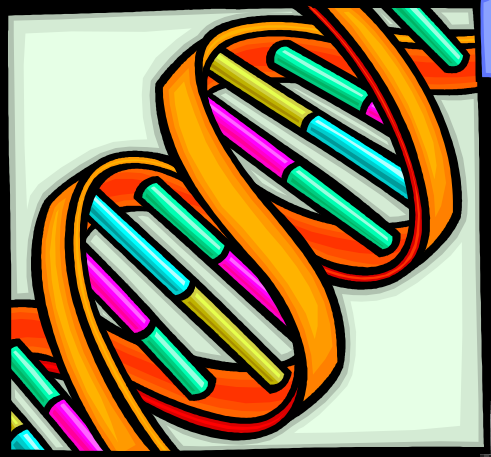
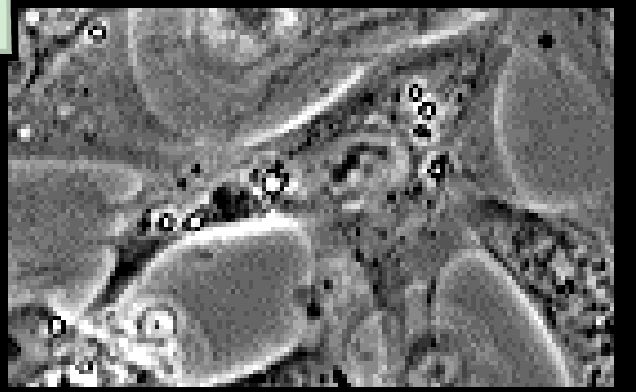
SME workshop - February 8, 2008

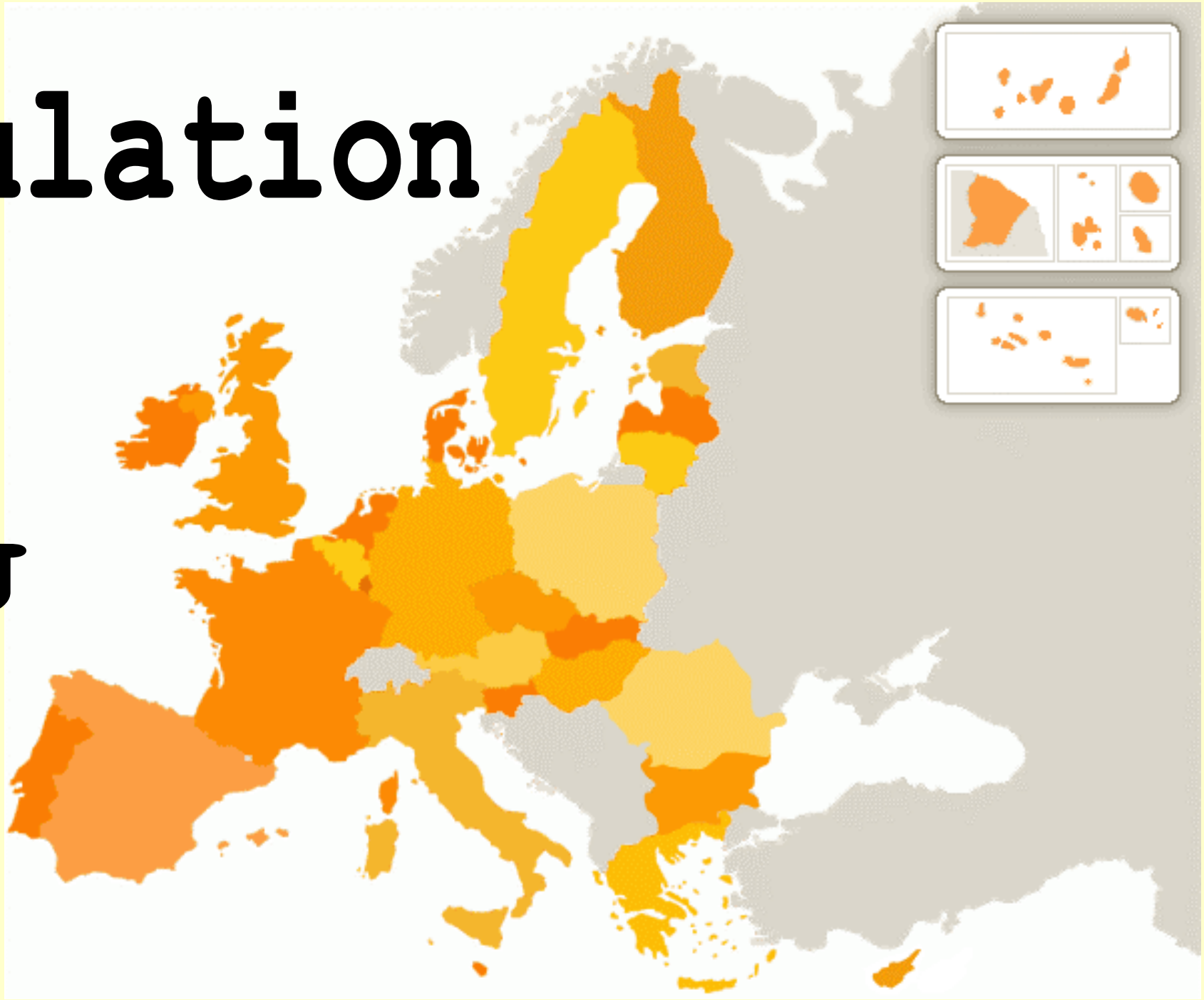
recent experience in quality assessment





Sol Ruiz
AEMPS

regulation in the EU



- Directives
- EMEA guidelines
- ICH guidelines
- European Pharmacopoeia

COMMISSION DIRECTIVE 2003/63/EC

of 25 June 2003

amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use

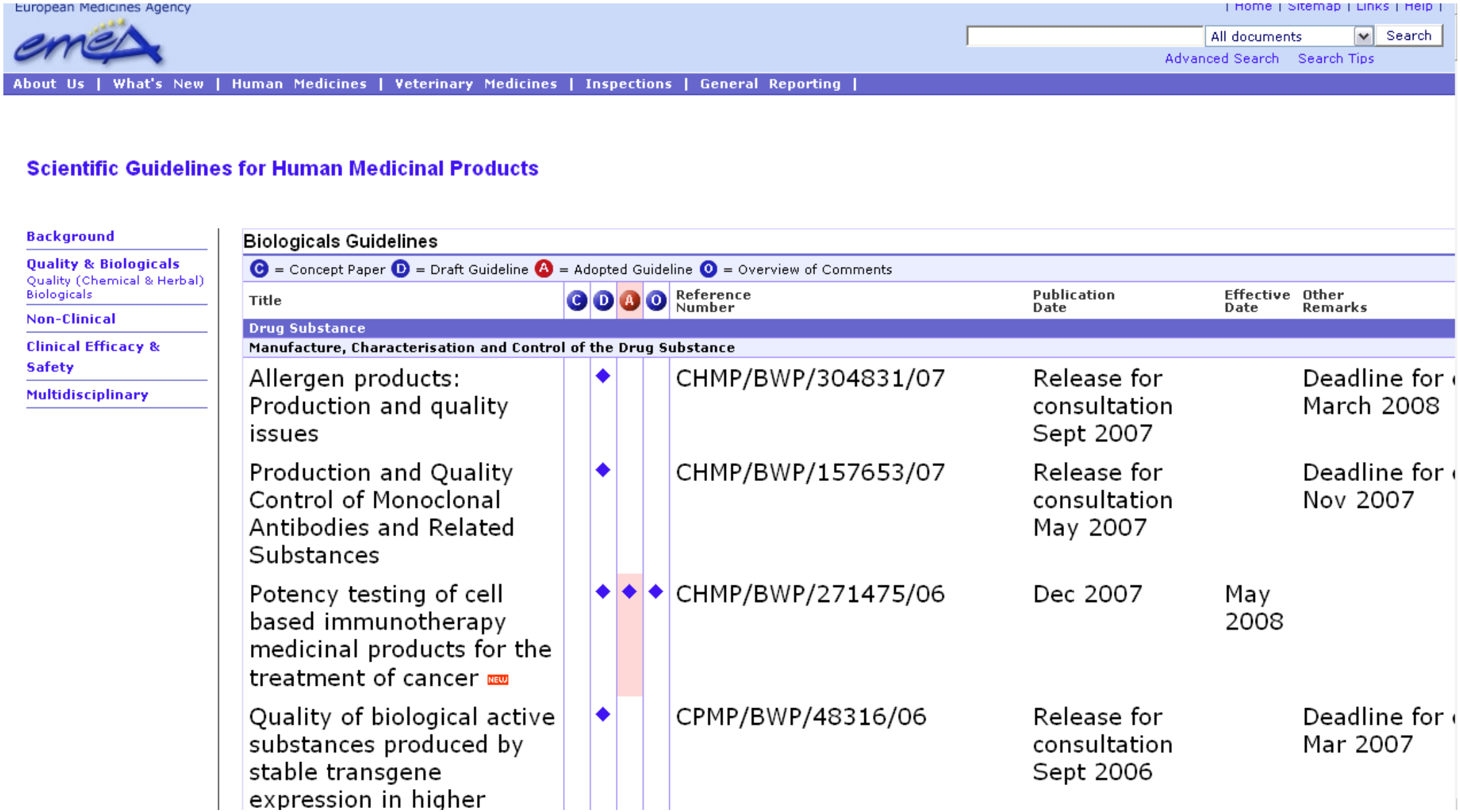
'*ANNEX I*

ANALYTICAL, PHARMACOTOXICOLOGICAL AND CLINICAL STANDARDS AND PROTOCOLS IN RESPECT OF THE TESTING OF MEDICINAL PRODUCTS

PART I

STANDARDISED MARKETING AUTHORISATION DOSSIER REQUIREMENTS

www.emea.europa.eu/htms/human/humanguidelines/biologicals.htm



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Scientific Guidelines for Human Medicinal Products

- Background
- Quality & Biologicals
  Quality (Chemical & Herbal)
  Biologicals
- Non-Clinical
- Clinical Efficacy & Safety
- Multidisciplinary

Biologicals Guidelines

C = Concept Paper D = Draft Guideline A = Adopted Guideline O = Overview of Comments

Title	C	D	A	O	Reference Number	Publication Date	Effective Date	Other Remarks
Drug Substance								
Manufacture, Characterisation and Control of the Drug Substance								
Allergen products: Production and quality issues		◆			CHMP/BWP/304831/07	Release for consultation Sept 2007		Deadline for March 2008
Production and Quality Control of Monoclonal Antibodies and Related Substances		◆			CHMP/BWP/157653/07	Release for consultation May 2007		Deadline for Nov 2007
Potency testing of cell based immunotherapy medicinal products for the treatment of cancer NEW		◆	◆	◆	CHMP/BWP/271475/06	Dec 2007	May 2008	
Quality of biological active substances produced by stable transgene expression in higher		◆			CPMP/BWP/48316/06	Release for consultation Sept 2006		Deadline for Mar 2007

www.edqm.eu/site/page_581.php

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case study 1
(live virus)

production

- Cell expansion from one vial of MCB
- Cells infected with one vial of MVSS. Incubation until full CPE is observed
- Cells harvested, sampled for testing, and split into several sublots (stored frozen)
- Freeze-thaw to release the virus
- Virus clarified by centrifugation and purified
- Buffer exchange; purified sublots concentrated
- Each sublot is sterile filtered, sampled for testing and stored frozen
- Acceptable sublots (based on testing results) thawed and pooled
- Drug substance sterile filtered, sampled for testing and filled

development

Changes introduced during development include:

- New MCB (Master Cell Bank)
- New MVS (Master Viral Seed)
- Scale-up of the production process
- Change in MOI (multiplicity of infection)
- Division of bulk harvest into sublots for purification
- Dialysis replaced TFF (tangential flow filtration)
- Addition of a freeze and hold step for sublots
- Addition of a filtration and hold step to drug substance (but later removed)
- Change in the filling facility for the drug product

in process controls

Stage of manufacture	Test	Method	Specification
Expansion of cells	Confluency following each expansion step	Microscopic inspection	
	Viability following each expansion step	In House method	
Infection and bulk harvest	Cell count prior to infection	In House method	
	Confluency prior to infection	Microscopic inspection	
	Cytopathic effect prior to harvest	Microscopic inspection	
Virus release and primary purification	Density of CsCl solution	Weighing	
	Density of CsCl solution	Weighing	
	1st UC gradient tube weight	Weighing	
	2nd UC tube weight	Weighing	
Secondary purification	pH of buffer	Potentiometry	
	pH of buffer/glycerol	Potentiometry	
	Conductivity of buffer	Conductivity meter	
	Conductivity of buffer/glycerol	Conductivity meter	
	Residual azide	In House method	
	pH of retentate and filtrate after flushing with WFI	Potentiometry	
	Normalised water permeability	Calculation	
	Conductivity of filtrate following buffer conditioning	Conductivity meter	
	Conductivity of filtrate following diafiltration	Conductivity meter	
Pooled sublots	Bioburden	Ph Eur	

Operating Parameters	Process Step	In-process Controls
Load rate Pool dilution factor Elution flow rate Pool hold temperatur	**Column: Cation exchange chromatography** **SP Sepharose HP resin**	RP-HPLC purity CEX-HPLC purity SE-HPLC purity *E coli* protein Bacterial endotoxin Aerobic bioburden Step yield Pool volume Position of start collect Peak shape

characterization

Identity:

SDS-PAGE and qualitative PCR

Content:

Total virus particles

Potency:

In vitro potency assay (rat cell line)

Impurities:

Process-related
Product-related
Potential contaminants

DS Specifications

Test	Method	Specification	Testing Facility
Physicochemical:			
pH	Ph Eur		
Content:			
Total virus particles/ml	In House method		
Identity:			
PCR	Contractors method		
Virus proteins (SDS-PAGE, coomassie stain)	In House method		
Purity:			
Host cell protein (ELISA)	Contractors method		
Residual host cell DNA (PCR)	Contractors method		
Caesium chloride (Inductively coupled plasma mass spectrometry)	Contractors method		

Changes in the production of the FP (filling):

- Facility 1 (Country A):

- Batches used in pre-clinical and early clinical studies
- Filling into plastic cryovials without freezing

- Facility 2 (Country B):

- From batch X (pivotal toxicology) onwards
- Filtered and frozen at F1, sent to F2, filled into
  Type I borosilicate glass vials

- Facility 1 (Country A):

- From batch Y (commercial supply)
- Filtered and filled directly into glass vials

Specifications of the FP

Test	Method	Specification	Testing Facility
General:			
Appearance	Ph Eur		
pH	Ph Eur		
Extractable volume	Ph Eur		
Subvisible particles	Ph Eur		
Content:			
Total virus particles/ml	In-House method		
Purity:			
Particle: infectivity ratio	In-House method		
Potency:			
Potency assay	In-House method		
Safety:			
Endotoxin	Ph Eur		
Sterility	Ph Eur		
Abnormal toxicity	Ph Eur		

assessment report

Major objections

Cell Banks

- Different cell banks used during development
- Insufficient characterisation of early used banks
- Lack of comparability studies between historical cell banks and final MCB
- Insufficient stability data for the final MCB

Viral Stocks

- Several viral stocks used during development
- The proposed commercial viral stock had not been used in clinical trials
- Insufficient characterisation of previous stocks
- Lack of comparability studies between historical stocks and final viral stock

Major objections (Cont.)

Characterisation

- Tests proposed are insufficient (additional tests required)
- Analytical procedures need complete validation

Production process (DS and DP)

- Processes and tests need full validation
- Proper comparability studies are needed
- Consistency of proposed production processes needs to be proven

Stability

- Additional data needed to support the proposed shelf-life

case study 2

(recombinant MoAb)

Recombinant antibody conjugated with a cytotoxic anti-tumour agent

- The cytotoxic agent is produced by fermentation followed by chemical modification
- The antibody is produced in a recombinant murine cell line

day 180 AR

- **A Major Objection remained was raised to the blood-derived component used during the production process of the MoAb**
  - Other Concerns raised on the cytotoxic agent
  - Other Concerns raised on the MoA
  - Other concerns raised on adventitious agents safety evaluation
- Several Commitments requested

Human plasma-derived component not acceptable

- Strict requirements described in the legislation and guidelines regarding the amount of information to be provided (e.g. testing of plasma pools, selection and screening of donors, epidemiological data from blood collection centers, traceability)
- Information difficult to obtain for a third party
- MAH was in the process of getting an alternative source in which this product is covered by a PMF

Conclusion: acceptable when this change is implemented

Viral safety

- Viral validation studies (evaluation of virus reduction/removal) – Doubts on how the validation studies were carried out (i.e. if two independent runs with material representative for the final commercial process had been performed -as required in ICH Q5A).

- Data on small non-enveloped viruses not in compliance with the requirements described in CHMP/BWP/268/95. Company's proposal: change to a smaller pore size filter (revalidation needed)

- Downscaling of viral validation study not specified (critical issue as it questions the validity of the data obtained)

Residual host cell proteins

- Initial test method: semi-quantitative Western blot assay. Not considered acceptable as validation not sufficiently documented
- An ELISA method was later developed but NOT validated yet
- Applicant proposed to conduct method validation after approval (as a post-marketing commitment)

Conclusion: **proposal not acceptable. Point not solved**

case study 3

(cell therapy product)

CT product

Critical issues: **quality and safety; traceability**

- ❑ Cell Manipulation
- ❑ Reagents
- ❑ Relevant controls
- ❑ Traceability system

CT product

Production process and facilities / equipment

Minimal manipulation: BM aspiration, separation of cells, culture, washing, filtrate and resuspension.

Processing under GMP conditions (under controlled microbiological safety) within 12- h of extraction (stability of the BM aspirate shown up to 24 h at 4°C). Transportation to the point of use in pre-filled syringes under controlled conditions.

Measures described to avoid cross-contamination (e.g. only one sample processed at a time, use of different incubators).

IPC are described (cell count, viability, identity). Results provided.

CT product

Reagents of biological original: irradiated FBS (TSE Certificate - PhEur), human albumin (authorized as a medicinal product), trypsin. Appropriate quality requirements (e.g. GMP). Specifications described, certificates of analysis provided (including sterility testing).

Drug product specifications described: cell count, viability, identity (several positive and negative markers used), pyrogens, mycoplasma, sterility. Results provided. Detailed SOPs provided. Dose and mode of administration described.

Processing is described as a continuous process from the starting material procurement to administration to the patient (2-3 h). Stability study not considered necessary.

Measures to ensure traceability described. Critical

critical issues

QUALITY

Viral/microbiological safety

Control of the manufacturing process / reagents

Consistency of production

Identity, purity, potency and stability

Comparability

sme workshop
8 february 2008

thanks!