GMP Training Course

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EU GMP Requirements

Biological medicinal product for human use

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Agenda

- **Relevant and legally binding documents**
  - EU GMP Annex 2
    - If sterile: Annex 1
    - If herbal: Annex 7
    - If human blood/ plasma derived: Annex 14
  - European Pharmacopoeia
  - PIC/ S

EU GMP Annex 2

Draft

EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

Brussels, 03 September 2007/rev.

EudraLex
The Rules Governing Medicinal Products in the European Union

Volume 4
Good Manufacturing Practice
Medicinal Products for Human and Veterinary Use

Draft Annex 2:
Manufacture of Biological Medicinal Products for Human Use

Document History	
Concept Paper published	May 2005
Pre-consultation of Biologics Working Party	April 2007
Draft agreed by GMDP Inspectors Working Group to release for public consultation.	July 2007
Deadline for comments to entr-gmp@ec.europa.eu and GMP@emea.europa.eu	14 March 2008 (revised)

EU GMP Annex 2

- **Definition**

Biological medicinal product: is a medicinal product in which the active substance is a biological substance.

Biological substance: is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physicochemical-biological testing, together with the production process and its control.

EU GMP Annex 2 - Scope

Table 1. Manufacturing activities within the scope of Annex 2.

Type and source of material	Example product	Application of this guide to steps (shown in grey) used in this type of manufacturing			
Animal sources: non-transgenic	Heparin, insulin, enzymes, proteins, allergen extract, somatic cell therapy, tissue engineered products	Collection of organ, fluid, or tissue	Cutting, mixing, and / or initial processing	Isolation and purification	
Animal sources: transgenic	Recombinant proteins, somatic cell therapy, tissue engineered products	Master and working transgenic bank	Collection, cutting, mixing, and / or initial processing	Isolation, purification and modification	
Human sources	Somatic cell therapy, stem cell therapy, gene therapy, gene silencing, tissue engineered products	Donation, procurement and testing of cells / tissues[1]	Establish MCB, WCB or cell pool	Isolation, purification, ex-vivo manipulation integration into vector incorporate into matrix	
Plant sources: transgenic	Mammalian proteins, vaccines, allergen extract	Master and working transgenic bank	Growing, harvesting, fermentation (if applicable)	Initial extraction	Isolation, purification, modification

EU GMP Annex 2 – Scope cont.

Plant sources: non-transgenic	Allergens	Collection of plants and/or pollens[2]	Initial isolation and purification	Purification and modification
Fermentation	Microbial vaccines: BCG, tetanus, diphtheria, enzymes, proteins	Establishment of MCB and WCB	Cell culture and/or fermentation	Isolation, purification, inactivation
Virus bioreactors / cell culture	Virus vaccines MMR, smallpox, influenza	Establishment of MCB, WCB, MSL, WSL	Cell culture and/or fermentation	Inactivation, isolation and purification
Biotechnology: fermentation/ cell culture	Recombinant products: EPO insulin, MAb, allergens, sub-unit vaccines	Establishment of MCB and WCB	Cell culture and/or fermentation	Isolation, purification, modification

EU GMP Annex 2

- **What is so special about biological products ?**
  - Variability of natural sources
  - Most likely to be prepared aseptically
  - Limited purification techniques
  - Potentially hazardous to men

EU GMP Annex 2

- **What are the main considerations ?**
  - Risk to the product
    - External contamination which can not be removed / detected
    - Internal contamination (inactivated products contaminated by non-inactivated product)
  - …minimized by means of
    - Containment
    - Clean room: positive pressure
    - Segregation of products („Dedicated equipment“)
    - Campaign production

EU GMP Annex 2

- **What are the main considerations ?**
  - Risk from the product
    - „Biological Safety Level“
  - … minimized by means of
    - Containment
    - Clean room: negative pressure (surrounded by positive pressure)
    - Avoidance of air recirculation
    - Effective decontamination procedures

EU GMP Annex 2

- **Part A – General Guidance**
- **Part B – Specific Guidance on selected product types**

EU GMP Annex 2

- **Part A – General Guidance**
  - Personnel
  - Premises and equipment
  - Animals
  - Documentation
  - Production
  - Starting Materials
  - Seed lot and cell bank system
  - Operating principles
  - Quality control

EU GMP Annex 2

- **Part B – Specific Guidance on selected product types**
  - Allergens
  - Animal immunosera products
  - Vaccines
  - Recombinant products
  - Monoclonal antibody products
  - Gene therapy products
  - Somatic and xenogeneic cell therapy products
  - Transgenic animal products
  - Transgenic plant products
  - Tissue engineered products (…under development …)

EU GMP Annex 2

- **Catchwords**
  - TSE (transmissible spongiform encephalopathies)
  - Definition of batch
  - Traceability
  - Viral safety

European Pharmacopoeia

- **5.1.7 Viral Safety**
- **6 General monographs**
  - i.e. Products with risk of TSE
  - i.e. vaccines for human use
  - …

PIC/ S
(Pharmaceutical Inspection Convention)

- **Inspection of biotechnology manufacturers (Aide Mémoire) (2007)**

Thank you !

Link to documents

- **EU GMP** http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol4_en.htm
- **PIC/ S** http://www.picscheme.org/