



Sept. 18, 2006

Division of Dockets Management  
Food and Drug Administration  
HFA-305  
5630 Fishers Lane – Room 1061  
Rockville, MD 20852

**Re: Docket No. 2002F-0316 (formerly 02F-0316); Food Additives Permitted for Direct Addition to Food for Human Consumption; Bacteriophage Preparation; OBJECTIONS, HEARING AND STAY REQUEST**

To whom it may concern:

Under the provisions of 21 CFR §12.24, Food & Water Watch is requesting a stay of action and a formal evidentiary public hearing for the purposes of revoking the Food and Drug Administration's above-referenced Final Rule, published in the Federal Register at 71 FR 47729-47732 (Aug. 18, 2006). We request the Rule be stayed until the final disposition of our objections.

We seek to present at a public hearing evidence that raises genuine and substantial issues of fact and that questions in a material way the rationale of FDA's Final Rule. Our objections submitted herein plainly satisfy the standard for providing a formal hearing under the criteria in 21 CFR §12.24(b)(1) through (b)(6). The regulatory change FDA has promulgated is based on numerous arbitrary and capricious analytical failures and should be revoked.

Due to significant shortcomings and factual misrepresentations in the Final Rule, potential risks to public health posed by FDA's decision have not been sufficiently examined. The stay and hearing are further necessitated because of inordinate delays by the agency in producing public records, including the Petition and agency memos cited in the Rule.

**1. THE AGENCY FAILED TO FOLLOW ITS OWN GUIDELINES FOR ASSESSING THE SAFETY OF FOOD ADDITIVES**

CFR §170.20(a) states that FDA "will be guided by the principles and procedures...stated in current publications of the National Academy of Science-National Research Council." The regulation states the agency is permitted to follow other procedures, but only if based on "available evidence...the procedures used give results as reliable as, or more reliable than, those reasonable expected from the use of the outlined procedures."

In the Final Rule, the agency makes no certification it followed the procedures in the current NAS-NRC publication regarding food additives – "Risk Assessment/Safety Evaluation of Food Chemicals." Neither does it state that different procedures were used. If different procedures were used, the Rule does not certify they are as reliable as the NAS-NRC procedures, which CFR §170.20(a) requires.

Additionally, 21 CFR §170.22 requires FDA to establish a 100-fold safety factor for food additives – "Except where evidence is submitted which justifies use of a different safety factor."

In the Final Rule, the agency makes no certification it established a 100-fold safety factor, neither does it state that a different safety factor was used. If a different safety factor was used, the Rule does not provide evidence to justify using a different factor, as required by 21 CFR §170.22.

Further, the agency failed to comply with the testing protocols set forth in the Redbook (a.k.a. "Toxicological Principles for the Safety Assessment of Food Ingredients.")

The Redbook states that Concern Levels are to be assigned to a proposed food additive. This determination is based on "the extent of human exposure (dose) and the toxicological effects on various biological systems (nature of effect, target, magnitude of response per unit dose, etc.). The Concern Level (I, II or III) then determines the toxicity tests recommended for assessing the safety of the additive.

In the Rule, FDA does not state whether a Concern Level was assigned to the bacteriophage preparation.

Even if the bacteriophage preparation were assigned the lowest Concern Level of I, the recommended toxicity tests for this level were not conducted, based on the Rule and supporting agency documents. According to the Redbook, the tests for Concern Level I are:

- Short-term tests for genetic toxicity, including a test for gene mutations in bacteria, an *in vivo* test for chromosomal damage using mammalian hematopoietic cells, and either an *in vitro* test with cytogenetic evaluation of chromosomal damage using mammalian cells or an *in vitro* mouse lymphoma thymidine kinase<sup>+/-</sup> gene mutation assay; and
- A short-term feeding study (at least 28 days duration) in a rodent species, including an evaluation of potential neurotoxicity and immunotoxicity. Observations and clinical tests are to include neurologic disorders, behavioral changes, autonomic dysfunctions, body weight, ophthalmological examination, hematology, clinical chemistry, urinalyses, necropsy and microscopic examination. The study should include at least 10 rodents per sex per group.

Reference 3 in the Rule (Feb. 1, 2006 memo from the Division of Petition Review to R. Davy) cites five studies – none of which fulfill the Redbook's recommendations for even a Concern Level I food additive.

Four of the five studies were conducted in Eastern European countries. The Petitioner introduces the Eastern European studies by saying on page 001673 of the Petition that “the Petitioner is well aware that most of these studies do not possess the desirable rigor of a well controlled and well-documented study such as would be commonly carried out in the United States.

Notwithstanding, the studies do provide presumptive evidence of the safe use of a wide range of bacteriophage preparations, including sustainably crude ones, in severely ill patients of all ages.”

Three of these studies involved the use of a bacteriophage on humans to address medical conditions, none of which are related to the bacteria *L. monocytogenes*. One study examined the immunobiological characteristics of a *Klebsiella* bacteriophage preparation on lab animals, and then also examined the therapeutic activity of the bacteriophage on humans. And the final study included in this memo, conducted in the U.S., tested the efficacy of a single *L. monocytogenes* bacteriophage on lab animals.

In one human study conducted by Babalova et al, the bacteriophage was used as a phagoprophylaxis to prevent dysentery among children. As the Petitioner describes on page 001674 of the Petition, “the paper does not specifically discuss the absence of adverse effects, however, none were reported in the context of the extensive study.” The objective of this study was to study the efficiency of the dry bacteriophage preparation for dysentery and not to study the allergenicity or toxicity of the bacteriophage preparation.

In the other three human studies presented, the bacteriophage preparations were intended for use as phage therapy to treat bacterial infections already present in humans.

Bogovazova et al. had two objectives. First the study examined the immunobiological characteristics of a purified *Klebsiella* bacteriophage and an unpurified *Klebsiella* bacteriophage by administering the preparations to mice and guinea pigs. The Petitioner states in the Safety Narrative on page 001674 that “this study is particularly pertinent since it examined preparations of bacteriophages with higher protein and endotoxin content than LMP-102™.” However, different bacteriophages are used in this study, and based upon the information presented in this article, the study does not appear to meet the Redbook requirements for a short-term toxicity study due to the following deficiencies: the number of laboratory animals used was not included; the report did not mention the use of both genders of laboratory animals, and; the only organs reported to undergo histological analysis were the lungs, myocardia, liver, spleen, kidneys, adrenal glands, and skin. The report did not mention conducting the following clinical and observational tests: neurologic disorders, autonomic dysfunctions, ophthalmological examination, and urinalyses. The study reports that it adhered to the State Testing Program, approved by the USSR Health Ministry (decree #437 of July 25, 1989), but information was not available to compare these standards to the level of rigor of the Redbook standards.

The second objective of the Bogovazova study was to examine the therapeutic activity of the *Klebsiella* bacteriophage for the treatment of conditions caused by the bacteria *K. Pneumoniae*, *K. ozaenae* and *K. rhinoscleromatis*. Clinical trials were conducted on humans after the toxicity testing of this phage preparation. This part of the study was concerned with the efficacy of treating the bacterial infections with the phages. The Petitioner states on page 001675 of the

Petition that “the study specifically states not only that the phages were effective, but that there were no side effects as well.”

Pavlenishvili and Tsertsvadze conducted a human study on using short-term bacteriophage treatment on newborns and infants with gram-negative sepsis. The bacteriophage preparation was intended for use against the bacteria *Klebsiella*, *Serratia* and *Enterobacter*. The study states that no toxic or allergenic reactions resulted from this treatment; however, the purpose of this study was not to test for toxicity, but to study the efficiency of using this combined bacteriophage to treat and prevent gram-negative sepsis.

Similarly, the final human study included in the memo, conducted by Lazareva et al., treated burn patients with a bacteriophage preparation targeting staphylococci, streptococci, protei, *Pseudomonas aeruginosa* and *E. coli*. The Petitioner describes on page 001673 of the Petition that “phage-related side effects were not reported.” Again, the purpose of this study was to test the efficacy of the treatment for burn patients and not to test toxicity.

We find it misleading to present studies that report on the efficacy of bacteriophage preparations in treating humans with identified bacterial infections – other than *L. monocytogenes* – rather than testing the safety of the bacteriophage preparation for widespread use.

The fifth study was an animal study in which Carlton et al. used a *L. monocytogenes* bacteriophage called “P100.” Because the FDA documents made available to us have been redacted, we cannot determine whether this is one of the six bacteriophages contained in the approved additive. Regardless, the study does not meet the standards of a short-term feeding test described in the Redbook. Among many deficiencies, the duration was only 8 days; only 5 animals per sex per group were included; only a small fraction of the required tissue examinations were conducted; and the following observations and clinical tests were not conducted: neurologic disorders, autonomic dysfunctions, ophthalmological examination, hematology, clinical chemistry and urinalyses.

No FDA documents indicate that any short-term genetic toxicity tests for the approved additive were conducted.

The Redbook states, referring to Petitioners: “You can use an alternative approach if such an approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach contact the FDA staff responsible for implementing this guidance.”

In the Final Rule, FDA does not present an alternative approach, nor does it indicate whether the Petitioner discussed an alternative approach with the agency. Again, if the agency used an alternative approach, the Final Rule does not demonstrate that it satisfied the requirements of the applicable statutes and regulations, which the Redbook requires.

**FDA failed to abide by safety procedures and testing protocols at the core of its mandate – procedures that are prescribed by federal regulations and guidelines. In their absence, what regulations, guidelines and testing protocols did the agency follow to conclude that foods treated with a bacteriophage preparation are safe for human consumption? We are requesting a formal evidentiary public hearing on this issue.**

## **2. KEY PORTIONS OF THE FINAL RULE ARE BASED ON CONJECTURE**

Instead of complying with federal regulations and guidelines to assess safety, FDA relies on conjecture in concluding that foods treated with a bacteriophage preparation are safe for human consumption. This conjecture simply mirrors unsupported assumptions made by the Petitioner that the agency made no independent effort to corroborate.

The Rule acknowledges that Listeriolysin O (LLO), one of the main virulence factors of *L. monocytogenes*, “may potentially be present as a residue in this food additive after the manufacturing process.” The agency speculates that any residual LLO “does not present a toxicological concern” for three reasons:

- LLO is “likely to be inactivated by the cholesterol” in treated meat.
- LLO is “likely to be inactivated by the low pH...within the human stomach.”
- LLO is “expected to be rapidly and irreversibly degraded by proteolytic enzymes that may be presented in the diet or in the stomach.”

Concerning the cholesterol issue, neither FDA nor the Petitioner provide any experimental data to support this conclusion – namely, the actual level of cholesterol in meat necessary to inactivate the levels of LLO likely to be present in the bacteriophage preparation.

The Petitioner cites a number of articles describing the effect that cholesterol has on the cytolytic activity of LLO. A cholesterol-dependent cytolysin (CDC), LLO requires membrane cholesterol in order to be cytolytically active. As cited by the Petitioner, an *in vitro* study conducted by Jacobs et al. found that the introduction of exogenous cholesterol significantly reduced the cytolytic activity of LLO. However, Giddings et al. states that “the mechanism by which cholesterol affects the cytolytic activity of the CDCs remains ambiguous even though the dependence of the CDC cytolytic mechanism on the presence of membrane cholesterol is the defining property of these toxins.” And in their study, Jacobs et al. discovered that “the inhibition of lysis by cholesterol is not due to decreased binding of listeriolysin to target membranes, but rather to an interference with a subsequent step leading to polymerization of the toxin.” This mechanism is not yet fully understood by researchers.

Therefore, it is disturbing that neither the Petitioner nor FDA report the amount of cholesterol present in RTE meat or cite any experimental data to support the claim that the cholesterol on RTE will inactivate the LLO residue that may be present in the bacteriophage preparation.

Concerning the pH issue, FDA makes this conclusion despite acknowledging that studies analyzed by the agency did not examine pH levels similar to those present in the human gastric system. The agency explicitly state in Reference 1 of the Final Rule (June 3, 2005 memo from the Division of Petition Review to R. Davy) that “no studies were performed at lower pH levels that are more consistent with that of the gastric environment.” Beauregard et al. cited in Reference 1 and the Petition found LLO to be optimally active at pH values ranging from 4.9-6.7. Other studies supported this finding. However, Matar et al. found that variant LLO strains 1/2a and 4b are optimally active at a pH of 8. The variation between the optimal pH of different LLO strains indicates that a more thorough study should be conducted on how the pH of the human stomach will affect LLO that could be present as a residue in the bacteriophage preparation.

Finally, concerning the enzyme issue, neither FDA nor the Petitioner provide any experimental data to support this conclusion – namely, the identity and quantity of host defense mechanisms necessary to inactivate the levels of LLO likely to be present in the bacteriophage preparation. As described in Reference 1, the host defense mechanisms – including stomach acid, normal gut microflora and cell mediated immunity – can be effective in preventing *Listeria* and LLO. However, 2,500 people become infected with *Listeria* each year in the United States, so this is clearly not providing a defense for everyone. In the same article cited by the Petitioner, Doyle explains that certain populations are more susceptible to *L. monocytogenes*, as their host defenses or immune response may be affected by other factors. Pregnant women and the elderly are two populations mentioned by the author. Therefore, it is essential that a study be conducted to ensure that populations who may have less effective immune reaction to *L. monocytogenes* or LLO residue will not be affected by the application of this bacteriophage preparation on RTE meats.

**It is inconceivable that FDA would approve the Final Rule based on vast conjecture. We are requesting a formal evidentiary public hearing on this issue.**

### **3. THE EFFICACY STUDIES OF THE BACTERIOPHAGE PREPARATION ARE INADEQUATE IN MEETING THE GOALS OF THE ZERO TOLERANCE POLICY FOR *L. MONOCYTOGENES* IN READY-TO-EAT FOODS.**

21 U.S.C. § 342(a),(1) states that the detection of any *L. monocytogenes* in either of two 25-gram samples of RTE food renders the food adulterated. Given this policy, it would be expected that the approved bacteriophage preparation would need to result in at least a 5-log reduction of *L. monocytogenes* on RTE food, a value used by FDA for unpasteurized juice and the U.S. Department of Agriculture’s Food Safety and Inspection Service (FSIS) as a performance standard for roast beef.<sup>1</sup> However, this is not the case.

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<sup>1</sup> “Food Safety A to Z Reference Guide: Comprehensive List of Terms.” FDA Center for Food Safety and Applied Nutrition, 2001. <http://www.cfsan.fda.gov/~dms/a2z-1.html>.

An inconsistency in FDA's enforcement of this standard was found in information presented under the Memorandum of Understanding (MOU) for the joint FSIS and FDA ingredient approval process. On FDA's webpage of questions and answers about the approved additive, LMP-102™, it is explained that, "FDA is authorized to determine the safety of substances, as well as prescribe safe conditions of use. FSIS is responsible for evaluating the suitability of the use of new ingredients (when the use involves meat or poultry products). 'Suitability' relates to the effectiveness of the substance in performing the intended technical purpose of use, at the lowest level necessary, and the assurance that the conditions of use will not result in an adulterated product or one that misleads consumers. In regard to *L. Monocytogenes* control, the guidance has been at least a 1-log reduction (for an antimicrobial agent used to reduce or eliminate *Listeria*) and no more than 2 logs growth during a product's shelf life (for an antimicrobial agent that is intended to suppress the growth of *Listeria*)."

This guidance is elaborated upon in FSIS' "Compliance Guidelines to Control *Listeria Monocytogenes* in Post-Lethality Exposed Ready-To-Eat Meat and Poultry Products."<sup>2</sup> This document refers to the level of sampling conducted by FSIS – and not the steps required to achieve the goals of the zero tolerance policy. If the log reduction is less than 2, then FSIS conducts relatively more sampling than if the log reduction is greater than 2. However, this risk-based guidance does not ensure safety for consumers. Nowhere do the Compliance Guidelines state what level of log reduction is necessary to completely eliminate *L. monocytogenes*, which is the intention of the zero tolerance policy – namely, the detection of zero bacteria.

The guidance for suitability of antimicrobial agents to control *L. monocytogenes* – a minimum 1-log reduction – is inconsistent with the zero tolerance policy for *L. monocytogenes* in RTE foods, as stated in 21 U.S.C. 342 (a)(1). It would be expected that the antimicrobial agent should completely eliminate *L. monocytogenes* present in RTE foods if it were providing "assurance that the conditions of use will not result in an adulterated product or one that misleads consumers."

The Petition contains a similar flaw. The Petitioner's data found in Table 15 on page 000049 of the Intended Technical Effects section of the Petition, presents the log reductions of the bacteriophage preparation versus the water control after 24 hours, 72 hours, and 168 hours. Log reductions ranged from 1.0 - 2.75 depending on the type of meat product and the time of study. However, nowhere does the Petitioner state that the bacteriophage treatment will completely eliminate *L. monocytogenes*, which, again, is the very intention of the zero tolerance policy. The various levels of log reductions may dictate whether FSIS conducts more or less sampling, but the reductions provide no assurance that bacteriophage-treated RTE meat will be bacteria-free.

Other methods exist to achieve a log reduction greater than the maximum 2.75-log reduction produced by LMP-102™, and they carry far fewer potential unintended consequences than bacteriophages.

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<sup>2</sup> "Compliance Guidelines to Control *Listeria Monocytogenes* in Post-Lethality Exposed Ready-To-Eat Meat and Poultry Products." FSIS, May 2006.

A few examples include:

- Surface-treating hot dogs with a mixture of pressurized steam and hot water at 121° C achieved a 3-log reduction<sup>3</sup> (See Attachment 1).
- Dipping hot dogs in liquid smoke and heating them for 1 minute at 165° F showed a 3-log reduction<sup>4</sup> (See Attachment 2).

Given that the ultimate goal of any bacteria-reduction program is to prevent illness and death, approving treatments of marginal value is contrary to FDA's mandate. The agency, in fact, acknowledges that higher log reductions will likely reduce the incidence of death.

According to the FDA/USDA 2003 risk assessment on *Listeria*, “[I]nclusion of a treatment that produced a 1-log reduction in contamination at retail would reduce the number of predicted cases in the elderly population by 50%, from 227 to 120, and a 2-log treatment would result in a 74% reduction.” It follows that the inclusion of a treatment that produced higher log reductions would further reduce the number of predicted cases of *L. monocytogenes* among vulnerable populations.

**Given the zero tolerance policy for *L. monocytogenes* detection established in the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 342(a)(1), FDA should not approve the bacteriophage preparation, LMP-102™. We are requesting a formal evidentiary public hearing on this issue.**

#### **4. RESEARCH USED TO SUPPORT THE RULE HAS NOT BEEN PUBLISHED IN PEER-REVIEWED JOURNALS**

21 CFR §170.3(i) states: “Safe or safety means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.” Key research submitted by the Petitioner to ostensibly support its Petition has not been published in a peer-reviewed journal.

The only studies conducted using the approved substance, LM-102™, were performed by the Petitioner, Intralytix, Inc. The only studies made available to Food & Water Watch were found on pages 000041-000049 of the Petition in a section entitled, “Intended Technical Effect.” In the efficacy studies conducted by Intralytix, Inc., the Petitioner inoculated 12 different types of RTE meat with three strains of *L. monocytogenes*, applied the bacteriophage preparation to one group and a water control to another group, and compared the presence of *L. monocytogenes* between the two groups. No studies made available to Food & Water Watch involved animals being fed

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<sup>3</sup> Murphy, R.Y. et al. “Eradicating *Listeria monocytogenes* from fully cooked franks by using an integrated pasteurization-packaging system.” *Journal of Food Protection*, 68(3):507-511, March 2005.

<sup>4</sup> Robertson, W. and Muriana, P.M. “Reduction of *Listeria monocytogenes* on hotdogs using liquid smoke extracts.” Institute of Food Technologists Annual Meeting, July 12-16, 2004, Las Vegas.

food treated with LM-102™. The information on how effective the approved substance is at reducing the presence of *L. monocytogenes* is critical to the decision to approve this bacteriophage preparation as a food additive. The methods used for these studies were *not* published in a peer-reviewed journal, and therefore were not reviewed by independent scientists.

Given the potential risk that bacteriophage treatments may not amply reduce levels of *L. monocytogenes* – which causes 500 deaths and 2,500 illnesses in the US per year – it is impossible for reasonable certainty among competent scientists to have been achieved if key research was not reviewed by independent experts and published in a peer-reviewed journal.

**The lack of peer review of key research fatally compromises the integrity of the Final Rule. We are requesting a formal evidentiary public hearing on this issue.**

## **5. THE AGENCY FAILED TO FOLLOW ITS OWN REGULATIONS FOR MAKING INFORMATION PUBLICLY AVAILABLE**

FDA’s regulations, at 21 C.F.R. § 171.1 (h), provide:

(1) The following data and information in a food additive petition are available for public disclosure, unless extraordinary circumstances are shown, after the notice of filing of the petition is published in the FEDERAL REGISTER ...

(i) All safety and functionality data and information submitted with or incorporated by reference in the petition.

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(4) For purposes of this regulation, safety and functionality data include all studies and tests of a food additive on animals and humans and all studies and tests on a food additive for identity, stability, purity, potency, performance, and usefulness.<sup>5</sup>

Despite the fact that the agency stated in its Final Rule that it has met these requirements,<sup>6</sup> FDA did not make the Petition and any of safety and functionality data available at the time the

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<sup>5</sup> Emphasis added. *See* 40 Fed. Reg. 40,682, 40,699 (1975) (“The Commissioner will make available for public disclosure all safety and functionality data relating to any color additive or food additive at the time of filing of the petition, so that public comment can be prepared meaningfully and submitted prior to publication of the final regulations.”)

<sup>6</sup> “In accordance with § 171 (h) (21 CFR 171.1 (h)), the petition and the documents that the FDA considered and relied upon in reaching its decision to approve the petition are available for inspection at the Center for Food Safety and Applied Nutrition by appointment . . . .”

Petition was filed.<sup>7</sup> While we did not ask for this data at the time of the initial notice, we are aware that this was not made publicly available at that time because as of the submission of these objections, FDA has still not made much of this information, including much of the Petition, available.

When we asked for all of safety and functionality data on August 28, 2006, after the Final Rule was published, we were told that the voluminous document had confidential information and was not available because as in the process of being redacted – despite the fact that the agency has had access to the primary petition for over four years.

The only data that has thus far been disclosed to us is select portions of the Petition and underlying data that we deduced might be important and thus we have specifically requested that this information be provided after expedited redacting.

**This failure to make safety and functionality data available for public disclosure before or after the Final Rule is contrary to FDA regulations. We are requesting a formal evidentiary public hearing on this issue.**

## **6. THE AGENCY FAILED PROVIDE ADEQUATE AND TIMELY NOTICE**

21 U.S.C. § 348 (f) (1) provides for 30 days for adversely affected parties to object to an order granting or denying a food additive petition. This time period is vital for public review of the petition, and as at least one observer has noted: “The primary opportunity for public debate on a food additive petition comes only after the FDA issues its order”<sup>8</sup> (See Attachment 3).

In order for an adversely affected party to be able to fully evaluate and comment on the final order, FDA is required to provide timely notice of the standards it used for evaluating the petition and how the data justifies the agency’s conclusion<sup>9</sup> (See Attachment 4).

FDA has failed to meet this burden. In its final rule, the agency cited four references that justified much of the agency’s determination that the petition met its safety standards. For example, FDA states: “Potential residues of *L. monocytogenes* other than [Listeriolysin O] do not present a safety concern (Ref. 1).”<sup>10</sup> The agency makes other claims such as:

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<sup>7</sup> It is likely that FDA has also failed to disclose more than simply functionality and safety data, and thus is out of compliance with other subsections of 21 C.F.R. § 171.1 (h) not excerpted. But without access to the information, it is difficult to divine under which categories the withheld information falls.

<sup>8</sup> Lars Noah & Richard A. Merrill, *Starting From Scratch?: Reinventing the Food Additive Approval Process*, 78 B.U.L. Rev. 329, 374 (1998).

<sup>9</sup> See *Marshall Minerals, Inc. v. FDA*, 661 F.2d 409, 418 (5th Cir. 1981) (applying to food additive petitions the same adequate and timely notice requirements available in other contexts under the Food, Drug and Cosmetic Act, such as New Animal Drug Applications, and quoting *American Cyanamid Co. v. FDA*, 606 F.2d 1307, 1314 (D.C. Cir. 1979)).

<sup>10</sup> 71 Fed. Reg. 47,729, 47,730 (Friday, August 18, 2006).

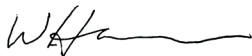
Lysogenic phages, as opposed to those that are lytic, have the capacity to integrate into the host genome and may facilitate transfer of toxin or drug resistance genes between bacteria cells. FDA has determined that the phages contained in the petitioned food additive are lytic based on the petitioner's information on host lysis characteristics and on genome analysis of each phage (Ref. 4).

And while these statements, if they were provided along with access to the referenced material and the petition, might have provided adequate notice to evaluate the agency's claims, the agency wholly failed to provide this additional information at the time of the Final Rule. As mentioned above, much of the Petition is still not available. What Food & Water Watch has been able to access, the memos referenced by the agency and select portions of the Petition, FDA only made available – after much pleading – 13 and 21 days respectively after the start of the statutorily-required 30-day comment period.

**Thus, FDA has ignored requirements to provide adequate and timely notice. We are requesting a formal evidentiary public hearing on this issue.**

Taken together, these flaws in FDA's Final Rule raise vital issues of fact and greatly undermine the rationale of the regulation. Due to these material flaws, potential risks to public health have not been sufficiently examined. We request that a formal evidentiary public hearing on each of the above objections be held at the earliest possible date, and the Final Rule be stayed until the hearing is held and a new decision issued.

Respectfully,



Wenonah Hauter  
Executive Director  
Food & Water Watch

Cc: Dr. Robert Brackett, FDA CFSAN

Dr. Laura Tarantino, FDA CFSAN