# Regulatory aspects of phage therapy

ECCMID meeting

21th April 2018

Alan Fauconnier

# Disclaimer

- Currently, Alan Fauconnier works as a scientist at the WHO, in the Vaccine Prequalification team.
- Formerly, he was quality/CMC assessor at the Federal Agency for Medicines and Health Products (FAMHP), the Belgian regulatory authority competent for medicinal products.
- Alan Fauconnier was also delegate at the Biologics Working Party (BWP) of the CHMP (EMA).
- However, this presentation represents a personal view, which may not necessarily reflect the view of the WHO, the FAMHP, the BWP, the CHMP, the EMA, the EDQM and/or any other regulatory body.



culture in vivo

# EU medicinal products regulation

- enshrined in Directive 2001/83/EC as amended
- Medicinal products (MP) are defined as:

  *Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or*

  *Any substance or combination of substances which may be used or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.*

- as opposed to the medical devices, tissues and cells, blood components, cosmetics, food supplements etc…





culture in vivo

# EU medicinal products regulation

- distinction between medicinal products
  - '*either prepared industrially or manufactured by a method involving an industrial process*'
  - 'handmade', e.g. magistral formulas prepared in a pharmacy





culture in vivo

# EU medicinal products regulation

**MP prepared industrially**

- in the scope of 2001/83/EC
- regulation laid down in Community Code
- submitted to marketing authorisation application (MAA)
- Art 8 : '*qualitative and quantitative particulars of all the constituents of the medicinal product*' to be provided in the MAA
- …

**Magistral formulas**

- out of the scope of 2001/83/EC
- submitted to national provisions





culture in vivo

# Prêt-à-porter approach

Phage therapy medicinal products (PTMP) may consist of

- predetermined formulation of phage(s)
- predefined qualitative and quantitative composition
- large-scale uniform therapy
- intended for the treatment of several patients

→ "prêt-à-porter approach" *

This approach matches with the usual medicinal product regulatory requirements.
will not be addressed here.

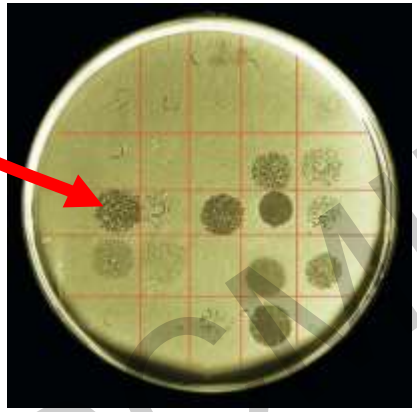
* Pirnay *et al* (2010) *Pharm Res.*



culture in vivo

# Alternative approach

Library of phages: each phage is tested on the bacteria isolated from the patient



On the basis of the « phagogram », a cocktail of phages will be formulated in a medicinal product for treating an infection with the corresponding bacterial isolate.

meaning that:

- cocktails customized for patient
- adapted over time if the phage resistance profile of bacteria is evolving.
- new phages could be added to the collection



culture in vivo

# Sur-mesure approach

- tailor-made/customized medicinal products
- to be administered possibly only just once
- “sur-mesure approach"*

does not fit well with the current regulatory framework

* Pirnay *et al* (2010) *Pharm Res*.

# PTMP regulatory status

- PTMP meet the medicinal product definition
- but face regulatory hurdles issued from
  - the wide range of active substances that could possibly be used (i.e. the different phages of the library)
  - the dynamic nature of the library (new phages could be added on an ongoing basis)
  - the "moving" qualitative and quantitative of composition of the finished product, stemming from the combinatorial possibilities of PTMP formulations.





culture in vivo

# Possible regulatory avenues

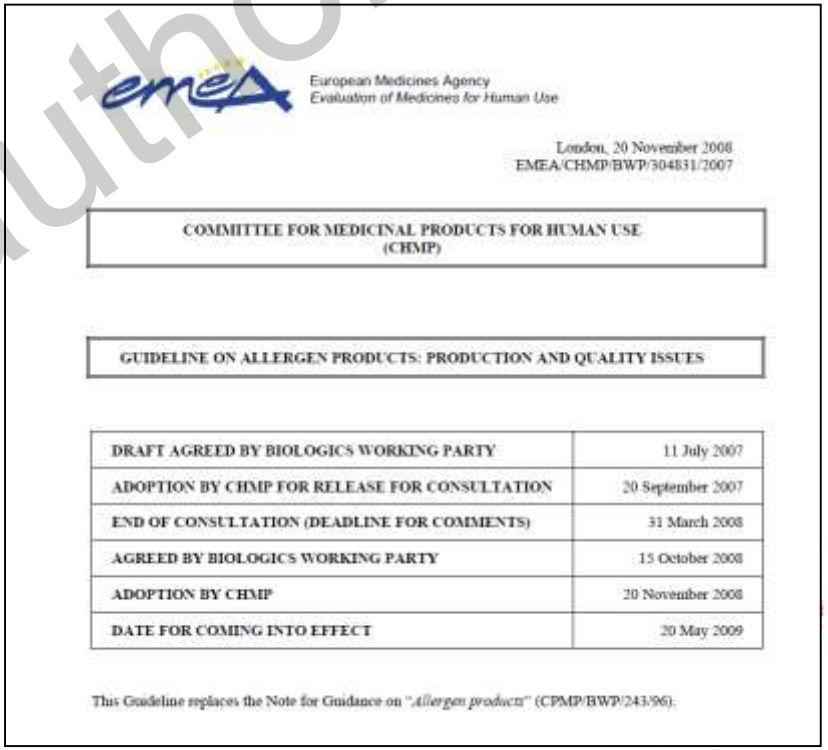
- **Homologous group concept (for allergen products)**
- **Biological Master File**
- **Magistral formula**
- ‘Specials’ scheme or ‘named-patient program’
- Multi-strain veterinary dossier
- Autogenous veterinary vaccines

* Fauconnier (2018) *Methods Mol Biol.*

# Homologous group approach

Instead of deeply characterizing each individual phage, focusing on a limited number of type species.

The concept of *Homologous groups* already exists. It was originally developed for the allergen products (EMEA/CHMP/BWP/304831/2007).



European Medicines Agency
Evaluation of Medicines for Human Use

London, 20 November 2008
EMEA/CHMP/BWP/304831/2007

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON ALLERGEN PRODUCTS: PRODUCTION AND QUALITY ISSUES

| | |
|---|---|
| DRAFT AGREED BY BIOLOGICS WORKING PARTY | 11 July 2007 |
| ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION | 20 September 2007 |
| END OF CONSULTATION (DEADLINE FOR COMMENTS) | 31 March 2008 |
| AGREED BY BIOLOGICS WORKING PARTY | 15 October 2008 |
| ADOPTION BY CHMP | 20 November 2008 |
| DATE FOR COMING INTO EFFECT | 20 May 2009 |

This Guideline replaces the Note for Guidance on "*Allergen products*" (CPMP/BWP/243/96).

# Homologous group approach

Allergen extracts prepared from different species, different genera or different families, and finished products which are derived from these allergen extracts and for which clinical experience already exists may be grouped into homologous groups…

One member of a homologous group is selected as the representative species…

To a limited extent, data on quality, safety and efficacy can be extrapolated from the representative source to other members of the homologous group…

This new concept limits the extrapolation to groups defined and justified by scientific criteria…





culture in vivo

# Ideal regulatory world?

Hybrid regulatory approach for PTMP, lying between

- extensive regulatory requirements for the operations which involve an industrial process, i.e. the manufacture of the active ingredients (the phage stocks),
- a magistral formula approach for the formulation of a personalized tailor-made cocktail of phages, which constitute the finished medicinal product.





culture in vivo

# Industrially-prepared versus custom-made

- Industrially prepared active ingredients
  - Licensing process: approval of regulatory authorities (RA)
  - Quality and safety (non-clinical) driven
  - GMP compliance
  - Release by a Qualified Person (QP release)
  - Under responsibility of industry and RA
- Custom made finished product
  - Magistral formula
  - Efficacy and safety (clinical) driven
  - Under the responsibility of prescriber and the (hospital) pharmacist



culture in vivo

# What could be done at the Community level ?

Licensing only a standalone part of the dossier, namely the active ingredient (= drug substance or DS), instead of granting to the finished product (= drug product or DP) as a whole is referred to as a "Master File".

In the EU, the concept of Master File is used for chemical entities but not allowed for biological medicinal products.

→ novel regulatory pathway would be needed in the EU

# Biological Master File concept

**BMF***

- would consist of a licensing procedure
- industrially prepared active ingredients
- ensures appropriate control of (at least) part of the process, in contrast to the weakly controlled magistral formula process
- introduces liability of DS manufacturer and RA
- valuable in other contexts
- SME-supportive

* Fauconnier (2017) *EMBO reports.*



culture in vivo

# What has been done at the national level ?

In the absence of Community provisions, a regulatory pathway for PTMP has been set up at the Belgian national level,

- based on the magistral formula national legislation
- and on the legal provisions over Scientific-Technical Advice (STA)
- result of a close collaboration between
  - the Laboratory for Molecular and Cellular Technology (LabMCT) of the Queen Astrid Military Hospital, being the manufacturer of the PTMP
  - the FAMHP, acting as the RA
  - Sciensano (formerly IPH), acting as a national control laboratory (NCL)





culture in vivo

# The magistral formula approach

In Belgium:

- active ingredients and raw materials used for the preparation of magistral formulas should meet official compendial requirements (Ph.Eur., Belgian, other), if any.
- if no official monograph available, they should be provided with a certificate of analysis (CoA) issued by an official approved laboratory.
- CoA based on an in-house monograph
- under the responsibility of the prescriber (safety, efficacy) and pharmacist for malpractices (quality).
- No GMP requirements
- No pharmacovigilance (PhV) requirements



culture in vivo

# The magistral formula approach

In the absence of a compendial document issued from an official pharmacopoeia…

- LabMCT drafted an in-house general monograph
- monograph revised and amended by both the RA and the NCL through the STA procedure
- peer reviewing by external experts (ANSM)
- made publicly available (Pirnay *et al* (2018) *Viruses*)
- living document (version 1.0)

*viruses*

MDPI

Communication

## The Magistral Phage

Jean-Paul Pirnay [1,*], Gilbert Verbeken [1], Pieter-Jan Ceyssens [2], Isabelle Huys [3], Daniel De Vos [1], Charlotte Ameloot [4] and Alan Fauconnier [4,5]

1 Laboratory for Molecular and Cellular Technology, Queen Astrid Military Hospital, Brussels, Belgium; gilbert.verbeken@mil.be (G.V.); daniel.marie.devos@mil.be (D.D.V.)
2 Bacterial Diseases, Unit Antibiotic Resistance, Scientific Institute of Public Health, Rue Engeland straat 642, 1180 Brussel, Belgium; pieterjan.ceyssens@wiv-isp.be
3 Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, O&N2, Herestraat 49, Box 521, 3000 Leuven, Belgium; isabelle.huys@pharm.kuleuven.be
4 Federal Agency for Medicines and Health Products, Place Victor Horta 40/40, 1060 Brussels, Belgium; charlotte.ameloot@fagg-afmps.be (C.A.); alan.fauconnier@mrwbru.be (A.F.)
5 Cultum In Vivo ASBL, rue du Progrès, 4, boîte 7, 1400 Nivelles, Belgium
* Correspondence: jean-paul.pirnay@mil.be; Tel.: +32-2-264-4444

Received: 15 January 2018; Accepted: 3 February 2018; Published: 6 February 2018

**Abstract:** Since time immemorial, phages—the viral parasites of bacteria—have been protecting Earth's biosphere against bacterial overgrowth. Today, phages could help address the antibiotic resistance crisis that affects all of society. The greatest hurdle to the introduction of phage therapy in Western medicine is the lack of an appropriate legal and regulatory framework. Belgium is now implementing a pragmatic phage therapy framework that centers on the magistral preparation (compounding pharmacy in the US) of tailor-made phage medicines.

**Keywords:** antibiotic; antimicrobial resistance; magistral preparation; compounding pharmacy; phage therapy; regulatory framework; personalized medicine

### 1. The Age of the Superbug

On 21 September 2016, the UN General Assembly convened a meeting on antimicrobial resistance (AMR) at the UN headquarters in New York. It was only the fourth time the General Assembly addressed a health emergency. This high-level meeting resulted in a UN resolution focused on combatting the AMR health threat. World leaders acknowledged that global AMR poses a fundamental long-term threat to human health, the production of food, and sustainable development. Based on scenarios of rising drug resistance for six pathogens, experts estimated that by 2050 the burden of AMR could rise to 10 million people dying every year and an economic cost of $100 trillion [1].

Commercial antibiotics that are currently used in public health, animal, food, agriculture and aquaculture sectors, are immutable chemicals that are based on natural antibiotics produced by soil bacteria or fungi to—depending on their concentration—either combat competitors, communicate with other organisms, or act as pleiotropic effectors of metabolic pathways. It was, therefore, to be expected that bacteria would be extremely proficient at evolving resistance to such antibiotics, especially when these are excessively and often unnecessarily used. Selective pressures imposed by humans have resulted in the emergence of "superbugs", or bacteria that are resistant to virtually all commercial antibiotics. Experts fear that society could return to a pre-antibiotic era, when simple infections could wipe out entire populations and surgical interventions were life threatening. Today, it seems that all "easy" antibiotics have been exploited and industry has been reluctant to put new efforts into the discovery and development of new classes of antibiotics. These are expensive to develop and are bound to offer a poor return on investment as they are only taken for a short period and their use is likely to be restricted in the future.

# The general monograph

Two-tiered system consisting of:

- the monograph on *Phage Active Pharmaceutical Ingredients*, laying down general requirements
- in addition, specific requirements might be included in individual monographs.

GENERAL MONOGRAPH – VERSION 1.0 **Phage active pharmaceutical ingredients**

## PHAGE ACTIVE PHARMACEUTICAL INGREDIENTS

DEFINITION

Phage active pharmaceutical ingredients (APIs) are pharmaceutical raw materials containing naturally occurring bacteriophages (phages in short), which are viruses that infect bacteria. Phages are composed of proteins that encapsulate a DNA or RNA genome, and may have relatively simple or elaborate structures. Phages replicate within a bacterium following the injection of their genome into its cytoplasm.

Phage APIs are intended for use as active ingredients of phage magistral preparations for *in vivo* treatment of bacterial infections (phage therapy).

Phage APIs are available as aqueous physiological solutions containing natural lytic phages (e.g., saline or glucose solutions) that may contain a buffer or as dried or freeze-dried powder. As active ingredients of magistral preparations, they are intended to be diluted or reconstituted and/or combined with the necessary excipients, in a hospital pharmacy officina, immediately before use on a named patient basis. Dosage forms may consist of capsules, creams, ointments, liquid preparation for oral use, cutaneous application, inhalation or parenteral administration, etc. The excipients needed to formulate these dosage forms must allow the required phage activity during the intended application period.

Each phage API contains one phage strain and various phage strains APIs may be combined into one magistral preparation to broaden the spectrum of activity of the medicine.

*The magistral preparation of phage therapy products is a practical way for medical doctors to personalize antibacterial treatments.*

*This monograph does not apply to phage derived products such as phage endolysins. It does not necessarily apply to phage products for veterinary use or for decontamination purposes.*

*In addition to the requirements specified in this general monograph, specific requirements for production, in process testing and release testing might be included in individual monographs.*

PRODUCTION

*MANUFACTURING PROCESS*

Phage APIs are generally obtained by propagation in host bacterial strains and are purified using appropriate methods shown to preserve the biological properties of the phages. Phage APIs are manufactured under conditions designed to minimise microbial contamination and phage degradation.

Purification procedures need to be designed to minimize the content of harmful bacterial or culture medium components (e.g., bacterial endotoxins and animal products).

*The manufacturing process must be described in detail (equipment, materials, culture media, additives, culture conditions, purification steps,...) in standard operating procedures (SOPs) and must be validated to confirm that the process can reliably output phage APIs of a determined standard.*

*The following manufacturing process has shown to be suitable for the small-scale production of qualitatively acceptable and safe phage APIs. It is indicative and based on the state of the art and available knowledge from peer reviewed scientific literature.*

*The manufacturing process comprises various stages.*

***De novo* phage isolation.** Natural phages are generally isolated from environmental samples such as sewage and river water or from clinical samples. Usually, the sample, culture medium and phage sensitive host bacteria (typically $10^7$-$10^8$ colony forming units (cfu)) are mixed in a sterile container and incubated under appropriate conditions (typically at 37°C for 1-3 h). If justified, a small volume of chloroform is added and the container is further incubated at 4°C for a short period of time (typically for 1 h). Host bacteria are removed using membrane filtration (0.2-0.5 µm) or by centrifugation. Usually, phages are isolated on bacteriophage sensitive bacteria following the 'double agar overlay method'. Phage lysate is mixed with lukewarm (typically 45°C) culture medium containing 0.5-1% agar and a suspension of bacteriophage sensitive host bacteria (typically $10^7$-$10^9$ cfu/ml) in a sterile container. This mixture is transferred to a sterile cell culture container with culture medium containing 1-3% agar and incubated under appropriate conditions (typically at 37°C for 12-36 h). The resulting plaques ('clear' zones formed in a lawn of bacterial cells due to lysis by phages) with different morphology are transferred to sterile culture media in sterile containers and incubated under appropriate conditions (typically at 37°C for 1-3 h). If justified, a small volume of chloroform is added and the containers are further incubated at 4°C (typically for 1 h). For each container, a dilution series (typically log(0) - log(-8)) is made in sterile containers filled with culture medium. A part from each dilution is mixed with lukewarm (typically 45°C) culture medium containing 0.5-1% agar and a suspension of bacteriophage sensitive host bacteria (typically $10^7$-$10^9$ cfu/ml) in a sterile container. This lysate mixture is transferred to cell culture containers with culture medium containing 1-3% agar and incubated (typically at 37°C for 12-36 h). Plates showing 1-10 plaques are visually analysed. Again, all plaques with different morphology are transferred to sterile culture medium in sterile containers and incubated (typically at 37°C for 1-3 h). This complete cycle is repeated until phage lysates with one plaque morphotype, containing one phage clone, are obtained (homogeneous plaques).

*If warranted, phages can be incited to evolve in vitro to exhibit broader host range or higher lytic activity under physiological conditions (e.g., temperature and pH).*

**Phage seed lots.** Phage seed lots are usually prepared using a slightly modified double-agar overlay method. If justified, another adequate solidifying agent than agar can be used. Monoclonal phage lysate (typically containing $10^8$-$10^9$ plaque forming units (pfu)) is mixed with lukewarm (typically 45°C) culture medium containing 0.5-1% agar and a suspension of phage sensitive host bacteria (typically $10^7$-$10^9$ cfu/ml) in a sterile container. This mixture is transferred to a sterile cell culture container with culture medium containing 1-3% agar and incubated (typically at 37°C for 12-36 h). If justified, a small volume of chloroform is added and the container is further incubated at 4°C (typically for 1 h). The top agar layer is recuperated and transferred to a sterile container. *Alternatively, buffer solution is added to the top agar layer. The cell culture container is shaken (typically for 1-3 h) and the buffer solution is recuperated.* Bacterial cells and cell debris are removed, usually by centrifugation (e.g., 20 min at 6 000*g*) followed by membrane filtration (0.2-0.5 µm). Phage seed lots can be stored using validated preservation/storage (cooling, cryopreservation, freeze-drying,..) methods.

**Phage APIs.** Phage APIs are prepared in the same way as phage seed lots, but starting from characterised and quality controlled phage seed lots instead of phage lysates. If justified, other agreed manufacturing methods can be used. In addition, biobuden as well as the levels of impurities, including endotoxins (especially for Gram negative host bacteria) are minimized using appropriate methods (e.g.

1

# The monograph on Phage APIs

- DEFINITION
- PRODUCTION
  - Manufacturing process
    - *De novo* phage isolation
    - Phage seed lots
    - Phage APIs
  - Quality system and production environment
  - Equipment and materials
    - General
    - Host bacterial

# The monograph on Phage APIs

- TESTS
  - Host bacteria
    - Identification (microbiology)
  - Phage seed lots
    - Identification (genomic sequencing)
    - Phage enumeration (qPCR)
    - Phage purity
    - Detection of genetic determinants conferring toxicity, virulence, lysogeny or antibiotic resistance (genome analysis)





culture in vivo

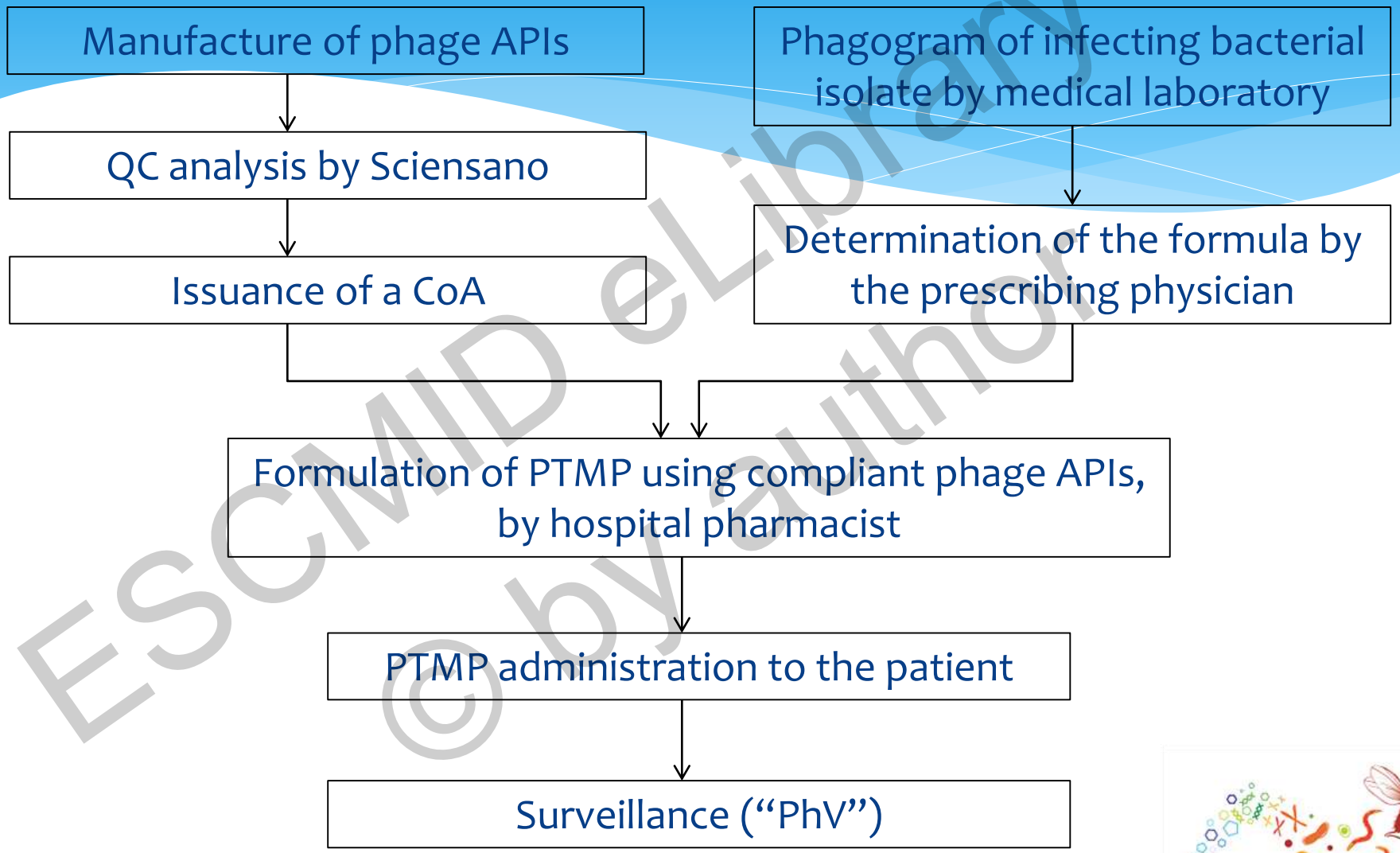
# The monograph on Phage APIs

- TESTS ff.
  - Phage APIs
    - Identification (PCR, qPCR)
    - Quantitative assessment of phages (qPCR)
    - Bioburden determination (EP 2.6.12)
    - Bacterial endotoxins (EP 2.6.14)
    - pH (potentiometric according to EP 2.6.14)
    - Water content (where relevant)
    - Impurities (chloroform, where relevant)

# The monograph on Phage APIs

- STORAGE (see individual monographs)
- SHELF LIFE (stability indicating methods, see individual monographs)
- LABELLING
- SURVEILLANCE (centralized reporting system and register for therapeutic phage applications)

# The magistral formula in practice



# Concluding remark

- Phage therapy has a place within the therapeutic armamentarium against bacterial infections
- Regulation needs to be adapted to phage therapy and not vice versa.
- No specific regulatory framework is available (yet) but several currently existing procedures may represent a source of inspiration.
- The (currently non existing) concept of Biological Master File could putatively meet both the society expectations for quality, safety and efficacy as well as the practitioners and patients needs for a customized personalised medicine.
- In the meantime, a magistral formula "enhanced" pathway may provide a pragmatic approach that opens the door to the regulatory-compliant use of PTMP.





culture in vivo

# Thanks for your attention

## Contact

Alan Fauconnier
Culture in vivo ASBL
Rue du Progrès, 4 boite 7
B-1400 Nivelles
Belgium
Email: alan.fauconnier@invivo.be

# Back up slides





culture in vivo

# Multi-strain dossier

From VT regulation

*Vaccines against avian influenza, Bluetongue and Foot-and-Mouth disease represent a special case in terms of the need for rapid and frequent change in the strains included and therefore do not fit well within the general regulatory model for vaccines*



culture in vivo

# Multi-strain dossier

Description of non fixed final composition

* **II.A. Qualitative and quantitative particulars**

  *The applicant has to define the maximum number of antigens that can be included in the vaccine and specify the quantity for each antigen. If a fixed amount of antigen is not targeted during the formulation process, minimum and maximum quantities for each antigen should be specified.*



culture in vivo

# The ‘Specials’ scheme

The named-patient use programs as meant in Article 5.1 of Directive 2001/83/EC, also referred to as ‘Specials’ scheme, allows supplying unlicensed medicinal products.

In UK:

- to meet the special needs of an individual patient
- under the responsibility of a HCP
- ‘specials’ license applying to the manufacturing site (and not the product itself)
- GMP manufacturing
- No QP release
- No PhV requirements

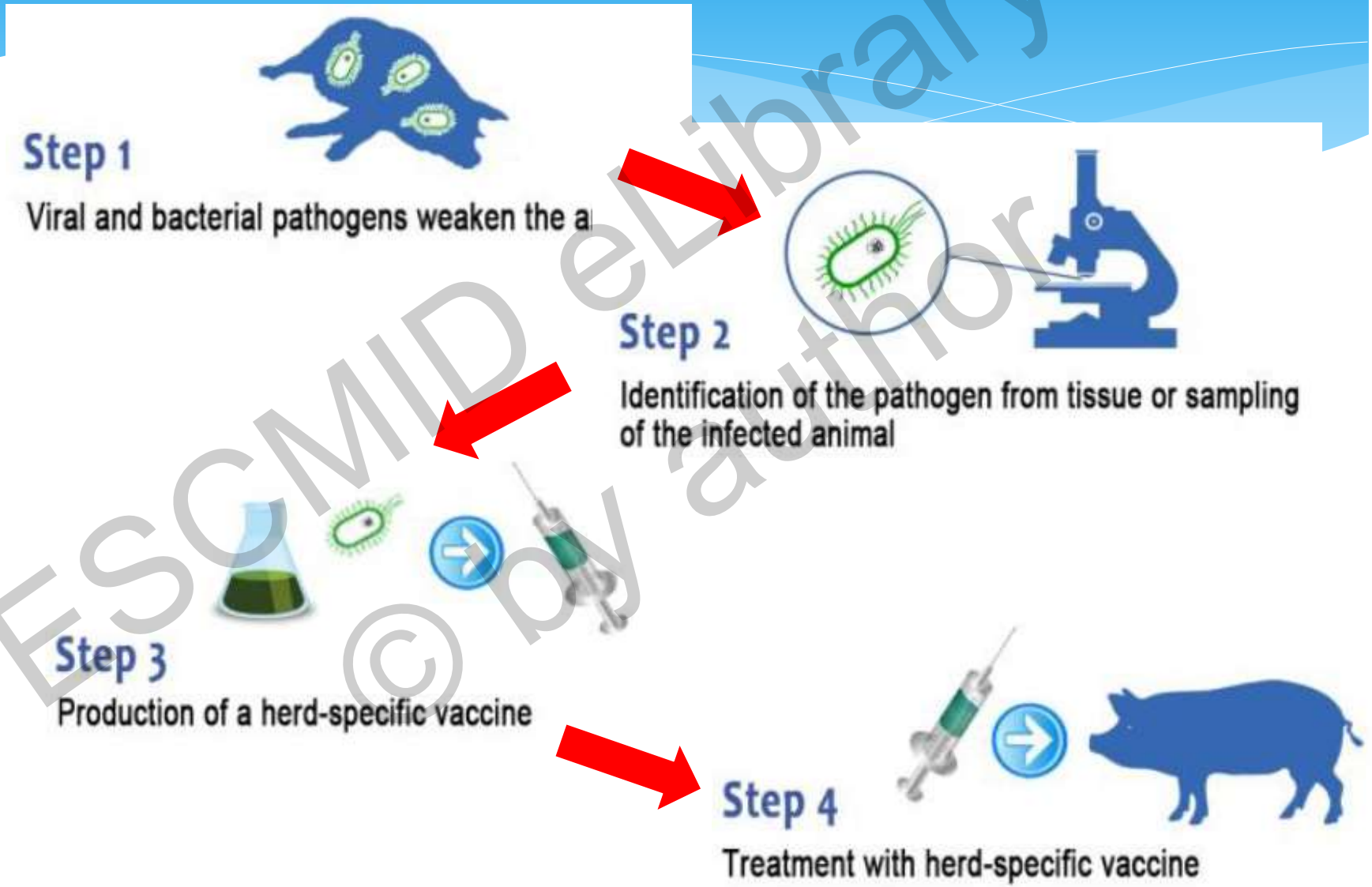




culture in vivo

# Autogenous vaccines

## Inspiration from the veterinary regulation:



# Autogenous vaccines

From VT regulation

In FR:

- tailor-made for a particular infectious event
- on veterinary prescription
- authorisation granted to a QP (and not the product itself)
- Good Preparation Practices for autogenous vaccines
- labelling must include a.o. :
  - denomination of the pathogen
  - qualitative composition
  - PhV in place



culture in vivo