KEI Engagement on NIH Exclusive Licenses and the Need for Increased Transparency and Public Safeguards in Licenses

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Overview

United States taxpayers have entrusted the National Institutes of Health (NIH) with conducting research and developing technologies that benefit the public's health and wellbeing. In order to do so, the NIH is supported with $45 billion in taxpayer funding. The Bayh-Dole Act was enacted to promote the commercialization of federally-funded inventions, while including critical safeguards to ensure that America's interest in innovation was balanced with access for the public who supported that innovation.

Before an agency such as the NIH may license a federally-owned invention, it must notify the public of its intent to do so, consider any objections submitted during a public comment period, and determine that certain statutory criteria have been met, including that "the proposed scope of exclusivity is not greater than reasonably necessary to provide the incentive for bringing the invention to practical application[.]"[1]

Knowledge Ecology International (KEI) is a nonprofit non governmental organization that focuses on solutions to ensure affordable and accessible medicines. KEI has pushed the NIH for greater transparency of the process through which the NIH grants exclusive licenses to private companies for taxpayer funded inventions. Through the licenses, the NIH grants

[1] 35 USC § 209(a)(2).

exclusive rights to potentially ground-breaking and budget-breaking medical technologies to companies to further develop and commercialize. It is critical that the NIH use this mechanism to ensure that any resultant technology is affordable and accessible to the public.

Beginning in 2015, KEI has engaged the NIH on these licenses through the public comment period required by the Bayh-Dole Act. As of June 2023, KEI had drafted and submitted comments to the NIH regarding 105 proposed exclusive licenses. A list of the comments submitted is included in the Annex. KEI has also previously raised our concerns regarding the NIH's exclusive licensing practices with the House of Representatives' Committee on Oversight and Reform in 2019.[2]

KEI's comments to the NIH have included in-depth reviews of the technologies to be licensed, discussions of the companies seeking the licenses, critiques of the lack of transparency on the part of the NIH in noticing the licenses and responding to public requests for information, and comments on the licensing terms.

Beginning with the Federal Register notices themselves, the NIH appears to consider the public comment period for exclusive licenses to be a pro forma box to be checked in the process of handing over taxpayer-funded technologies to private companies with few public safeguards. The content of the notices comply with the Bayh-Dole requirements, but give the public very little data on which to assess the need for the technology to be licensed exclusively, or whether the company to receive the license is qualified to develop the product. Typically the only information given on the company is the name and a city and state location. Sometimes, the company listed has little to no web presence, and may not even be listed in the respective state's business registry.

In the presentation of the technology to be licensed, the NIH's Federal Register notices list the intellectual property and its assignee, the field of use covered by the license, the territory (most often worldwide), and a paragraph describing what the technology may be useful in treating.

The public that may wish to comment on the proposed licenses is left with many questions that are critical for informing whether exclusive licenses are necessary to incentivize development of the technologies or how the NIH has come to that determination and whether a particular company is the appropriate partner to further its development and ensure any resultant technology is accessible and affordable to the US public, or that other terms in a license are reasonable or appropriate.

Presented with this dearth of information, prior to the close of the comment period KEI has repeatedly asked for more information about the technology, proposed terms of the license, and the company set to receive the license. Examples of questions asked by KEI include:

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2 https://www.keionline.org/wp-content/uploads/KEI_Letter_HouseOversightCommittee_-NIH_Lack_of_Transparency_22July2019.pdf

1. At what development stage are the inventions listed?
2. Are there any clinical trials of the licensed technology planned or already conducted?
3. Has the government funded any clinical trials relevant to these technologies? If so, please provide NCT numbers.
4. If the government has provided funding, how much has been spent by the government on these trials? Can you please provide relevant grant and/or contract numbers?
5. Is the term in the proposed licenses to be life of patent or less than life of patent?
6. In working towards executing this license, has the NIH sought advice from the Attorney General (as is required under 40 USC § 559) to determine if the "disposal to a private interest would tend to create or maintain a situation inconsistent with antitrust law"?
7. Is there a Cooperative Research and Development Agreement associated with this technology?
8. What analysis did the NIH undertake, if any, in order to conclude that exclusivity is a reasonable and necessary incentive?
9. How will the NIH ensure that the scope of exclusivity is not broader than reasonably necessary?
10. Would this technology be eligible for a priority review voucher?
11. Who are the principals in this company? For example, are the leading shareholders US residents or non-US residents?
12. Do any former NIH employees have leadership roles in the company?
13. (If proposed licensee is foreign firm) Is the NIH in any concurrent negotiations to waive the domestic manufacturing requirement (35 USC 204) for this license?

There were many times that the NIH did not provide responses to our questions. Indeed KEI received an email that was evidently intended for an NIH colleague, but was sent to us by mistake, instructing them not to reply to us.[3]

When the NIH did provide a response to our questions, it was often with limited responses, for example answering a question about how the NIH determined that an exclusive license was necessary to incentivize the development of a particular technology by responding that that "has been addressed previously", in earlier exchanges about other exclusive licenses.[4] If the NIH were properly assessing whether licensing a technology on an exclusive basis is necessary for a particular invention, it could not have been "addressed previously". It appears that the NIH does not conduct any analysis of what terms and exclusivity are actually necessary to incentivize the development of any of the publicly funded innovations it is offering up on the auction block to private companies.

KEI Exchange with the NIH Regarding EnZeta License

[3] https://www.keionline.org/wp-content/uploads/Attachment-C-10Jan2020.pdf

[4] https://www.keionline.org/wp-content/uploads/KEI-NIH-Questions-86FR50895-License-Sana-Biotechnology.pdf

In 2023, the NIH has posted two notices in the Federal Register for the "Prospective Grant of an Exclusive Patent License: Manufacture, Distribution, Sale and Use of T-Cell-Based Immunotherapies for Solid Tumors" (88 FR 20544 in April and 88 FR 54629 in August). Both licenses were to be granted to entities with "EnZeta" in the name: EnZeta, Inc. and EnZeta, Immunotherapies, Inc.

Upon receiving an alert on April 5, 2023 that a notice would be published the next day, KEI immediately emailed Richard Girards, Jr. seeking information about EnZeta, Inc. as the firm did not appear to have a website or any other publicly available information. Mr. Girards replied on April 6, 2023 providing limited answers and directed us to search the Delaware state business registry (which yielded very limited information that we had to pay for). KEI asked further questions on April 7th, to which we did not receive a reply either before or after the comment period closed on April 21, 2023.[5] This exchange regarding EnZeta is one of many similar exchanges KEI has experienced when trying to obtain basic information about these exclusive licenses.

The NIH has recently posted another Federal Register notice (88 FR 54629) for nearly the same technologies, this time to EnZeta Immunotherapies, Inc. Again, no firm by this name appears in a Google search, and a search of the Delaware business registry returns very limited results. KEI asked the NIH a set of questions about the prospective license and how this notice related to the April EnZeta notice.[6] The NIH has responded to those questions in a timely manner, but has provided limited information.

For example, KEI's first question asked how the August notice related to the April notice, since they are both to EnZeta-named companies for overlapping IP for T-cell-based immunotherapies for solid tumors. The NIH declined to answer that question, stating "...we have determined that these queries either call for or inextricably implicate business confidential information that NIH is legally precluded from divulging."[7]

KEI has experienced exchanges such as this numerous times when trying to obtain basic information about these exclusive licenses. In order for the public to assess and comment on the necessity and appropriateness of the licenses, the NIH must be more transparent in the information both in the Federal Notices and in their responses to public questioning.

Increased Transparency in Public Notices for Exclusive Licenses

In addition to the information already provided, the NIH should include in the public notices regarding exclusive licenses:

[5] The full exchange with the NIH regarding the April EnZeta notice is available here: https://www.keionline.org/39002
[6] https://www.keionline.org/38976
[7] https://www.keionline.org/wp-content/uploads/NIH-Response-KEI-Questions-EnZeta-17Aug2023.pdf

1. A written analysis, or a discussion of the analysis that was undertaken, of how exclusivity has been deemed “reasonable and necessary” under 35 U.S.C. § 209,

2. The terms of the prospective license, including scope and time period of exclusivity, as well as royalty rate to be earned from the agreement, should be made public,

3. A description of the inventions' stage of development,

4. In order to increase transparency in the cost of drug development, the NIH should make available information on the total funds the government has spent on research and any clinical trials, including total and per patient cost,

5. A description of how the NIH solicited the licensee and an analysis of how it has vetted the licensee. The information should include physical addresses for the company’s headquarters and the names of principals in the company. The NIH should also disclose what steps it has taken to ensure that the licensee has the infrastructure, know-how, experience, staff, and funds necessary to begin work on the invention as soon as the license is granted.

6. The NIH should disclose what safeguards it is taking to protect the public interest in this technology, and to ensure that prices charged will not be significantly higher in the United States than in other high income countries.

License Safeguard Term Requests in KEI Comments

In our comments, KEI asked that if the NIH decided to proceed with the exclusive license that the licenses include public interest safeguards. The content of the comments was tailored to the particular technology and company, but examples of terms that KEI requested be incorporated by the NIH included:

- Reference pricing,
- Limitations on geographic scope,
- Transparency, related to the 2019 WHO resolution on transparency (WHA72.8),
- Transparency of R&D outlays, sales/revenue,
- Domestic manufacturing waiver (for foreign firms),
- Non-exclusive/WHO/Medicines Patent Pool licenses,
- Acknowledgement of federal funding,
- Global registration and affordability,
- Limitations on exclusivity term,
- 40 U.S.C. § 559 - Attorney General consultation,
- Transfer of know-how and biologic resources; research permissions,
- 35 U.S.C. § 209 analysis,

- Limiting exclusivity to non-US high income countries,
- Requirement that US prices are set to ensure affordable Medicare co-pays,
- Requirement that US prices do not exceed the estimated value of treatment,
- Limitations on the geographic scope of test data rights,
- Working the patent requirement,
- Products should be priced such that access is not restricted by payors.

Below are brief discussions of and examples of language for selected terms noted above.

Affordable Access for US Patients

Reference pricing. KEI included requests for the NIH to incorporate reference pricing to ensure affordable access to treatments for US patients in 101 of the 105 comments submitted. Below is an example of that request:

> "a provision in the license that requires that any medical technology using the patented invention be available in the United States at a price that does not exceed the median price in the seven largest economies by GDP that have at least 50 percent of the GNI per capita as the United States, using the World Bank Atlas method."

As KEI noted in our comments numerous times,

> "The above is a modest safeguard. The US government has recently incorporated similar terms in agreements related to COVID-19 vaccines and other technology contracts. For example, in the contract with Sanofi Pasteur (Sanofi) for a COVID-19 vaccine, the federal government included a term that stated that Sanofi will not sell the vaccine to any member of the G7 or Switzerland at a price lower than what the U.S. government paid. The NIH should apply this standard to its exclusive licensing practices, and prevent licensees from charging U.S. residents a higher price for products embodying the licensed invention than they charge residents of these high-income countries."

Limitations on years of exclusivity. KEI proposed that the NIH include limitations on the term of the exclusivity, tied to the revenue generated by the product sales. As KEI suggested in 71 comments,

> "We propose that the exclusivity of the license be reduced when the global cumulative sales from products or services using the inventions exceed certain benchmarks. For example, the period of exclusivity in the license could be reduced by one year for every $500 million in global cumulative revenue after the first one billion in global sales. This request is consistent with the statutory requirements of 35 USC § 209, which requires that "the proposed scope of exclusivity is not greater than reasonably necessary to provide the incentive for bringing the invention to practical application.""

Limiting exclusivity to non-US high income countries. KEI also proposed that the NIH include in its licenses a term that would limit exclusivity to the European Union, Japan and other high-income countries, but not extend to the United States. This would ensure that countries

that did not fund the R&D underlying the inventions would bear the costs of the exclusivity, while the US residents would not.

Limitations on US prices. KEI asked the NIH to seek terms that would put limitations on US prices of products, ensuring that 1) Medicare co-pays for the products are affordable, 2) that prices do not exceed the estimated value of treatment, and 3) that products are priced such that access is not restricted by payors.

Transparency

KEI's requests regarding transparency cover several areas, including clinical trial costs, R&D outlays more broadly, sales, and revenue, and also urge the NIH to include terms that adhere to the resolution on transparency adopted by the World Health Organization Member States (WHA72.8). KEI notes that this resolution was enthusiastically supported by HHS at its adoption.

Transparency of R&D outlays. In its exclusive licenses, the NIH should require that licensees file an annual report to the NIH, available to the public, on the research and development costs associated with the development of any product or service that uses the inventions, including reporting separately and individually the outlays on each clinical trial. This is not a request to see a confidential company business plan or license application but rather that going forward licensees (and any sublicensees) be required to report on actual R&D outlays to develop the subject inventions. Reporting on actual R&D outlays is important for determining if the NIH is meeting the requirements of 35 U.S.C. § 209, that "the proposed scope of exclusivity is not greater than reasonably necessary to provide the incentive for bringing the invention to practical application[.]" Specifically, having data on actual R&D outlays on each clinical trial used to obtain FDA approval provides evidence that is highly relevant to estimating the risk-adjusted costs of bringing NIH licensed inventions to practical application.

Transparency of sales, revenue, grants, and credits. Through these licenses, the NIH should also require reporting on units of sales and revenue for sales, by country, as well as annual reporting on grants and research contracts received from government agencies, with data on the funding agency, the identifier of the grant or contract, and the amount of the grant or contact. Reporting would also include tax credits associated with R&D for the product, including the U.S. orphan drug tax credit, broken out by the type of credit and the expenditure the credit was associated with (such as a specific trial), as well as other government R&D subsidies.

Domestic Manufacturing Waiver

Innovations that are licensed under the Bayh-Dole Act must include a requirement that the products be "substantially" manufactured in the United States. Companies can obtain a waiver of this requirement. For licensees based outside the United States, KEI asked about and requested the NIH disclose whether the company had sought waiver of the domestic manufacturing requirement. When KEI asked about a potential waiver of the domestic

manufacturing requirement in questions to the NIH prior to the close of the comment period, the NIH would refuse to provide that information.[8]

Global Access

Limitation on geographic scope of exclusivity and test data rights. In order to ensure affordable access in low and middle income countries, KEI asked the NIH to ensure that the exclusive licenses did not extend to countries with a per capita income less than 30 percent that of the United States. In the "United States Public Health Service Technology Transfer Policy Manual, which outlines the technology transfer policies for the NIH, FDA, and CDC, the manual sets out as a policy objective, that "PHS seeks to promote commercial development of inventions in a way that provides broad accessibility for developing countries." KEI's proposal seeks to give action to those words.

Additionally, KEI requested in its comments that the NIH to include provisions that would require the licensed patent holders to waive any exclusive rights regarding test data and any patent-registration linkage rights that may exist in any country with a per capita income less than 30 percent of U.S. per capita income. This is important because a number of trade agreements and bilateral pressures force low and middle income countries to enact laws granting exclusive rights in test data, in most cases, without the possibility of exceptions, even in cases involving excessive prices.

Non-exclusive, World Health Organization, and Medicines Patent Pool licenses. KEI has urged in its comments to the NIH that:

> "The NIH should retain a right to grant the WHO, the Medicines Patent Pool or other governments the rights to use the patent rights to procure the medical technology from competitive suppliers, including technology transfer, in LMICs, upon a finding by HHS or the WHO that people in these markets do not have sufficient access to the medical technology."

Global registration and affordability. KEI has asserted that, "The licenses should require the licensee to disclose the steps that each will take to enable the timely registration and availability of the medical technology at an affordable price in the United States and in every country with a demonstrated need, according to the Centers for Disease Control and Prevention (CDC) and/or the World Health Organization (WHO), either by supplying a country directly at an affordable, publicly disclosed price and with sufficient quantities, or by providing technology transfer and rights to all intellectual property necessary for third parties to do so."

NIH Due Diligence and Fostering Further Innovation

Acknowledgement of federal funding. In order to recognize the contributions that taxpayers make in the support of biomedical R&D, KEI urged that the licensee should be required to

[8] For example: https://www.keionline.org/36442

include, when issuing statements, press releases, and other documents describing the development of any product that includes the licensed inventions, a statement that describes the role of the licensed inventions and the total and proportionate contribution of federal funding to the research and development performed to bring the inventions to market.

40 U.S.C. § 559 - Attorney General consultation. Per 40 U.S.C. § 559, the NIH is required to seek the advice of the Attorney General regarding antitrust issues when disposing of property. Patents with a market value more than $3 million fall under this requirement. When KEI asked whether the NIH had sought the advice of the Attorney General, the NIH would either not answer the question, or asserted that the requirement did not apply to their licensing practices.

35 U.S.C. § 209 analysis of the necessity of exclusivity. 35 U.S.C. § 209 has several restrictions on the grant of an exclusive license. In Section 209(a)(1), the agency has to determine if exclusivity is a reasonable and necessary incentive to induce the investments to bring an invention to practical application. Additionally, if some exclusivity is warranted, the agency still has to determine the scope of exclusivity, and is required to ensure that that the proposed scope of exclusivity is not greater than reasonably necessary.

No exclusive license should be granted until the NIH conducts an economic analysis to determine if exclusivity can be limited to less than the life of the patent, as was the case, for example, for all extramural-funded patents when the Bayh-Dole Act was passed in 1980, and under previous NIH Directors, as in the case of the ddI license for an HIV drug.

When asked by KEI the NIH has never provided a copy of the analysis carried out to determine that an exclusive license was necessary to induce investments, nor have they described how they conducted their analysis. Indeed, in other responses to KEI, the NIH has appeared to admit to not conducting analyses for each prospective license by stating that answers to questions about the analyses have been addressed in earlier licenses.[9]

Transfer of know-how and biologic resources, and research permissions. In order to address research by third parties on the inventions to be licensed, in many of our comments KEI proposed the NIH explicitly permit researchers worldwide to use the inventions for research purposes, regardless of whether or not research has a grant or contract from a U.S. government agency, and for both profit or non-profit organizations. KEI also urged the NIH to require the licensee to provide transfer of manufacturing know-how and access to relevant biologic resources, to any firm designed by the United States.

Examples of Notable Exclusive Licenses

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9 https://www.keionline.org/wp-content/uploads/KEI-NIH-Questions-86FR50895-License-Sana-Biotechnology.pdf

CAR T Therapy for B-cell Cancers - Kite Pharma/Gilead Sciences

On Monday July 29, 2019, KEI submitted joint comments[10] to the NIH on behalf of KEI, Social Security Works (SSW), Universities Allied for Essential Medicines (UAEM), Union for Affordable Cancer Treatment (UACT), and Clare Love, a cancer patient, regarding two proposed exclusive licenses to Kite Pharma/Gilead Sciences for CAR T technologies to treat cancers.[11]

Both licenses concerned CAR T technologies that target both CD19 and CD20 proteins and were for the treatment of B-cell derived human cancers, which include Non-Hodgkins Lymphoma (NHL), acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL). At the time, Kite/Gilead already had on the market Yescarta, a CAR T therapy to treat B-cell derived cancers. Yescarta was also developed from NIH-licensed technologies and was introducted at a price of $373,000 per treatment.

The dual targeting of CD19 and CD20 would provide more comprehensive therapy to B-cell cancers than treatments that have been approved that only target CD19, such as Yescarta. Granting a license to these technologies on an exclusive basis presents a troubling anti-competitive consolidation of these technologies with a company that has repeatedly been shown to charge extremely high prices for its treatments. Particularly in this case, KEI urged the NIH's compliance with 40 U.S.C. § 559, which requires the NIH to solicit the Attorney General's advice regarding antitrust issues in the disposal of government property.

Since 2012, Kite/Gilead have entered into several Cooperative Research and Development Agreements (CRADAs) and exclusive licenses related to CAR-technologies. In 2016, the New York Times chronicled the close relationship between the NIH and Kite/Gilead in an article titled, "NAME."[12]

As KEI noted in our comments, "The NIH license of yet another B-cell CAR T treatment to Gilead/Kite for the treatment of hematological malignancies will increase concentration, and protect Yescarta and Kymriah from price competition at a time when the new cell- and gene-therapies present emerging threats to health care budgets, and the high prices for treatments, which have nothing to do with R&D or cell manufacturing costs, are associated with rationing."

Ebanga - Ridgeback Therapeutic's Ebola treatment

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[10] https://www.keionline.org/wp-content/uploads/Kite-Gilead-NIH-License-comments-29July2019.pdf

[11] "Prospective Grant of an Exclusive Patent License: Autologus Therapy Using Bicistronic Chimeric Antigen Receptors Targeting CD19 and CD20" (84 FR 33272) and "Prospective Grant of an Exclusive Patent License: Allogeneic Therapy Using Bicistronic Chimeric Antigen Receptors Targeting CD19 and CD20" (84 FR 33270).

[12] https://www.nytimes.com/2016/12/19/health/harnessing-the-us-taxpayer-to-fight-cancer-and-make-profits.html

On March 30, 2021, KEI filed comments regarding the "Prospective Grant of an Exclusive Patent License: Development, Production, and Commercialization of Ebola Neutralizing Single Monoclonal Antibody for the Treatment of Ebola Virus Disease in Humans" (86 FR 14331) to Ridgeback Therapeutics.[13] Ridgeback has risen in profile in recent years, as it obtained and leveraged rights to COVID-19 treatment NAME.

In the 2021 license, the field of use of the license conveyed the rights to the, "development, production, and commercialization of Ebola neutralizing monoclonal antibody mAb114, as a single antibody not in combination with other monoclonal antibodies, for the treatment of Ebola virus disease in humans."[14]

Ridgeback's Ebola treatment Ebanga (ansuvimab-zykl, formerly referred to as mAb114) was approved by the FDA on December 12, 2020, prior to the publication of the notice and grant of this exclusive license. Ridgeback also received a priority review voucher (PRV) for the treatment as well under the material threat medical countermeasure PRV as well as an orphan drug designation and approval.

The US government provided significant support and incentives for the development of mAb114, including sponsoring and conducting key clinical trials, granting Ridgeback rights to the technical data, and agreeing to contracts worth up to $168 million. The Ridgeback press release concerning Ebanga notes,

> "Ebanga development has been funded in whole or in part with federal funds from the Department of Health and Human Services; Office of the Assistant Secretary for Preparedness and Response; Biomedical Advanced Research and Development Authority, under Contract Numbers 75A50119C00059 and 75A50120C00009."[15]

As previously noted, when granting patent licenses to federally-owned inventions, the NIH may only grant an exclusive license when exclusivity is a necessary incentive and must limit the scope of patent licenses, including the period of exclusivity, to that which is reasonable and necessary. 35 U.S.C. §209(a)(1)-(2).

How was a license on an exclusive basis necessary to incentivize commercialization when the product was already approved by FDA? The clinical trials were already completed and/or underway, Ridgeback had rights to clinical trial data, and the company already brought in $168

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[13] https://www.keionline.org/wp-content/uploads/KEI-Comments-NIH-Exclusive-License-Ridgeback-30March2021.pdf

[14] "Prospective Grant of an Exclusive Patent License: Development, Production, and Commercialization of Ebola Neutralizing Single Monoclonal Antibody for the Treatment of Ebola Virus Disease in Humans" (86 FR 14331).

[15] https://www.businesswire.com/news/home/20201222005421/en/Ridgeback-Biotherapeutics-LP-Announces-the-Approval-of-EbangaTM-for-Ebola

million through contracts just to bring the invention to market. Granting exclusive rights in this case was in no way reasonable or necessary.

ANNEX

TABLE:
Overview of Requests in KEI Comments on NIH Prospective Exclusive Licenses