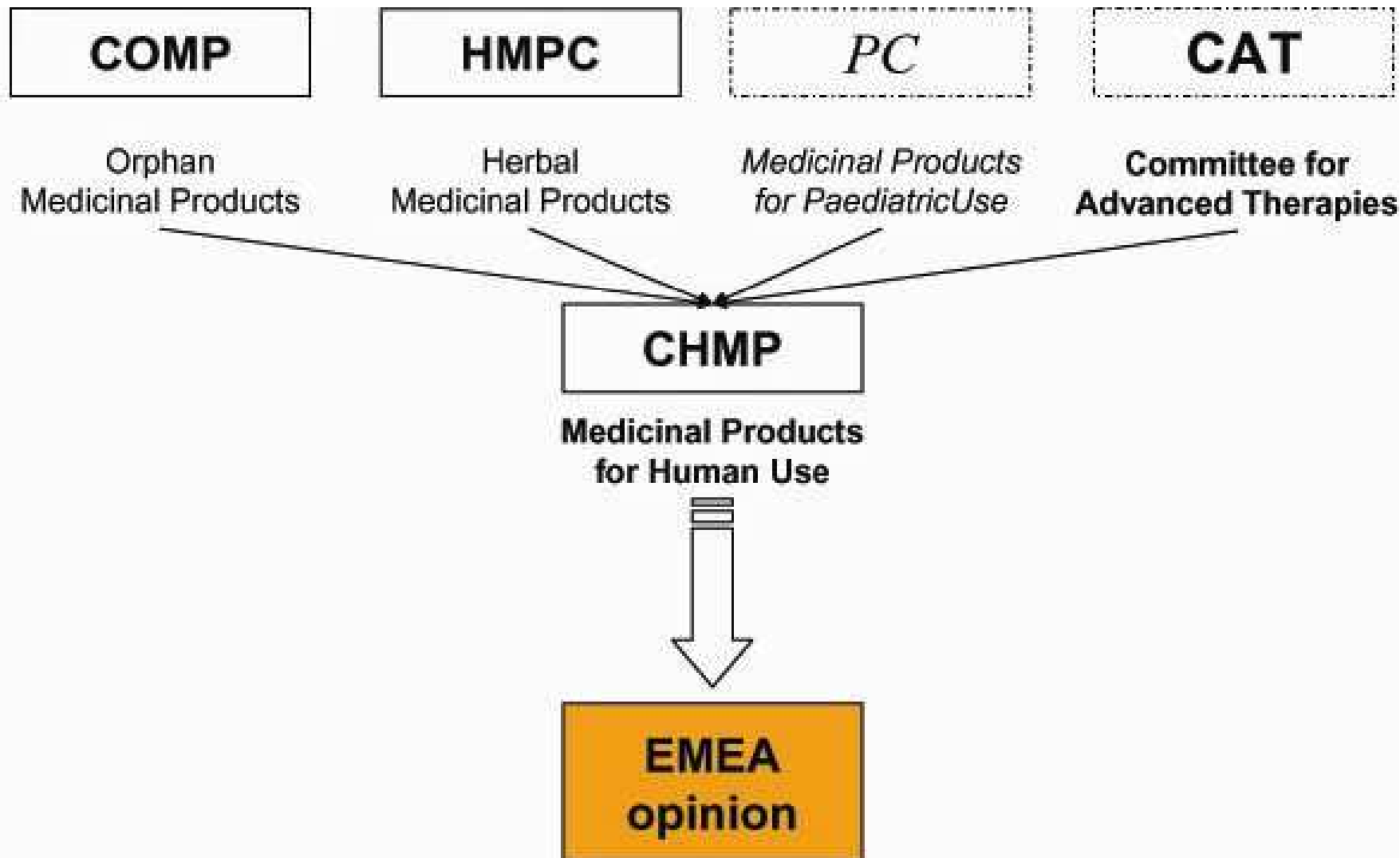
## Committee for Advanced Therapy (CAT)

New committee within the EMEA

Pooling of Community expertise

Multidisciplinary group: biotechnology, medical devices, risk management, ethics .....

# Regulations on advanced therapies : EMA Committees



# Regulations on advanced therapies : Competitiveness aspects, new

## General provisions :

Stemming from existing legislation:

- Direct access to Community market
- Harmonised data protection
- Orphan status linked to market exclusivity
- Accelerated ('fast-track') assessment
- Conditional marketing authorisation

New in the proposal:

- Scientific Advice (90% fee reduction)
- Scientific recommendation on advanced therapy classification

# Regulations on advanced therapies : Competitiveness aspects, new

## Specific provisions for SMEs :

- Existing legislation: Reg. (EC) No 2049/2005:
  - Fee reductions and deferrals
  - Handling of translations
  - General administrative assistance (EMEA SME Office)
  - Workshops/Training sessions
- New in the proposal:  
Certification of quality and non-clinical data

## Regulations on advanced therapies : Competitiveness aspects, new

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- Clear rules, smooth procedures and a level playing field for all manufacturers
- Particular attention to certain categories of stakeholders, most notably hospitals and SMEs
- Detailed requirements and guidance also influence the implementation and its economic impact
- Keep the pace with new scientific developments

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# Adv. Ther.: Bottleneck, key issues, challenges : development of Advanced Therapies

## Special clinical investigation centers for GT and CT

- A very few in Europe (TG), → traveling of patients (difficult due to their pathology, lack of familial environment, costing)
- unharmonised rules on confinement in EU

**Register of patients:** To be harmonized, (a minimum of informations by disease), to reach patients as fast as possible, to inform them....

## Regulation:

Unique IMPD file - centralised mutual recognition → same entity will evaluate CTA & NDA

SUSSAR to be declare only at the EMEA not EMEA + National  
EC could be still national (cultural differences to be respected)

**GMP Production sites for clinical trials:** a very few in EU for GT & CT,  
with low capacities

**Funds !!!** (Pharma, biotech, National, European, Venture Capital, business angels, private equity partners.....)



# Adv. Ther.: Bottleneck, key issues, challenges

## At compassionate use/ MAA step

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- European centralised MAA: OK

- ATU/ Compassionate use (EMA): who will pay? currently different across countries, and discussions on harmonisation!

*It is to be taken into account that most to advanced therapies are on small companies or Academics! Hands!!!*

- Care and logistic organisation for access to treatment:

- Confinement to be lightened when possible! (in France ), vector shedding

- A very few medical referenced and specialised sites for TG and TC → travel, cost, environment, ....

- Information: on treatments, clinical sites.. → patient association and Industry

- Reach patients: European registers, data base...

- Reimbursement not harmonized across countries → inequity in access to treatment across MS

Different type and way of reimbursement across countries when compassionate authorization, and when MAA  
Discrepancies across MS, for obtention of reimbursement (price/ reimbursement negotiations, delays, indications...)

- Funds!!: Costs of these advanced therapies are quite high! How to deal with each MS for reimbursement: Social security/ welfare, private mutual insurance? European funds? National funds? Private insurance? ....

# Conclusions

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- EU Regulatory is coming → advanced therapies are really coming
- Objective to facilitate and harmonize EU rules for development and MAA
- Clear Objectives to get equity across countries to get access to treatment
- Main issues : harmonisation across MS, funds, different ways of reimbursement across MS

# Thank you

