KEI and MSF comments regarding the Notice published in the Federal Register on February 22, 2016, [81 F.R. 8728], entitled 'Prospective Grant of Exclusive License: Production of Attenuated Respiratory Syncytial Virus Vaccines

March 8, 2016

Knowledge Ecology International (KEI) and Doctors Without Borders/Médecins Sans Frontières USA (MSF) are responding to the Notice published in the Federal Register on February 22, 2016, entitled 'Prospective Grant of Exclusive License: Production of Attenuated Respiratory Syncytial Virus Vaccines' [81 F.R. 8728], available at: https://federalregister.gov/a/2016-03486.

The Notice indicated that:

> Requests for a copy of the patent application, inquiries, comments and other materials relating to the contemplated license should be directed to: Peter Soukas, Senior Technology Licensing Specialist, Technology Transfer and Intellectual Property Office, National Institute of Allergy and Infectious Diseases, 5601 Fishers Lane, Suite 6D, Rockville, MD 20852-9804, Tel: (301) 594-8730 or email: ps193c@nih.gov.

Despite contacting the above-named individual at the National Institute of Allergy and Infectious Diseases (NIAID) on February 22, 2016 — the day the Notice appeared in the Federal Register — and having made numerous subsequent efforts to obtain information about the proposed license, we have yet to receive copies of the patent applications or receive any information from the NIAID Technology Transfer and Intellectual Property Office about the proposed licensing terms or the technology that is to be licensed. We object to the lack of transparency surrounding this proposed license, and ask for an additional two weeks to submit further comments, so that NIH can provide information to KEI and MSF for a full and thorough evaluation. However, we will also provide comments now, to meet the current deadline of March 8, 2016.

About the commenters

Knowledge Ecology International (KEI) is a non-governmental organization based in Washington, DC, with an office in Geneva, Switzerland, that advocates for access to affordable medicines, with a focus on human rights and social justice. For more information, see: http://keionline.org.

Doctors Without Borders/Médecins Sans Frontières USA (MSF) is an international independent humanitarian medical organization that delivers medical care to people excluded from healthcare in more than 60 countries. MSF needs access to effective, affordable and adapted vaccines to be able to deliver care. For more information: http://www.doctorswithoutborders.org/

Why the vaccine may be important

In the February 22, 2016 Federal Register Notice, the NIH provided a compelling narrative of the importance of respiratory syncytial virus (RSV) and the NIH-developed vaccine:

> Respiratory syncytial virus (RSV) is the most important cause of viral acute lower respiratory infection (ALRI) in infants and children worldwide and is responsible for over 30 million new ALRI episodes worldwide and up to 199,000 deaths in children under five (5) years old. In the United States, the virus infects nearly all children at least once by the age of two (2) and is the most common cause of bronchiolitis and infant pneumonia, causing up to 125,000 hospitalizations of children each year. RSV disease burden is less understood in the developing world, but available data indicates that the virus causes a significant proportion of childhood ALRI in these parts of the world, particularly in the first months of life. The drug palivizumab (Synagis) can help prevent RSV disease in high risk infants, but it cannot treat or cure already-serious RSV infection. No vaccine exists today to prevent RSV due to an incomplete understanding of the body's immune response to the virus, which has challenged and delayed RSV vaccine development efforts.
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> The methods and compositions of this invention provide a means for prevention of RSV and/or parainfluenza virus (PIV) infection by immunization with live attenuated, immunogenic viral vaccines against RSV and/or PIV.

According to a CDC fact sheet[1], each year, on average, in the United States, RSV leads to:

- 57,527 hospitalizations among children younger than 5 years old,
- 2.1 million outpatient visits among children younger than 5 years old, and
- 177,000 hospitalizations and 14,000 deaths among adults older than 65 years.

[1] http://www.cdc.gov/rsv/research/us-surveillance.html

RSV presents significant health and economic burdens in both high- and low-resource settings, making the development of an efficacious vaccine a highly beneficial public health intervention. Prophylactic vaccines are of particular importance to the public, since people with compromised immune systems also benefit from the protective effects of herd immunity acquired through population wide vaccination programs.

The NIH role in the development of the vaccine

The NIH has been involved in RSV research for over 25 years. In particular, the attenuated RSV vaccines referred to in the Notice (from patent applications entitled (1) Production of Attenuated Respiratory Syncytial Virus Vaccines Involving Modification of M2 ORF2, (2) Genetically Stable Live Attenuated Vaccine for Respiratory Syncytial Virus (RSV) with an Attenuation and Temperature Sensitive Phenotype Conferred by an Amino Acid Deletion, (3) Versions of Respiratory Syncytial Virus (RSV) Vaccine Candidate LID Delta M2-2 with Increased Attenuation, (4) Improved RSV F Protein for Expression from a Heterologous Vector, (5) Attenuated RSV Vaccine Strains in which the NS1 and/or NS2 Genes have been Shifted to Promoter-Distal Positions) arose from a culmination of years of publicly funded clinical and basic research. Developing a suitable vaccine candidate for a pediatric population is especially difficult primarily because there is a risk of disease enhancement. Therefore live attenuated RSV vaccines or gene based vectors (Adenovirus or Parainfluenza virus) are the currently preferred route. As it stands, the only live attenuated RSV vaccines indicated for pediatrics in the clinical phase of development are sponsored by the NIH.[2]

Notably, the recombinant live attenuated RSV vaccine candidate LID Delta M2-2 (IND IND # 15713 - Held by RCHSPB/NIAID/NIH) is being studied in phase 1 clinical trials sponsored by NIAID as part of the IMPAACT 2000 initiative. Initial results from these trials presented in October 2015 showed that although additional attenuation would be needed, the vaccine induced high titers of neutralizing antibodies in children.

The vaccine candidates used in these initiatives and other NIAID sponsored clinical trials (NCT01893554, NCT01968083, NCT01852266, NCT02040831, NCT02237209, NCT01459198, and NCT02601612) stem from the important work led by Dr. Peter Collins, chief of the RNA Viruses Section Laboratory of Infectious Diseases at NIAID. In fact, his research has identified temperature sensitive mutations and improvements to genetic stability for the generation of attenuated vaccine candidates, such as RSV_ΔNS2/Δ1313/1314L.

[2] http://sites.path.org/vaccinedevelopment/files/2015/12/RSV-snapshot-Dec2015v5.pdf

Why patent license terms are important

We are concerned that the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), and Department of Health and Human Services (HHS) exclusive licensing of patent rights of this promising vaccine candidate to Sanofi will result in:

1. Sanofi pricing an important vaccine out of the reach of routine use in pediatric and/or adult populations;
2. Sanofi abusing the granted monopoly to charge excessive prices, something the NIH has been loath to address after previous licenses have been issued;
3. Sanofi requiring U.S. residents to pay more than other countries for a vaccine developed at public expense (see http://keionline.org/xtandi for a petition to the NIH relating to a prostate cancer drug invented at UCLA on federal grants, and priced far higher in the United States than in any other country); and
4. Delays in the entry of competitive suppliers for the manufacturing and distribution of the vaccine that will increase affordability and reduce supply shortages,
5. Barriers to innovation, including enhancements that make the vaccines more effective in low resource settings.

The price will greatly affect the accessibility of the vaccine in the United States and abroad. In 2015, all 193 countries at the World Health Assembly passed a landmark resolution demanding more affordable vaccines. More than 50 developing countries spoke out against high vaccine prices and about the difficulties of introducing new vaccines.

The rising price of vaccines is an increasing concern for MSF and developing countries. Last year, MSF released its vaccine pricing report, *The Right Shot: Bringing Down Barriers to Affordable and Adapted Vaccines*, available here: http://www.msfaccess.org/our-work/vaccines/article/2345, which showed that in many developing countries with the addition of new vaccines, it is now 68 times more expensive to vaccinate a child than in 2001.

The price of the end product is a crucial detail in terms of fairness to U.S. residents who need the vaccine, U.S. taxpayers who paid for years of research to develop the vaccine, and U.S. patients who rely on herd immunity.
It is worth noting that RSV prevention efforts have already been affected by the high price of an existing prophylaxis, palivizumab.

Palivizumab is a monoclonal antibody that reduces the incidence of RSV infection. The current retail price of the drug is $2,690 (CVS with coupon) for a single dose vial.[3] *The Redbook*, a medical guidance document prepared by the Committee on Infectious Diseases (COID) of the American Academy of Pediatrics (AAP), states that the cost of palivizumab far exceeds its economic benefit,[4] implying its use should be limited.

A July 2, 2014 article in the New York Times by Elisabeth Rosenthal, titled the "Price of Prevention: Vaccine Costs Are Soaring,"[5] describes the crisis in vaccine prices as follows:

> Vaccination prices have gone from single digits to sometimes triple digits in the last two decades, creating dilemmas for doctors and their patients as well as straining public health budgets. Here in San Antonio and elsewhere, some doctors have stopped offering immunizations because they say they cannot afford to buy these potentially lifesaving preventive treatments that insurers often reimburse poorly, sometimes even at a loss.
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> Childhood immunizations are so vital to public health that the Affordable Care Act mandates their coverage at no out-of-pocket cost and they are generally required for school entry. Once a loss leader for manufacturers, because they are often more expensive to produce than conventional drugs, vaccines now can be very profitable.
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> Old vaccines have been reformulated with higher costs. New ones have entered the market at once-unthinkable prices. Together, since 1986, they have pushed up the average cost to fully vaccinate a child with private insurance to the age of 18 to $2,192 from $100, according to data from the Centers for Disease Control and Prevention. Even with deep discounts, the costs for the federal government, which buys half of all vaccines for the nation's children, have increased 15-fold during that period.

Federal regulations on the use of exclusive licenses

The discretion to grant exclusive rights in government owned patents is subject to statutes and regulations, including 37 C.F.R. § 404.7, titled "Exclusive, co-exclusive and partially exclusive licenses."

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[3] http://www.goodrx.com/synagis
[4] American Academy of Pediatrics, Red Book Online: Report of the Committee on Infectious Diseases, 30th edition. 2015. p.667- 676
[5] http://www.nytimes.com/2014/07/03/health/Vaccine-Costs-Soaring-Paying-Till-It-Hurts.html

Standards for the United States

Before granting exclusive rights for the **U.S. market**, the NIH must satisfy the conditions in 37 C.F.R. § 404.7(a)(1)(ii)(A-C), which read:

> (A) The public will be served by the granting of the license, in view of the applicant's intentions, plans and ability to bring the invention to the point of practical application or otherwise promote the invention's utilization by the public.
>
> (B) Exclusive, co-exclusive or partially exclusive licensing is a reasonable and necessary incentive to call forth the investment capital and expenditures needed to bring the invention to practical application or otherwise promote the invention's utilization by the public; and
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> (C) The proposed scope of exclusivity is not greater than reasonably necessary to provide the incentive for bringing the invention to practical application, as proposed by the applicant, or otherwise to promote the invention's utilization by the public[.]

It would be easier to evaluate the NIH proposal for an exclusive license if we were given information about the technology being licensed, the investment and progress made by the NIH in the development of the vaccine, and the terms of the exclusive license.[6]

In the absence of such information, we can offer the following comments.

1. **37 C.F.R. § 404.7(a)(1)(ii)(A),**

   The public will be served by the granting of the license, in view of the applicant's intentions, plans and ability to bring the invention to the point of practical application or otherwise promote the invention's utilization by the public.

As regards 37 C.F.R. § 404.7(a)(1)(ii)(A), the term “practical application” is defined by statute as requiring that the invention’s “benefits are to the extent permitted by

[6] Among the efforts to obtain information were these five questions posed on February 22, 2016. http://keionline.org/node/2421

1. What provisions exist in the license to protect US residents against excessive or unreasonable pricing?
2. What provisions exist in the license to ensure access in developing countries?
3. What are the royalty arrangements?
4. How much money did the government spend on these inventions?
5. How much do you reckon the company receiving the license will have to spend on further development?

law or Government regulations available to the public on reasonable terms" [35 U.S.C. § 201(f)]. We do not know the "applicant's intentions, [or] plans" as regards the price of an RSV vaccine. We do know that U.S. residents routinely face higher prices than patients in other countries, and we believe that this is unreasonable, particularly for an invention that benefited from U.S. government funding, and we also know that the HPV vaccine was priced so high it has not been as widely used as it should have been.

Before an exclusive license is signed, the NIH needs to negotiate with Sanofi on the price of the vaccine, and ensure that the price is reasonable, given the role of the federal government in financing the invention, and the actual investments that Sanofi is expected to make in the development of the product.

Any price for U.S. residents that is higher than the median price charged by G7 countries is unreasonable.

Any price that restricts access is not reasonable.

Any price that is so high that Sanofi earns excessive profits on this federally funded invention is not reasonable.

2. 37 C.F.R. § 404.7(a)(1)(ii)(B)

> *Exclusive, co-exclusive or partially exclusive licensing is a reasonable and necessary incentive to call forth the investment capital and expenditures needed to bring the invention to practical application or otherwise promote the invention's utilization by the public;*

To properly evaluate this requirement, it would be important to know how much money is required to bring the vaccine from its current state of development to the market, and the terms of the license, including the number of years of exclusive rights, and to have a notion about the prices that Sanofi will charge.

Given the huge impact that a vaccine can have on federal programs including but not limited to Medicaid and Medicare, and global health programs the U.S. government supports, the NIH should at least explain why it is giving Sanofi a monopoly on the vaccine, as opposed to conducting the clinical trials itself, and being in a stronger position to obtain much lower prices for the vaccine.[7]

[7] Particularly given the government's past unwillingness to use its rights in federally funded patents post licensing to a commercial drug manufacturer.

3. 37 C.F.R. § 404.7(a)(1)(ii)(C)

> *The proposed scope of exclusivity is not greater than reasonably necessary to provide the incentive for bringing the invention to practical application, as proposed by the applicant, or otherwise to promote the invention's utilization by the public;*

As noted above, to fully evaluate this requirement, it would be important to know how much money is required to bring the vaccine from its current state of development to the market, and how large is the potential market. It is possible that everyone in the world is the potential market.

One way to satisfy the requirements of 37 C.F.R. § 404.7(a)(1)(ii)(C) would be to grant an exclusive license that was limited in term and in the geographic area. For example, the exclusive rights in the license could expire after the vaccine manufacturer earns a multiple of what the NIH estimates to be the risk adjusted cost of obtaining FDA approval. The FDA could also require the patent holder to provide technology transfer to any subsequent manufacturer licensed by the NIH.

If the NIH automatically provides a term equal to the life of the patents, and world wide rights in the patents, without any concessions on prices, it is ignoring the requirement that "t*he proposed scope of exclusivity is not greater than reasonably necessary to provide the incentive for bringing the invention to practical application."*

Standards for Foreign Countries

Before granting exclusive rights in foreign markets, the NIH must meet the obligations of 37 C.F.R. § 404.7(b)(1)(i-iii).

4. 37 C.F.R. § 404.7(b)(1)(i-iii)

> (b) (1) Exclusive, co-exclusive or partially exclusive foreign licenses may be granted on a Government owned invention provided that;
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> (i) Notice of the prospective license, identifying the invention and prospective licensee, has been published in the Federal Register, providing opportunity for filing written objections within at least a 15-day period and following consideration of such objections received during the period;
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> (ii) The agency has considered whether the interests of the Federal Government or United States industry in foreign commerce will be enhanced; and

(iii) The Federal agency has not determined that the grant of such a license will tend substantially to lessen competition or create or maintain a violation of the Federal antitrust laws.

The residents of the United States are not indifferent to the access to vaccines globally, and the United States has a special interest in increasing affordable and appropriate access to vaccination in developing countries, as evidenced in part by the U.S. government support and funding of GAVI[8], PAHO Revolving Fund and other programs.

Any future vaccine developed with NIH funding should not only be affordable but also effective and adapted to resource limited setting and developing countries contexts (e.g. thermostable).

The NIH should not only consider the needs of patients in the United States. Given the potential importance of this vaccine for children everywhere, it will be important that the terms of the license (1) ensure the pricing is affordable in developing countries, or even better, allow for competition and technology transfer to competitive suppliers, and (2) obligate the developer to address the special needs of developing countries, and/or to permit others to make such modifications and improvements as are necessary.

Conclusion

At a minimum, the NIH should provide more disclosure and a truly open consultation with health experts, advocates for patients and third party payers to review the commitments Sanofi has offered, or should make, to address the concerns expressed above regarding (1) the impact of an exclusive license on the pricing and affordability of the vaccine, and (2) the need to adopt the vaccine for the special needs of low income populations.

To meet the requirements of 37 C.F.R. § 404.7(a)(1)(ii)(C), the NIH *must* demonstrate that the rights granted to Sanofi are "*not greater than reasonably necessary"* than are required to induce Sanofi to conduct the trials and the vaccine registration that the NIH could do, but wants to outsource to Sanofi, in return for the grant of the exclusive rights.

[8] Press release: Gavi applauds Obama Administration budget request for vaccine programmes Funding will support historic US$ 1 billion, 4-year U.S. pledge to Gavi to help protect millions of children from deadly diseases through vaccination, February 2, 2015. http://www.gavi.org/Library/News/GAVI-features/2015/Gavi-applauds-Obama-Administration-budget-request-for-vaccine-programmes/

Even better would be for the NIH to reject the use of exclusive licenses, and to conclude the development of the vaccine either with its own funding, or by approaching third-party payers (in the public and private sectors) to share the costs of the final development of the vaccine. Those providing funding to conclude the vaccine development could be offered access at concessionary prices and possibly share in the eventual licensing income from non-exclusive licensing of the patents.

It is important to fully protect the public interest when licensing these patents.

Respectfully submitted,

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