Emerging issues in research tool licensing

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Abstract This paper presents a brief examination of the current trends and issues in the licensing of patented research tools, as well as perspectives on 'reach through' licensing of research tools.

Keywords: research tool, licensing, reach-through, National Institutes of Health, royalty

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Introduction

The National Institutes of Health (NIH) defines research tools as:[1]

> All tools that scientists use in the laboratory, including cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry, and DNA libraries, closes and cloning tools (such as PCR [polymerase chain reaction]), methods, laboratory equipment and machines.

The primary users, or potential licensees, of research tools tend to be research institutions, molecular biology laboratories, biotechnology companies and pharmaceutical companies. As the licensing of patented research tools continues to evolve, the NIH is expected to play a significant role in shaping the structure of research tool licensing. This is predicated, in large part, on the NIH's far-reaching funding of research programmes in both the non-profit and private sectors.

The NIH has identified three primary stakeholders with an interest in research tool licensing practices. Each group of stakeholders tends to have a different view on the licensing of research tools, from both a license-in and license-out perspective. These stakeholders were identified as follows:[2]

- bench scientists;
- university technology transfer professionals; and
- private firms.

Bench scientists are the 'front-line' scientific community that typically utilises a variety of research tools in developing new drug discoveries. Bench scientists have expressed increasing frustration regarding dealings with complicated legal agreements in the licensing of patented research tools. This disillusionment, in part, is based on the lack of formal business and/or legal training required to negotiate and interpret such agreements. Some also take the position that such tools should be freely available. Less frequently in the position of licensors, some are similarly willing to freely distribute research, while others seek to profit from their patented inventions.

University technology transfer professionals as a whole tend to express concern over licensor indemnification issues and the desire for licensors to participate in profits from new drug discoveries. Indemnification of licensors against liability stemming from university research is often problematic and prohibited by governing state law. These professionals are apparently concerned with the administrative burden in connection with

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the licensing of research tools. Universities, however, generally maintain they are able to successfully conclude licences to patented research tools, in particular with other universities.

Private firms, such as biotechnology or pharmaceutical companies, typically take the position that complicated research tool negotiations impede the advancement of new drug discoveries. Furthermore, private firms are of the opinion that universities are often inconsistent in their licensing practices by charging private firms licensing fees for such tools that they otherwise freely distribute to academic researchers. Conversely, private firms frequently transfer such tools to universities for nominal compensation, influenced largely by their typically strong ties to academic institutions.

The NIH's position

The NIH has issued certain guiding principles for obtaining and disseminating biomedical research resources for those receiving funding.[3] First, the NIH is interested in preserving academic research and publication freedom, safeguarding appropriate authorship, and ensuring timely disclosure of scientists' research findings.

Second, the NIH seeks to ensure appropriate implementation of the Bayh–Dole Act, which allows universities to increase their income through the transfer of technology to private industry for commercialisation. Third, the NIH wishes to minimise impediments to academic research through royalty-free research tool licensing. This includes attempting to streamline the transfer of technology via simplified, informal agreements. Finally, the NIH encourages the dissemination of research resources developed with NIH funding.

Taken as a whole, the NIH's position is to encourage the dissemination of research resources freely among academic institutions that receive NIH funding. Conversely, the NIH is of the opinion that universities should attempt to extract as much value as possible from licensing research resources to private firms.

Current research tool licensing trends

Proponents of the licensing of patented research tools point to a number of benefits conferred to the licensee. From a purely monetary perspective, licensing provides the patent owner compensation that may be used for further research and provides a return on investment. Along the same lines, this encourages the development of new research tools and facilitates potential new drug discoveries; thereby benefiting society as a whole. In addition, benefits may be gained from the safety testing facilitated by research resources.

Those less favourably disposed to the licensing of patented research tools for profit indicate that it impedes or deters research and development activity by creating an unnecessary 'thicket' of intellectual property rights to navigate in connection with new drug discovery efforts. In addition, concern has been voiced that such licensing can lead to an expensive 'stacking' of royalties from the use of a number of research tools in new drug research. Furthermore, licensees often do not want to disclose confidential information regarding their R&D efforts that is often required in connection with negotiating a licence.

Given the above considerations, it is useful to examine current research tool licensing practices with respect to the previously identified parties-in-interest. From an overall perspective, it appears that research tools are being actively patented and licensed for consideration by the various stakeholders, and are not, in fact, being widely distributed for use on a royalty-free basis. Therefore, an important consideration is the appropriate structure of royalty-bearing licences.

Prevailing industry licence practices tend to emphasise non-exclusive licences, with some combination of up-front and milestone payments. With respect to universities, the

licences often include a component of compensation in the form of sponsored research, in addition to any other agreed-upon consideration.

One aspect of licensing that has become the subject of increasing debate is the inclusion of 'reach-through' royalty provisions as part of the patented research tool licensing structure. A reach-through royalty is a series of running royalty payments based on an agreed-upon percentage of end-product drug sales. In other words, some licensors are now requesting a participation in the profits of end-user drug sales that may have, in part, been developed with the assistance of a licensed research tool.

While reach-through licence provisions are still largely atypical, the concept has been subject to increasing controversy regarding its necessity and economics. Proponents of reach-through licences argue the logic of such a provision on various fronts. The prevailing and arguably strongest rationale is that if the licensed research tools lead directly to a new drug discovery, it is reasonable for the patent owner to participate in the end-user drug profits.

A second related argument is that with continuing substantial increases in drug pricing, new drugs often yield significant profits. The actual manufacturing cost of the drugs is often minimal, with the more significant costs having been incurred in the research and development and US Food and Drug Administration (FDA) approval phases. Therefore, the incremental profits to drug companies are potentially quite substantial after the R&D costs to develop the drug have been fully recouped. In turn, the patent owner's participation in the profits from new drug sales provides an incentive for the development of new research tools.

Furthermore, proponents reason that research tools often provide affordable solutions to problems that occur in drug development and can often expedite the approval and commercialisation of the drug. Therefore, there is a societal benefit component to the argument.

Resistance to the concept of reach-through licensing is based on a number of considerations. The research and development of new drugs is an expensive and time-intensive process, and often involves the usage or application of a wide variety of research tools and resources. As such, there is an industry-wide concern that if a firm were to license a number of tools bearing reach-through provisions, it would serve only to increase the cost of the development and manufacture of new drugs. In this way, it could lead to an expensive 'stacking' of royalties for the drug manufacturer that could significantly reduce its corresponding profit margins and return on its R&D investment.

There is also a general agreement that the vast majority of research tools, while useful, do not typically directly lead to a new drug discovery. As such, drug companies generally do not believe a reach-through licence would be appropriate if the tool is not fundamental to the new drug development.

The current prevailing industry practice is avoidance of reach-through licences. However, evidence shows that licensees are at least willing to consider such a structure if the research tools lead directly to a new drug discovery. In this situation, a typical reach-through licence would incorporate perhaps an up-front payment with a participation in end-user drug profits in the form of a running royalty. Reach-through royalty rates are typically in the range of 0.5–3 per cent of the sales of the subject drug.[4]

Infringement of patented research tools

Another perspective on research tool licensing trends can be viewed through the 'eyes' of the US courts, as discussed in recent case decisions relating to the infringement of patent research tools. While few cases involving research tools have reached the US courts and resulted in judicial determination, they do offer some guidance as to the US court's perspective on

appropriate licensing structures. Two recent cases that involve the infringement of patented research tools include:[5]

- *Ajinomoto Co. v Archer Daniels Midland Co.* (228 F.3d 1338, Fed Cir. 2000); and
- *Sibia Neurosciences, Inc. v Cadus Pharmaceutical Corp.* (225 F.3d 1349, Fed Cir. 2000).

In *Ajinomoto Co. v Archer Daniels Midland Co.* the patented research tool involved a genetically modified bacterial strain that enhanced the production of amino acids, specifically threonine. In this case, the court found in favour of the plaintiff and did, in fact, award a reasonable royalty based on a reach-through licence. In this case, the US court awarded a fixed royalty of US$1.23 per kilogram of threonine produced by the infringer. The royalty rate was based on the production cost savings afforded by the patented technology. Although the case was appealed, the reach-through royalty was not challenged.

Sibia Neurosciences, Inc. v Cadus Pharmaceutical Corp. involved the infringement of a screening method for identifying compounds that interact with cell surface proteins. In this matter, the US court awarded US$18m in damages made up of two components: (a) a US$100,000 flat fee per molecular target validated by the patented screening method and (b) a reach-through royalty based on net sales of future drug products discovered for a ten year period by the defendant using the patent screening method. However, on appeal Sibia's patent was found to be invalid and, therefore, the US Appellate Court did not address the lower US court's finding regarding the damages award.

These recent cases seem to indicate that the US courts are at least willing to consider the prospect of a reach-through licence. It also appears that lost profits damages are an unlikely remedy, as the plaintiffs in such cases are typically research companies, rather than developers and manufacturers of drugs. Furthermore, as additional infringement matters are adjudicated it is likely the US courts will look to industry licensing norms in deciding damages issues and the determination of the appropriate outcome of the hypothetical negotiation in such cases.

Evolution of research tool licensing

As discussed above, various factions have conflicting positions regarding the licensing of patented research tools. Should research tools be licensed at all or made freely available? When research tools are licensed, what is an appropriate royalty payment structure? We would like to suggest some options the reader may wish to consider in the licensing of patented research tools.

It is important to keep in mind that every licensing situation has unique aspects. Both the licensor and the licensee must consider their requirements and expectations in connection with such negotiations in order to execute a transaction that is mutually beneficial from an economic perspective.

The first issue a licensee must address is what benefits will be conferred by licensing of the research tool. The licensor and licensee must also consider whether the licence is to be exclusive or non-exclusive. From that basis, in addition to other important considerations, both parties can proceed with reasonable expectations as to its requirements and limitations. A well-structured licence can take into account potential benefits conferred by the licensed technology by including various provisions that serve to address the concerns of the industry at large.

In our experience, industry convention leans towards inclusion of an up-front payment in connection with research tool licences. However, we suggest the consideration of other multifaceted provisions. Such provisions can be mutually beneficial to the respective parties to the agreement. For example, a provision could provide additional compensation to the licensor should the research tool confer further advantage to the licensee. In addition, the licence can include anti-stacking provisions, as well as caps or limits as to the amount and duration of royalties paid by the licensee.

Hypothetical case examples

Although we recognise that each licensing situation is unique, we present two hypothetical case studies, based in part on consulting work performed by the authors, for readers to consider.

Hypothetical case 1

- University owns the rights to patented research tool involving process for isolating protein and peptides.
- Biotechnology company desires to license the research tool in connection with the development of a new treatment for diabetes.
- University contemplates non-exclusive licence with biotechnology company to enable to license it to other parties.

Proposed licence structure:

- Up-front payment in form of cash or sponsored research.
- Milestone payment upon FDA approval of new drug.
- Reach-through royalty in the range of 1–3 per cent of new drug sales – triggered if research tool is directly involved in new drug discovery; royalty range on a sliding scale depending on aggregate of up-front and milestone payments.
- Anti-stacking provision whereby royalty rate is reduced by 50 per cent if the licensee must pay total royalties in excess of 3 per cent of new drug sales.
- Running royalty payments limited to shorter of (a) the first five years after commercialisation of drug or (b) the expiration of the research tool patent.
- Running royalty payments capped at US$1.5m per year, with any royalties in excess of the yearly cap credited in full towards future years.

The above case study includes multiple mutually beneficial provisions that are triggered by various outcomes. The multifaceted provisions also serve to protect and mitigate the risk to the licensor and licensee. It is, therefore, suggested that parties involved in the negotiation of patented research tools consider such conventions in consummating related licence agreements.

Hypothetical case 2

- It is assumed that the research tool patent expires on 31st December, 2013.
- It is expected that the research tool will shorten by 24 months the time to filing a new drug application with the FDA.
- A major drug discovery is anticipated.
- The costs incurred to develop the research tool totalled US$5m.
- The patent on the new drug extends to 31st December, 2017, and it is expected that minimal profits will be realised thereafter by the drug company.

Figure 1 illustrates the above schedule. Clearly, the primary value of the research tool to the drug development company (licensee) is a reduction in time from the pre-clinical testing phase to commercialisation of the new drug. This can be measured by comparing the present value of the profits from use of the research tool to the present value of the profits without use the research tool. Figure 2 illustrates the described present value calculations.

As illustrated in Figure 2, it was assumed that new drug revenues would be US$68m in the first year, 2008, with the research tool and a nominal sales growth rate of approximately 5 per cent per annum. It was further assumed that without use of the research tool, the revenue stream would not begin until 2010, or two years later than the first scenario. The licensor profit margin is assumed to be 75 per cent under both scenarios. The profit stream under both scenarios was discounted to present value (as of 31st December, 2000) using a 30 per cent discount rate to account for the risk associated with new drug development. As illustrated in Figure 2, the present value of the incremental benefit from use of the research tool is approximately US$11.2m.

Once the value of the research tool has been measured, negotiations to apportion the value between the licensee and licensor

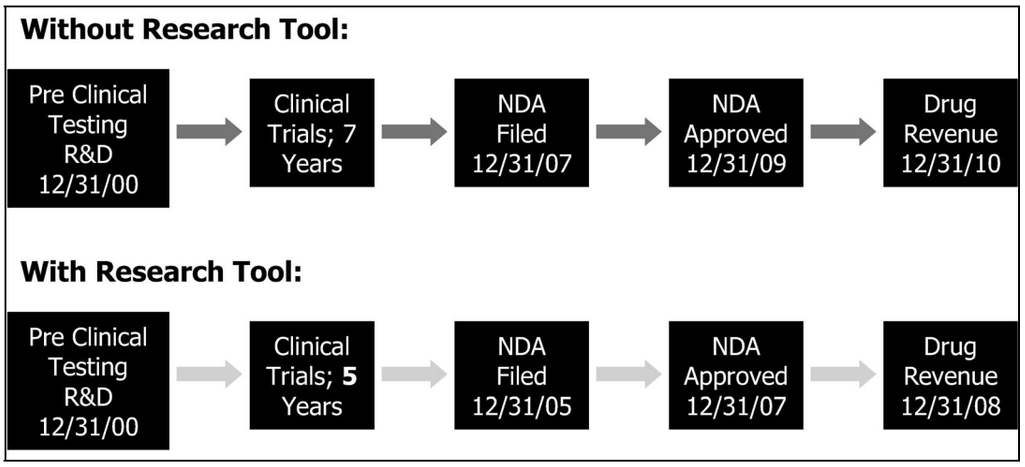


Fig. 1 Value of research tool. NDA Timeline

Without Research Tool

In $ USD	12/31/08	12/31/09	12/31/10	12/31/11	12/31/12	12/31/13	12/31/14	12/31/15	12/31/16	12/31/17
Sales	0	0	75,000,000	78,750,000	82,687,500	86,821,875	91,162,969	95,721,117	100,507,173	105,532,532
Profit Margin (%)	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%
Profit	0	0	56,583,300	59,412,465	62,383,088	65,502,243	68,777,355	72,216,223	75,827,034	79,618,385
PV @ 30% Discount (12/31/00)	0	0	4,104,448	3,315,131	2,677,606	2,162,682	1,746,781	1,410,862	1,139,542	920,400

Total Present Value **$17,477,451**

With Research Tool

In $ USD	12/31/08	12/31/09	12/31/10	12/31/11	12/31/12	12/31/13	12/31/14	12/31/15	12/31/16	12/31/17
Sales	68,000,000	71,400,000	74,970,000	78,718,500	82,654,425	86,787,146	91,126,504	95,682,829	100,466,970	105,490,319
Profit Margin (%)	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%
Profit	51,000,000	53,550,000	56,227,500	59,038,875	61,990,819	65,090,360	68,344,878	71,762,122	75,350,228	79,117,739
PV @ 30% Discount (12/31/00)	6,252,063	5,049,743	4,078,639	3,294,285	2,660,769	2,149,083	1,735,797	1,401,990	1,132,377	914,612

Total Present Value **$28,669,358**

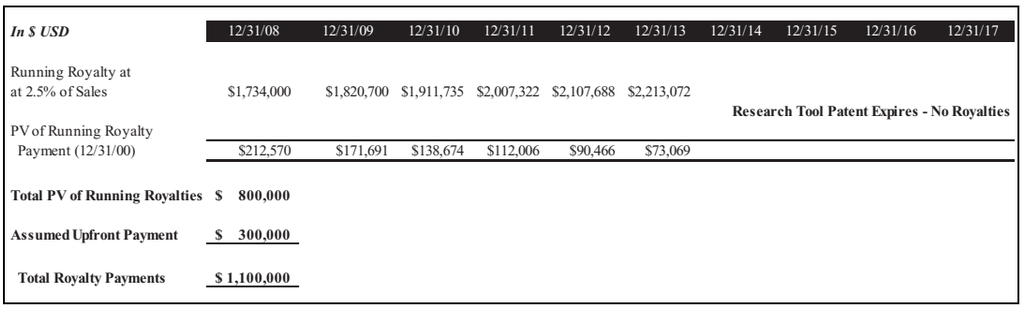
Present Value Difference (Value of Research Tool) **$11,191,907**

Research Owner Wants 10% of Value **$1,100,000**

Fig. 2 Proposed licence structure

can proceed. In this example, it is assumed that the parties agreed that licensor was to receive 10 per cent of the US$11.2m in value accrued to the licensee from use of the research tool, or approximately US$1.1m.

Based on this apportionment, Figure 3 illustrates a potential reach-through licensing scenario, which is equivalent, on a present value basis, to US$1.1m. It was assumed that the licensee required an up-front payment of US$300,000. It was further assumed that the remaining US$800,000 in expected royalties would be received via a reach-through running royalty. A running royalty rate equal to 2.5 per cent of new drug revenue, combined with an up-front payment of US$300,000, would provide the licensor with the required US$1.1m in royalties, on a present value basis. If the licensee required a lower up-front payment, then the reach-through royalty rate would be lower. The research tool owner will attempt to mitigate its risk by requiring the largest possible up-front payment.



In $ USD	12/31/08	12/31/09	12/31/10	12/31/11	12/31/12	12/31/13	12/31/14	12/31/15	12/31/16	12/31/17
Running Royalty at at 2.5% of Sales	$1,734,000	$1,820,700	$1,911,735	$2,007,322	$2,107,688	$2,213,072				
								Research Tool Patent Expires - No Royalties		
PV of Running Royalty Payment (12/31/00)	$212,570	$171,691	$138,674	$112,006	$90,466	$73,069				
Total PV of Running Royalties	**$ 800,000**									
Assumed Upfront Payment	**$ 300,000**									
Total Royalty Payments	**$ 1,100,000**									

Fig. 3 Potential reach-through licensing scenario

Conclusion

The licensing of patented research tools evokes differing positions depending on the stakeholder concerned. It is also apparent that while few infringement matters have been adjudicated, it is expected that the US courts will look to industry licensing practices in making judicial determinations as to damage awards. Furthermore, the appropriateness of reach-through royalty provisions in connection with research tool licences is situation-dependent, and the authors do not advocate a specific position. It is our hope, however, that we have presented relevant emerging issues for the reader or practitioner to consider, as the licensing of research tools continues to evolve.

Disclaimer

This paper reflects the opinions of the authors and not those of Intecap Inc. The concepts and theories covered are not intended to be all-inclusive on the topic of research tool licensing. They are for illustrative purposes and may not necessarily represent approaches the authors or InteCap would recommend in any particular matter. The reader should keep in mind that each situation should be evaluated in light of its own facts and circumstances.

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