

KEI Comment 2: Request for Information Regarding the Draft Interagency Guidance Framework for Considering the Exercise of March-In Rights (NIST–2023–0008)

Topic: The draft guidance must address the common cases in which patent landscapes for a product with some Bayh-Dole rights are mixed.

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Introduction

The draft guidance for march-in rights provides a useful discussion of the need to establish whether patented inventions meet the requirements of a subject invention, and calls attention to the fact that patent holders often do not disclose federal funding in inventions, and that in some cases fact finding is necessary to determine if federal rights exist. The guidance also states that “a complicated intellectual property landscape could reduce the likelihood of successful licensing.”

The guidance is technically correct in noting that a march-in request can be unsuccessful if the intellectual property landscape is complex, but it fails to explore or even consider the tools the federal government can use to overcome this barrier.

The problem of mixed rights in relevant patents is important and deserves a more thoughtful discussion in the guidance. This should encompass a specific discussion of the obvious tools the federal government has to address such cases.

It is unnecessarily challenging to know which products rely on any subject inventions, and the guidance should recommend actions to make the systems of disclosures work better, not only for funding agencies but also for the public.

The fact that many biomedical products with subject patents also have complex patent landscapes should not be presented as a deal breaker for the use of the federal march-in rights.

Failures to disclose

Funding agencies are relatively cavalier over the reporting requirements of government rights in patents. Obvious failures to disclose, even when third parties bring the issue to funding agencies, rarely result in remedial actions, and almost never result in any meaningful sanctions.

Non-standard disclosures on patent applications

In many cases, a patent application will include, in the text of the patent, a reference to “Government Interest” in a subject patent. But there is no guarantee that the disclosure will use those terms. The data on government rights collected by the Chief Economist illustrates the surprisingly large number of different ways the disclosures have been reported in the text of the patent, making it challenging to locate the disclosures through keyword searches. And sometimes the disclosures are only found in an assignment to a federal agency or in a certificate of correction to a patent.

Certificates of Correction

After a patent is published by the federal government, patent holders can request a correction. The U.S. patent office issues a significant number of Certificates of Correction. In 2017, James Love published “Errors in Patent Grants: More Common in Medical Patents,”¹ an essay that discussed the frequency of correcting errors in published patents. These corrections may cover anything in the patent, such as the names or addresses of inventors, assignees, or the claims, and they can also include belated disclosures of federal rights in the patents.

¹ Errors in Patent Grants: More Common in Medical Patents, *Bill of Health*, October 21, 2017. <https://blog.petrieflom.law.harvard.edu/2017/10/21/errors-in-patent-grants-more-common-in-medical-patents/>.

The sheer number of such corrections was surprising, particularly for medical patents than for other technologies, and higher also for non-profit institutions than for for-profit companies. In examining patents published from 2000 to 2015 (queried on October 20, 2017), 11.1 percent of all patents had at least one Certificate of Correction. For every medical category searched, the proportion of patents with corrections ranged from 21 to 27 percent. Below are the proportions of patents with Certificates of Correction from seven non-profit research organizations.

Table 1: Frequency of Certificates of Corrections for patents granted from 2000 to 2015

Search term	Patents granted	Patents with COFC	Percentage with COFC
City of Hope	374	127	34%
Cold Spring Harbor	156	48	31%
Kettering	633	187	30%
Yale University	801	211	26%
Wisconsin Alumni Research Foundation	2867	734	26%
Massachusetts institute of technology	5412	1317	24%
University of Pennsylvania	1618	352	22%

None of the Certificates of Correction issued and published by the patent office are text searchable, necessitating manual inspection of the image file of the patent in order to determine the nature of the correction.

The timing of these corrections vary significantly. They can come a few months after the patent is published, or several years later. These are some examples.

- In the case of Gleevec, a controversially high priced cancer drug,² the disclosure of federal funding was 18 years after the patent grant, rendering it too late to be considered for a march-in case.³
- In 2016, Carl June issued six corrections to disclose federal funding in five CAR-T patents, with the disclosures ranging from 9 to 17 months after the patents were granted.⁴

² Experts in Chronic Myeloid Leukemia, “The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts, Blood (2013) 121 (22): 4439–4442.

³ James Love, “Novartis, Dana Farber, Oregon Health & Science University Wait 18 Years to Disclose NIH Funding in Key Gleevec Patent”, Bill of Health, October 11, 2019.

⁴ Patents 8,916,381; 8,975,071; 9,101,584; 9,102,760; 9,102,761.

- James Wilson and his co-inventors took 101 months to disclose federal funding in patent 7,790,449 and 137 months to disclose federal funding in patent 7,282,199, both involving the use of Adeno-associated Virus (AAV) Serotype 8 Sequences Vectors in gene therapy.
- Warner Lambert took 81 months to disclose federal rights in patent number 5,563,175 for the drug Lyrica.
- The University of Western Australia waited from 39 to 97 months to disclose federal rights in four patents involving the drug Exondys 51.
- The University of Pittsburgh waited 56 to 135 months to disclose federal funding in three patents on the drug Vizamyl.

Non-disclosures

There are many patents where disclosures of federal funding have never been made, despite ample evidence that such disclosures are warranted. These include patents on new technologies such as CRISPR and blockbuster products, like Sovaldi⁵ or Keytruda⁶, where KEI has been waiting years for federal agencies to respond to petitions asking for investigations into failures to disclose. KEI has asked BARDA, DARPA and the NIH to investigate failures to disclose federal funding. Although the NIH appears to have done some follow-up on a few cases, it has ignored others.

In one case, the University of Pennsylvania stated that patents relating to the dosing of a drug did not qualify as a subject invention, because the federal funding originated from an infrastructure grant, even though the title of the grant itself explicitly named a single product that was the subject of the patent.⁷

Non-standard rights

Not all grants or research contracts have the standard federal rights clauses in contracts.

In some cases, the federal government can expand the federal rights, through the use of the exceptions circumstances clause in Section 202(a).⁸ Recently, some agencies have sought to use

⁵ James Love, KEI request that HHS take ownership of US Patent 7,964,580 on sofosbuvir, now held by Gilead, for non-disclosure of NIH grants, March 14, 2018. <https://www.keionline.org/27205>

⁶ Claire Cassidy, KEI Requests the NIH to Investigate Failure to Disclose Federal Funding in Opdivo and Keytruda Patents, December 20, 2019. <https://www.keionline.org/32076>

⁷ KEI Staff, Six University of Pennsylvania and Daniel J. Rader patents on Juxtapid (lomitapide) failed to discuss multiple NIH grants, March 19, 2018. <https://www.keionline.org/27300>

⁸ 2020:2 KEI Briefing Note: The Federal Government's Authority to Restrict or Eliminate Contractors' Rights to Federally-Funded Inventions in "Exceptional Circumstances".

“Other Transactions Authority” (OTA) exemptions from the Bayh-Dole Act to write non-standard intellectual property provisions.

In many of the recent COVID-19 contracts, involving billions of taxpayer dollars, the U.S. government bypassed the Bayh-Dole Act through OTA funding agreements. Many of these agreements include a modified version of the march-in right.⁹

The OTA agreements are particularly vexing because of the combination of non-standard clauses and the secrecy of the clauses in the redacted contracts, as well as redactions of specific patent numbers.

Complex patent landscapes

KEI is currently developing a database for small molecule drugs that have at least one patent in the FDA's Orange Book that have federal rights disclosed.

The data includes patents that have acknowledged federal rights, excluding inventions that should but do not disclose such rights.

To determine if a patent has federal rights, KEI first examines whether there is a disclosure in the original published patent, either as an assignment to a federal agency or a disclosure of federal funding in the text of the patent. Additionally, each patent is cross-checked to see if there is a relevant Certificate of Correction on the federal funding issue, or a subsequent assignment to a federal agency.

It's worth noting that the patent landscape is a moving target, with companies adding and removing patents from the Orange Book over time, making corrections to the disclosures or recording assignments of interests to federal agencies.

This research is ongoing. Thus far KEI has examined 56 products approved as NDAs (New Drug Applications).

The NDA drugs are typically the first place people look for march-in rights because they are the only category of products where the patent landscape is reasonably transparent from initial registration. The data on the 56 products is attached as a spreadsheet file, and KEI will update and expand the data later, and publish the data for public viewing here:

<https://DrugDatabase.info/govt-orangebook-patents>

The small molecule cases are probably the ones mostly likely to have clear rights, as compared to biologic drugs or cell or gene therapies, where patent thickets can be more intense.

⁹ 2020:3 KEI Briefing Note: Other Transaction Agreements: Government Contracts that May Eliminate Protections for the Public on Pricing, Access and Competition, Including in Connection with COVID-19.

One key finding to present today is that roughly 4 of 5 NDA products with at least one patent with federal rights has a complex patent landscape.¹⁰ This means that if the federal government were to disregard every product without clear rights in all Orange Book patents, it would greatly reduce the usefulness of the march-in right.

That said, not all patents in the Orange Book are equal. Patents may involve different uses of the same product, allowing a generic to be sold for some indications but not others, or different delivery mechanisms. It’s also widely recognized that some listed patents have questionable validity or relevance.

In the case of the Xtandi march-in case, there are four Orange Book patents, but one, added much later, only involves a minor formulation for a tablet. Xtandi was approved by the FDA in 2012. The formulation patent was not granted by the FDA until December 12, 2023—more than 11 years after Xtandi was on the market. Moreover, that patent only applies to one possible presentation of the drug.

In the Norvir march-in case, a total of 19 patents ended up being published in the FDA Orange Book. The first patent was granted in 1996, and the last one in 2014, 18 years later. At the time of the 2004 Norvir march-in case, there were just five 5 patents listed by Abbott in the Orange Book for its approved ritonavir capsule product. Four of the patents disclosed rights, but one—U.S. Patent No. 6,232,333—did not. Like the Xtandi case, it was a formulation patent. Daniel Ravicher provided evidence on behalf of the march-in petitioner, Essential Inventions, that “the existence of the ‘333 patent in no way detracts from the importance or utility of the Ritonavir Petition.” (See ANNEX below).

Biologic drugs, vaccine and cell and gene therapies

The patent landscapes for biologic drugs, blood products, vaccines, cell and gene therapies and diagnostics tests are generally less transparent than the drugs in the FDA Orange Book.

Only a handful of biologic drugs have disclosed patents in the FDA Purple Book. The number of patents listed are often large. For biologic drugs with large numbers of patents, the odds of having a clear patent landscape for patents with Bayh-Dole rights is very small.

Table 2: Purple Book Patents (December 2023)

Proprietary Name	Proper Name	BLA Number	Applicant Name	Patents	Initial registration	Max expiration	Span in years
Rituxan	rituximab	103705	Genentech	15	Nov 26, 1997	Jul 31, 2035	37.7
Herceptin	trastuzumab	103792	Genentech	4	Sep 25, 1998	Aug 7, 2031	32.9

¹⁰ The FDA can grant a patent term extension (PTE) for some patents. The PTE patents are generally considered more important than many of the subsequent patents that are filed. In our group of 56 products with at least one patent with disclosed federal rights, 46 products had one or more PTE-associated patents. Those 46 products had 74 PTE patents in all. Of the 74 PTE patents, 50 (two-thirds) reported federal rights.

Neulasta	pegfilgrastim	125031	Amgen	1	Jan 31, 2002	Jun 21, 2030	28.4
Humira	adalimumab	125057	AbbVie	66	Dec 31, 2002	Nov 14, 2034	31.9
Avastin	bevacizumab	125085	Genentech	22	Feb 26, 2004	Jul 31, 2035	31.4
Tysabri	natalizumab	125104	Biogen	32	Nov 23, 2004	Jun 1, 2036	31.5
Lucentis	ranibizumab	125156	Genentech	11	Jun 30, 2006	Nov 5, 2035	29.3
Stelara	ustekinumab	125261	Janssen Biotech	12	Sep 25, 2009	Sep 24, 2039	30.0
Actemra	tocilizumab	125276	Genentech	35	Jan 8, 2010	Jul 31, 2035	25.6
Prolia and Xgeva	denosumab	125320	Amgen	23	Jun 1, 2010	Jul 21, 2037	27.1
Eylea	aflibercept	125387	Regeneron Pharmaceuticals	52	Nov 18, 2011	Aug 18, 2040	28.8

For the new cell and gene therapies, there is a significant role for Bayh-Dole subject inventions, in part because the federal government plays an outsized role in subsidizing the R&D for newer technologies. That said, the issue of complex patent landscapes is important here too.

A notable example of a complex patent landscape is the gene therapy Zolgensma. When first brought to the market, AveXis (a company acquired by Novartis before Zolgensma approval) licensed four patent portfolios, one from Nationwide Children’s Hospital, one from a spin-off company licensing University of North Carolina patents, one from another spin-off company licensing University of Pennsylvania patents, and a fourth from a French charity. The three US portfolios included patents with Bayh-Dole rights, but the patents owned by the French charity did not. Subsequent to Zolgensma market entry, new patent suits emerged, including one involving two subsidiaries of Sanofi suing Novartis.¹¹

March-in rights can be used with other federal rights in patents

March-in rights can be leveraged alongside other federal rights embedded in patents. Even when all the patents on a product are deemed essential for making and selling a product, the government has options, including additional rights for non-voluntary uses of patents, beyond the march-in right.

The most important and powerful option the federal government has involves two government use rights.

The Bayh-Dole Act provides that each patent with a march-in right also includes a paid-up worldwide royalty-free license to the federal government. This license is specifically for use “by or for” the federal government. Additionally, the federal government holds a more general right for use “by or for” the federal government that does not depend upon who funded an invention.

¹¹ Genzyme Corp. v. Novartis Gene Therapies, Inc., Civil Action 21-1736-RGA (D. Del. Feb. 13, 2023) <https://casetext.com/case/genzyme-corp-v-novartis-gene-therapies-inc>

Each of these rights, the march-in or the government use rights, has a purpose and role, and it is noteworthy that the guidance erred in not addressing how they can be used together, particularly in cases involving complex patent landscapes.

The federal government's Section 202 and 209 royalty-free license

The Bayh-Dole Act gives the federal government a worldwide royalty-free right to use the inventions it funds, as outlined in 35 U.S.C. § 202 (Disposition of rights) and § 209 (Licensing federally owned inventions). For cases where the contractors own the patent, the provision is Section 202(c)(4), and when the federal government owns the patent, the provision is Section 209(d)(1).

The paid-up license “by or on behalf” of the federal government has been used by funding agencies in a variety of settings, including to enable research activities on federally funded inventions, and in procurement contracts. Whether or not these licenses have been used in connection with the purchase of drugs, vaccines or other medical products is unclear, but they have certainly not been used for any of the several cases where third parties, including consumer, health or patient groups, have asked.

The paid-up §202 and §209 licenses have narrower scopes compared to the march-in right in terms of the use, requiring the use to be “by or for” the government. The §202 and §209 licenses have other advantages. They are not subject to automatic stays during appeals, and they are not limited to specific grounds, as is the case with the Section 203 march-in license.

Pros and cons of zero royalty licenses

Often the availability of a zero royalty license is a positive. Not only does this reduce the cost to the government, but it can also greatly reduce the expense and effort to administer a license. There is no need to monitor the quantities or revenues of products sold, and activities like research benefit from the relatively simplicity of such authorizations. That said, in cases where the payment of royalties to right holders is preferable, the Section 202/209 licenses can be a somewhat awkward mechanism. While funding agencies have been comfortable insisting on royalty-free research licenses, they have been less inclined to deny inventors royalties from patents on commercial products.

The federal government's right to use any patented invention using 28 U.S.C. 1498

In 1918, the Congress enacted legislation to permit the federal government to use or authorize third parties to use any U.S. granted patent, subject to payment of compensation to patent holders. The current version of the legislation is 28 U.S.C. 1498(a).

A detailed legislative history of the statute by former Judge Arthur J. Gajarsa is provided in the March 14, 2012 U.S. Court of Appeals for the Federal Circuit decision in *Zoltek Corp. v. U.S.* One of

the primary motivations for the new law was to eliminate the ability of patent holders to obtain injunctions against federal contractors for non-consensual use of patented inventions.

The 1498 statute covers the use of any “invention described in and covered by a patent of the United States by a contractor, a subcontractor, or any person, firm, or corporation for the Government and with the authorization or consent of the Government,” and limits the remedy of the patent holder to an “action against the United States in the United States Court of Federal Claims for the recovery of his reasonable and entire compensation.”

The federal government’s use of this authority often involves an explicit authorization and consent clause in a contract. This can be done by merely including this phrase in a contract: “This contract includes by reference FAR 52.227-1.”

The reference is to the Federal Acquisition Regulation 52.227-1, which reads, in part, “The Government authorizes and consents to all use and manufacture, in performing this contract or any subcontract at any tier, of any invention described in and covered by a United States patent.”

The US government used FAR 52.227-1 dozens of times during the COVID-19 pandemic for a variety of drugs, vaccines, diagnostic tests and other medical countermeasures. One of the contract recipients, Moderna, used the federal government’s authorization and consent to manufacture and sell COVID-19 vaccines which were provided to the U.S. public.

The federal government has used FAR 52.227-1 hundreds of times in recent years, as documented in the attached sheet (linked [here](#)).

Table 3: Features of march-in, Bayh-Dole government license and Section 1498 government use rights

	Section 203 march-in right	Sections 202/209 government use right	28 U.S.C. 1498 government use right/ FAR 52.227-1
Covered patents	Federally funded “subject inventions”	Federally funded “subject inventions”	Any invention described in and covered by a United States patent
Grounds	Four grounds set out in 35 U.S.C. 203	No grounds or finding of abuse needed	No grounds or finding of abuse needed
Uses	Any use, including commercial activity for which the US government plays no role	Use that is for or on behalf of the United States government	Any use by or for the government. Statute states: “the use or manufacture of an invention described in and covered by a

			patent of the United States by a contractor, a subcontractor, or any person, firm, or corporation for the Government and with the authorization or consent of the Government, shall be construed as use or manufacture for the United States.”
Injunctions/stays during appeals	Automatic stays during appeals for two grounds, failure to achieve practical application or meet requirements for public use specified by Federal regulations. No automatic stay for public health or failure to meet US manufacturing obligations.	No mandatory stay	No injunction possible
Royalties	Terms that are reasonable under the circumstances, set by federal funding agency	Zero	Reasonable compensation, set by the United States Court of Federal Claims.
Geographic scope	Worldwide as it relates to a subject invention	Worldwide as it relates to a subject invention	US granted patents

Using all three rights to address complex patent landscapes or to avoid injunction or stays

The march-in right has two important advantages over the 1498 government use statute and one important advantage over the Section 202/209 government use license.

The march-in right can be used to sell in any market, and is not limited to cases where the use is by or for a government program or agency. In the area of biomedical inventions, the government can make products available to everyone, such as the Moderna mRNA COVID-19 vaccine. The government can also have a more limited role, such as providing reimbursements through Medicaid, Medicare, the VA, or any number of special programs with specific eligibility requirements, or play no role at all in the market.

March-in works for the larger market segment

For a drug like Xtandi, there is a very large percentage of patients on Medicare, and a government use is particularly powerful leverage. But for a disease like spinal muscular atrophy or cervical cancer, with younger populations, the role of private insurance is more significant, and a march-in right can reach more patients than existing government programs.

For products such as a battery technology (the subject of many subject inventions) or a software product, the government role in the market may be quite limited, and the march-in right is more useful than a government use license.

March-in case royalties are set by the funding agency rather than a court

A march-in right has another advantage over the 1498 license. Royalties are set by the funding agencies rather than the court, providing an important degree of certainty on the costs of the exception. This is in contrast to the 1498 cases where the compensation is set by a court.

There is also an important distinction between the march-in and the 1498 government use license as regards to the foreign uses of an invention. The 1498 government use license only applies to U.S. patent rights, while the march-in right applies to rights in subject inventions. Like the Section 202/209 licenses, the march-in right can work globally.

The 1498 government use right when used with the Section 202/209 licenses

The uncertainty over the compensation to patent holders is an unwanted risk when using the 1498 authorization and consent. But the combination of the 1498 license with the royalty free Section 202/209 licenses reduces that risk.

Secretary Tommy Thompson, working with his aide Alex Azar, considered using the 1498 license to acquire stockpiles of generic ciprofloxacin. Thompson was concerned over the uncertainty of the cost of using Section 1498, knowing that the court process could take years to be resolved. In cases where a product has a complex patent landscape with some patent Bayh-Dole rights and others lacking such rights, a 1498 case is less daunting since the royalties on the Bayh-Dole patents are set at zero.

Using the march-in, Section 202/209 and 1498 licenses together

The effective use of the march-in, Section 202/209, and 1498 licenses together is necessary in important cases. The President's video announcing the march-in guidance emphasized that the march-in right would be used to lower drug prices for US residents.¹² For that to actually happen, and not be one more empty and unfilled promise to deal with drug prices, the government needs to leverage, when necessary, all of its available rights and resources. (For an example of strong executive action getting things done, during COVID 19 the federal government invoked the Defense Production Act to modify existing supply contracts and as noted made extensive use of FAR 52.227-1).

For a majority of products where the federal government has funded key inventions, it is necessary to use the combination of Sections 202/209 and 1498 to deal with non-Bayh-Dole rights in patents on the same product, if the government is going to actually lower prices for products in a meaningful way.

ANNEX: Daniel B. Ravicher's April 29, 2004 Analysis of Patents Relevant to the Ritonavir March-in Petition

The letter to Dr. Mark Rohrbaugh of the NIH, available at:
<https://www.essentialinventions.org/drug/ravicher04292004.pdf>

These are excerpts:

PUBPAT has undertaken a review of the patents pertaining to Abbott Laboratories' ritonavir drug products. In total, there are 5 patents listed by Abbott in the Orange Book for its approved ritonavir capsule product. Of those 5, the Ritonavir Petition would, if granted, provide access to 4, leaving only one patent, U.S. Patent No. 6,232,333 ("'333 patent"), as a potential barrier to making an effective generic ritonavir capsule product. Table 1 below sets forth the Orange Book patent listing for Abbott's ritonavir capsule product and also indicates which of those patents are subject to the Ritonavir Petition.

The '333 patent, unlike each of the other 4 patents listed for Abbott's ritonavir capsule, does not claim the active ingredient, ritonavir, itself. Rather, it merely claims a pharmaceutical composition containing ritonavir. Upon initial review, we have serious doubts about the validity of the '333 patent and its applicability to an effective generic ritonavir product. One issue regarding the '333 patent's validity is that its Abstract and Specification purport to teach an invention providing "improved bioavailability." Yet, no such limitation is present in any of the '333 patent's claims. Such a missing

¹² @potus. "We're taking on price gouging." *Instagram Video*. December 7, 2023. Accessed February 6, 2024. <https://www.instagram.com/reel/C0jdm8GNKTS/?igsh=MTg3dmJkbzBkdWN4bg%3D%3D>

limitation means that the scope of the claims is much broader than what the patent otherwise purports to cover. This breadth of the claims increases the likelihood that they are invalid.

Regardless, the existence of the '333 patent in no way detracts from the importance or utility of the Ritonavir Petition. Access to the technology claimed in the 4 other patents that pertain to ritonavir is absolutely necessary to making an effective ritonavir capsule product available to the American public on fair terms. Further, a potential producer of a generic ritonavir product is much more likely to challenge the '333 patent if it stands alone as the sole patent at issue than if the other 4 patents must also be dealt with. This is especially true since the '333 patent has such glaring validity issues and may be much more easily designed around than the other 4 patents since it does not cover the active ingredient ritonavir itself.

In conclusion, there is absolutely no patent related reason to quell support of the Ritonavir Petition.