EMA Workshop on the therapeutic use of bacteriophages

London, June 8th 2015

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Presentation outlines

- Foreword : Company overview / phage therapy field,
- Strategy for the management of bacteria banks, phage banks, drug substances, drug products,
- Quality control scheme,
- Practical point of view from a CMO: experience-based considerations.

Clean Cells' overview

Founded in 2000

Located near Nantes, France

Team = 50 persons

GLP and GMP certified

Objective: To become a key player in biopharmaceutical development for human medicine and animal health

- Business 1: Quality controls of Biopharmaceuticals,
- Business 2: Manufacturing of biological products for clinical trials.

Clean Cells & Phage therapy

Participation in the Phagoburn's consortium

Selection of relevant lytic phages

Selection of appropriate production bacteria

GMP-production and quality controls of the phages

Use in clinical trial / burn patients
Plan = First patient in July 2015

Pherecydes Pharma (sponsor of the clinical trial)

Clean Cells

Clinical centers

The research leading to these results has received funding from the European Community's Seventh Framework Programme FP7 (2007-2013) under grant agreement n°601857

SEVENTH FRAMEWORK PROGRAMME

Phage production framework

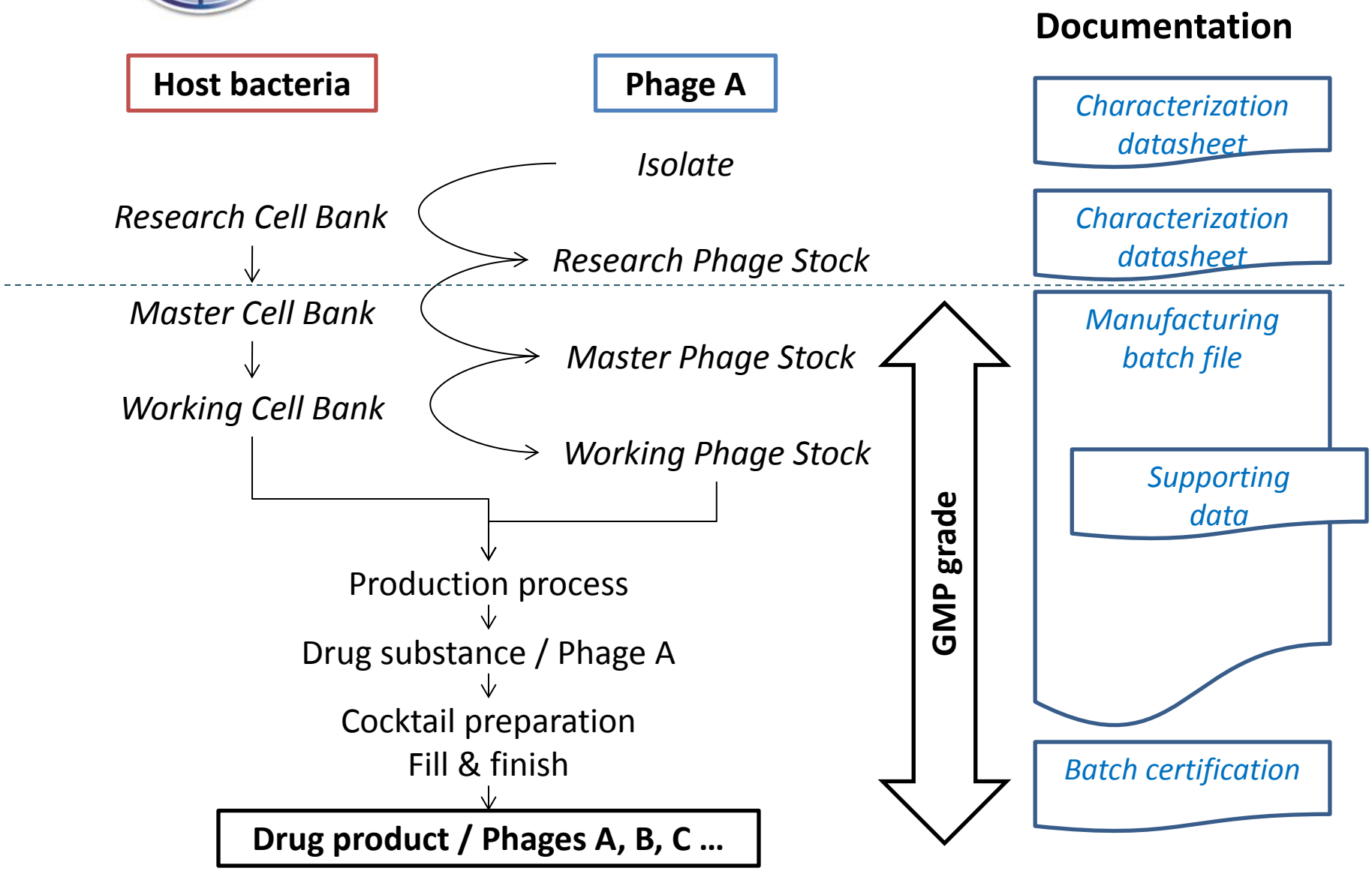
Phage products are considered as:

- Anti-infectious products,
- Biological products,
- Sterile products.

Practical organisation:

- Management of production bacteria as cell banks : R&D, Master and Working,
- Management of phages as stocks : R&D, Master and Working,
- Drug Substance Process and Drug Product Process with several steps, under GMP organization.

Phage production strategy



Phage GMP production

Parameter	Pre-requisites
Biological starting material	Full characterization available
Raw material (e.g. medium)	Selected and controlled
Single-use consumables	Selected and controlled
Classification of the production area	Class A in class C for the banks, Isolator (class A) for drug substances & products Constant environmental monitoring
Human resources	Trained staff
Equipments	Qualified
Quality controls	Validated methods (except for supporting data)
Production	Validated method + Media Process Test / Media Fill Test + Pilot runs

GOAL = Manufacturing under control

Quality control scheme

• Objective of QC: ensure the quality of the biological material and of the process at different steps

Bacteria: strategy inspired from European Pharmacopoeia 5.14

QC	Methods	RCB	MCB	EOPC
Viability	Titration	+	+	-
Identity	Full genome sequence	+	-	-
	Strain Characterization -16s DNA sequencing	+	+	-
	Genotyping – RAPD-PCR based method	+	+	+ *
Purity	Plating	+	+	-
	Absence of bacteriophages	+	+	-

* In case of production failure

Additional criteria = fit for production of the phage(s)

Quality control scheme

Phages: strategy inspired from viral vaccine strains characterization

QC	Methods	Research Phage Stock (RPS)	Master Phage Stocks (MPS)	Drug substance	Drug product = cocktail
Viability	Titration	+	+	+	+
Identity	Host range	+	+	-	-
	Full genome sequence	+	-	-	-
	DNA restriction profile	+	-	-	-
	Genotyping – RAPD-PCR based method	+	+	+	-
	Protein profile	-	-	+	-
	Morphotype by e.m.	+	-	-	-
Purity	Sterility	+	+	+	+
	Endotoxins	-	-	+	+
	Host Cell DNA	-	-	+	+
	Total proteins	-	-	+	+
	Visual aspect	-	-	+	+
Other	pH	-	-	+	+
	Volume	-	-	-	+
	Integrity of container	-	-	-	+

Experience-based considerations

- Amplification: Short duration ~17h, reduced risk of genetic instability
  Scale-up appears feasible

- Purification: Tangential Flow Filtration +/- chromatographic purification
  = f (simplicity, yield, impurities)
  TFF : robust platform process

- Sterile filtration: Feasible without impacting phage titer
  Significant advantage for multiple indications

- Fill & Finish: Aseptic step (under isolator)
  Glass vials, alternative contents possible

- Stability: > 12 months, in saline buffer
  Storage +5°C
  Rather stable and easy-to-store product

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Clean Cells

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