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Survey on the therapeutic use of bacteriophages: summary of the responses Pharmaceutical Committee 07/11/2019

Background

Bacteriophage therapy was proposed as an agenda point for the Pharmaceutical Committee by the FAMHP (Belgium).

An increased interest of the academic and health care sector is observed in this domain, especially in treatment of infections caused by multi resistant bacteria.

Given the very specific nature of this type of product and the specific features of bacteriophage therapies, the regulatory/legal framework to develop and/or use these products is often not fully appropriate or (partially) lacking in order to adequately ensure their overall quality, safety and efficacy. Therefore, an appropriate legal / regulatory framework is needed.

To facilitate the discussion at the Pharmaceutical Committee, a small survey on this topic was send to the members states' (MS) national competent authorities (NCAs).

Responses were received from 18 NCAs, namely those of the following MS:

Germany, France, Belgium, Denmark, Czech Republic, Spain, Slovenia, Estonia, Cyprus, Greece, Malta, the Netherlands, Sweden, Lithuania, Portugal, Lichtenstein, Italy, Hungary.

Below, the responses are summarised and suggestions are made of points for further discussion.

Discussion of the responses

1. *Question 1*

Do you agree that bacteriophages that are used in phage therapy should be considered as medicinal products, as defined in Art 1.2 of Directive 2001/83/EC? If not, please explain.

Summary of the responses

The majority of the responding NCAs consider bacteriophages for phage therapy as medicinal products (15 of 18 NCAs).

The main argument is that they are " presented as having properties for treating …disease in human beings", which makes them medicinal products according to Article 1.2.(a) of Directive 2001/83/EC.

Reference is also made to a pharmacological action, which would be an additional argument according to Article 1.2(b)

Three member states responded that they have not yet decided on this issue (the Netherlands, Sweden and Malta).

Point for discussion

Does the Pharmaceutical Committee agree that bacteriophages used in phage therapy should be considered as medicinal products, as defined in Art 1.2 of Directive 2001/83/EC?

2. *Question*

Do you agree that placing on the market of these bacteriophages requires a marketing authorisation, as defined in Art 6 of Directive 2001/83/EC? If not, please explain.

Summary of the responses

The NCAs that consider bacteriophages for phage therapy as medicinal product (see question 1) are in general of the opinion that a marketing authorisation is required.

Some NCAs add that Directive 2001/83/EC (and thus also the obligation of a marketing authorisation) only applies to "medicinal products … prepared industrially or manufactured by a method involving an industrial process" (Art 2 of the Directive). In the domain of phage therapy this is the case for phage cocktails with a pre-defined composition. It is also stated that for those phage cocktails the necessary regulatory flexibility should be foreseen to easily adapt the composition to overcome resistance.

Those NCAs are of the opinion that for personalised phage therapies, where a number of phages are selected from a phage bank / library in function of the specific infection of the patient, the Marketing authorisation concept is probably not applicable and an alternative regulatory framework should be explored.

Different NCAs are of the opinion that a transparent regulatory framework is needed. This is for example illustrated by different scientific advice requests on the regulatory status of bacteriophages.

Points for discussion

Does the Pharmaceutical Committee agree on the need of a transparent regulatory framework for bacteriophage therapy?

If so, is it agreed that a different regulatory approach is required for:

- ✓ Industrially manufactured phage cocktails with a pre-defined composition (that would require a marketing authorisation), versus
- ✓ personalised phage therapies, where specific phages are selected from a phage bank / library for a single patient?

If so, how can the necessary flexibility be to easily adapt the composition of phage cocktails to overcome resistance?

What are options of tools to regulate personalised phage therapies and what should be the requirements to demonstration of clinical benefit and safety?

3. *Question*

Have you granted (a) marketing authorisation(s) for bacteriophages or is/are such authorisation application(s) ongoing? If so, please add relevant references (e.g. MA numbers, composition, indications).

Summary of the responses

None of the responding member states has a valid marketing authorisation or an application for marketing authorisation for bacteriophages.

The Czech Republic had an authorisation for medicinal product Stafal (solution) until 29th February 2008. The active substance of Stafal was: Phagi particulae contra staphyllococcus polyvalens 1 x 10^7 in 1 ml, therapeutic form: solution and the therapeutic indication was: treatment of staphylococcal infection, local application.

Points for discussion

No specific issues for discussion.

It can be noted that, although there are no existing marketing authorisations, different companies are developing phage cocktails with the objective to go for marketing authorisation. Presentations during the "Phage Futures Europe symposium" on 25-26/09/2019 (Brussels) illustrate that those companies are planning phase I and/or phase II trials and developing GMP production facilities.

4 *Question*

Have you approved clinical trials for phage therapy, or is such procedure ongoing? If so, please add relevant references (e.g. EudraCT numbers).

Summary of the responses

France and Belgium approved the now closed phase 1/2 Phagoburn (2014-000-714-65) clinical trial patients with burn wound infection (Jault et al. Lancet Infectious Diseases, 2019). This multi-centre study (FR, BE, Switzerland) has received funding from the EU Commission.

None of the other responding member states reported trials with bacteriophages.

Point for discussion

The lack of randomised controlled clinical trials was already highlighted in the summary of the EMA Workshop on the therapeutic use of bacteriophages of 2015 [1]. This concern was also expressed during the recent "Phage Futures Europe" symposium.

Does the Pharmaceutical Committee agree that there is a need to promote adequate clinical demonstration to avoid maintaining empirical approach of bacteriophage therapy?

[1] Workshop on the therapeutic use of bacteriophages, 8 June 2015, London
https://www.ema.europa.eu/en/events/workshop-therapeutic-use-bacteriophages

5. *Question*

Can bacteriophage therapy in your country be considered as unlicensed medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (magistral formula), as described in art 3 of Directive 2001/83/EC? If so, please clarify under which circumstances and which requirements are in force with regard to these preparations and to the phages themselves (e.g. are they considered to be "substances for pharmaceutical use" which need to comply with the monograph "substances for pharmaceutical use" of the European Pharmacopoeia, GMP requirements, etc.)?

Summary of the responses

Six (6) of the responding NCAs confirm that bacteriophages for phage therapy could be prepared as magistral preparation, as described in Art 3 of Directive 2001/83/EC, under the condition that the national requirements for magistral preparations are respected.

The other NCAs consider magistral preparation not an option. Different of those NCAs explain that this by the fact that there is no official pharmacopoeia monograph.

Point for discussion

Is it correct that the lack of an official monograph is the main hurdle to accept magistral preparations of bacteriophages in many MS?

Does the Pharmaceutical Committee is of the opinion that the concept of personalised phage therapy in the form of magistral preparations could be accepted on the basis of Resolution CM/Res(2016)1 of the Council of Europe on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients?

6. *Question*

Have you authorised bacteriophage therapy by any other regulatory tool (e.g. compassionate use, named patient access)? If so, please specify.

Summary of the responses

Most member states do not have alternative regulatory tools to authorise bacteriophage therapy.

In France, compassionate use of bacteriophages is possible through hospital preparations and it is expected that the ANSM could ultimately delivered Temporary Authorisation for Use for products issued from an industrialised manufacturing process.

In the Czech Republic, a "Specific Therapeutic Programme (STP)" (kind of compassionate use access, import of medicinal product authorised in other EU country) was approved till 30th April for the Stafal drug product, authorized in the Slovak Republic.

Point for discussion

No specific points for discussion.

7. *Question*

Do you have national guidance(s) on bacteriophages, for example regarding Good Manufacturing Practices? If so, please specify.

Summary of the responses

None of the Member States has national guidance(s) on bacteriophages in place.

In Germany, the development of specific quality requirements is in progress.

A proposal to elaborate a general chapter on bacteriophages in the European Pharmacopoeia was submitted at the EDQM by the Belgian authorities with the support of the French authorities. A monograph developed by the Belgian Queen Astrid hospital was added to the proposal as a potential basis.

Point for discussion

Does the Pharmaceutical Committee supports the elaboration of a dedicated chapter of the EU Pharmacopoeia on bacteriophages, to achieve harmonised requirement on the quality aspects across EU?

Is there a need to map phage banks across the EU?

8. *Question*

Have you approved in your member state the use of any bacteriophage therapies that were falling under the EU definition of a genetically-based organism (GMO)?

Summary of the responses

None of the member states has approved bacteriophage therapies that were falling under the EU definition of a genetically-based organism (GMO).

The remark is made that for such products the centralised procedure would be mandatory.

Point for discussion

No specific points for discussion.