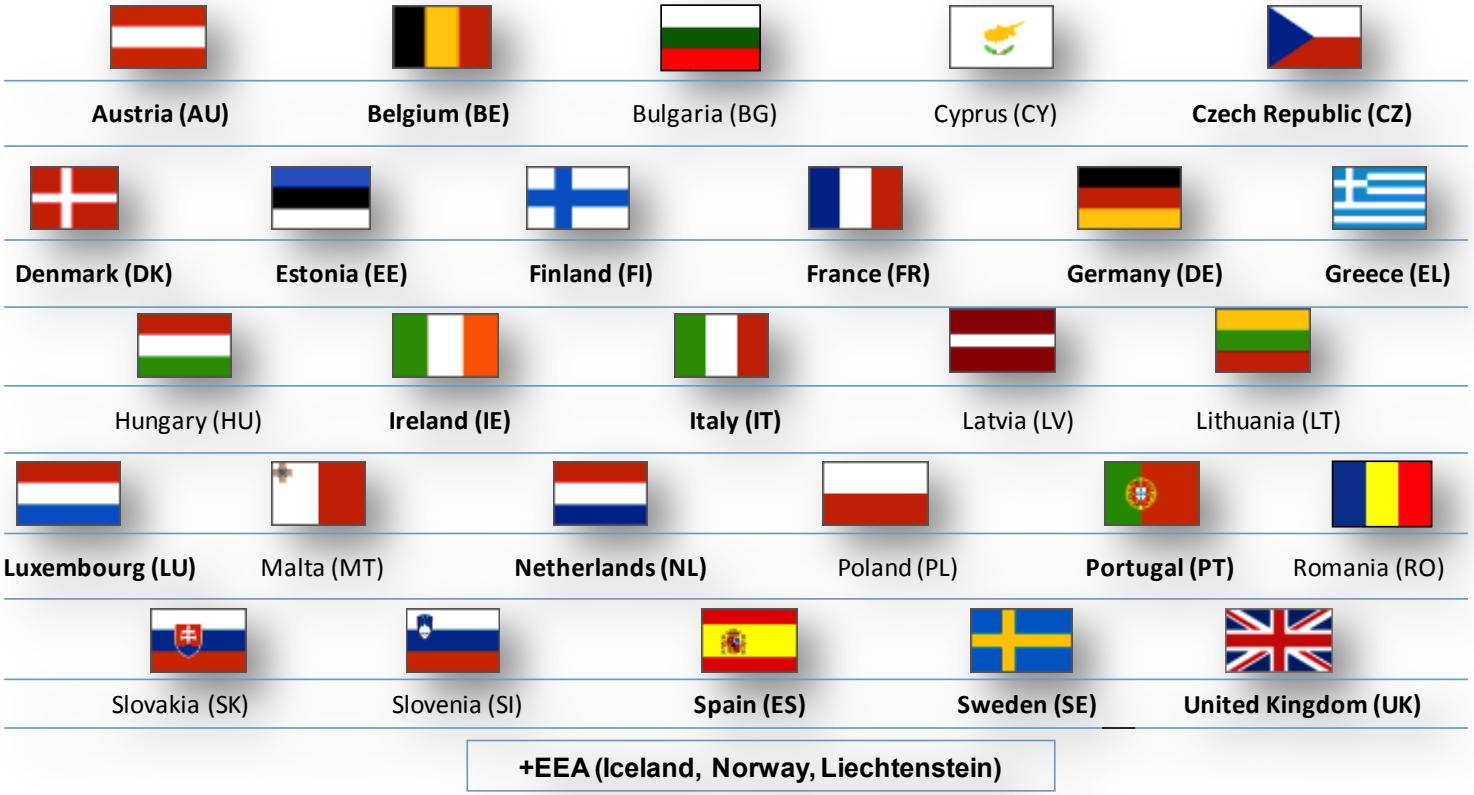
Regulation of Regenerative Medicine in the EU (incl.UK)



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The European Union

- 27 member states (30 incl. EEA)
- Combined population c. 500 million
- Single market authorisation from EMA valid for entire EU/EEA

- Not a federal state
- Clinical trials remain a <u>national</u> responsibility

European Union (EU)

European Economic Area (EEA)

EU Agencies and Responsibilities

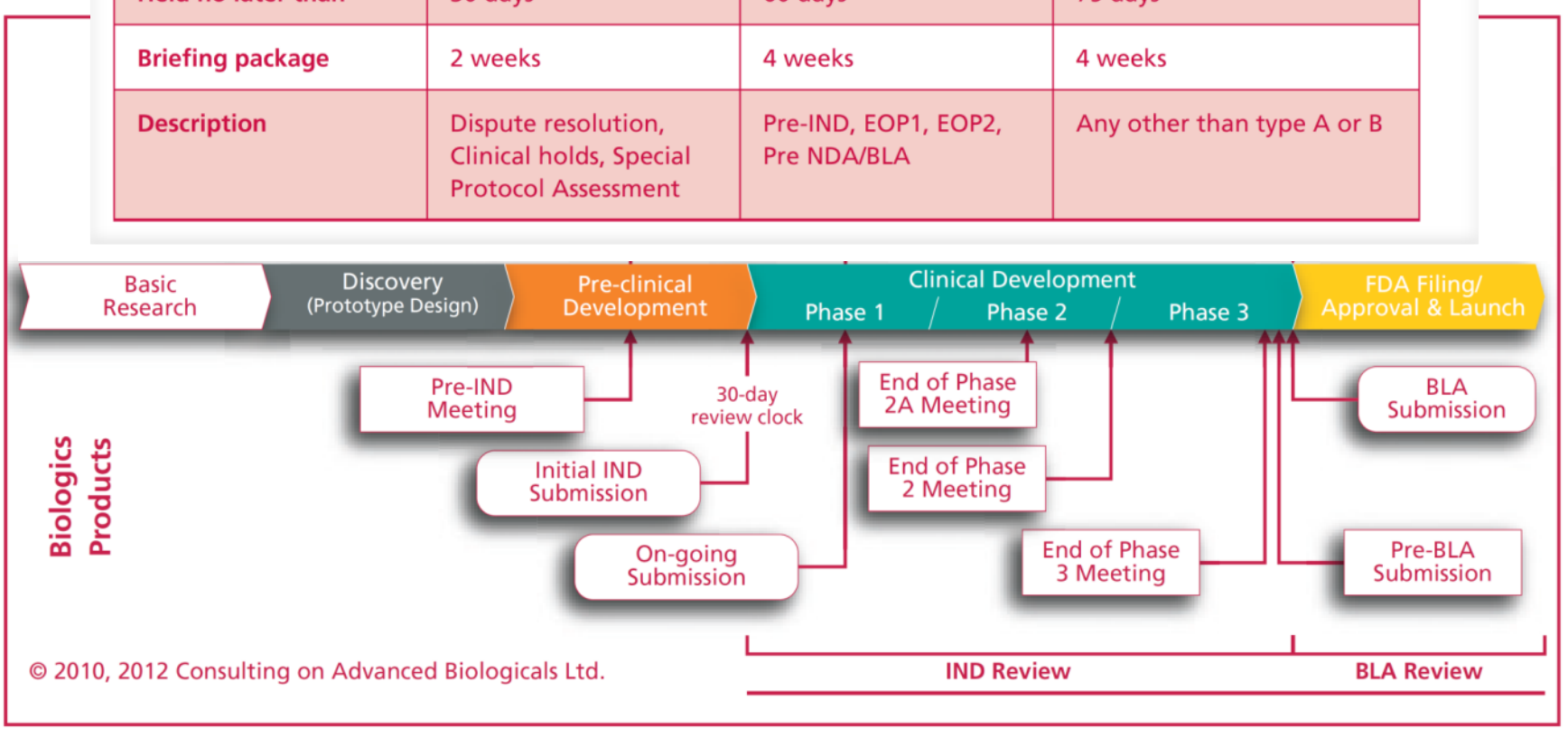
- In US all these activities covered by the FDA
- In EU, >30 national agencies and the EMA.
- Procedures within national agencies can differ.
- UK:
  - MHRA – medicines and medical devices
  - HTA – tissues and cells (donation, procurement and testing only when medicine)
  - HFEA – Fertility (gametes only)

	NCA [a]	EMA
Manufacturing (GMP) licence	✔	
EUTCD [b]	✔	
Orphan designation		✔
Innovation Task Force		✔
SME registration		✔
Classification [c]	✔	✔
Certification [d]		✔
Scientific advice	✔	✔
CTA	✔	
MAA		✔
Variations (post MAA)		✔
Pharmacovigilance	✔	✔

Agency Interactions in the US

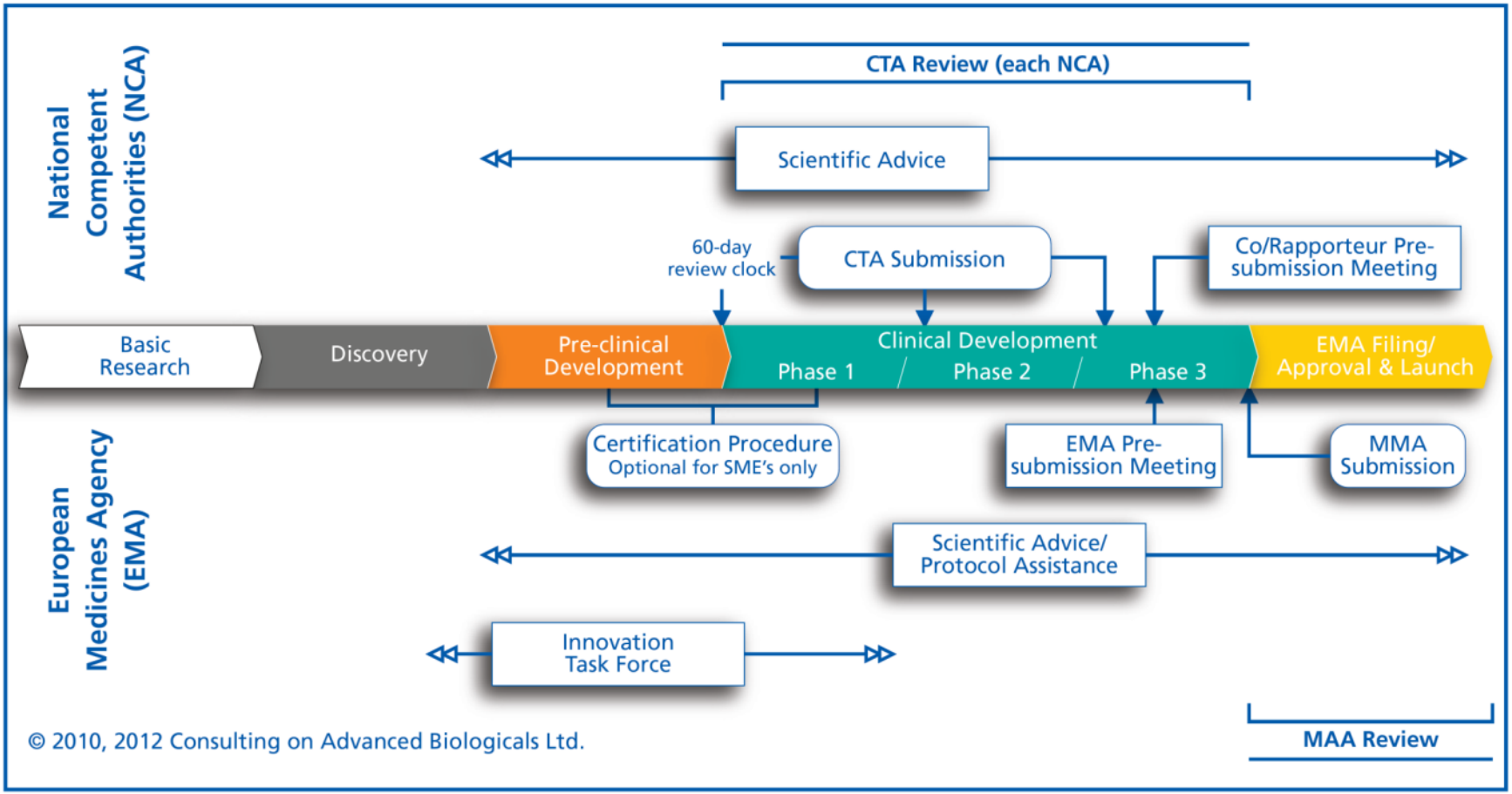
Table 6 FDA meeting types

Type	A	B	C
Confirming of scheduling	14 days	21 days	21 days
Held no later than	30 days	60 days	75 days
Briefing package	2 weeks	4 weeks	4 weeks
Description	Dispute resolution, Clinical holds, Special Protocol Assessment	Pre-IND, EOP1, EOP2, Pre NDA/BLA	Any other than type A or B



Adapted from http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf

Agency Interactions in the EU



ATMP's Currently Under Review at the EMA

International non-proprietary name (salt, ester, derivative, etc.) / Common Name	Therapeutic area[1]
Aclidinium (bromide)	Medicines for obstructive airway diseases
Aflibercept	Antineoplastic medicines Ophthalmologicals
Autologous cultured chondrocytes	Other medicines for disorders of the musculo-skeletal system
Autologous oral mucosal epithelial cells	Ophthalmologicals
Autologous peripheral blood mononuclear cells activated with PAP-GM-CSF	Immunostimulants
Somatropin	Pituitary and hypothalamic hormones and analogues
Spheroids of human autologous matrix-associated chondrocytes	**Other medicines for disorders of the musculo-skeletal system**
Strontium ranelate / colecalciferol	Medicines for bone diseases

MACI, Genzyme

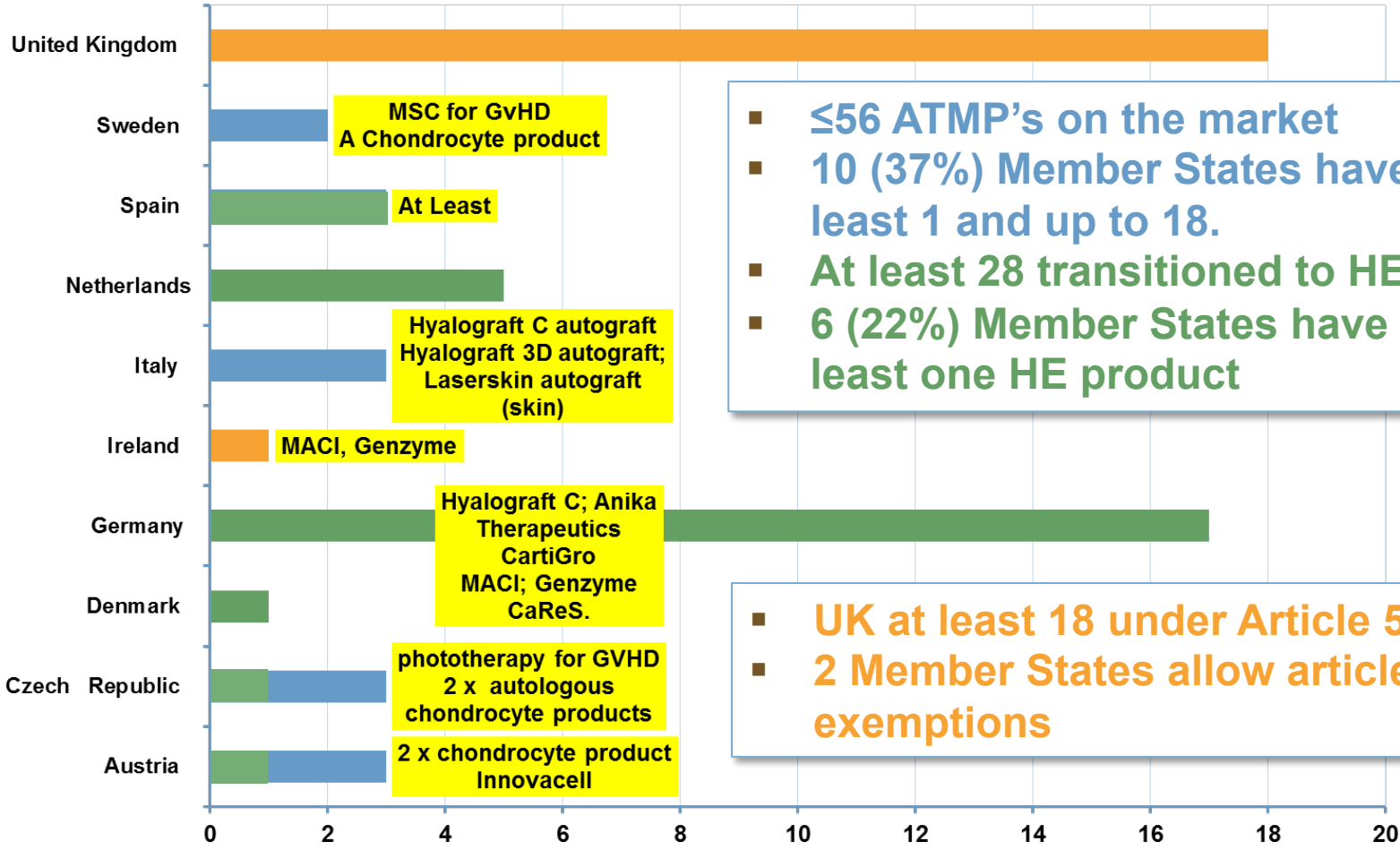
Cellseed, CellSeed Inc.

Provenge, Dendreon

Chondro-sphere (ACT 3D), co.don

Note: *assumptions as to developer/product may be incorrect.*

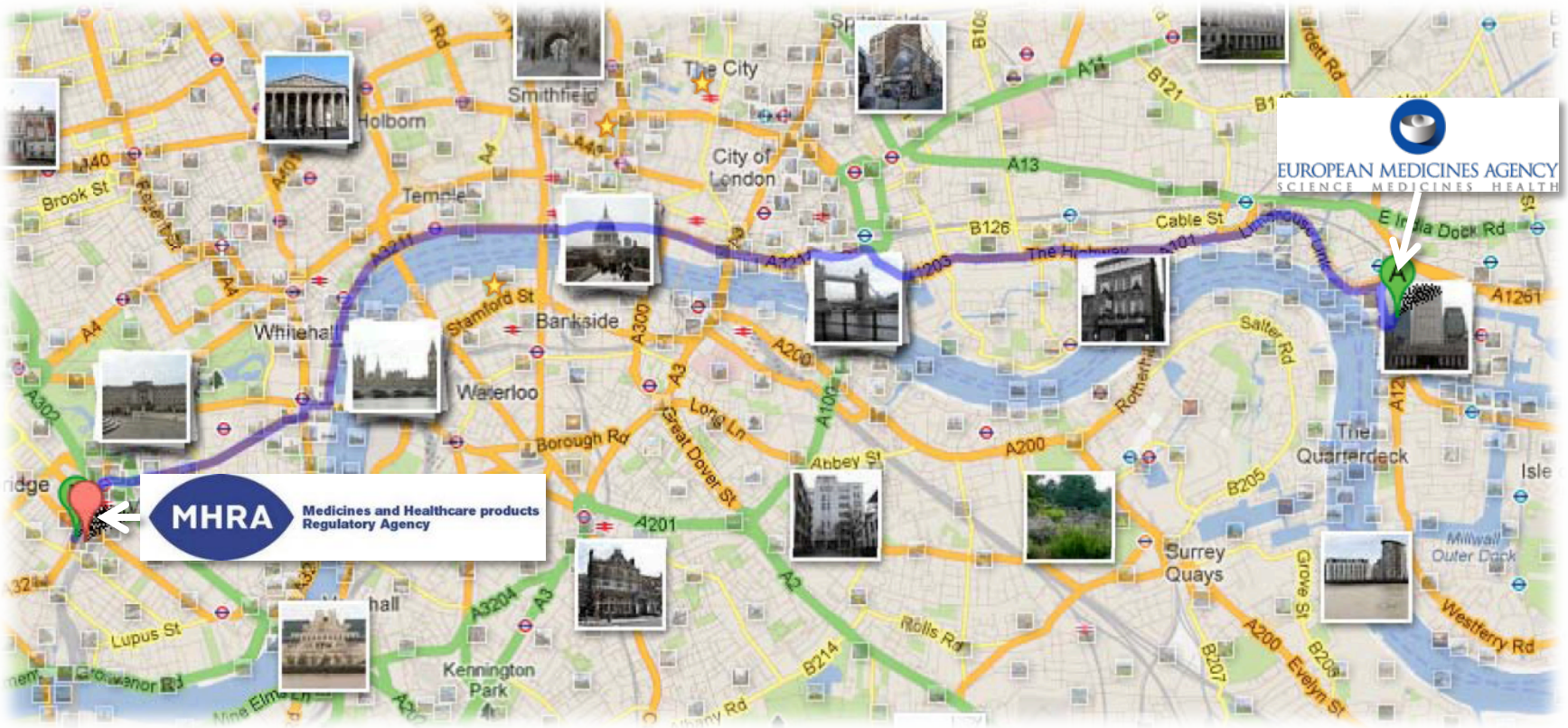
EU Commission Survey results Oct 2012



- ≤56 ATMP's on the market
- 10 (37%) Member States have at least 1 and up to 18.
- At least 28 transitioned to HE
- 6 (22%) Member States have at least one HE product

- UK at least 18 under Article 5(1)
- 2 Member States allow article 5(1) exemptions

The Medicines Centre of the EU

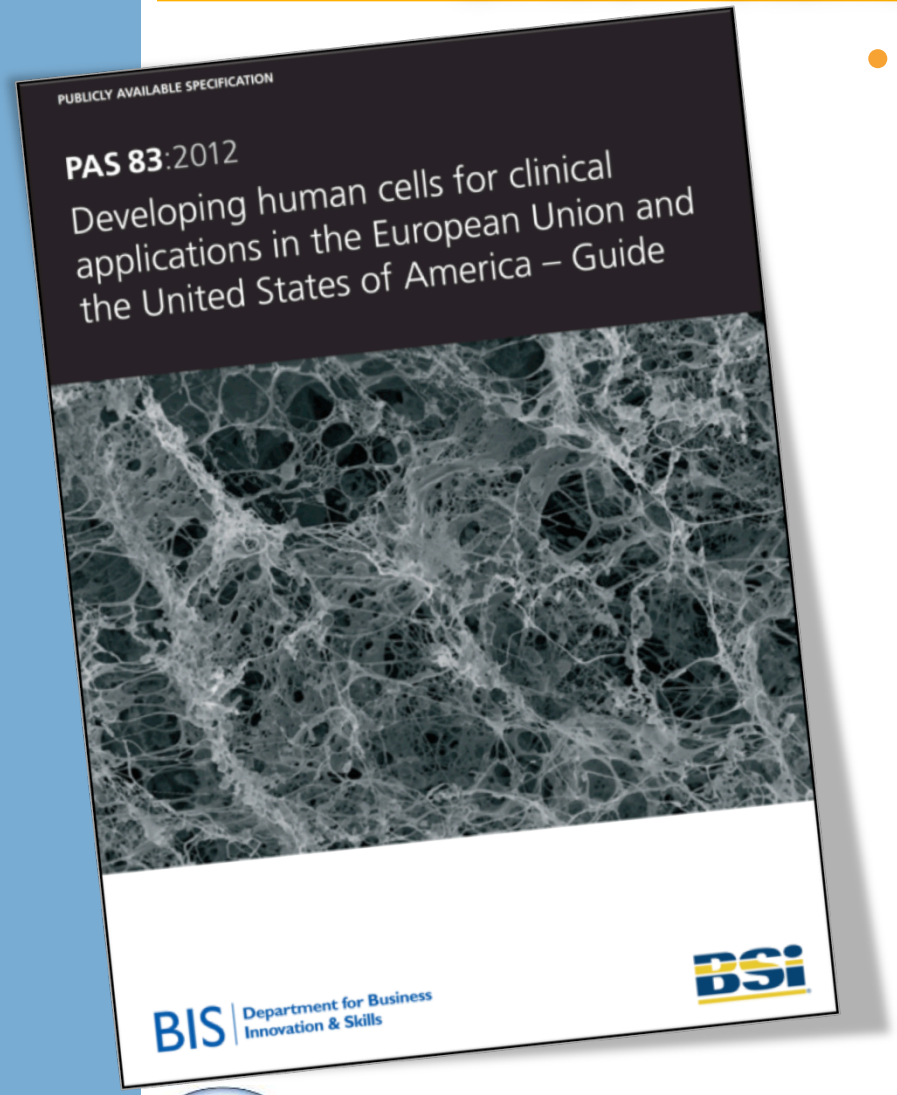


Consulting on Advanced Biologicals

What's Needed for a CTA

- Essentially same as an IND
  - but a CTA for each trial not phase
- Scientific and regulatory principles are the same
  - ICH (EU, US, Japan)
- All agencies in the EU use CTD
- Centralised system for recording clinical trials
  - EUDRACT (assigned unique trial number).
- Ethics approval
- Fees (variable)
- QP declaration of GMP compliance.
- Actual paperwork varies a little between member states.

PAS 83 (2012)
British Standards Institution



- High level overview of:
  - Legal Framework
  - Product development
  - Available guidelines and other useful links.

Free download from BSI:
http://shop.bsigroup.com/en/forms/PASs/PAS-83/

Link also provided along with other PAS's here:
http://www.advbiols.com/Publications.php

CAB

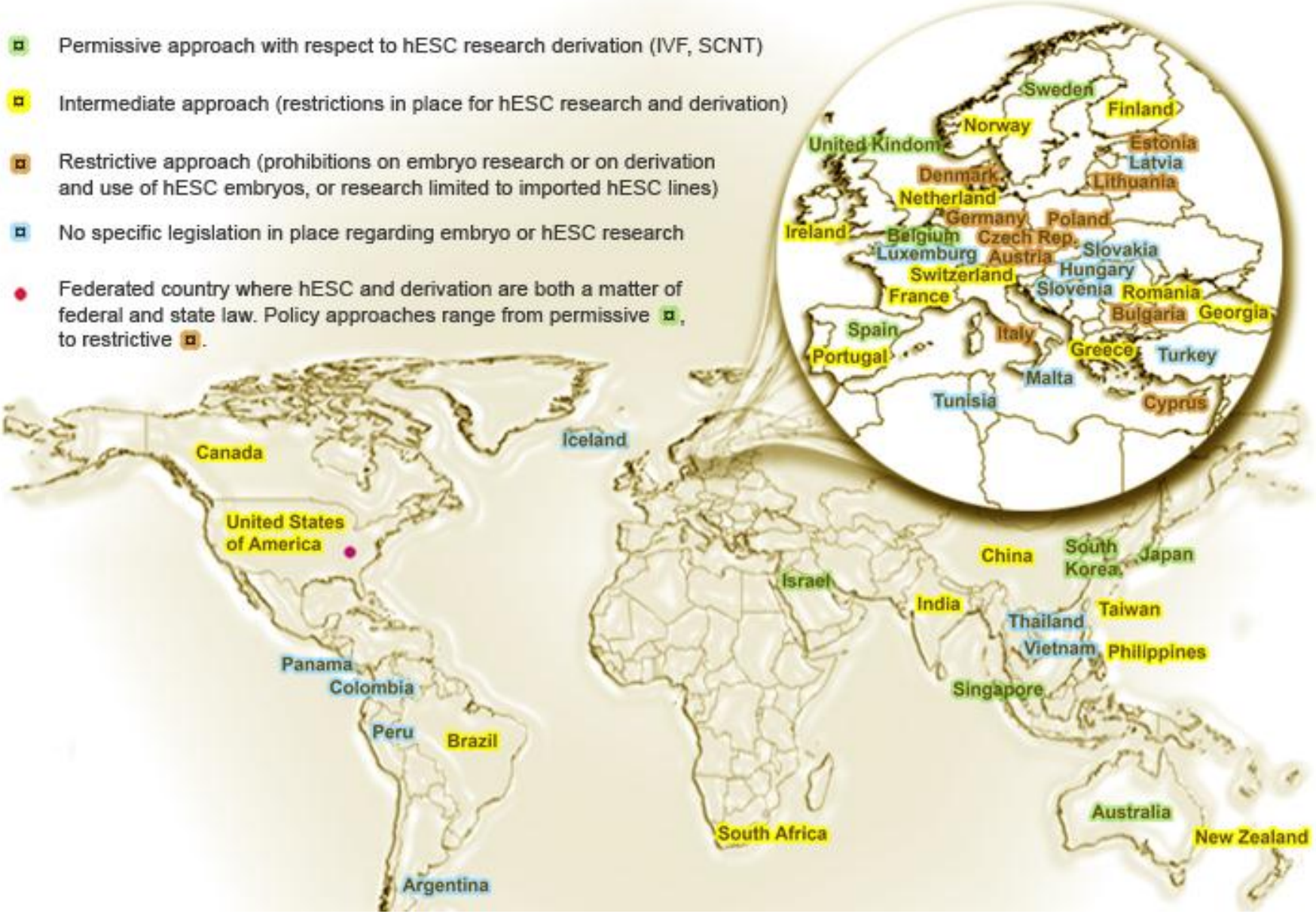
Consulting on Advanced Biologicals

UK Summary

- MHRA has significant experience with regenerative medicine products
  - cell and gene therapy products.
  - hESC (ACT, Stargardt's Macular Dystrophy)
  - approval timelines are good
  - Pragmatic science-led assessment

- MHRA undertake significant share of EMA work
  - Number of key positions on committees
- The system in the UK is harmonised with the rest of the EU

Back-up Slides



http://www.stemgen.org/mapworld.cfm

Product	INN/description	Indication/s (Therapeutic area)	Company	Submission Date	Opinion	Finalisation Date
Apligraf	*Graftskin*	*Venous leg ulcers*	*Novartis (Licensing deal with Organogenesis)*	*Apr 2001*	*Unknown*	*Withdrawn 2002*
Cerepro	*adenovirus-mediated Herpes Simplex Virus-thymidine kinase gene*	*High grade glioma*	*Ark Therapeutics*	*Oct 2005*	*Negative*	*Withdrawn Jul 2007*
ChondroCelect	characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins	cartilage defects of the femoral condyle of the knee	Tigenix	Jun 2007	**Positive**	**Jun 2009**
Advexin	*contusugene ladenovec*	*Li-Fraumeni syndrome*	*Gendux Molecular Limited*	*Sep 2007*	*Negative*	*Withdrawn Dec 2008*
Contusugene Ladenovec Gendux	*contusugene ladenovec*	*recurrent or refractory squamous cell carcinoma of the head and neck*	*Gendux Molecular Limited*	*Jul 2008*	*Negative*	*Withdrawn Jun 2009*
Cerepro	*adenovirus-mediated Herpes Simplex Virus-thymidine kinase gene*	*High grade glioma*	*Ark Therapeutics*	*Jan 2009*	*Negative*	*Dec 2009*
Glybera	alipogene tiparvovec (vector = AAV)	Hyperlipoproteinemia Type I	AMT B.V. (now uniQure biopharma B.V.)	2009	***Positive***	**Jul 2012**
Undisclosed	*Autologous oral mucosal epithelial cells*	*(Ophthalmologicals)*	*Undisclosed*	*2011*	*TBD*	*TBD*
Hyalograft C	*Cultured autologous chondrocytes on hyaluronan based scaffold*	*(Other medicines for disorders of the musculo-skeletal system)*	*Anika Therapeutics*	*2011*	*Unknown*	*Withdrawn Jan 2013*
Undisclosed	*Autologous peripheral blood mononuclear cells activated with PAP-GM-CSF*	*(Immunostimulants)*	*Undisclosed*	*2012*	*TBD*	*TBD*
Undisclosed	*Autologous cultured chondrocytes*	*(Other medicines for disorders of the musculo-skeletal system)*	*Undisclosed*	*2012*	*TBD*	*TBD*
Undisclosed	*Spheroids of human autologous matrixassociated chondrocytes*	*(Other medicines for disorders of the musculoskeletal system)*	*Undisclosed*	*2013*	*TBD*	*TBD*

Product	INN/Description	Type	Indication/s	Company	Type	Approved
Integra Artificial Skin	Artificial Skin Burn Wound Covering	Engineered Skin	Dressing, Wound And Burn, Interactive	Integra Lifesciences Corp.	PMA	Mar 96
Carticel	Autologous Cultured Chondrocytes	Chondrocyte	Repair of symptomatic cartilaginous defects of the femoral condyle	Genzyme	BLA	Aug 97
Dermagraft	Bioengineered Temporary Covering	Engineered Skin	partial thickness burns (mid-dermal to indeterminate depth)	ATS/S&N (now Shire)	PMA	Oct 97
Apligraf	Graftskin	Engineered Skin	venous leg and diabetic ulcers	Organogenesis	PMA	May 98
Epicel	Cultured epidermal autografts	Engineered Skin	Deep dermal or full thickness burns (≥30%)	BioSurface Technology (now Genzyme)	HDE	Nov 98
TransCyte	Human fibroblast-derived temporary skin substitute	Engineered Skin	Dressing, Wound And Burn, Interactive	ATS/S&N (now Shire)	PMA	Dec 98
OrCel	Interactive Wound And Burn Dressing	Engineered Skin	Dressing, Wound And Burn, Interactive	Ortec Internation (now Forticell)	PMA	Aug 01
Provenge	Sipuleucel-T	Immunotherapy	asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.	Dendreon Corporation	BLA	Apr 10
LaViv	Azficel-T	Skin rejuvanation	For the improvement of the appearance of moderate to severe nasolabial fold wrinkles in adults.	Fibrocell Technologies, Inc.	BLA	Jun 11
Hemacord	Hematopoietic Progenitor Cells, Cord	Cord blood	unrelated donor hematopoietic progenitor cell transplantation	New York Blood Center	BLA	Nov 11
Gintuit	Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen	Engineered Skin	treatment of mucogingival conditions in adults	Organogenesis	BLA	Mar 12
DuCord	Hematopoietic Progenitor Cells, Cord	Cord Blood	unrelated donor hematopoietic progenitor cell transplantation	Duke University	BLA	Apr 12
HPC, Cord Blood	Hematopoietic Progenitor Cells, Cord	Cord Blood	unrelated donor hematopoietic progenitor cell transplantation	Clinimmune Labs	BLA	May 12