Phage Therapy

Talk 3 — Sustainable Manufacturing Platform
From phage bank to GMP release, and the case for a platform approach

Frenk Smrekar
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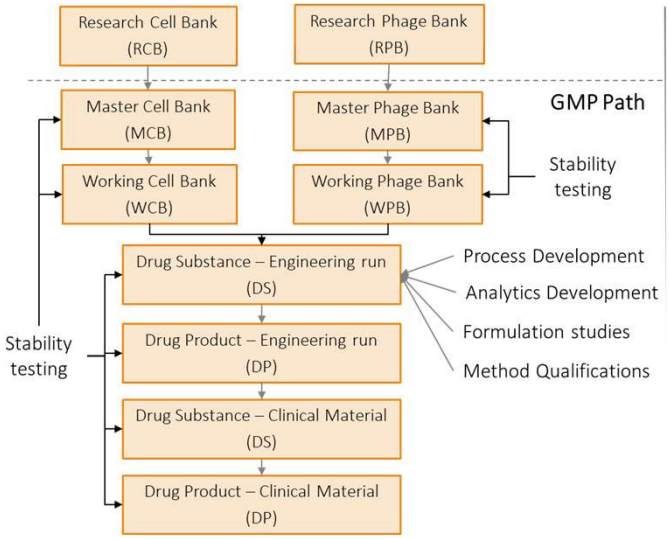
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Agenda

1. Making a living medicine **reproducible**
2. The **manufacturing challenge** in one slide
3. The **phage bank**: foundation of reproducibility
4. **DS/API:** Upstream: the host strain is a critical material
5. **DS/API:** Downstream: purification to releasable quality
6. GMP release **specifications** for a variable product
7. **Reproducibility vs variability** — drawing the line
8. The **platform model** in practice
9. **Scale**, turnaround and cost
10. **Decentralised / magistral** manufacturing

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Sustainable Manufacturing Platform



GAMRIC Global AMR Innovators Conference

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Making a living medicine reproducible

Production host:
- Bacteria
- Clinical strain (BSL1, BSL2)
- Non-optimized production strains

Production process:
- Two stage complexity: bacteria properties, phage properties
- High contribution to variability of process

Manufacturing is where the reproducibility constraint becomes concrete — specs, not slogans.

Two regimes to keep distinct:
- industrial fixed product vs
- on-demand personalised preparation.

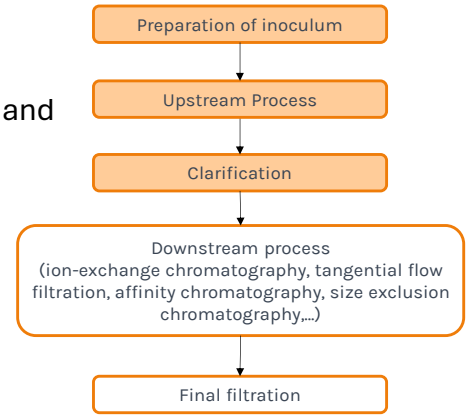
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The manufacturing challenge in one slide

Product is:
- phage

+
- host-derived impurities (endotoxin, host DNA and protein, cell debris).

Variability enters at every step:
- host strain,
- propagation,
- titre,
- purification.



Endotoxin is the gating impurity for systemic (IV) use.

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The phage bank: foundation of reproducibility

General guidance:
- A sequenced,
- characterised,
- curated collection — master and working banks, analogous to cell banks.

Selection criteria:
- strictly lytic,
- no lysogeny,
- no toxin or AMR genes,
- broad / complementary host range, stability.

Full genome and phenotype on file — an identity you can return to.

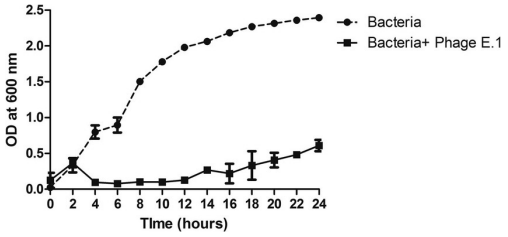
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Active Pharmaceutical Ingredient (API) – Drug Substance (DS)
<u>Upstream</u>: the host strain is a critical material

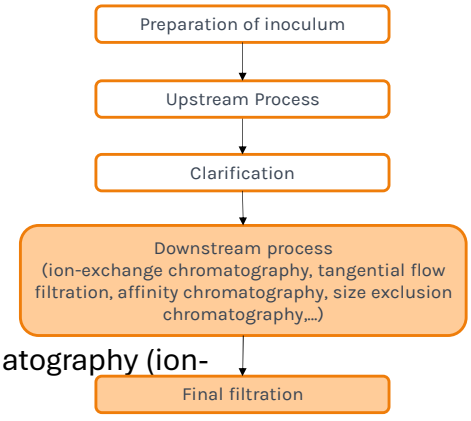
Propagation host should ideally be a safe, well-characterised production strain (or non-pathogenic surrogate).

<u>Important factors:</u>
- Two-stage process: bacteria growth + phage growth
- Host-pair specifics
- Burst size
- Resistance
- Genetic stability

Controlled host = controlled input.



Downstream: purification to releasable quality



<u>Target:</u>
- Remove endotoxin,
- host DNA
- Host cell protein;
- concentrate active phage.

<u>Process options:</u>
- GMP/Scalable: tangential-flow filtration, chromatography (ion-exchange);
- Not GMP/Scalable: historically CsCl gradients (poorly scalable).

<u>Trade-off:</u>
- yield and infectivity vs purity
- over-processing can kill the product.

GMP release specifications for a variable product

Identity:
- genome sequence

Potency:
- Biological activity
- measure of biological activity (not titre alone)?
- Orthogonal methods?

Purity / safety:
- endotoxin,
- residual host DNA
- Host cell proteins,
- Sterility/bioburden/Subvisible particles, etc..

The hard part: setting and justifying specs when inputs legitimately vary.

Reproducibility vs variability — drawing the line

Controllable:
- process parameters,
- host strain,
- in-process controls,
- release specs.

Inherent:
- some biological batch-to-batch variation will remain.

Consistency: a validated process producing components within specification, not identical batches.

The platform model in practice

A validated process:
- a characterised bacteria bank
- a characterised phage bank
- Defined API/DS process (upstream/downstream)
- Defined DP process
- Same quality expectations

Comparability and change:
- control let you add or swap phage without starting from zero.

This is the technical basis for “approve the platform, deploy many products.”

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Scale, turnaround and cost

Industrial fixed cocktail:
- batch scale,
- long shelf life,
- classic supply chain.

Personalised preparation:
- small batches,
- days-to-weeks turnaround against an acute clinical need.

Cost of goods, stability and cold chain differ sharply between the two models.

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Decentralised / magistral manufacturing

Work-flow:

- Produce phage active substance to GMP centrally;
- Supply to hospital pharmacies for magistral compounding
- Combines centralised quality control with local, patient-specific assembly.

Raises questions of consistency, oversight and traceability across sites?

Actually Higher quality & process expectations than for IMP/clinical trial material