# Changing phage cocktails to match developing resistance

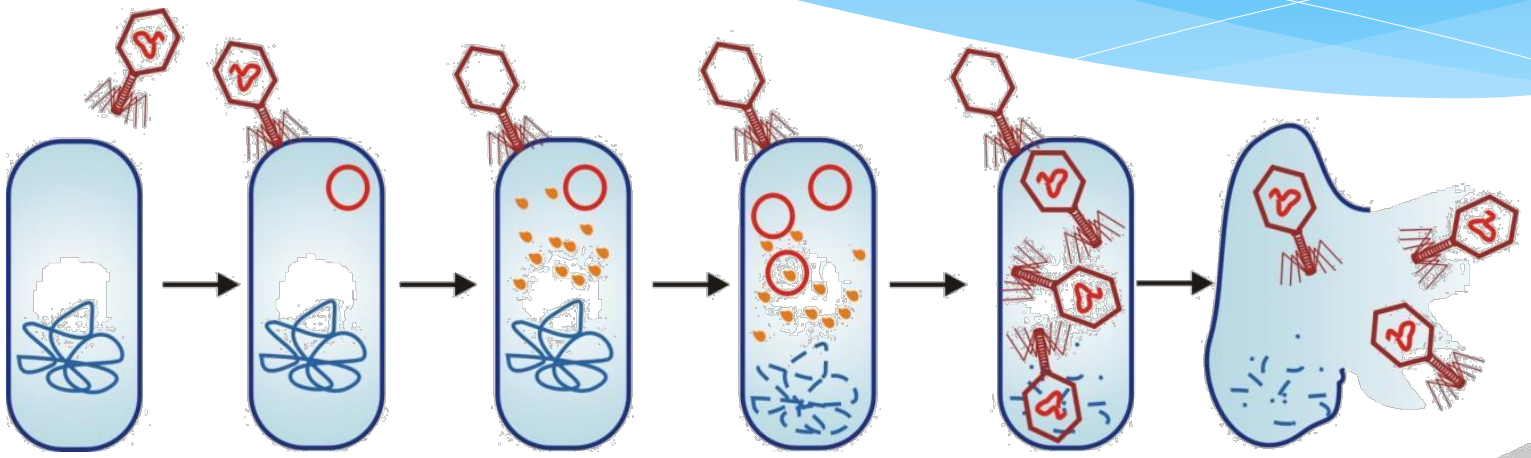
EMA Workshop on the therapeutic use of bacteriophages
London, 8 June 2015 (09:00-16:15), Room 3E

Gilbert VERBEKEN, Queen Astrid Military Hospital, Burn Wound Centre, LabMCT, Brussels, Belgium

# Opening remark

Bacteriophage therapy is a therapy concept

# Current industrial approach: bacteriophage anti-bacterials



**'Prêt à Porter'**

**Medicinal product development by a pharmaceutical company**

**Time: several months to years**

**Cost: high**

**(Patented) phage cocktail based on previously relevant strains**

Phage cocktail

**GMP produced medicinal product for broad application**

**Pre-clinical (animal) tests**

**Phase I, II, III clinical human tests**

**Review and approval**

**Marketing**

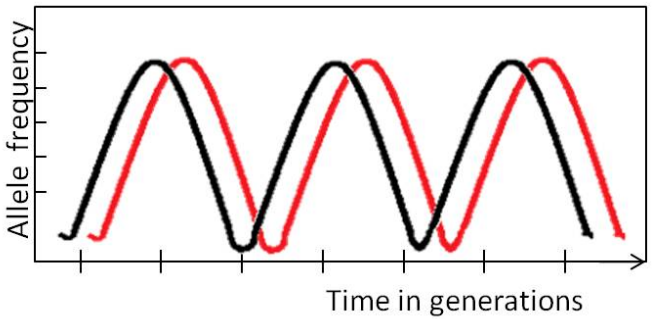
TM

**Phase IV safety**

**Eventually, a rapid updating and licensing procedure may be adopted (e.g. influenza vaccines)**

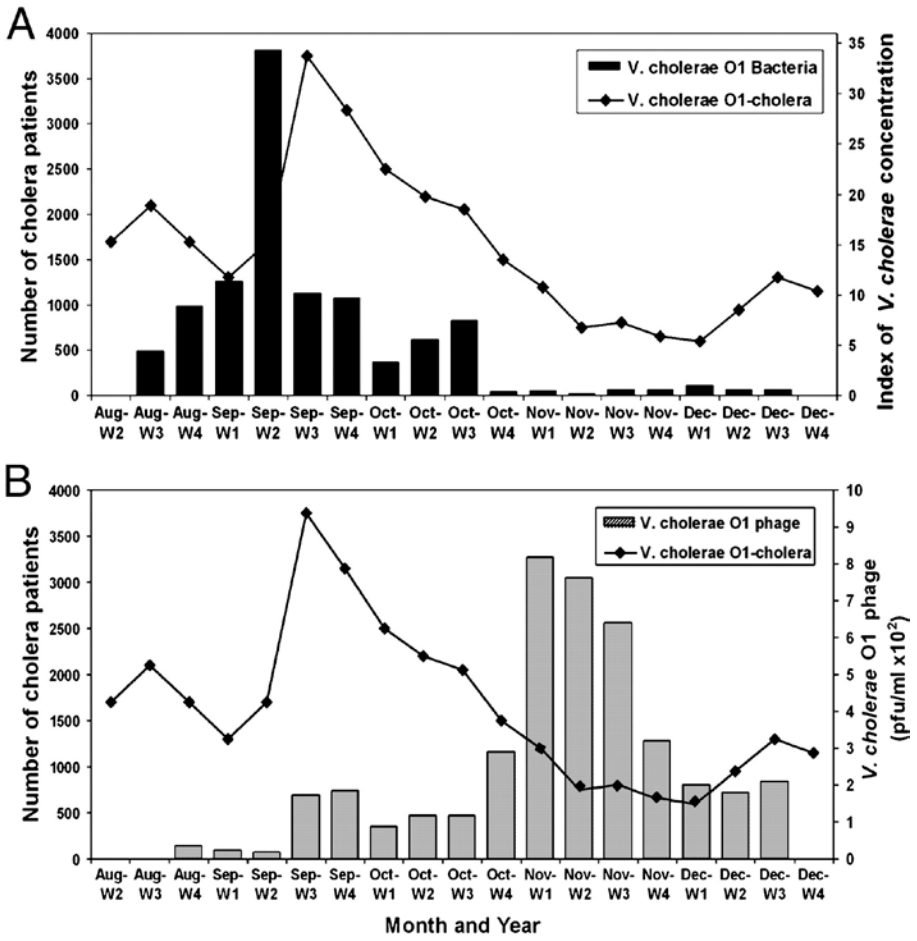
# Bacteriophage therapy: full sustainable potential

- Dynamic bacterial-bacteriophage interactions (co-evolution)
- Bacteriophages are controlling bacteria in nature
  - Bacteriophages will rapidly and drastically reduce the population of the most abundant bacteria, thus preventing the best competitors from building up a high biomass




**Negative frequency dependent selection** in the coevolution of hosts and parasites; black curve: host; red curve: parasite

# Bacteriophage therapy: full sustainable potential




## Example: Cholera infection

"**Host-mediated bacteriophage amplification** during Bangladesh cholera epidemic (2004) likely contributed to increased environmental bacteriophage abundance, **decreased load of environmental *V. cholerae*** and, hence, the collapse of the epidemic"

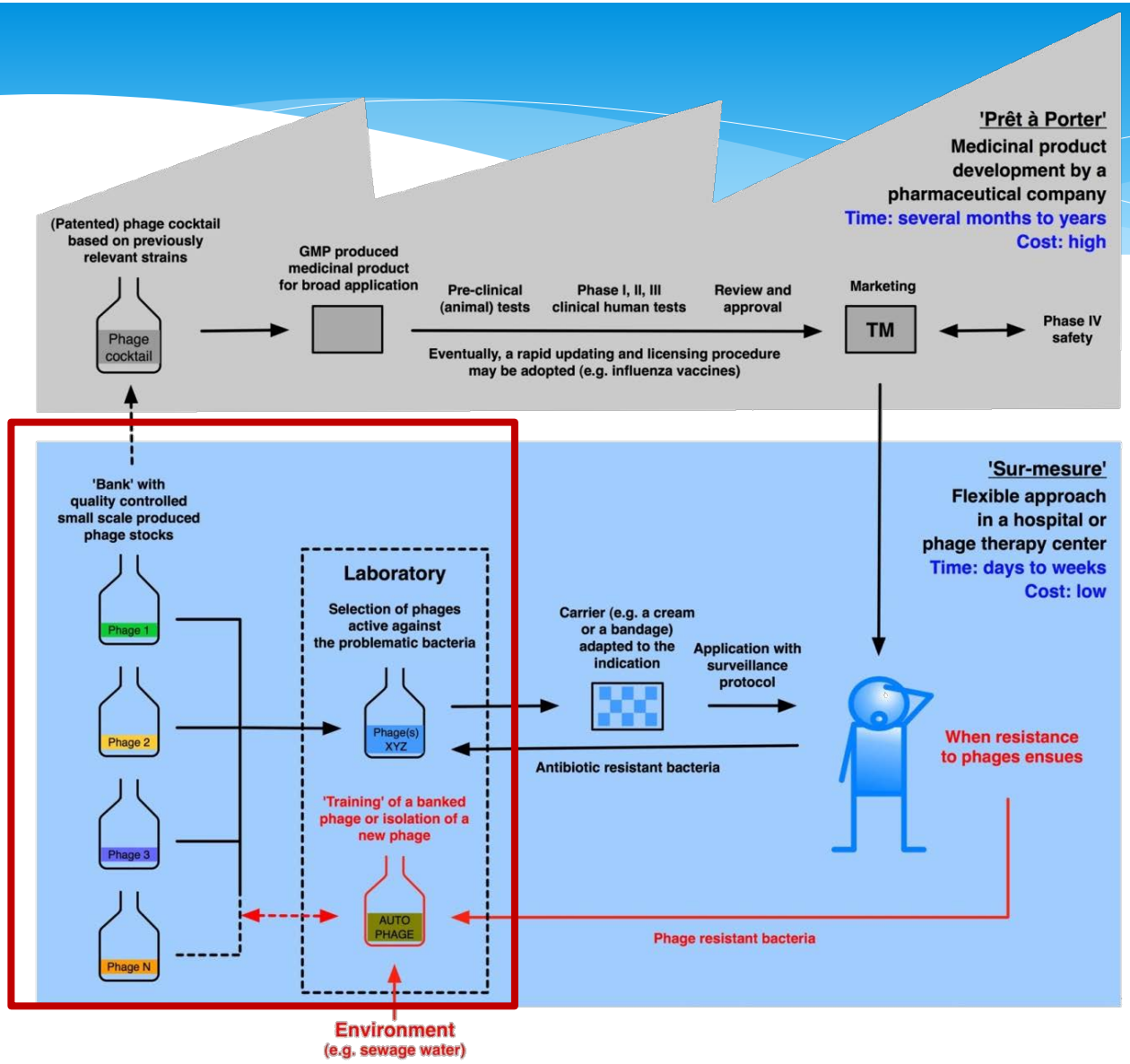
Faruque *et al.* Self-limiting nature of seasonal cholera epidemics: Role of host-mediated amplification of phage. Proc Natl Acad Sci U S A. 2005 Apr 26;102(17):6119-24.

# A rational and sustainable bacteriophage therapy concept

- Fully exploit the potential of bacteriophages
- Resistance issues (similar to antibiotics) require oversight
- Lack of strong IP protection

⇩

- **Timely small scale productions and distributions** (cottage industry) of personalised bacteriophage preparations (e.g. for MDR hospital outbreak, EHEC outbreak, ...)
- These bacteriophage preparations should adhere to well defined and **bacteriophage relevant standards of safety, quality and efficacy**




The **evolutionary bacterial-bacteriophage dynamics** can only be put to full advantage in therapy when **using a timely and flexible approach**

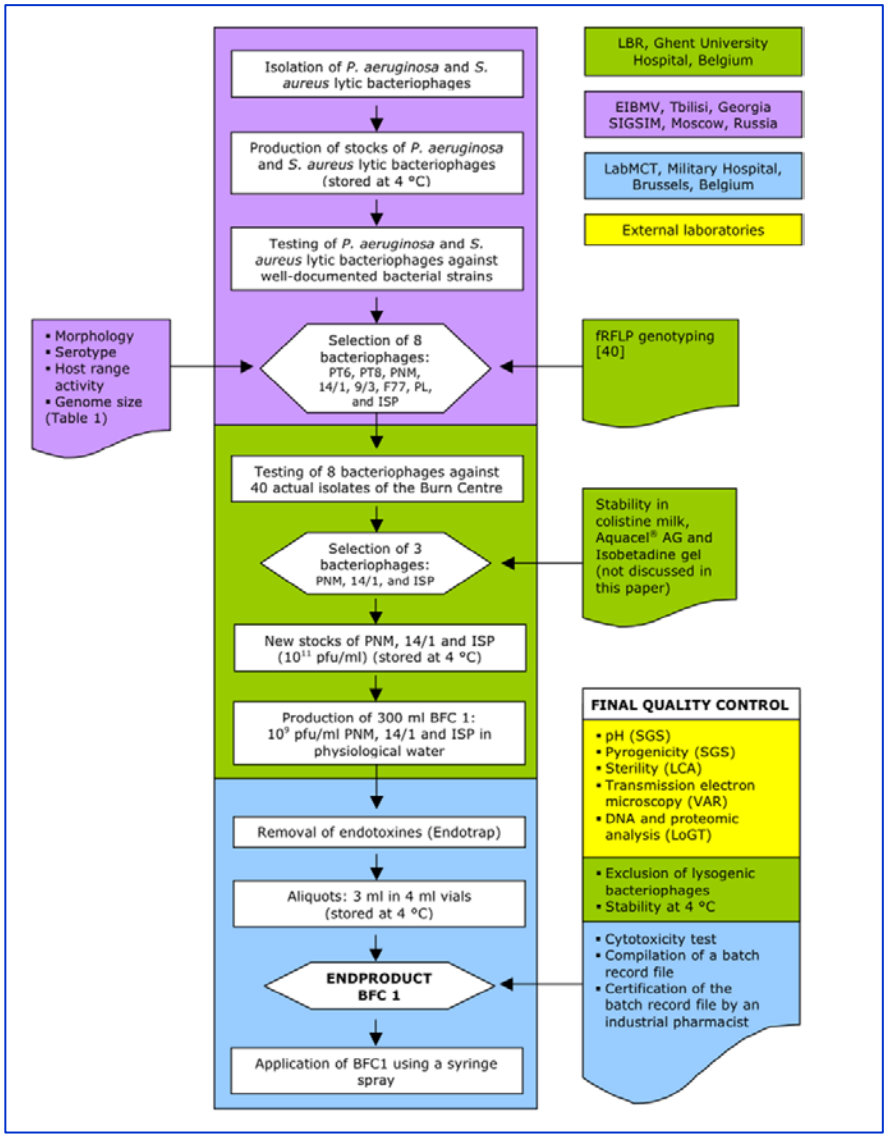
# Timely and flexible approach

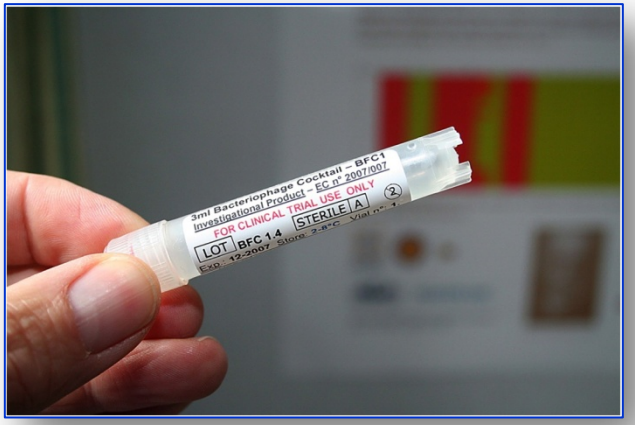
- **The ineffective bacteriophages can either be "trained,"** a term used in the Georgian Eliava Institute of Bacteriophage, Microbiology and Virology (EIBMV) to indicate the selection of bacteriophage mutants more active against the bacteriophage-resistant bacteria, or replaced by new active bacteriophages

- **New bacteriophages are generally selected from the environment** (e.g. sewage water), but in some cases they can be isolated from clinical samples containing the problematic bacterium

- In bacteriophage therapy centres in Georgia and Poland, **therapeutic bacteriophage banks containing many different natural bacteriophages** are kept and regularly updated

# Qualitative production




## Example: BFC- 1 (2007)

Merabishvili *et al.* **Quality-controlled** small-scale production of a **well-defined** bacteriophage cocktail (2 *P. aeruginosa* + 1 *S. aureus*) for use in human clinical trials. PLoS One. 2009;4(3):e4944

# Safety and quality control

**Characterisation of bacteriophages:**

* Determine morphotype
* Complete DNA and proteome analysis (confirm absence of lysogeny and toxin genes)
* Test host bacteria used in production for absence of (lysogenic) phage (mitomycin test)

**QC tests performed by qualified accredited laboratories on the preparation :**

* Phage titre (agar overlay method)
* pH (according to EP)
* Cytotoxicity (ISO10993-5)
* Pyrogenicity (10 ml/kg Rabbit, according to USP)
* Sterility (according to EP)
* Confirm morphology and activity towards targeted bacteria (TEM)

OPEN ACCESS Freely available online

PLoS one

# Quality-Controlled Small-Scale Production of a Well-Defined Bacteriophage Cocktail for Use in Human Clinical Trials

**Maya Merabishvili[1,2,8], Jean-Paul Pirnay[2]*, Gilbert Verbeken[2], Nina Chanishvili[1], Marina Tediashvili[1], Nino Lashkhi[1], Thea Glonti[1], Victor Krylov[3], Jan Mast[4], Luc Van Parys[5], Rob Lavigne[6], Guido Volckaert[6], Wesley Mattheus[6], Gunther Verween[2], Peter De Corte[2], Thomas Rose[2], Serge Jennes[2], Martin Zizi[5,7], Daniel De Vos[2], Mario Vaneechoutte[8]**

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Pharm Res
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PERSPECTIVE

# Quality and Safety Requirements for Sustainable Phage Therapy Products

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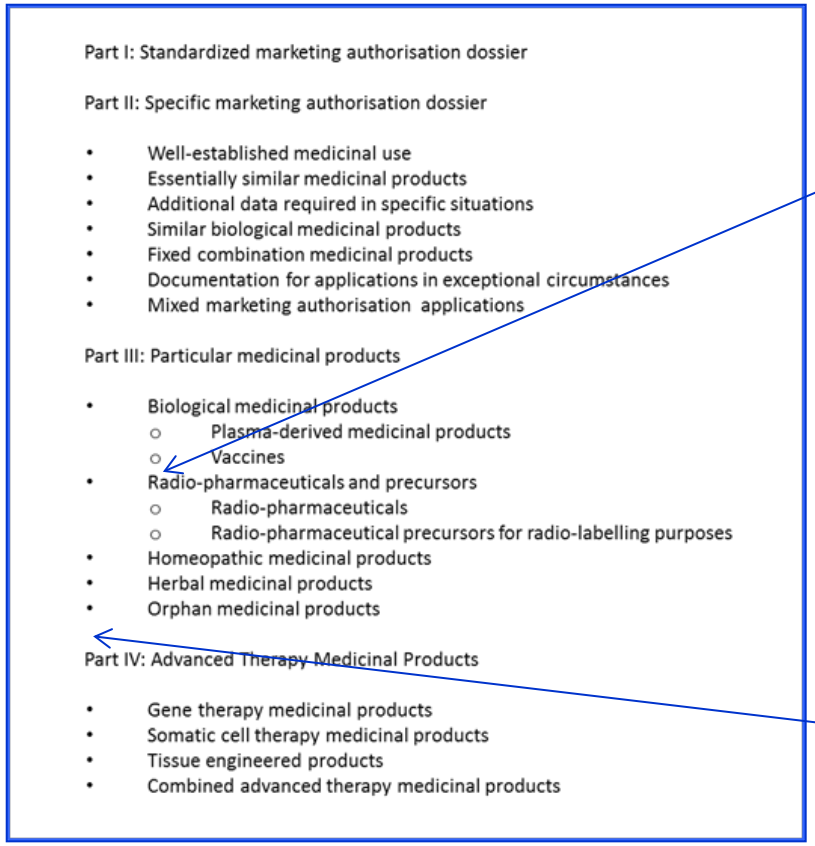
# “Vaccines” pathway ?



Part I: Standardized marketing authorisation dossier

Part II: Specific marketing authorisation dossier

- Well-established medicinal use
- Essentially similar medicinal products
- Additional data required in specific situations
- Similar biological medicinal products
- Fixed combination medicinal products
- Documentation for applications in exceptional circumstances
- Mixed marketing authorisation applications

Part III: Particular medicinal products

- Biological medicinal products
  - Plasma-derived medicinal products
  - Vaccines
- Radio-pharmaceuticals and precursors
  - Radio-pharmaceuticals
  - Radio-pharmaceutical precursors for radio-labelling purposes
- Homeopathic medicinal products
- Herbal medicinal products
- Orphan medicinal products

Part IV: Advanced Therapy Medicinal Products

- Gene therapy medicinal products
- Somatic cell therapy medicinal products
- Tissue engineered products
- Combined advanced therapy medicinal products

+ o Bacteriophage therapeutic products

( > “Prêt-à-Porter” frame )

Conditional! >>>>>>>>>>>>>>>>>>>>>>>>>>>>>

Then also define a Biological Medicinal Products “Hospital - Exemption” (BMP -H.E.) under the actual Biological Medicinal Products legislative frame ( > “Sur-Mesure” frame )

+ • Bacteriophage therapeutic products

( > “Prêt-à-Porter” frame + > “Sur-Mesure” frame )

# European Medicinal Product Directive 2001/83/EC

Art. 3.7 > **This Directive shall not apply to:** Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is prepared on a non- routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient

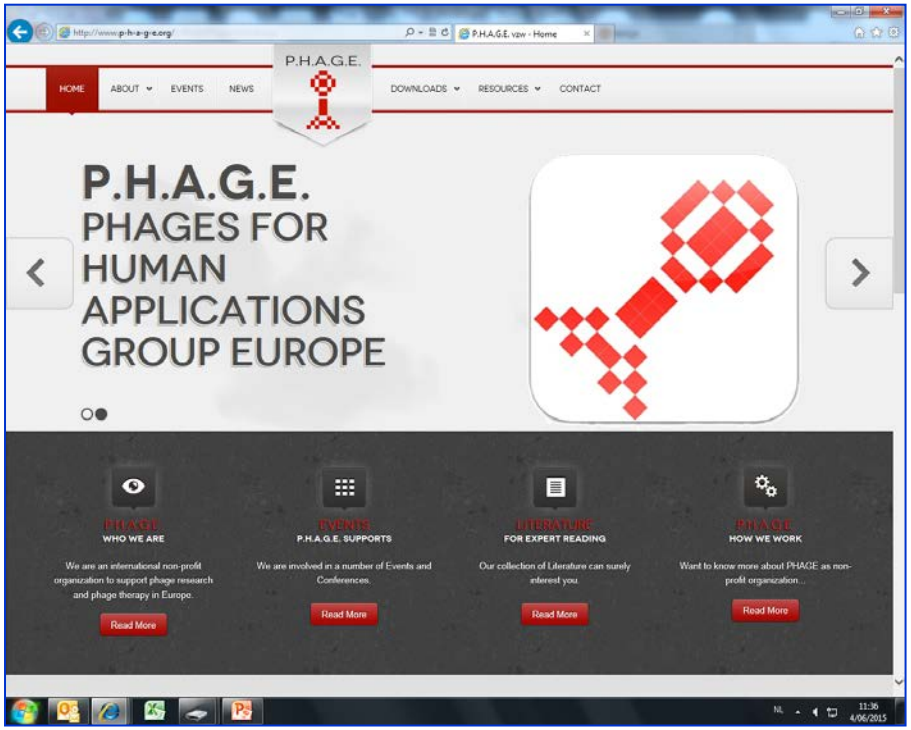
Art. 2.1 > **Scope:** This Directive shall apply to medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process

Art. 5.1 > **A Member State may**, in accordance with legislation in force and to fulfil special needs, **exclude from the provisions of this Directive** medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorized health-care professional and for use by an individual patient under his direct personal responsibility

>>> Develop a new bacteriophage therapy European directive (next to MPD 2001/83/EC) ?

# Phages in Interaction IV: September 29th 2015, Leuven, Belgium

# Thanks




http://www.p-h-a-g-e.org

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Also to colleagues at:

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- Royal Military Academy
- KU Leuven
- UGent
- Free University Brussel