# GMP Phage Production for Clinical Trials

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# AmpliPhi Bioscience Corporation

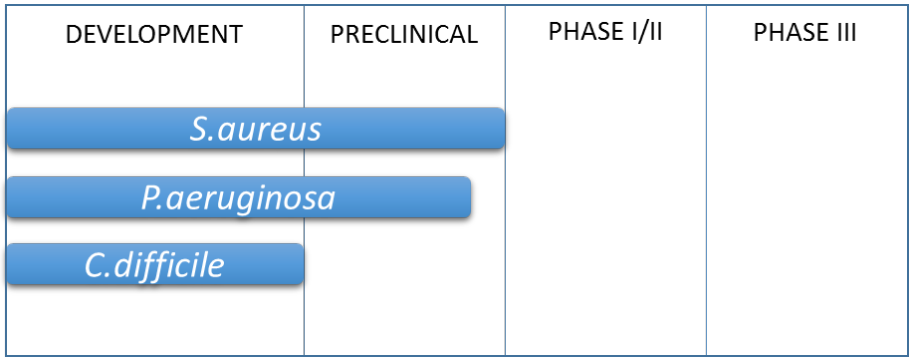
## Mission

- AmpliPhi is biopharmaceutical company focused on the development of an internally generated pipeline of naturally occurring viruses called bacteriophage (phage) for the treatment of bacterial infection.

## Organization

- Headquarters: United States
- Research: Australia, United States
- Process Development and Manufacturing: Slovenia

## Pipeline

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# AmpliPhi – GMP Facility

## Location

- Ljubljana, Slovenia

## Technical details

- Bacteriophage dedicated GMP facility built in 2014
- Size - 600 $m^2$
- Specific area:
  - Clean rooms (Grade D, C, B, A)
  - QC Laboratories
  - GMP storage
  - Process Development Lab
  - Offices

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# AmpliPhi Facility- GMP Compliant

- GMP compliant to manufacture - JAZMP
  - Active Pharmaceutical Ingredient (API) – Drug Substance
  - Human Investigational Medicinal Product (IMP) – Drug Product
- Registration of production of API in EU Database
  - According to: Directive *2011/62/EU* from 8th of June 2011
  - API: Bacteriophages

jazmp

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*Agency for medicinal products and medical devices of the Republic of Slovenia*

CERTIFICATE NUMBER: *450-3/2015-1*

**CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER**

**Part 1**

Issued following an inspection in accordance with :
Art. 15 of Directive 2001/20/EC

The competent authority of Slovenia confirms the following:
The manufacturer: ***Ampliphi, biotehnične raziskave in razvoj d.o.o.***
Site address: ***Litijska cesta 259, Ljubljana, 1261, Slovenia***

Has been inspected under the national inspection programme in connection with manufacturing authorisation no. ***800-3/2015-7*** in accordance with Art. 13 of Directive 2001/20/EC .

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on ***2015-01-29*** , it is considered that it complies with :

- The principles and guidelines of Good Manufacturing Practice laid down in Directive 2003/94/EC [1]

This certificate reflects the status of the manufacturing site at the time of the inspection noted above and should not be relied upon to reflect the compliance status if more than three years have elapsed since the date of that inspection. However, this period of validity may be reduced or extended using regulatory risk management principles by an entry in the Restrictions or Clarifying remarks field. This certificate is valid only when presented with all pages and both Parts 1 and 2. The authenticity of this certificate may be verified in EudraGMP. If it does not appear, please contact the issuing authority.

[1] *The certificate referred to in paragraph 111(5) of Directive 2001/83/EC and 80(5) of Directive 2001/82/EC, shall also be required for imports coming from third countries into a Member State.*
[2] *Guidance on the interpretation of this template can be found in the Help menu of EudraGMDP database.*
[3] *These requirements fulfil the GMP recommendations of WHO.*

Online EudraGMP, Ref key: 29261 Issuance Date: 2015-05-19 Signatory: Mr. Janez Obreza Page 1 of 3

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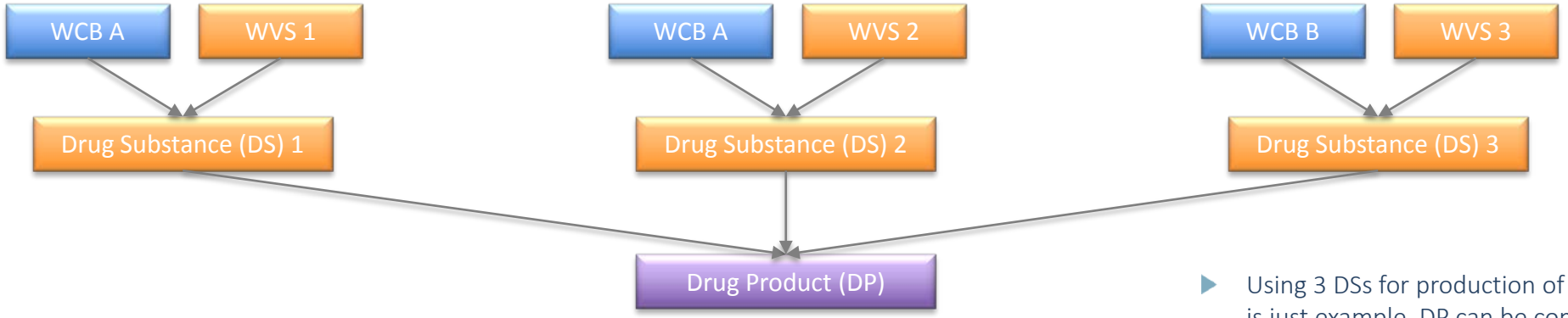
# Phage Manufacturing Process: Flow chart summary


- The same procedure is used for preparing MCBs and WCBs - for Bacteria A and B
- The same procedure is used for preparing MVSs and WVSs – for Phage1, 2 and 3

Example of preparing Drug Product:




- Using 3 DSs for production of Drug Product is just example. DP can be composed for as many DSs as required.

Drug Product is aseptically prepared according to EU GMP Guide Annex 1 Manufacture of Sterile Medicinal Products

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# Product Specifications: R&D vs GMP

| | **Research and Development Level**<br>General characterization assays | **GMP Level**<br>Tendency to use well-defined, validated, reproducible methods |
|---|---|---|
| Cell Banks | Identity, Potency, Purity, Antibiotic resistance, Spontaneous release of lysogenic phages and other specific methods that are relevant to produce a well characterized and safe product. | Identity, Potency, Purity, etc.<br><br>**Testing according to industry standards for Cell Banks.** |
| Phage Banks | Identity, Potency, Host range, Sequencing, Absence of "undesired" genes and other specific methods that are relevant to produce well characterized and safe bacteriophages. | Identity, Potency, Purity, Adventitious agents, etc.<br><br>**Specific phage testing as activity enhancing methods (e.g. Appelman method,…) are not performed at GMP level.** |

***We must separate early phage characterization vs required routine analysis of cell and phage banks produced in GMP environment.***

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# Drug Substance and Drug Product: Production, Release and Stability

- Production:
  - Scalable, robust, well specified process documented with Batch Records.
- Release
  - Identity, potency, removal of impurities (e.g. HCP, DNA, endotoxins), etc.
  - QC methods for release have to be qualified. Special care to Medial Fill validation – required for sterile fill of Drug Products.
- Stability:
  - Products on stability program
    - Cell Banks, Viral Banks, Drug Substances, Drug Product
  - Guidelines to be followed:
    - ICH Q1A, ICH Q5C

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# GMP production process as a platform

- Process can be divided into two stages:
  - Selection of candidate (host and phage) for GMP production
    - Efficacy criteria
    - Safety criteria
    - Industrial scale-up criteria
  - Platform of GMP manufacturing process
    - Existing or additional manufacturing host
    - Upstream process optimization
    - Downstream process adjustments

***It is vital that the GMP production process supports changes in the composition of a phage cocktail.***
***Criteria for these changes must be pre-established.***

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# Final thoughts

- Investigators/companies should conduct placebo controlled clinical trials using phage manufactured under GMP with accepted efficacy endpoints to meet modern standards demonstrating safety and effectiveness.
- Regulatory flexibility will be required to address the unique aspects of bacteriophage development. For example, the substitution of the most effective phage into an approved product without the need for additional clinical trials.
- It would be unfortunate to overly-burden a promising approach to treating antibiotic resistant microorganism because creative development/regulatory strategies cannot be embraced.

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# Questions

Thank you for your attention.

Any questions?



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