EU v US Regulation
Impact on Global Development

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Objectives

- Identify differences between EMA (EU) and FDA (US):
  - legal framework
    - Impact on global development
  - Scientific expectations
    - Impact on global development
- Highly Interactive
  - This will only work if you join in.
  - Please offer examples of how this affects you
- Output
  - List of issues
  - Summary report

Objectives

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health Systems and Products
Medicinal products – authorisations, EMA

Brussels,
Sanco.ddg1.d.5(2012)

PUBLIC CONSULTATION PAPER

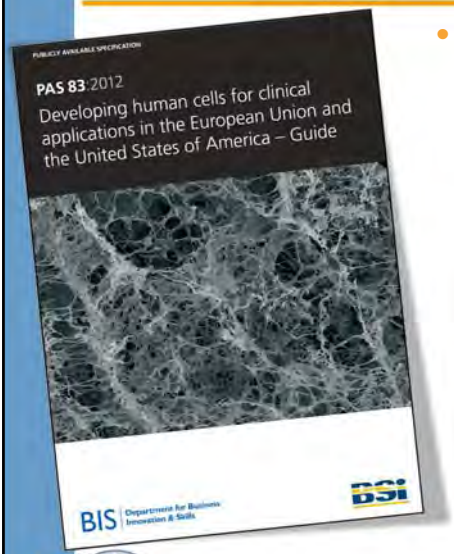
ON THE REGULATION ON ADVANCED THERAPY MEDICINAL PRODUCTS

Deadline for Public Consultation: 31 March 2013

What sorts of issues?

- The legal framework
  - Understandably different
  - Broadly achieves the same objective
  - Subtle differences can cause difficulties
- Procedures
  - Administrative differences – different forms, timelines etc
  - EU complexity (not a Federal State)
    - Myriad of different agencies
- Scientific principles
  - Underlying principles harmonized through ICH
  - Specific expectations/requirements conveyed through guidelines.

PAS 83 (2012)
British Standards Institute



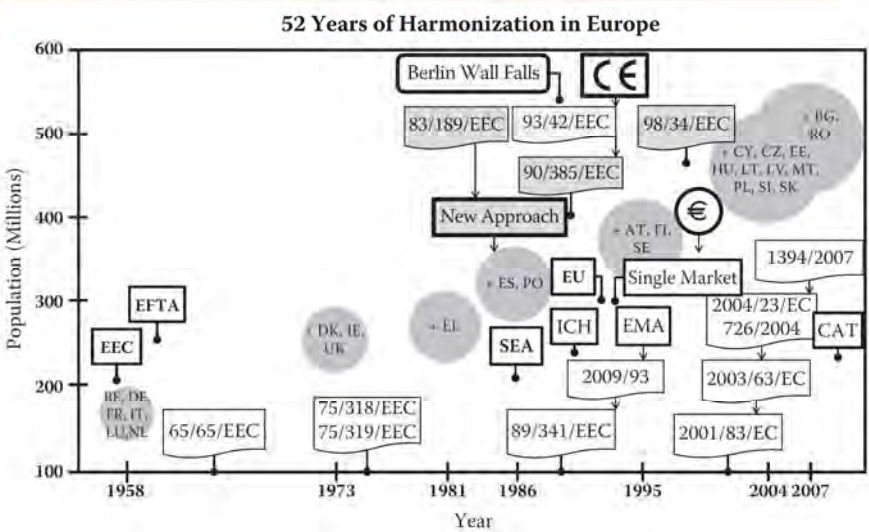
- High level overview of:
  - Legal Framework
  - Product development
  - Available guidelines and other useful links.

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

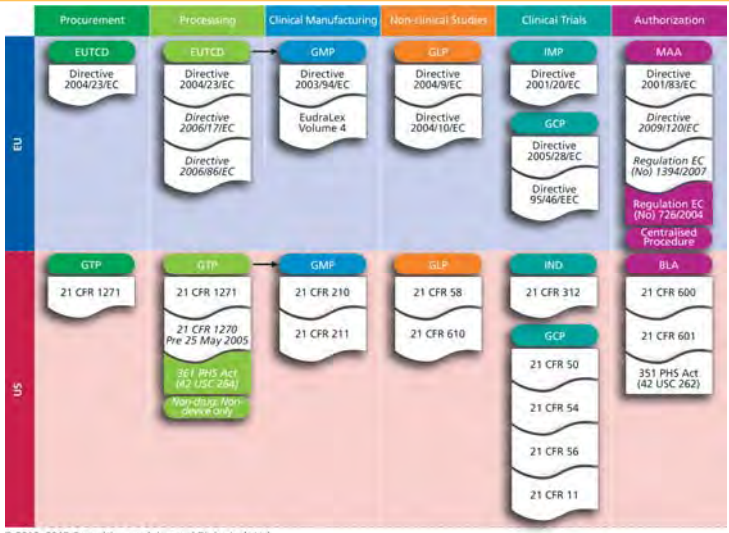
CAB

Harmonisation in Europe 1958-2009
A healthcare products perspective



From: Chapter 19 A CATalyst for Change *Regulating Regenerative Medicines in Europe*
http://www.crcpress.com/product/isbn/9781439836064;jsessionid=mhKy2DXbsRPGj8OFCaw42A**

Legal Framework



CAB

Consulting on Advanced Biologicals

Concept of minimal/substantial manipulation well-aligned.

	EU	US
Minimal manipulation	Cells or tissues in which the biological characteristics, physiological functions or structural properties relevant for the intended clinical use have not been substantially altered. The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations. [Adapted from Directive 2001/83/EC, Annex I, Part IV.2 (Directive 2009/120/EC) and Regulation (EC) No 1394/2007 Article 2(c)] Manipulations referred to in the first indent of Article 2(1)(c): • cutting; • grinding; • shaping; • centrifugation; • soaking in antibiotic or antimicrobial solutions; • sterilization; • irradiation; • cell separation, concentration or purification; • filtering; • lyophilization; • freezing; • cryopreservation; • vitrification. [Regulation (EC) No 1394/2007 Annex I]	(1) For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement; and (2) For cells or non-structural tissues, processing that does not alter the relevant biological characteristics of cells or tissues. [21 CFR 1271.3(f)] Minimally manipulated include those that have been subjected to the following procedures: • cutting; • grinding; • shaping; • centrifugation; • soaking in antibiotic solution; • sterilization by ethylene oxide treatment or irradiation; • cell separation; • density gradient separation; • lyophilization; • freezing; • cryopreservation; • selective removal of B-cells, T-cells, malignant cells, red blood cells, or platelets; [Adapted from: 66 Fed Regulation 5447, 5457 (Jan 19, 2001)]

"We do not agree that the expansion of mesenchymal cells in culture or the use of growth factors to expand umbilical cord blood stem cells are minimal manipulation."
[Federal Register: January 19, 2001 (Volume 66, Number 13)] [Rules and Regulations] [Page 5447-5469]
http://www.fda.gov/ohrms/dockets/98fr/011901a.htm

g on Advanced Biologicals

Concept of Homologous Use also well-aligned

	EU	US
Homologous use	***NOTE*** *The term homologous isn't used in the EU but the same principle is applied with the following wording:* Somatic Cell Therapy: cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor. [Directive 2001/83/EC, Annex I, Part IV.2 (Directive 2009/120/EC)] Tissue Engineered Product: not intended to be used for the same essential function or functions in the recipient as in the donor. [Regulation (EC) No 1394/2007 Article 2(c)]	The repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor. [21 CFR Part 1271.3(c)]

- Terminology slightly different, but definitions suggest the same concept.

Examples

- Cord blood banks
  - Minimal manipulation, same essential function but FDA rules mean unrelated allogeneic donors fall under BLA
    - These would remain under EUTCD only in the EU
- Living cells cannot be medical devices in the EU
  - Limitations on which human-derived substances can be used in devices.
  - Skin equivalents such as Apligraf would be ATMP's in the EU.
    - But would Apligraf be regulated as a PMA today (i.e. Gintuit, same process different presentation; but is MoA same)?

Open Discussion

- Have you experience of significant differences in classification of your product between the EU and US?
  - Do you suspect you might have a different classification if you've not yet asked?

EUTCD v GTP

- These two systems aim to achieve the same, and are quite similar.
  - Donor testing rules very similar
  - Donor eligibility – differences
  - GTP/GMP more integrated than EUTCD/GMP
    - Does this pose problems?
  - Procedural differences – EU complexity.

Donor Testing – Broadly aligned

		HIV-1 [a]	HIV-2 [a]	HBV [a]	HCV [a]	Syphilis	HTLV-I [b]	HTLV-II [b]	Chlamydia trachomatis	Neisseria gonorrhoea
Autologous somatic cells [c]	EU	■	■	■	■	■	■			
	US									
Allogeneic somatic cells	EU	■	■	■	■	■	■			
	US	■	■	■	■	■				
Leukocyte-rich cells and tissues	EU	Category not defined								
	US	■	■	■	■	■	■	■		
Gametes: sexually intimate partner for reproduction [d]	EU									
	US									
Gametes: other donors	EU	■	■	■	■	■	■		■	
	US	■	■	■	■	■			■	■

Actual test methods can get confusing

Virus	Test	Directive 2006/17/EC	Additional National	NCA's	FDA Licensed Tests?*
HIV 1 and 2	Ag		Yes	CZ, FR, MT, RO	
	Ab	Yes			Yes
	NAT		Yes (HIV-1)	DK, EE, IT, HU, PT, SK	Yes (HIV-1)
Hepatitis B	Ag	Yes			Yes
	Ab	Yes			Yes
	NAT		Yes	DK, ES, IT, HU, PT	Yes
Hepatitis C	Ag				
	Ab	Yes			Yes
	NAT		Yes	DK, DE, ES, IT, HU, PT	Yes
Syphilis		A validated testing algorithm must be applied to exclude the presence of active infection.			Yes
HTLV-1	Ag				
	Ab	Where risk	Yes**	BG, DE, EL, ES, FR, HU, RO	Yes
	NAT				

* http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/TissueSafety/ucm095440.htm

** Donor comes from area of high prevalence (Directive 2012/39/EU, amending 2006/17/EC)

Donor Eligibility - TSE Risk

Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products, FDA 2007

LIST OF BSE-AFFECTED COUNTRIES APPLICABLE TO DONOR DEFERRAL

European Countries to be Used for Deferral of Donors Based on Geographic Risk of BSE

Albania, Austria, Belgium, Bosnia-Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Liechtenstein, Luxembourg, Macedonia, Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, United Kingdom[1], and Yugoslavia.

[1]For purposes of this guidance, the United Kingdom should include all of the following: England, Northern Ireland, Scotland, Wales, the Isle of Man, the Channel Islands, Gibraltar, and the Falkland Islands.

Donor Eligibility

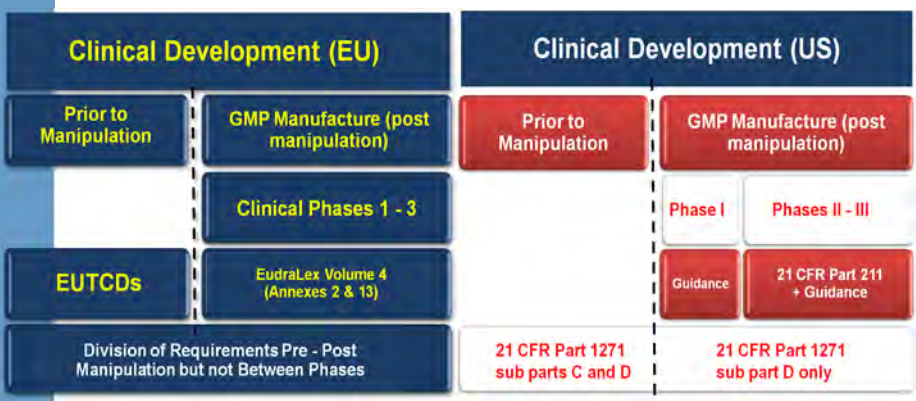
- Since EU donors for allogeneic products are excluded, developers need to source from US donors or other regions acceptable to the FDA.
  - EU do not exclude any particular region
- Have you had discussions with the FDA about the use of donors (including hESC) from outside the US for allogeneic cell products?
  - What feedback have you had?

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

Open Discussion

- You have a hESC line which was derived before 2005 in the UK
- You don't know who the donors were for the gametes
- You don't have full provenance for the line, but quite a lot of information.
- Murine feeder cells were used in the past, but not now.
- Could this cell line be acceptable
  - To EMA?
  - To FDA?

GMP



Many thanks to Patrick Ginty for this slide.

GMP

- In EU full GMP from the start
  - Risk-based approach to inspections but in many cases you will be inspected when you apply for a license (sometimes even outside EU)
  - No MRA between EU and US (yet)
- Need a Qualified Person (QP) to release investigational medicinal product, or an authorised product.
  - Must be located in the EU
  - Including import of IMP from outside EU
  - Makes a declaration of compliance with GMP, so will need to audit your facility etc

Drug Master Files

- While the EU has a system for drug master files, these cannot be used for biological active substances.
  - Active Substance Master File (ASMF) or European Drug Master File (EDMF)
- Consequently no mechanism for auxiliary reagents to use this, e.g. freezing solutions, media etc.
  - Need to work with supplier to get appropriately detailed information.
    - No mechanism to reference US DMF's

EU Risk Based Approach (RBA)

- For ATMP's the EMA has acknowledged the need for a risked based approach
- Not out of align with FDA, but nothing similar.
  - Would the FDA fins this helpful to include?
- An EMA guideline is available to suggest how to approach this
  - Its optional but likely to be useful.
  - Document in M2 identifying risks and directing the assessors to the evidence in the dossier
    - Shows that you have considered all the risks
    - Provides your justification for the level of evidence you have generated.

FDA: Target Product Profile

- Very useful concept
  - Personally recommend you consider this from the start, and update regularly
- Nothing equivalent in the EU
  - Likely to be considered useful by assessors so you could consider including in discussions with EU regulators
    - Has anyone done this?

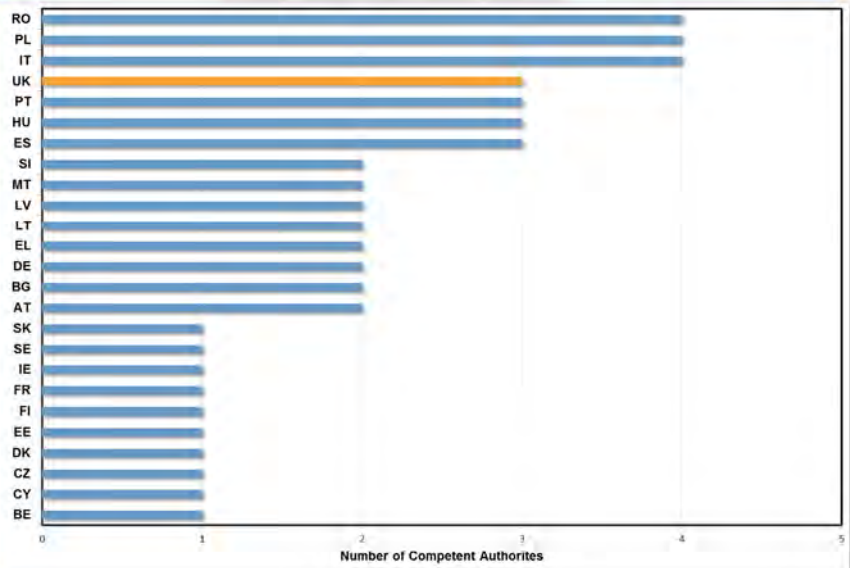
EU Agencies and Responsibilities

- In US all these activities covered by the FDA
- In EU, >30 national agencies (next slide) and the EMA.
- Procedures within national agencies can differ considerably.

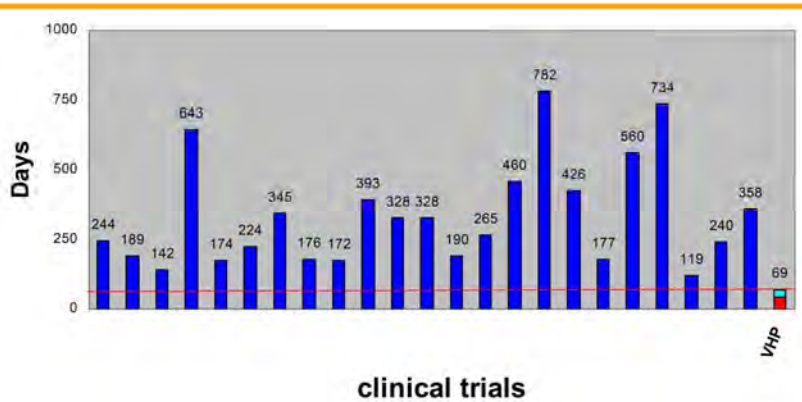
	NCA [a]	EMA
Manufacturing (GMP) licence	✔	
EUTCD [b]	✔	
Orphan designation		✔
Innovation Task Force		✔
SME registration		✔
Classification [c]	✔	✔
Certification [d]		✔
Scientific advice	✔	✔
CTA	✔	
MAA		✔
Variations (post MAA)		✔
Pharmacovigilance	✔	✔

Number of Competent Authorities

Medicines, Medical Devices, Organ Transplantation, Tissues and Cells, Reproduction, Blood



Clinical trials in the EU



- Approval times of multinational CT's with 18 member states (first application to last approval)
- Source H Krafft presentation on VHP, May 2010

Revision of Clinical Trials Directive

- Concern about the drop in clinical trails in the EU.
- Stakeholders identify complexity as an issue

Good News: Proposed Changes

EUROPEAN COMMISSION

Brussels, 17.7.2012
COM(2012) 369 final

2012/0192 (COD)

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

(Text with EEA relevance)

http://ec.europa.eu/health/human-use/clinical-trials/index_en.htm#rlctd

New Clinical Trials Regulation: Highlights

- Submission of a single common application (forms and dossier) through a new common EU portal
  - Portal to be established by the Commission
  - Single submission whether 1 or 27 CTA's
- Indicate lead (Reporting) Member state and concerned Member States
- Single payment per agency

New Clinical Trials Regulation: Process

- Involves only the participating MS
  - Applies to single MS studies and multi-state CTs
- Two-part assessment process leading to single decision per MS
  - Part I: scientific technical aspects
  - Part II: national aspects
- Part I: Coordinated process led by Reporting Member State (rMS)
  - Lead MS proposed by the Sponsor
- National concerned MS (cMS) assessment of Part II

Possible Timelines for Regulation

- Adoption of COM Proposal July 2012
- First reading & plenary vote: Q2/3 2013 ??
- Earliest approved text by 2014 ??
  - New Parliament in 2014
- Implementation by 2016 ??
  - Regulation comes into force 2 years after publication
- Timelines will be determined by the political landscape & political agenda
  - Medical devices
  - Data Privacy Directive

Open Discussion

- What problems have you experienced when dealing with multiple countries?
- Are there lessons from any particular agency that should be adopted by others?
- Both IND and IMPD can or should be in CTD format, does this mean the same documents can be used for the EU and US?
  - What sections need changes and why?

Open Discussion

- **Outside the box**: If the VHP experiment in the EU shows 27 countries can coordinate and review a single application together – could we envisage doing the same with other countries, e.g. between US and EU and Canada?
  - Would we want this?
  - What are the barriers?
  - Are we sufficiently aligned for it to work?

Non-clinical Development

- General principles harmonised through ICH.
  - In particular ICH S6 – preclinical safety evaluation of biotech products
- Value of animal studies hotly debated
- General perception that the FDA more inclined to push for animal studies
  - Some differences in opinion within the EU
- General acceptance that GLP cannot always be applied in full
- Tumorigenicity studies difficult to design and interpret
  - Difficult to argue against.
- PK/PD generally not relevant
- Biodistribution studies problematic

Non-clinical Development - Discussion

- Have you experienced differences of opinion between EMA and FDA as to need for animal studies?
  - Are primate studies ever warranted? What sorts of situations?
- Can in vitro experiments alone substitute for animal studies?
- Can you envisage a product being authorised where no animal studies have been conducted?
  - If you enter the clinic without animal data, does it even make sense to undertake studies later?

Clinical Development

- General principles harmonised through ICH
  - ICH E series
  - Harmonised guidance on ethnic factors in the acceptability of foreign clinical data

Clinical Development - Discussion

- What issues lead to differences in opinion as to the suitability of clinical studies for both regions?
  - Perception the FDA is less keen on [pivotal] data generated outside the US than EMA
    - Is this true?
  - Are both agencies aligned on the use of comparators?
- Are two pivotal trials really necessary?
  - What are the risks of a single pivotal?
- Is there really a need for adaptive licensing to allow for provisional licensing and allow for long-term efficacy data to be considered later?
- Adaptive design seems to offer efficiencies, why have so few been undertaken?

EU: Paediatrics

- The Paediatric Regulation (Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use) was adopted on 12 December 2006 and entered into force on 26 January 2007. Its main provisions started to apply from July 2008 (Article 7) and January 2009 (Article 8), respectively.

EU: Paediatrics

The key objectives of the Regulation are:

- to ensure high-quality research into the development of medicines for children;
- to ensure, over time, that the majority of medicines used by children are specifically authorised for such use;
- to ensure the availability of high-quality information about medicines used by children.

EU: Paediatric Regulation

- Established a paediatric committee (PDCO) at the EMA
- Requirement to submit data on paediatric in accordance with an agreed paediatric investigation plan (PIP) at MAA and for line extensions (new indications)
- system of waivers where medicine is unlikely to benefit children
- system of deferrals of the timing of the requirement to ensure that medicines are tested in children only when it is safe to do so and to prevent the requirements delaying the authorisation of medicines for adults;
- a reward for compliance with the requirement in the form of a six-month extension to the supplementary protection certificate;

EU: Paediatric Regulation

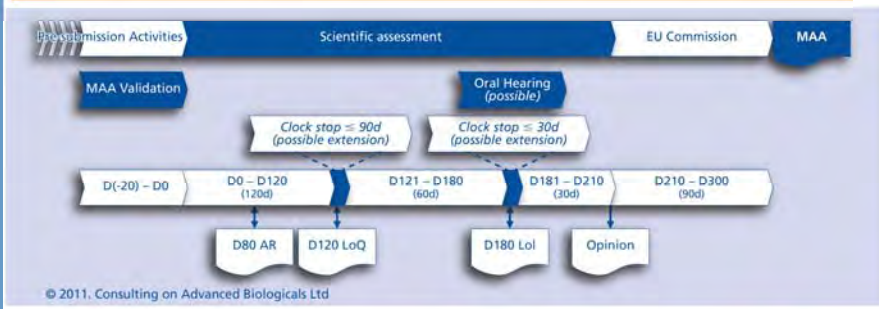
The key measures included in the Regulation are:

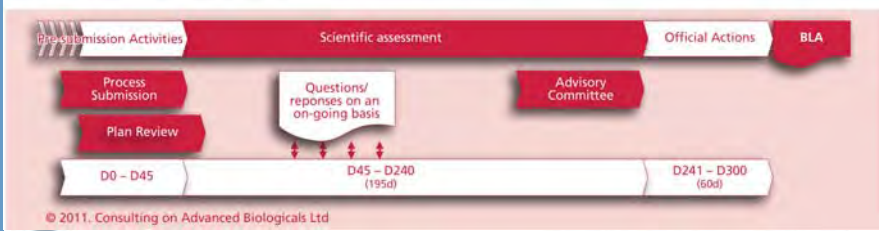
- for orphan medicines, an additional two years of market exclusivity added to the existing ten years awarded under the EU's Orphan Regulation;
- measures to strengthen pharmacovigilance and maximise the impact of existing studies on medicines for children;
- an EU inventory of the therapeutic needs of children to focus the research, development and authorisation of medicines;
- a system of free scientific advice for the industry, provided by the EMA;
- a public database of paediatric studies (http://art45-paediatric-studies.ema.europa.eu/clinicaltrials/)

EU: Paediatrics

- Importantly, you cannot submit an MAA in the EU without a PIP or PIP waiver
- You should plan to do this at least 1 year before submission to do this.

Market Authorisation Process





Market Authorisation

- Procedures for authorisation (BLA and MAA) are very different
- Timelines are theoretically similar but EU has clock stops. In the EU:
  - The procedure cannot take more then 210 days of assessment time – set in law.
  - Because of the way the EMA operates, it will also not be shorter
    - Accelerated approval process with shorter timelines
    - Emergencies – e.g. pandemic flu etc.
  - All additional time is therefore based on the required duration of clock stops to address questions.

Open Discussion

Probably a bit early to discuss differences with the licensing process – but:

- **Outside the box**: Cooperation on licensing of medicines in the EU started with a mutual recognition process and eventually led to the creation of the EMA.
- Could we envisage a mutual recognition process with other countries, e.g. between US and EU and Canada?
  - Would we want this?
  - What are the barriers?
  - Are we sufficiently aligned for it to work?

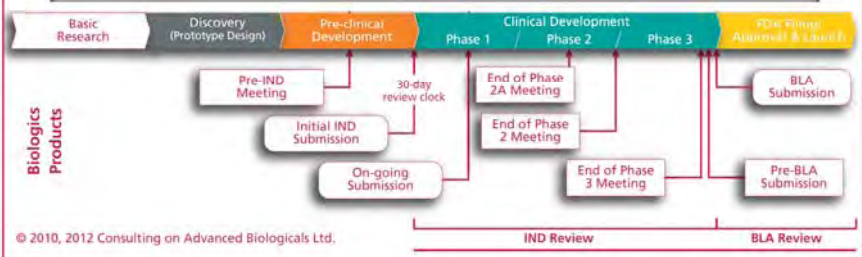
Other Procedural Differences

- Final release testing should be undertaken in the EU
- Batches imported into the EU must be re-tested on import
  - They can then be freely distributed around the EU
  - *Unresolved issue for Cellular Therapeutics*

Agency Advice in the US

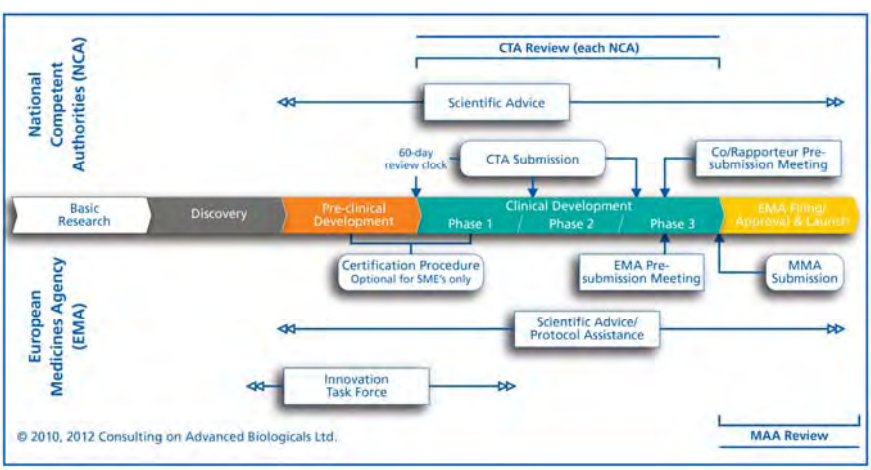
Table 6 FDA meeting types

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 Advice in the EU



EMA: Scientific Advice and Protocol Assistance

SUBMISSION DEADLINES FOR SAWP MEETINGS IN 2012

Start of procedure SAWP meeting	Presubmission meeting					SAWP 1 (start of procedure)	SAWP 2 (reports discussed)	Finalisation day 40 (adoption at CHMP)	SAWP 3 if needed (Meeting with company)	Finalisation day 70 (adoption at CHMP)
	YES			NO						
	Deadline for submission of:									
	Letter of Intent [1] by	*Dates of pre - submission meeting*	Final request by	Letter of Intent [2] by	Final request by					
03 – 05 Jan 12	13 Oct 11	*07 Nov - 09 Dec 11*	16 Dec 11	17 Nov 11	12 Dec 11	03 – 05 Jan 12	30 Jan – 01 Feb 12	13 – 16 Feb 12	27 – 29 Feb 12	12 – 15 Mar 12
30 Jan – 01 Feb 12	17 Nov 11	*05 Dec – 13 Jan 12*	23 Jan 12	08 Dec 11	16 Jan 12	30 Jan – 01 Feb 12	27 – 29 Feb 12	12 – 15 Mar 12	26 – 28 Mar 12	16 – 19 Apr 12
27 – 29 Feb 12	08 Dec 11	*09 Jan - 10 Feb 12*	20 Feb 12	19 Jan 12	13 Feb 12	27 – 29 Feb 12	26 – 28 Mar 12	16 – 19 Apr 12	23 – 25 Apr 12	21 – 24 May 12
26 – 28	19	*06 Feb -*	19	16	12	26 – 28 Mar	23 – 25	21 – 24	29 – 31	18 – 21