Research Tools Policies and Practices: Perspective of a Public Institution

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Introduction

The impact of the 1980 Bayh-Dole Act (35 U.S.C. §200-§212) on commercialization of medical inventions is indisputable. The act gave grant and contract recipients the ability to take title to inventions made under federally funded research. Associated with this ownership was the right to license the inventions to the private sector for commercial development. The Bayh-Dole Act resulted in a dramatic increase in the formation of commercialization partnerships between academia and industry and in the emergence of a great number of startup enterprises, many of them university spinoffs initiated by the academic inventors themselves.

Over the same time period similar legislation for federal laboratories such as the Stevenson-Wydler Act of 1980 and the Federal Technology Transfer Act (FTTA) of 1986 has also likewise resulted in increased commercialization activity based upon research conducted at the federal laboratories themselves.

The potential of profiting from traditional research activities, however, created the perception that academic institutions and their scientists may become reluctant to disclose their research results and freely share research resources developed under government grants, including those from the National Institutes of Health (NIH).

Furthermore, many were concerned that the proliferation in the number of such partnerships, sponsored research, and license agreements could lead to the private sector imposing restrictions adversely affecting academic freedom and the dissemination of research

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resources. A major area of concern was related to biological materials and research tools that are instrumental to scientific discovery and the life blood of biomedical research.

The commercialization concerns above seemed to some to create potential conflict with the basic intent of federal research funding and with the core philosophy of academic research that traditionally encouraged broad dissemination of research results and research resources. These two seemingly conflicting directives, commercialization on one hand and broad dissemination of research results on the other, created some confusion and ambiguities in the research community that required clarification to show how both objectives could be compatibly achieved.

As the primary federal agency for conducting and supporting biomedical research, the NIH felt that it was necessary to provide its grantees with guidance to assist them in balancing commercialization under Bayh-Dole in a way that would not inhibit further research and new scientific discoveries. Accordingly, the agency took upon itself the responsibility of formulating a formal policy regarding dissemination of biomedical research resources. A working group tasked with this mission was established in 1997 under the directive of the then director of the NIH, Harold Varmus, MD.

A first draft of the policy was proposed by the working group and published in the *Federal Register* in August 1997 to obtain comments from the biomedical community as well as the broader public. In view of the feedback, the NIH published its revised final policy notice on December 23, 1999, (http://www.ott.nih.gov/pdfs/64FR72090.pdf). Since its publication, the notice, entitled "Sharing Biomedical Research Resources: Principles and Guidelines for Recipients of NIH Research Grants and Contracts" (also known as the NIH research tools policy) has served as a useful reference document for the biomedical research community, assisting researchers in developing balanced strategies related to dissemination of research resources, both as providers of such resources and as recipients.

This 1999 *Federal Register* notice was issued as a grants policy, to be incorporated into the NIH grants policy statement. Moreover, following the issuance of these guidelines Congress amended the Bayh-Dole Act to emphasize the obligation of recipients to balance between the above-mentioned two directives as articulated in the policy and the objective

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section of the law as quoted here: "It is the policy and objective of the congress to use the patent system to promote the utilization of inventions arising from federally supported research and development … to ensure that inventions made by nonprofit organizations and small-business firms are used in a manner to promote free competition and enterprise *without unduly encumbering future research and discovery*" (35 U.S.C. §200).

This chapter is presented in three parts. "Part 1: The NIH Research Tools Policy" provides a detailed description of the NIH research tools policy. This part includes different strategies and proposed language that can be used in transactional and collaborative agreements.

"Part 2: NIH Technology Transfer Practices" discusses the practices implemented by the NIH technology transfer community with regard to research tools. Although these NIH intramural research tool practices themselves derive separately from the Stevenson-Wydler Act and the FTTA (rather than the Bayh-Dole Act), they provide some very practical experience in this area based upon the substantial size and large number of inventions coming from the NIH intramural research program.

"Part 3: More on the NIH Patenting and Policy Positions Related to Research Tools" provides examples of policy positions taken by the NIH over the years as they relate to patenting of research tools. This part highlights the NIH's continuing dedication to improving policies related to dissemination of research tools.

The chapter is designed to provide practical advice and specific language related to the dissemination of research tools. The three parts that follow this introduction endeavor to provide sufficient information so that future collaborative research may better lead to expeditious product development without hindrance to academic research and further scientific discoveries in the spirit of the Bayh-Dole Act.

Part 1: The NIH Research Tools Policy

The NIH research tools policy as published in the December 23, 1999, *Federal Register* encompasses four principles and a set of implementation guidelines as summarized below. Before discussing the principles and guidelines it is important to define what research tools are and how they should be utilized.

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What Are Research Tools and How Should They Be Utilized?

Research tools, also called research resources or research materials, are biological or other materials that are:

- primarily useful for research purposes, such as in data related to the elucidation of disease mechanisms or to drug discovery;
- by definition finished products that often do not require further development time and development costs in order to be utilized; or
- broadly enabling inventions, useful in developing multiple products in numerous disciplines, rather than a single project-specific or product-specific use.

Common examples of research tools include:

- antibodies
- expression plasmids and proteins derived from them
- cell receptors
- cell lines
- animal models (e.g., knockout mice)
- laboratory and drug-screening methods or protocols
- certain software

It should be appreciated that certain biological materials can serve dual purposes, i.e., they can be classified as research tools, but they can also be used for commercial applications as therapeutic or vaccine candidates or as diagnostics that require major investment of capital and time for further development and regulatory approval. These distinctions associated with such materials may be accommodated through inclusion of appropriate language in licensing agreements, which is discussed in "The Guidelines" section of Part 1 and in the "Licensing" section of Part 2 of the chapter.

As will be discussed further in this chapter, inventors should seek the assistance of their technology transfer professionals to thoroughly analyze the potential utility of biological materials developed by them in order to be able to choose a strategy that will best comply with the NIH research tool policy as discussed in this chapter while also protecting the interest of the inventors and their institutions.

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The Principles

The first principle of the NIH research tools policy is "Ensure Academic Freedom and Publication."[1] This principle is concerned with the need by NIH recipients to preserve academic freedom even when a partnership with industry is involved. The following points are the essentials of this principle:

- Recipients have the obligations to preserve academic freedom and disclose their research findings in a timely manner through publications, public presentations, and the like.
- Recipients should avoid signing collaborative agreements that unduly limit their freedom to collaborate and publish or that otherwise grant overreaching rights to a third-party provider of research materials.

With respect to preserving academic freedom under sponsored research situations, this point reinforces an earlier NIH guidance to recipients. In July 1994 the NIH published a notice in the *Federal Register* entitled "Developing Sponsored Research Agreements: Considerations for Recipients of NIH Research Grants and Contracts" (59 FR 5567; November 9, 1994, and *NIH GUIDE*, Vol. 23, No. 25, July 1, 1994).

This earlier document emphasizes that for NIH-funded research, it is essential that "Grantees must ensure that the timely dissemination of research findings is not adversely affected by the conditions of a sponsored research agreement."

The first principle discussed here further elaborates on this issue as summarized in the next two bullets:

- In the case of a sponsored research agreement between a recipient and an industrial partner, some reasonable restrictions are acceptable to avoid conflicting obligation with other industrial sponsors. Furthermore, brief delays in publications of research results are acceptable when patent protection is warranted or for the purpose of ensuring that the sponsor's proprietary information is not disclosed.
- Excessive publication delays or requirements for editorial control, approval of publications, or withholding of data when imposed by the commercial partner all undermine the credibility of research results and should be avoided.

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The second principle, "Ensure Appropriate Implementation of the Bayh-Dole Act," emphasizes the obligations of recipients to cooperate with the spirit of Bayh-Dole in dealing with patenting and licensing of new inventions. It highlights the following:

- NIH-funded research is subjected to laws and regulations as codified by the Bayh-Dole Act *(35 U.S.C. 200 et seq.)*.
- In accordance with this act, recipients are expected to (a) maximize the use of their research findings by making them available to the research community and the public and (b) when warranted and suitable, transfer inventions to the private sector for commercialization, which may sometimes require patent protection.
- While the practice of patenting and licensing of inventions is encouraged by the Bayh-Dole Act to stimulate commercialization, there are sometimes other appropriate means of implementing the Bayh-Dole act as stated below.
- Recipients should consider alternative strategies other than seeking patent protection for materials whose primary use is as research tools, as they are by their very nature fully developed and do not require further investment of time and capital be utilized. Such research tools are usually transferred between academic institutions for internal research under material transfer agreements (MTAs) in transactions that do not involve financial compensations.
- Unpatented research tools can also be transferred to the private sector on a nonexclusive basis via internal-use license agreement. Such agreement may include financial compensation. Modifications to NIH policy allow recipients to elect title to such inventions even if unpatented.
- It is also consistent with Bayh-Dole to grant commercial licenses for research tools to companies for the purpose of sales and distributions of such reagents to the research community. Such commercial licenses may in certain circumstances be better justified on an exclusive basis if the technology requires further development by the commercial party to realize the invention's usefulness as a research tool.

The third principle in the NIH Policy, "Minimize Administrative Impediments to Academic Research," is concerned with the transfer of research tools to research groups, whether located at for-profit or not-for-profit institutions. It emphasizes the importance of establishing expeditious processes for the transfer of research resources.

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Furthermore, it advocates and proposes streamlining and simplification of transfer agreements. This third principle expands on the concepts of the first principle regarding collaborative relations between academia and industrial sponsors and the responsibilities of each party. The main points outlined in this principle are as follows:

- To expedite the transfer process, the standard uniform biological materials transfer agreement (UBMTA)[3] is acceptable. This master document can be further implemented by a convenient form of a simple letter agreement (SLA). In addition a freestanding SLA is strongly encouraged for the transfer of patented biological materials. A sample of such an agreement is provided in "The Guidelines."
- When a recipient acquires research resources from another party, the recipient should develop and implement clear policies that articulate acceptable conditions for acquiring resources and refuse to yield on unacceptable conditions that may excessively restrict academic freedom while remaining respective of the legitimate concerns of the for-profit provider.
- For-profit organizations must minimize obligations that seek to impose. In these transfers all providers should avoid imposing reach-through royalty or product rights as conditions on transfer (i.e., rights to products invented through the use of research tools provided by them), unreasonable restraints on publication and academic freedom, and improper valuation of tools.

The fourth principle, "Ensure Dissemination of Research Resources Developed with NIH Funds," is meant to ensure broad and timely dissemination of research tools by recipients. Furthermore, recipients should not agree to limitations in their agreements with third parties that have the potential to restrict the dissemination of NIH-funded research tools.

- Recipients are expected to manage interactions with third parties that have the potential to restrict recipients' ability to disseminate research tools developed, in whole or in part, with NIH funds (research tools obtained from human tissues may require restrictions to ensure consistency with donor consent and protection of human subjects as per 45 CFR Part 46).
- In cases where recipients are involved with transfer or collaborative agreements with third parties, recipients are encouraged to share the principles outlined in the NIH policy notice with these third parties.

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- In instances where the for-profit institution is seeking access for internal-use purposes, recipients are encouraged to transfer research tools developed with NIH funding to such institutions without seeking option rights or royalties on the final product.

The Guidelines

This section provides technology transfer professionals, scientists, and research administrators with practical strategies, procedures, forms, and proposed language related to the four principles discussed above to facilitate their implementation. These proposals are merely guidelines. It is expected that they may be modified depending on specific scenarios.

Disseminating Research Resources Arising out of NIH-Funded Research

As per the discussion above regarding the third principle, a model transfer letter agreement is shown in Exhibit 1.[4] This SLA is primarily suitable for transfer of materials amongst academic institutions and other not-for-profit entities. It is designed for transfers under terms no more restrictive than the well-known UBMTA.[5] If the materials are patented or licensed to an exclusive provider, other arrangements may be used, but commercial license rights, royalty reach-through, or product reach-through rights back to the provider are inappropriate.

Exhibit 1: Material Transfer/Simple Letter Agreement

In response to RECIPIENT's request for the MATERIAL [insert description] _____ the PROVIDER asks that the RECIPIENT and the RECIPIENT SCIENTIST agree to the following before the RECIPIENT receives the MATERIAL:

1. The above MATERIAL is the property of the PROVIDER and is made available as a service to the research community.

2. THIS MATERIAL IS NOT FOR USE IN HUMAN SUBJECTS.

3. The MATERIAL will be used for teaching or not-for-profit research purposes only.

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4. The MATERIAL will not be further distributed to others without the PROVIDER's written consent. The RECIPIENT shall refer any request for the MATERIAL to the PROVIDER. To the extent supplies are available, the PROVIDER or the PROVIDER SCIENTIST agree to make the MATERIAL available, under a separate Simple Letter Agreement to other scientists for teaching or not-for-profit research purposes only.

5. The RECIPIENT agrees to acknowledge the source of the MATERIAL in any publications reporting use of it.

6. Any MATERIAL delivered pursuant to this Agreement is understood to be experimental in nature and may have hazardous properties. THE PROVIDER MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE MATERIAL WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER PROPRIETARY RIGHTS. Unless prohibited by law, Recipient assumes all liability for claims for damages against it by third parties which may arise from the use, storage or disposal of the Material except that, to the extent permitted by law, the Provider shall be liable to the Recipient when the damage is caused by the gross negligence or willful misconduct of the Provider.

7. The RECIPIENT agrees to use the MATERIAL in compliance with all applicable statutes and regulations.

8. The MATERIAL is provided at no cost, or with an optional transmittal fee solely to reimburse the PROVIDER for its preparation and distribution costs. If a fee is requested, the amount will be indicated here: _____ The PROVIDER, RECIPIENT and RECIPIENT SCIENTIST must sign both copies of this letter and return one signed copy to the PROVIDER. The PROVIDER will then send the MATERIAL.

Provider Information and Authorized Signature

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Provider Scientist:_____
Provider Organization: _____
Address:_____
Name of Authorized Official: _____
Title of Authorized Official: _____
Certification of Authorized Official: This Simple Letter Agreement ____ has _____ has not [check one] been modified. If modified, the modification is attached.

_____
(Signature of Authorized Official) (Date)
Recipient Information and Authorized Signature
Recipient Scientist: _____
Recipient Organization: _____
Address: _____
Name of Authorized Official: _____
Title of Authorized Official: _____
Signature of Authorized Official: _____
Date: _____
Certification of Recipient Scientist: I have read and understood the conditions outlined in this Agreement and I agree to abide by them in the receipt and use of the MATERIAL.

_____
(Recipient Scientist) (Date)

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Similarly to this model agreement, when for-profit entities are seeking access to NIH-funded tools for internal-use purposes, recipients should ensure that the tools are transferred with the fewest encumbrances possible. The model SLA may be expanded for use in transferring tools to for-profit entities or an internal-use license agreement may be drafted where compensation may be appropriate. For example, NIH has expanded the model (Exhibit 1a)[6] to handle circumstances relating to the transfer of model organisms where crossbreeding may occur. Additionally, animal welfare conditions or other special issues may apply to these transfers.

Exhibit 1a: Additional MTA/SLA Language for Transfer of Transgenic Organisms

This is in response to RECIPIENT's request for the MATERIAL (specifically, the name of the gene or allele mutation that makes the organism(s) unique) _____, found within the _____ (organism strain, species, et.), the PROVIDER asks that the RECIPIENT and the RECIPIENT SCIENTIST agree to the following before the RECIPIENT receives the MATERIAL:

…

8. If the RECIPIENT anticipates that it will generate cross-bred or genetically-modified organisms incorporating the PROVIDER's modified allele(s), RECIPIENT may transfer such cross-bred or genetically-modified organism(s) to non-profit institutions under the terms of a material transfer agreement that notifies the not-for-profit institution of the existence of PROVIDER's rights to the modified allele(s) and restricts the use of the transferred organism(s) by the not-for-profit recipient to teaching or not-for-profit research purposes only. This Agreement does not transfer any of PROVIDER's patent, invention, or other intellectual property rights in the organism(s) to RECIPIENT. Additionally, to the extent that any other party has any patent, invention or other intellectual property rights in the organism(s), these rights are not transferred to RECIPIENT by PROVIDER…

Consistent with the principles, in situations where recipients are engaged in collaborative and/or sponsored research with third parties, they are expected to craft agreements with such third parties in a way that is consistent with Bayh-Dole and their obligations to the NIH, including their obligations to share research resources with the rest of the research community as freely and openly as possible. Samples of such language are provided below in Exhibit 2.[7]

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Exhibit 2: Sample Language in Sponsored Research Agreements

The project covered by this agreement is supported with funding from the National Institutes of Health. Provider agrees that upon publication, unpatented unique research resources arising out of this project may be freely distributed.

In the event an invention is primarily useful as a research tool, any option granted shall either be limited to a non-exclusive license or the terms of any resulting exclusive license shall include provisions that ensure that the research tool will be available to the academic research community on reasonable terms.

Provider agrees that Recipient shall have the right to make any materials and inventions developed by Recipient in the course of the collaboration (including materials and inventions developed jointly with Provider, but not including any Provider materials (or parts thereof) or Provider sole inventions) available to other scientists at not-for-profit organizations for use in research, subject to Provider's independent intellectual property rights.

Subject to Recipient's obligations to the U.S. government, including 37 CFR Part 401, the NIH Grants Policy Statement, and the NIH Guidelines for Obtaining and Disseminating Biomedical Research Resources, Recipient grants to Sponsor the following rights: …

Research tools that do not require extensive research and development (R&D) or capital investment to realize the invention's usefulness as a tool should not be licensed on an exclusive basis unless it is licensed to a commercial research reagents distributor and the distributor is committed to the broad dissemination of such tools. This strategy is sometimes advisable as it can facilitate a wide distribution of reagents in an effective manner.

In certain situations inventions that are biomedical materials can be exploited in multiple ways. They can be developed into vaccines, therapeutics, or diagnostic products on one hand or can be utilized as research tools on the other. In these cases, patenting of the materials may be warranted. A common example for this is antibodies. Antibodies can be developed into therapeutics against a variety of diseases or they can be used to develop laboratory reagents.

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In these situations, regulatory requirements may be necessary and thus entail significant investment of time and capital, therefore justifying exclusive licenses when the cost of commercial development so justifies. At the same time, antibodies can be used as research tools, e.g., in elucidating disease mechanisms or for drug discovery. In such cases, the biological materials may be licensed on different terms for different fields of use, i.e., exclusive license for therapeutics and vaccines, but nonexclusive licenses when licensed as a research tool. This point is further discussed in Part 2 of this chapter, under the "Licensing" section.

Furthermore, the exclusive licensee shall not be permitted to block the broad dissemination of the materials for the research community for research purposes, which may be accomplished through requiring the licensee to grant such research licenses, MTAs, or refraining from enforcing any relevant patents against nonprofit research institutions. Finally, the original licensor or owner of such materials may reserve the rights to grant such research licenses directly. These goals can be accomplished through incorporation of appropriate language into commercial license agreements. Examples of such language are provided in Exhibit 3.[8]

Exhibit 3: Language Directed to Research Licenses

"Research License" means a nontransferable, nonexclusive license to make and to use the Licensed Products or Licensed Processes as defined by the Licensed Patent Rights for purposes of research and not for purposes of commercial manufacture, distribution, or provision of services, or in lieu of purchase, or for developing a directly related secondary product that can be sold. Licensor reserves the right to grant such nonexclusive Research Licenses directly or to require Licenses on reasonable terms. The purpose of this Research License is to encourage basic research, whether conducted at an academic or corporate facility. In order to safeguard the Licensed Patent Rights, however, Licensor shall consult with Licensee before granting to commercial entities a Research License or providing to them research samples of the materials.

Licensor reserves the right to provide the Biological Materials and to grant licenses under Patent Rights to not-for-profit and governmental institutions for their internal research and scholarly use.

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Notwithstanding anything to the contrary in this agreement, Licensor shall retain a paid-up, nonexclusive, irrevocable license to practice, and to sublicense other not-for-profit research organizations to practice, the Patent Rights for internal research use.

The grant of rights provided herein is subject to the rights of the United States government pursuant to the Bayh-Dole Act and is limited by the right of the Licensor to use Patent Rights for its own research and educational purposes and to freely distribute Materials to not-for-profit entities for internal research purposes.

Licensor reserves the right to supply any or all of the Biological materials to academic research scientists, subject to limitation of use by such scientists for research purposes and restriction from further distribution.

Licensor reserves the right to practice under the Patent Rights and to use and distribute to third parties the Tangible Property for Licensor's own internal research purposes.

Acquiring Research Resources for Use in NIH-Funded Research

Agreements to acquire materials for use in NIH-funded research are expected to address the timely dissemination of research results. Recipients should not agree to significant publication delays, any interference with the full disclosure of research findings, or any undue influence on the objective reporting of research results. A delay of 30 to 60 days to allow for new patent application filing or review for confidential proprietary information is generally viewed as reasonable.

Under the Bayh-Dole Act and its implementing regulations (37 CFR 401), agreements to acquire materials for use in NIH-funded projects cannot require that title to resulting inventions be assigned to the provider. Recipients should therefore make sure that the definition of *materials* in MTAs or similar agreements with third-party providers does not include all derivatives and improvements of provided materials. Conversely, the language of such agreements should specify that recipients do not gain an ownership interest in such third party's provided materials as a result of the recipient's work with the materials. Exhibit 4[9] below provides possible definitions for use in such transfer agreements.

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Exhibit 4: Definition of* Materials *when Recipients Accept Research Tools

"Materials" means the materials provided as specified in this document. Materials may also include Unmodified Derivatives of the materials provided, defined as substances created by the Recipient which constitute an unmodified functional subunit or product expressed by the original material, such as subclones of unmodified cell lines, purified or fractionated subsets of the original materials, proteins expressed by DNA/RNA supplied by the Provider, or monoclonal antibodies secreted by a hybridoma cell line.

"Materials" means the materials provided as specified in this document. Materials may also include Progeny and Unmodified Derivatives of the materials provided. Progeny is an unmodified descendant from the original material, such as virus from virus, cell from cell, or organism from organism. Unmodified Derivatives are substances created by the Recipient which constitute an unmodified functional subunit or product expressed by the original material, such as subclones of unmodified cell lines, purified or fractionated subsets of the original material, proteins expressed by DNA/RNA supplied by the Provider, or monoclonal antibodies secreted by a hybridoma cell line.

"Materials" means the materials being transferred as specified in this document. Materials shall not include: (a) Modifications or (b) other substances created by the recipient through the use of the Material which are not Modifications, Progeny, or Unmodified Derivatives. Progeny is an unmodified descendant from the Material, such as virus from virus, cell from cell, or organism from organism. Unmodified Derivatives are substances created by the Recipient which constitute an unmodified functional subunit or product expressed by the original Material, such as subclones of unmodified cell lines, purified or fractionated subsets of the original Material, proteins expressed by DNA/RNA supplied by the Provider, or monoclonal antibodies secreted by a hybridoma cell line. [Source: Uniform Biological Materials Transfer Agreement; terms defined therein]

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Recipients are expected to avoid signing agreements to acquire research tools that are likely to restrict their ability to promote broad dissemination of additional tools that may arise from the research. This situation might occur if an agreement gives a provider an unrestricted exclusive license option to any new intellectual property arising out of the project. A new transgenic mouse developed during the project could fall under this license option and become unavailable to third-party scientists as a result.

In signing agreements such as MTAs, memoranda of understanding (MOU), research or collaboration agreements, and sponsored research agreements, recipients should consider adopting standard language that address this issue. The language provided in Exhibit 2 (in the discussion related to sponsored research), can be used in agreements that either acquire materials from or co-mingle funds with nongovernment sources.

Grant Back and Option Rights to Third-Party Material Provider

The points that follow further elaborate on the expectations from recipients in their dealing with providers from for-profit entities.

Agreements to acquire materials from for-profit entities for use in NIH-funded research may provide a grant back of nonexclusive, royalty-free rights to the provider to use improvements and new uses of the material that would infringe any patent claims held by the provider. The agreements may also provide an option for an exclusive or nonexclusive commercialization license to new inventions arising directly from use of the material. These should be limited to circumstances where the material sought to be acquired is unique, such as a patented proprietary material and not reasonably available from any other source.

A nonexclusive grant-back might be used, for example, to protect a for-profit entity that provides a proprietary compound from being blocked from using new uses or improvements of that compound discovered during the NIH-funded project. In providing license options, recipients must ensure that licenses granted to providers under such options are consistent with Bayh-Dole requirements, including the preference for U.S. industry requirements under exclusive agreements and reservation of government rights under 37 CFR Part 401.

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In determining the scope of license or option rights that are granted in advance to a provider of materials, recipients should balance the relative value of the provider's contributions against the value of the rights granted, cost of the research materials provided, and importance of the research results. The rights granted to providers should be limited to inventions that have been made directly through the use of the materials provided.

In addition, recipients should reserve the right to negotiate license terms that will ensure: (1) continuing availability to the research community under reasonable terms if the new invention is a unique research resource, (2) that the provider has the technical and financial capability and commitment to bring all commercially relevant applications in the field of use of the license to the marketplace in a timely manner, and (3) that if an exclusive license is granted, the provider will provide a commercial development plan and agree to benchmarks and milestones for any fields of use granted.

It is expected that agreements to acquire NIH-funded materials from not-for-profit entities for use in NIH-funded research will not include commercialization option rights, royalty reach-through, or product reach-through rights back to the provider. Such materials should be acquired under terms no more burdensome than the SLA or UBMTA, or, if the materials are provided to a for-profit entity, a SLA or MTA that does not request reach-through to either future products or royalties.

If the providing not-for-profit organization is constrained in sharing the material due to a pre-existing sponsored research agreement or license, NIH expects that such a not-for-profit provider to negotiate a suitable resolution with the private research sponsor or licensee. The co-mingling of NIH and sponsored research funds is allowed, however, each recipient is responsible for ensuring that conditions on the use of the sponsored funds do not interfere with the open dissemination of research tools or other terms and conditions of the NIH funding.

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While there is no specific model language provided to recipients pertaining to the guidelines under this section for working with for-profit entities, a useful example can be found from an NIH model agreement used in the intramural research program, the material cooperative research and development agreement (M-CRADA). This specific model can be found at the OTT Web site under "Forms and Model Agreements."[10]

Part 2: NIH Technology Transfer Practices

In addition to its function as a granting institution, the NIH also engages in intramural research and extensive technology transfer activities. As such, in its own biomedical research program, the NIH has adopted for its programs the same policies and guidelines that apply to recipients. These activities will be highlighted here.

For example, the NIH intramural research program utilizes the SLA or UBMTA as model MTAs for transfers of biological materials with a nonprofit research institution. Additionally, as a U.S. government agency, the NIH has the legal authority to grant licenses under license agreement instead of an MTA. Thus for NIH the grant of an explicit license to use biological materials for commercial purposes can only be accomplished through such means instead of an NIH MTA, which would only give the receiving party permission to use the biological materials without an explicit license.

The NIH OTT (www.ott.nih.gov) serves as the patenting and licensing arm for the NIH and FDA intramural programs. As such, OTT works in concert with technology transfer offices within the different institutes and centers at the NIH and U.S. Food and Drug Administration (FDA). The institute- and centers-based technology transfer activities focus on interactions with academic institutions involving MTAs, the initial referral of new invention reports to OTT, and establishing collaborative research with private companies.

The latter aspect involves agreements such as collaborative research and development agreements (CRADAs), M-CRADAs, or clinical trial agreements. CRADA mechanisms grant options to future inventions made under their research plans. A significant portion of the overall NIH technology transfer activities relate to transfer of biological materials. The practices implemented by the NIH with regards to these activities are highlighted below.

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Patenting

The NIH will generally seek patent protection for biomedical inventions that require further investment of capital and time to bring the invention to the point of commercial utilization. Many times these inventions require regulatory approval (such as from the FDA).[11] Inventions related to vaccines, therapeutics, and diagnostics generally fall into this category. Also included are devices and software with medical utility (e.g., imaging devices and instrumentation or software required by such instrumentation for enhanced signal resolution). Such devices usually require clinical trials to receive acceptance in the medical community. Conversely, the NIH will not seek patent protection for biomedical inventions that only have utility as research tools.

As previously noted, the NIH will seek patent protection for biomedical inventions that can be utilized for dual purposes, i.e., commercial product development (e.g., vaccine or therapeutics) and as research tool (e.g., drug screening and discovery), and further discussion regarding licensing of such dual-purpose inventions is discussed in the next section.

Licensing

At the NIH, research tools may be transferred to third parties under a variety of license agreements for government-owned inventions, whether patented or not (37 CFR Part 404), as listed below:

a. patent license agreements for commercialization (i.e., development of integrated drugs screening kits and systems or for sale and distribution of research reagents)
b. unpatented biological materials licenses for commercialization
c. internal-use licenses (patented or unpatented biological material)
d. commercial evaluation licenses

In all of its license agreements,[12] the NIH includes clauses that will ensure the continued ability to broadly disseminate the licensed materials for research applications, even where those materials are licensed exclusively for commercialization. This is accomplished by incorporating in such agreements specific definitions and clauses that preserve the right

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of the NIH to grant research licenses to third parties (academic or commercial), including to CRADA partners, or to require its licensees to do the same, as shown in Exhibit 5[13] (note that in its license agreements, OTT uses the term Public Health Service (PHS) rather than NIH, to also include the FDA, since OTT serves as the invention licensing arm of this agency).

Exhibit 5: Granting of Research Licenses

"Research License" means a nontransferable, nonexclusive license to make and to use the Licensed Products or Licensed Processes as defined by the Licensed Patent Rights for purposes of research and not for any purposes relating to or which could lead to commercial manufacture or distribution or in lieu of purchase.

PHS reserves the right to grant Research Licenses directly or to require Licensee to grant Research Licenses on reasonable terms. The purpose of these Research Licenses is to encourage basic research, whether conducted at an academic or corporate facility. In order to safeguard the Licensed Patent Rights, however, PHS shall consult with Licensee before granting to commercial entities a Research License or providing to them research samples of materials made through the Licensed Processes.

Licensee acknowledges that PHS may enter into future Cooperative Research and Development Agreements (CRADAs) under the Federal Technology Transfer Act of 1986 that relate to the subject matter of this Agreement. Licensee agrees not to unreasonably deny requests for a Research License from such future collaborators with PHS when acquiring such rights is necessary in order to make a Cooperative Research and Development Agreement (CRADA) project feasible. Licensee may request an opportunity to join as a party to the proposed Cooperative Research and Development Agreement (CRADA).

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This language sometimes causes concerns for potential commercial partners, who view research licenses as a potential mechanism by which an industry competitor may undermine its commercial position. Such concerns are typically addressed through education regarding the intent of the clauses in Exhibit 5 or by incorporating additional language to reassure licensee that PHS will consider its concerns in good faith (for example: "before

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granting such Research License PHS will consider Licensee's concerns in good faith") or to indicate that PHS may revoke a research license if NIH receives adequate evidence that a corporate licensee has extended its efforts beyond the scope of the research license.

Similarly, nonexclusive commercialization or internal-use licenses for nonpatented biological materials include a clause that allows the NIH the right to distribute the licensed materials to third parties for research purposes, as shown in Exhibit 6.[14]

Exhibit 6: Biological Materials License, Distribution of Material to Third Parties
This Agreement does not preclude PHS from distributing the Materials or the Licensed Products to third parties for research or commercial purposes.

The biological material license agreement (BMLA), either for commercialization or for internal use, makes clear distinction between *materials* and *licensed products*. They typically define *materials* as the biological materials provided by the NIH under the license agreement, and *licensed products* as the end products derived from them or in which they are used.

For example, a plasmid will constitute the *material* and the protein it expresses will be the *licensed product*. A similar relationship exists for a hybridoma cell line (material) and antibodies derived from it (licensed product). In a commercialization license, recombinant virus strains may be the material while the vaccine formulation made from it will constitute the licensed product. A commercialization BMLA will typically entail royalty payment on sales of licensed products. As you can see, it is always critical to make definitions as inclusive (or exclusive) as necessary to ensure the ability of the NIH to comply with its own guidelines regarding research tools.

In the spirit of its guidelines, the NIH license agreements encourage publication or presentation of research results stemming from the use of research tools through inclusion of, e.g., the clause of Exhibit 7.[15]

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Exhibit 7: BMLA Internal Use, Publication of Research Results

Licensee is encouraged to publish the results of its research projects using the Materials or the Licensed Products. In all oral presentations or written publications concerning the Materials or the Licensed Products, Licensee shall acknowledge the contribution of Dr. _____ and the PHS agency supplying the Materials, unless requested otherwise by PHS or Dr. _____.

As previously noted, the NIH will consider seeking patent protection for biomedical inventions that can be utilized for dual purposes, i.e., commercial development (e.g., vaccine or therapeutics) and as research tool (e.g., drug screening and discovery). In licensing of such inventions, the level of exclusivity will be commensurate with the field of use as exemplified in the customized sample shown in Exhibit 8.

Exhibit 8: Grant of Rights Language for Dual Purposes

PHS grants and Licensee accepts license grants for the Licensed Patent Rights as follows:

1) An exclusive license to make and have made, to sell and have sold, to use and have used, and to import *Licensed Product(s)* in the *Field of Use* of vaccines [therapeutics, diagnostics] against xxxxx.

2) A nonexclusive license to make and have made, to sell and have sold, to use and have used, and to import *Licensed Product(s)* in the *Field of Use* of research reagents.

3) A nonexclusive license to use *Licensed Product(s)* in *Licensee's* internal drug discovery program.

In agreements of this type, different earned royalty rates could well apply for product sales in the different fields of use. As an example, perhaps 5 percent for the exclusive license, 7 percent for the commercial nonexclusive license, and no earned royalties could be required for the internal use license. In this instance, a higher earned royalty rate might well apply for research reagent sales due to the technology being so much closer to

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a finished product in this field rather than the actual rate being a function of exclusivity or nonexclusivity. NIH license agreements with multiple fields of use (including internal use) typically contain other financial terms (e.g., execution, annual, or benchmark royalties).

Regarding patent costs reimbursement, the NIH will not generally seek such reimbursement for research reagent agreements, including those for internal use by a licensee as well as for commercial sale and distribution of research reagents by a licensee.

A complete collection of the model agreements of the NIH intramural program can be found at the OTT Web site under "Forms and Model Agreements."[16]

Part 3: More on the NIH Patenting, Licensing, and Policy Positions Related to Research Tools

In its leadership role, the NIH has continuously been involved with educating and advising the research community with respect to the interpretation and implementation of the Bayh-Dole Act and of the research tools guidelines as summarized in previous parts of this article. These activities are done through the Office of Policy for Extramural Research Administration (OPERA) as well as at OTT, with OTT as the lead office for the development of technology transfer policy.

The NIH has over the years published its positions regarding various issues related to patenting and licensing of research tools. Links to some of these published documents are provided on the OTT Web site (www.ott.nih.gov/policy) as well as on the OPERA Web site (http://grants.nih.gov/grants/intell-property.htm). There are a variety of useful policy documents and information listed for recipients, ranging from invention reporting requirements to electing title to biological materials. Some of the research tool-related positions of note are summarized below.

Best Practices for Licensing of Genomic Inventions

Genomic inventions include a wide array of technologies and materials such as cDNAs, expressed sequence tags, haplotypes, antisense molecules, small interfering Ranks, full-length genes and their expression products, methods for the sequencing of genomes, quantification of nucleic acid molecules, detection of single nucleotide polymorphisms,

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and genetic modifications. Commercial products that can be developed on the basis of these technologies include nucleic acid-based diagnostics, gene therapy applications, and DNA- and RNA-based therapeutics. With the growing importance of such inventions in product development, the NIH saw a need to provide additional, specific guidance on the topic.

Building on the established research tools guidelines already in place, the NIH published a final version of "Best Practices for Licensing of Genomic Inventions" (which also included guidance on patenting of such inventions) on April 11, 2005, following comments solicited and received from the public as well as grantees and academic, not-for-profit, and private-sector participants in the biomedical research and development communities.[17]

Patenting of Genomic Inventions

The NIH recognized that patent protection for genomic inventions, like other technology areas, tend to include claims that are broad in scope. However, such an outcome could adversely impact further innovations based on the original findings, which is one of the fundamental issues that led to the development of the research tools policy. As described earlier for research tools, the best practices guidelines advocated pursuing patent protection only if significant further investment in R&D by the private sector would be needed. If, as for research tools, this additional investment were unlikely to be needed, then the best practices indicated that patent protection need not be sought.

However, the best practices recognized that in the early stages of development, the commercial embodiments of the invention may not be clear or the need for patent protection may not be clear. Therefore, pursuit of patent protection in the early stages with reassessment prior to further, future filings may be a reasonable strategy. This scenario would best be implemented if there is periodic review of filings at key filing deadlines so these items are reviewed as a matter of course and a separate review strategy does not need to be implemented.

Licensing of Genomic Inventions

Whenever possible, licensing of genomic inventions should be on a nonexclusive basis, which favors and facilitates the widespread availability and accessibility of the invention to the scientific community. However, it is possible that exclusive licensing of genomic inven-

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tions will be appropriate, especially for nontool applications. In these instances, as previously described for research tools in general, it is important to appropriately tailor the scope of the license to allow for expeditious development of as many aspects as possible. As with any commercial development license, regardless of whether it is for research tools or not, the NIH believes in the inclusion of development benchmarks and milestones to allow for license modification or termination should appropriate progress not be made.

NIH/DuPont Memoranda of Understanding Related to Cre-lox and Oncomouse

To ensure dissemination of critical research tools to the research community as broadly as possible the NIH entered into two MOUs with the E.I. DuPont de Nemours and Co.

The first MOU with DuPont, signed July 1, 1998, relates to DuPont's patent concerning cre-lox, a site-specific recombination system that is used as a genetic tool to control site-specific recombination events in genomic DNA.[18] The cre-lox system has usefulness in basic research conducted or funded by NIH as well as utility for commercial application. The MOU grants the NIH with the right to use the patented system for research purposes. It further states that the NIH retains the right to transfer materials covered by the patent rights and made by it in its research program, to non-for-profit institutions including to recipients under an MTA for research purpose. In transferring materials to for-profit organization, the MTA for such entities must include language referring to the rights of DuPont in the inventions, and directing such for-profit recipients to take a license from DuPont. The terms of this MOU agreement were also made available to PHS-funded nonprofit institutions for use in their own agreements with DuPont.

The second MOU, signed in July 1, 1999, relates to patented transgenic nonhuman mammals and cells derived from them containing a recombinant activated oncogene sequence that have usefulness in basic research conducted or funded by NIH as well as utility for commercial applications.[19] The technology developed and patented by Harvard under a sponsored research agreement from DuPont was licensed exclusively by Harvard to DuPont. Under the MOU the NIH is granted the rights to use the Harvard intellectual property to make materials in its internal research.

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Furthermore NIH secured the rights to further transfer such materials under MTA to other non-for-profit research organizations for research purposes. A similar transfer to for-profit entities is also allowed according to the MOU, but the MTA for such entities must include language referring to the rights of DuPont in the inventions and directing such for-profit recipients to take a license from DuPont. The terms of this MOU agreement are also available to PHS-funded nonprofit institutions for use in their own agreements with DuPont.

The relevant biomedical patent rights for the cre-lox (and some but not all of the rights for the transgenic oncomouse patents) have now expired. The NIH strongly prefers that a company not require researchers at nonprofit institutions to take licenses to its patents, but when a company does so, these two MOUs remain useful examples of how the NIH research tool policy can assist researchers that need to utilize new technology with rapidly changing commercial applications.

Stem Cells

In 2001, PHS entered into an MOU,[20] later amended and re-stated in 2008, with WiCell Research Institute Inc. (WiCell), a Wisconsin-based company and an affiliate of Wisconsin Alumni Research Foundation (WARF), with ownership rights in primate embryonic stem-cell line materials developed at the University of Wisconsin. By virtue of funding some nonhuman primate studies conducted at the University of Wisconsin, the U.S. government obtained a Bayh-Dole license under intellectual property owned by WARF. Through the MOU agreement WiCell agreed to make the WARF intellectual property available to PHS-funded research programs for conducting biomedical research, including when materials from third parties were involved. These third-party suppliers were granted a limited, revocable research license for noncommercial research or teaching purposes only when providing materials to PHS research programs.

Additionally, the MOU provided a means for stem-cell line materials to be provided by WiCell to PHS for noncommercial research. The later amendment to the MOU also permitted the use of the transferred materials by PHS in research conducted with companies under the terms of CRADAs as well as the ability to transfer derivatives to third parties.

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The terms of these MOU agreements were also made available to PHS-funded nonprofit institutions for their own agreements with WiCell.

The NIH thus also strongly prefers that nonprofit institutions do not require researchers at other nonprofit institutions take licenses to their patents but when they do, this MOU also remains a useful example of how the NIH research tool policy can assist researchers that need to utilize new technology with rapidly changing commercial applications.

The Research Tool Web (a Guide to Pricing Research Tools)

To assist research institutions without much experience in valuing and licensing research tools to industry, the NIH OTT provided data to Pfizer Japan to establish a free online searchable database called "Research Tool Web" (http://www.research-tool.info/english/index.html) that contains the financial terms for more than 15 years of research tool licensing transactions completed by the NIH for its research tools. Although the company names are not included for confidentiality reasons, the tool along with key financial terms is included in the database. Research tool license agreements for both research tool resellers and research tool internal users are included. The transaction database can be searched for a specific individual tool or entire tool categories, such as animal models or antibodies.

While it is certainly possible to develop pricing models for research tools like the licensing of other inventions—most institutions find comparables to be the most convenient for research tools since transaction prices tend to be moderate based often on make-vs.-buy transactions by the company that is looking to obtain quick use of the tool itself from the research institution and not access to any patent rights. Thus comparable valuations are easy to come up with at large research institutions with a significant track record in research tool licensing. But what if your institution is small or doesn't have much experience to date in research tool licensing?

Thus the establishment of the Research Tool Web database is an effort to better facilitate the licensing of research tools to companies by providing benchmark valuations of research tools that institutions are seeking to distribute. By collecting historical data from

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institutions such as NIH that have a high annual transactional volume for research tools it should be possible to price a new tool transaction in a range that is reasonable and customary. This database can be used by both research tool buyers as well as research tool sellers to help facilitate and accelerate transactions that will bring these tools into rapid use in commercial development programs.

Pfizer's future plans for this database include adding additional languages other than English and Japanese as well as additional transactional terms from both the NIH and other institutions.

Conclusion

This chapter is an attempt to provide the research community with practical advice and guidelines regarding best practices related to the dissemination of research tools. It is critical that researchers select strategies that will balance between the motivation to commercialize research for the benefit of public health on one hand and the need to disseminate research resources to the general public as broadly and quickly a possible so as to encourage further research and discoveries. The chapter provides examples of strategies used at the NIH in its intramural technology transfer activities as well as in its extramural funding activities.

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Notes

1. For more details on these principles, see *Federal Register,* Vol. 64, No. 246, December 23, 1999, page 72091 (accessible at http://www.ott.nih.gov/pdfs/64FR72090.pdf).
2. The full text of these documents can be found at http://frwebgate3.access.gpo.gov/cgi-bin/TEXTgate.cgi?WAISdocID=00664624263+1+1+0&WAISaction=retrieve and http://grants.nih.gov/grants/guide/notice-files/not94-213.html, respectively.
3. The UBMTA model agreement and implementing letter can be found on the AUTM Web site (http://www.autm.net).
4. See http://www.ott.nih.gov/pdfs/slaform.pdf .

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5. The NIH is also a signatory to the UBMTA. See http://www.ott.nih.gov/forms_model_agreements/forms_model_agreements.aspx.
6. See http://www.ott.nih.gov/docs/MTA-TO_NIH_Model_Agreement.doc.
7. See *Federal Register,* Vol. 64, No. 246, December 23, 1999, page 72094 (accessible at http://www.ott.nih.gov/pdfs/64FR72090.pdf).
8. See *Federal Register,* Vol. 64, No. 246, December 23, 1999, page 72095 (accessible at http://www.ott.nih.gov/pdfs/64FR72090.pdf).
9. Ibid.
10. See http://www.ott.nih.gov/docs/Model%20NIH%20Materials%20Cooperative%20Research%20and%20Development%20Agreement.doc.
11. For additional information regarding the NIH patent policy, see http://www.ott.nih.gov/policy/phspat_policy.aspx.
12. For additional information about the NIH licensing policy, see http://www.ott.nih.gov/policy/phslic_policy.aspx.
13. This example can be found in the PHS exclusive patent license agreement (http://www.ott.nih.gov/pdfs/PHS-Patent-License-Exclusive-model-102005.pdf) as well as other model agreements.
14. This example can be found in the PHS biological materials license agreement (http://www.ott.nih.gov/pdfs/PHS-Biological-Materials-Agreement-License-model-102005.pdf) as well as other model agreements.
15. This example can be found in the PHS biological materials internal use license agreement (http://www.ott.nih.gov/pdfs/PHS-Biological-Materials-Agreement-License-Internal-Use-model-102005.pdf) as well as other model agreements.
16. See http://www.ott.nih.gov/forms_model_agreements/forms_model_agreements.aspx.
17. For further information see http://www.ott.nih.gov/policy/lic_gen.aspx.
18. http://www.ott.nih.gov/policy/cre-lox.pdf.
19. http://www.ott.nih.gov/policy/OncoMouse.pdf.
20. http://ott.od.nih.gov/pdfs/WiCellMOUhuman.pdf and http://stemcells.nih.gov/staticresources/research/registry/MTAs/Wicell_MOU.pdf.

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