Statement By Prof. Ignacio Chapela on the effects of Measure M on the availability of drugs and vaccines for people and animals in Sonoma County.

10/16/05

I am writing in connection to the current discussion about the relationship between Sonoma County's Measure M and vaccine production and use.

I am Associate Professor of Microbial Ecology at UC Berkeley, and have been engaged in research and education around environmental aspects of GMO release for the last 10 years, while I have also actively worked on policy aspects of genetic resources for more than 15 years. In the latter field, I was part of an ad-hoc committee of the National Academy of Sciences reviewing the potential impacts of the commercial release of GMOs into the environment, and have served in an advisory role to several national and multilateral agencies in this area. Further, I have taken part in the multiple discussions emerging in California, the Nation and the world on these topics, specifically around the viability and desirability of areas free of open-field transgenic releases into the environment. On occasion, I have been requested by the proponents of Measure M in Sonoma County to provide them with technical advice. From this engagement, I consider myself familiar with the Measure.

It has come to my attention that a technical challenge to Measure M has arisen posing delicate and important questions . The main question is whether the Measure would ban or otherwise restrict the research, development, use or other application of recombinant vaccines. Because this question lies in the diffuse interregnum between medical, veterinary and environmental disciplines, I realize that it can be very confusing and prone to misleading interpretations.

However, after careful analysis and consultation, I am convinced that there is no room for ambiguity: in my understanding Measure M would not affect any existing or foreseen vaccines, with the obvious exception of the open-field production of antigenic proteins by domestic plants or animals, an application which is clearly in need of more careful research and regulation, and which is rapidly losing interest from the scientific community. Below, I will develop my arguments for this position, which I hope you will find useful in your own deliberations.

The overarching principle: "alive and reproducing"?

The principle established by Edward Jenner through his daring experiment of infecting the boy James Phipps with cowpox to protect him from human smallpox in 1796 stands today still as basic to the concept of vaccination, and has two main tenets: (a) a vaccine must induce the patient's immune system to recognize and neutralize a target agent[1], (b) without the immunizing agent moving to infect other members of the patient's population. Both of these tenets must apply since an intervention which fulfils tenet (a),

[1] Jenner's focus on viruses has expanded today to other targets including other infectious agents, cancer cell-types, or even constitutive cell types, such as is the case with spermaticidal immunizations on trial as potential contraceptives. On principle, all these targets are equivalent.

but not (b) cannot be called a vaccination, but rather an intentional epidemic in the making, while an intervention fulfilling tenet (b) but not (a) is simply ineffective to prevent the development of the target agent.

All modern and foreseeable forms of vaccination conform to these two tenets, explicitly including the non-infectiousness of the immunizing agent (the "vaccine"). Because Sonoma County's Measure M refers exclusively to organisms that can reproduce in the environment ("transmit their DNA" in the language of the Measure), any vaccine conforming to the basic principle of non-infectiousness is clearly excluded from consideration.

Some of the older vaccines (e.g. chickenpox and MMR) and several new approaches to vaccination include the inoculation of a patient with various viral forms which may be considered "live", and might even replicate within the patient to a limited extent. However, in all cases currently available or under development, the immunizing agent does not leave the individual patient to move infect other organisms in the patient's population or other organisms of different species. In other words, these immunizing agents cannot be considered "reproducing" in the environment, even though they might even replicate within an individual. For this reason, Measure M would not apply to any of these vaccines.

Cases where confusion might arise regarding the applicability of Measure M.

Below I briefly review seven different classes of practices which could be considered unclear in the application of Sonoma County's Measure M. As this analysis shows, no major category of vaccine production or delivery available today or in the pipeline would be affected by Measure M, with the obvious exception of the proposal to grow open-field crops that express antigenic proteins or adjuvants.

1- Traditional (non-recombinant) "live" vaccines, such as the polio, rabies, smallpox and MMR vaccines. Several vaccination methods, including the greatly successful polio vaccine, are based on the inoculation of patients with viral particles which, although capable of reproduction, are predictably rendered non-infectious by virtue of dosage, administration route or natural attenuation. Although there might be the suggestion to transgenically modify these traditional vaccines, none of these live virus vaccines would be affected by Measure M because they cannot be said to be reproducing in the environment, which is the standard of definition of the measure. Some difference of interpretation could be found in this respect with those who consider replication of the virus in the individual patient as a form of "reproduction", even though at the environmental (epidemiological) level the virus materials administered in these vaccines are not reproductive since they are not passed on from the individual patient to the host population (human or animal) in general.

2- Several vaccines vectored in the canarypox virus, such as the commercially-available West Nile virus vaccine (Recombitek). Transgenically-modified viruses in the canarypox or other avipox vectors have been developed for immunization using "live" viruses, i.e. viruses which can replicate –at least partially- within the host patient. Avipox viruses are

complex and their reproductive viability is apparently dependent on the integrity of their genome and on the compatibility of the animal context in which they attempt to reproduce. The transgenic manipulation of avipox viruses is reported to result in their attenuation, i.e. their incapacitation to reproduce successfully in the host population[2]. The manufacturers of these vaccines have established that although the virus will produce virion particles within the individual patient inoculated with these recombinant vaccines, these virions are abortive and cannot further reproduce, especially not when passed on to other members of the population. For this reason, these viruses cannot be considered "live, reproducing" in the sense of Measure M, which is focused on the transmission of recombinant DNA in the environment. Because these viruses do not reproduce in the host population beyond the individual inoculated with the vaccine agent, they would not be affected by Measure M.

3- Vaccines for various targets, vectored by adenoviruses such as Merck's Ad5 vector. A typical example of this kind of viral vector is the Ad5 construct, which is explicitly designed and tested to be replication-defective. Although proteins are synthesized in the host cells deriving from genetic material introduced by the viral vector, no infective virus particles are passed on to the population of the host. To the extent that these viruses are epidemiologically-inert (i.e., they do not infect other members of the host population beyond the inoculated patient), they would be excluded, by definition, from the application of Measure M, which focuses on the reproduction of transgenic organisms in the environment.

4- Vaccines vectored by RNA-viruses, such as the Venezuelan Equine Encephalitis (VEE) virus. Although not the most favored strategy, RNA-viruses are currently being proposed as possible vectoring agents for recombinant immunization. Here again, the virus is rendered replication-incompetent through the deletion of capsid-encoding and other genetic regions necessary for replication. To the extent that the products of these viruses in the host cells are non-reproductive and non-infectious to other members of the host population (i.e. epidemiologically inert), these vaccination strategies would not be affected by Measure M.

5- DNA vaccines. Recent approaches to immunization include the direct introduction of naked- or adjuvant-associated DNA. Such DNA, often included as a plasmid construct, participates to a limited extent in the synthesis of RNA and proteins in the host which are thought to be responsible for the activation of the immune system. However, this participation is commonly restricted to specific tissues and is not enough to result in any form of reproducing living organisms which can be successfully passed on to other members of the host's population in the environment. Such non-reproducing DNA vaccines would naturally be excluded from the application of Measure M.

6- Immunogenic proteins (antigens and adjuvants) produced in bacterial or mammalian host cells in production plants. A growing and successful approach to vaccine production is the transgenic manipulation of cell cultures of bacteria or other organisms (including

[2] For a recent review, see: Skinner MA, Laidlaw SM, Eldaghayes I, Kaiser P, Cottingham MG. 2005. Expert Rev Vaccines. Feb; 4(1):63-76.

human tissue culture) by inserting DNA sequences from the target agent (virus, cancer cell-line, specific tissue) into the genome of such recipient cells. Such transformed cells thereby produce a subset of the viral proteins, which can then be used as the antigens for a successful vaccine. This particular case is clearly outside the scope of Measure M, since the stages of production for this kind of vaccine that require the use of living, reproducing organisms are always practiced in fermentation or tissue-culture plants, not the open, public environment. Undoubtedly, escapes of living reproducing organisms from these production facilities would be undesirable and would be covered by other statutes and regulations already in place.

7- Finally, there is only one kind of suggested vaccine production system which in my view would be clearly affected by Measure M. This is the production of antigenic proteins or DNA for vaccine use in plant hosts, under open-air field conditions[3]. Among these proposed practices are so-called "edible vaccines" which would be composed of food plants transgenically manipulated to express proteins of immunogenic value (as in 6 above). Because the transgenic crops thus produced would be live, reproducing organisms able to transfer their DNA out into the wider population of their conspecifics, this application would fall squarely within the scope of Measure M. I believe that you will agree that the open-field planting of commercial crops which have been transformed to express immunogenic proteins should be the subject of much more research before it would be authorized for widespread use, just as should be the case with pharmaceutical-producing transgenic crops.

In conclusion, it is my firm conviction that on principle and in practice, none of the existing, researched or even foreseeable vaccine applications of transgenic organisms would be affected by Sonoma County's Measure M, given that in all cases the genome containing the transgenic manipulation cannot be "transmitted through the reproduction of the recipient organism" in the environment, as defined by the Measure. The obvious exception, the attempt to produce antigenic proteins in open-field food crops is clearly covered under Measure M, as I believe it should.

I remain available for further comments at the address below.

Sincerely,

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[3] For an example, see Yusibov et al., 1997. Proc Natl Acad Sci U S A. 1997 May 27; 94(11): 5784–5788.