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Laura Kohli, JD Candidate

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Laura Kohli*

I. Abstract

The advent of CRISPR, with all its extraordinary potential, has exposed some seams and uncertainties in how U.S. patent law operates extraterritorially. The CRISPR-Cas system can be used to edit the human genome to correct diseases by way of a gRNA that guides a Cas enzyme to a certain DNA sequence location to make a corrective edit. Despite the presumption against extraterritorial patent protection, if an actor exports a component created in the U.S. that, when combined with other components abroad, will infringe a patented invention, the actor can be liable for infringement under 35 U.S.C. § 271(f). By way of an example, consider a patented invention that relates to a Cas9 protein and a DNA-targeting RNA with specific features (gRNA) to produce a modification of the targeted DNA molecule. If a party supplies a library of specific gRNAs for export to be combined with CRISPR-Cas9 in order to practice a patented invention as a whole, there may be 271(f) liability. Notably, the crux of the puzzle rests on the analysis of what a "component" is in such gene editing inventions. Courts could view Cas effector-encoding amino acid sequences, Cas protein

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domains, Cas effectors themselves, gRNA-encoding nucleotide sequences, exons, or gRNA molecules themselves as components. In this writing, I propose that sequences that encode the Cas effector proteins and the gRNAs be considered components for 271(f) liability purposes.

II. Introduction

This paper explores CRISPR-Cas technology and its ramifications for extraterritorial patent infringement under 35 U.S.C. § 271(f) ("271(f)"). I conclude that, to provide the most robust infringement protection extraterritorially, sequences that encode the Cas effector proteins and the gRNAs should be considered components for 271(f) liability purposes. Although there has been work done in the legal area of extraterritorial patent infringement under 271(f) as it relates to devices, software, and early biotech (PCR methods, antibodies, etc.), applicability of 271(f) to gene editing technologies remains unexplored. As such, this Note makes an important contribution by filling a gap in the legal literature regarding gene editing technologies that in the recent years have become an increasingly relevant technology field.

In this Note, I will explore how the 271(f) extraterritorial patent infringement backdrop translates to the space of gene editing with CRISPR-Cas nucleases. CRISPR-Cas is an important technology because it has "the power . . . to target and delete any sequence of DNA in the human genome."[1] Such revolutionary tool can be used to treat genetic diseases including sickle cell anemia as well as to correct "genes that contribute to acquired diseases, including AIDS, cancer and heart diseases."[2] Also, pertinent to the time of writing this Note, Broad Institute and Mammoth Biosciences (a University of California spin-off) are both in

the early stages of using CRISPR-Cas12 "for the detection of COVID-19."[3] CRISPR-Cas is also applicable in the area of agriculture to, for example, "edit crops to be more nutritious."[4] Today, there are a number of these CRISPR-Cas systems patented for use in gene editing. Considering the ever-expanding globalization and the size of the gene-editing fields noted above, the question of patent infringement is critical to the commercial viability of the technology.

The journey through this twofold matrix starts with Section III, which is an overview of the CRISPR technology, including the status of the ownership disputes around Cas9, and looking beyond into some recent developments relating to novel Cas nucleases. In Section IV, we will revisit the types of infringement including extraterritorial patent infringement under 271(f). Further, we will delve into applicability of extraterritoriality doctrine in the gene editing space, including some case law parallels that can be used as guideposts in determining what a "component" may mean in the CRISPR-Cas space. Finally, we will touch on the fact that the best patent practice in this underexplored area of the patent doctrine is to continue including both method and composition claims. This Note overall looks at how the current 271(f) backdrop may color infringement from the CRISPR-Cas perspective.

III. CRISPR Technology and Patent Warfare

a. Gene Editing and CRISPR

Genome editing broadly refers to the process of making targeted deletions, insertions, substitutions, or other modifications in genomes of a range of species to effectuate, for example, a correction of a disease-causing gene or expression of a desired trait.[5] The venture into editing human genes started in the late 1970s with gene replacement in yeast, followed

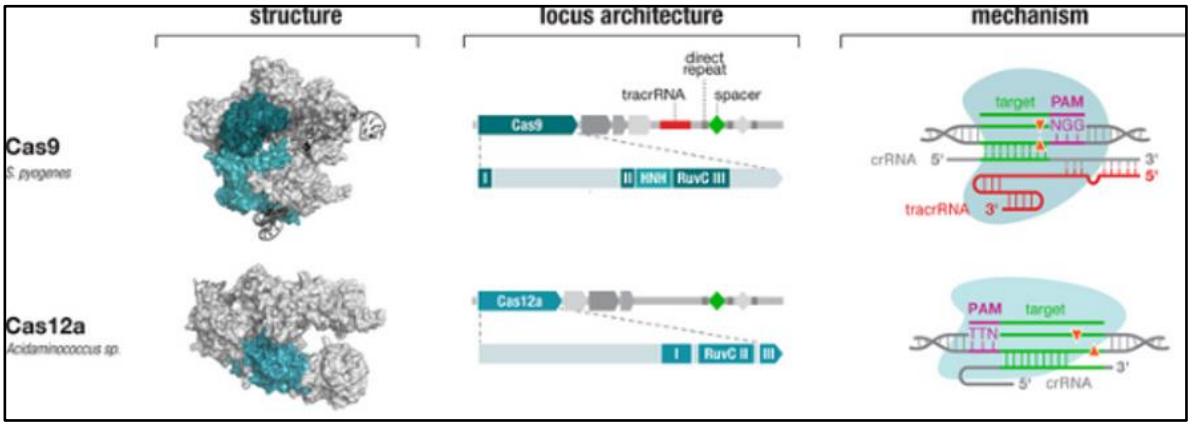
by numerous incremental discoveries which in 2007 culminated in finding that CRISPR-Cas (Clustered Regularly Interspaced Palindromic Repeat) functions as an adaptive bacterial immune system.[6] What this means is that the CRISPR system in bacteria functions as an immune system by "integrating short virus sequences in the cell's CRISPR locus, allowing the cell to remember, recognize and clear infections."[7] In early 2013, this system was finally harnessed as a tool to gene edit human and other eukaryotic cells by way of site-specific genome modifications.[8] This in turn brought on the advent of genome editing that to this day uses RNA-programmable CRISPR and a CRISPR-associated Cas protein (a Cas9 initially) to effectuate a targeted modification in a selected genome target.[9] Simplistically, a gene editing CRISPR-Cas complex comprises a Cas protein, an RNA guide sequence (gRNA), and other elements of the CRISPR machinery.[10] A Cas effector protein is an endonuclease capable of making a genomic cut that uses a gRNA sequence to bring the complex to a complementary target sequence location.[11] Thus, by changing a gRNA sequence, the CRISPR-Cas complex can essentially target and modify any part of the genome.[12]

Now that we have learned about the inception of CRISPR-Cas as a gene editing tool, we will next look at the various types of CRISPR-Cas effectors that, by way of their structural and mechanistic differences, open opportunities for many uses.

b. The Vast Universe of CRISPR

Although CRISPR-Cas9 was the initial frontier, today the field is peppered with a diverse assortment of CRISPR-Cas systems representing two classes that include a half a dozen Types and 33 subtypes of such systems.[13] Class 1 includes Types I, II, and IV, and Class 2 includes Types II, V, and VI.[14] These systems, depending on unique domains and

characteristics, can make single or double stranded cuts or nicks in RNA or DNA target sequences, creating a wide array of possible practical applications.[15] For example, Type II, which includes the original Cas9, contains "two nuclease domains that are each responsible for the cleavage of one strand of the target DNA" while Type V, which includes some of the most recently identified Cas12 effectors, contains only "a RuvC-like domain that cleaves both strands" of the target DNA.[16] Depicted below is a comparison of the domain architecture and gene editing process between CRISPR-Cas9 and CRISPR-Cas12a:



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This image highlights the difference in the locus architecture between the CRISPR Types. Specifically, it shows two Cas9 domains, as opposed to a single cleavage domain in Cas12a, that are involved in the editing process.[18] The two small red triangles in the rightmost image demonstrate that the types of ends produced by the different effector cuts also differ.[19] Specifically, the Type II Cas9 effector produces blunt ends while the Type V Cas 12a effector produces staggered ends.[20] These are just some of the differences that exemplify the vast universe of CRISPR-Cas, offering "many opportunities for engineering CRISPR-based technologies."[21]

Now that we are familiar with the vast universe of CRISPR-Cas proteins, we will briefly explore other gene editing technology and the reasons for CRISPR's superiority.

c. CRISPR- Democratizing Gene Editing?

CRISPR is not the first or the only gene editing tool that scientists have used.[22] Other foundational methods include transcription activator-like effector nucleases (TALENs), zinc-finger nucleases (ZFNs), homing endonucleases or meganucleases, and megaTALs.[23] Despite the availability of alternatives, CRISPR is special because it is "faster, cheaper, more accurate, and more efficient than other existing genome editing methods."[24] By way of an example, it takes "one working week" to prepare a library of thousands of gRNAs that can then be screened for best performance in guiding CRISPR to the desired target[25] while it takes "100 days to make a meganuclease."[26] The reason for that is that CRISPR technology relies on gRNAs, which are often around 20 nucleotide strands of RNA that are complementary to the target DNA, while, for example, making a meganuclease involves "sophisticated protein engineering."[27] Thus, in today's fast-paced environment, every time one desires to modify a different target in a genome, CRISPR offers the coveted time efficiency that is unparalleled with other gene editing technologies.[28] Also, CRISPR is much more efficient in making modifications than other technologies.[29] For example, it may take around a year to engineer a mouse to carry a specific mutation in more than one gene using ZFNs or TALENs, compared to a month using CRISPR.[30] Another reason for the attractiveness of CRISPR is that it is less expensive to make than other technologies.[31] In 2017, it was reported that it costs around $4,000-$5,000 to make a meganuclease, around $5,000-$10,000 to make a ZFN, less than $1,000 to make a TALEN, and strikingly less than

$100 to make CRISPR-Cas.[32] Considering that in 2019 the gene editing industry had a reported market size of $4.44 billion and is projected to grow to $15.79 billion by 2027,[33] the low cost, efficiency, and simplicity of use of CRISPR offers a way to democratize gene editing by making it more accessible to everyone.

Now that we can appreciate the benefits and the market size of CRISPR-Cas technology, next we will delve into the notorious CRISPR patent dispute that has plagued this technology for many years, creating costly uncertainty for those interested in utilizing it commercially.

d. CRISPR Patents

The CRISPR-Cas tool has been one of the most disruptive recent innovations, one that earned Emmanuelle Charpentier and Jennifer A. Doudna a Nobel Prize in Chemistry in late 2020 "for the development of a method for genome editing."[34] As such, it comes as no surprise that the CRISPR-Cas patent landscape has been marching in lockstep with the technology from its inception and now has reached a level of complexity not seen in any recent patent history.[35] For purposes of perspective, there are currently over 30,000 patents and patent applications that belong to over 14,000 patents families relating to CRISPR.[36] As a comparison, there are around 13,000 patents and patent applications that belong to close to 6,000 families in the much older gene editing field of ZFNs mentioned above.[37] Notably, it has been about eight years since harnessing CRISPR-Cas as a biotechnology tool and about six years since the "first of a series of US patents covering the use of the CRISPR technology in eukaryotes" was issued to the MIT/Broad Institute ("Broad").[38] However, the patent war between Broad, with F. Zhang at the forefront, and University of California,

Berkeley/University of Vienna ("UC"), with the 2020 Nobel Prize in Chemistry awardees J. Doudna and E. Charpentier at the forefront, has raged on.[39]

e. Broad vs. UC- Patent Warfare

CRISPR has been in the spotlight not only for what it offers scientifically but also for its "epic patent battle between two academic institutions."[40] Patent filings around CRISPR technology over the past few years offered the public a front row seat to the inner workings of patent disputes.[41] The key players in this institutional patent dispute, as already noted above, are Broad (contributor: F. Zhang) and UC (contributors: J. Doudna and E. Charperntier). The story of the CRISPR patent dispute starts with UC filing the first patent application on CRISPR-Cas system in prokaryotes in May 2012.[42] In December 2013, Broad filed its first patent application on CRISPR-Cas system in eukaryotes (including mammalian cells) and claimed priority to December 2012.[43] Importantly, Broad also took advantage of the tools available through the USPTO and filed an accelerated examination request along with its patent filing.[44] Such an accelerated prosecution strategy led Broad to obtain the very first CRISPR patent (US8697359) in April 2014.[45] UC took notice of the patent and filed for interference proceedings with the USPTO in January 2016.[46] UC's patent (licensed to UC's spin-off Caribou Biosciences) issued in February 2016.[47] And the interference saga began with the USPTO being tasked with deciding "the interference issue and award[ing] one (or none) of the parties his or her respective patents."[48]

Briefly, when two or more actors assert that they, but not the other filers, have invented a particular invention first, an interference may be instituted.[49] An interference, a pre-AIA relict that has now been replaced by somewhat different derivation proceedings, has two prerequisite conditions: "each inventive party must have patentable subject matter [and]

the patentable subject matter must actually interfere."[50] If the USPTO determines that both conditions are met, it declares an interference, and the matter generally moves to an administrative patent judge.[51] The proceeding itself "involves two stages: the preliminary motions phase and the priority phase."[52] The only two outcomes to an interference are either (1) "an award of priority to one of the parties" or (2) "a decision of no interference-in-fact."[53] Although priority is one of the issues that can be raised during an interference, "invalidity in view of prior art (lack of novelty, obviousness)[] and invalidity due to insufficiency of disclosure (lack of enablement, lack of written description)" can also be raised.[54] Put differently, when "the subject matter of a claim of one party would, if prior art, have anticipated or rendered obvious the subject matter of a claim of the opposing party and vice versa," then an interference exists.[55] Interference proceedings are immensely complex procedurally, time-consuming, and as costly as other inter partes proceedings.[56] At the conclusion of the initial proceedings, the losing party can then appeal to the US Court of Appeals for the Federal Circuit.[57]

Reportedly, Editas (Broad's commercial entity that licensed in Broad's patents) spent around $15 million in the first round of interference.[58] As a comparison, commentators suggest budgeting up to $1 million for a run-of-the-mill interference litigation.[59] Although what Editas spent may be a hefty amount, the potential revenue that an entity that holds patents on CRISPR technology is immense and well worth it in perspective.[60] In February 2017, the PTAB rendered its decision, favoring Broad in the interference proceedings because, in the USPTO's view, UC "had not provided an enabling disclosure to justify patent claims on the use in the complex cells and organisms [eukaryotes/mammalian cells] that Broad focused on."[61] This verdict offered an insight that there was no interference because "the eukaryotic CRISPR and other uses of the genome editor were separate inventions"

independently patentable by the respective entities.[62] Unsurprisingly, UC appealed its loss, but in September 2018, the US Court of Appeals for the Federal Circuit affirmed PTAB's decision, solidifying Broad's victory in the first interference proceeding.[63]

To recap, the first interference proceedings concluded with outcome 2 noted above—a decision of no interference-in-fact because "Broad's invention, directed to CRISPR-Cas9 in eukaryotic cells" was patentably distinct from UC's invention, directed to "the CRISPR-Cas9 system generically."[64]

Even with this victory, Broad still could not sit on its laurels because UC instituted a second interference proceeding in June 2019, this time seeking to establish priority—that UC invented CRISPR for use in eukaryotes first.[65] UC triggered the current second interference by filing "new claims … shortly after conclusion of the first interference, which have essentially the same scope as Broad's claims that survived the first interference."[66] The examiner concluded that "the new UC claims were allowable except for a potential interference with Broad's claims, and the PTAB subsequently declared the second interference on June 24, 2019."[67]

In May 2020, both parties argued in front of the PTAB, where Broad's motion to wipe out this second interference altogether was denied.[68] Briefly, as part of the motion, Broad argued for judgement against UC because "the same issues based on the same facts were already litigated in the first interference."[69] However, the PTAB noted that it did not decide "priority or patentability of either party" in the first interference.[70] Although this was a setback to Broad, it was only a small win for UC because this merely allows the parties to offer evidence such as laboratory notebooks and for parties to take depositions in order to establish who "invented the disputed CRISPR-eukaryote system first."[71] The time periods for submitting these priority motions and any oppositions run out in May 2021.[72]

Thus, to this day, the CRISPR-Cas9 battle continues. The result of this drawn-out patent dispute is uncertainty as to who owns the CRISPR technology and, in turn, from whom to obtain a license to practice the technology without potential infringement liability and how much a license may be worth.[73] In the market's attempt to decipher what the value of these CRISPR licenses may be, the stock prices of commercial entities associated with Broad and UC have fluctuated with PTAB's decisions, and, thus, may provide some indication as to the value of these CRISPR licenses.[74] For example, since PTAB's decision was favorable to Broad in the first interference, the stock of Editas (which has a broad exclusive license to CRISPR-Cas9 patents from Broad) "has gone up roughly 36%," which translates to an increase of about $265 million in Editas' market cap.[75] Concurrently, Intellia (one licensee of UC's CRISPR-Cas9 patents) lost in the neighborhood of $100 million of its market cap.[76] Thus, it may be extrapolated that the CRISPR-Cas9 patent portfolio is valued "somewhere between $100 million and $265 million."[77] With the patent warfare between Broad and UC still in full swing, we will next take a look at the associated CRISPR-Cas licensing maze.

f. Other Players in the CRISPR Field and the License Maze

The complexities of the CRISPR patent landscape do not end with Broad and UC. Often, where there is potential for a significant economic gain, there are many suitors aiming to claim at least a slice of the pie—CRISPR is no exception. Other major players include Toolgen Inc., which has licensed its patent portfolio on "fundamental aspects of the CRISPR-Cas system in eukaryotes and modifications for improved specificity" to Thermo Fisher Scientific.[78] And in 2017, MilliporeSigma obtained grants of relatively broad Australian and European patents around "methods for modifying a chromosomal sequence in a eukaryotic

cell by integrating a donor sequence involving at least one RNA-guided endonuclease, at least one RNA guide sequence and at least one donor sequence," which, in turn, makes the question about the freedom to operate even more complex.[79] Much of the early work on CRISPR came from Vilnius University and is now covered by patents, albeit limited to *in vitro* uses, which have been exclusively licensed to DuPont and cross-licensed to Doudna's Caribou Biosciences and Intellia Therapeutics.[80] Cellectis, a known player in the CAR-T field, has a patent for the "use of CRISPR in the preparation of CAR-T cells, one of the main ex vivo uses of CRISPR technology."[81] DowDuPont entered into a non-exclusive license deal with Broad for access to some foundational CRISPR IP relating to agriculture.[82] Interestingly, because DuPont already has arrangements with Vilnius University, Doudna's Caribou, and Broad, DuPont possesses access to a large chunk of CRISPR IP in their particular area of application.[83] What becomes apparent is that the CRISPR IP space has become a paradigmatic patent thicket, first described by Carl Shapiro as "a dense web of overlapping intellectual property rights that a company must hack its way through in order to actually commercialize new technology."[84]

The cost of CRISPR licenses cannot be overlooked. Although such costs can only be approximately gauged from some SEC filing information, this information provides a sense of the scale of such license costs. For example, Editas entered into an exclusive license agreement with Broad relating to some key CRISPR-Cas9 IP, where Broad is entitled to receive, in the aggregate for relevant territories and diseases, clinical and regulatory milestone payments totaling around $18.1 million and additionally $90 million on certain sales milestones.[85] Another example is the CRISPR Therapeutics (co-founded by Emmanuel Charpentier) deal with Vertex Pharmaceuticals.[86] A part of this deal gives Vertex a non-exclusive license to certain CRISPR-Cas9 IP use for treatment of human disease including

cystic fibrosis and sickle cell disease.[87] The terms of this license include "an up-front commitment of $105 million to CRISPR [Therapeutics], including $75 million in cash and a $30 million equity investment" and the possibility of an additional $420 million in milestone payments.[88,89] Considering that more than a single license may likely be required in any given scenario, using CRISPR-Cas9 for commercial purposes may be cost prohibitive to most. The paradox is apparent—CRISPR is the least costly and most efficient gene editing technology once in the laboratory, but the patent landscape has interfered with broad liability-free access to it and driven up costs of licensing it for commercial purposes.

Now that we have made our way through the CRISPR-Cas9 technology, its patent saga, and its associated licensing maze, we will look beyond to other CRISPR effectors that have been identified in the recent years.

g. Looking Beyond Cas9

In part, because the uncertainties attendant ownership of the CRISPR-Cas9 system and the cost of obtaining licenses even if ownership is clear, groups have ventured out to identify other CRISPR effectors that may function as well or even better than Cas9. In the Class II type V CRISPR space, Arbor Biotechnologies has been active in identifying new effectors.[90] Arbor researchers have identified and characterized Cas12c, Cas12g, Cas12h, and Cas12i, most of which "demonstrate RNA-guided double-stranded DNA (dsDNA) interference activity" including Cas12i, which effectuates dsDNA nicking.[91] What this means is that these new CRISPR-Cas effectors have the potential to become additional—and possibly more efficient and accurate tools than Cas9—in the CRISPR toolbox. For example, Cas12i "could enhance double-nicking applications for high-fidelity genome editing."[92] That

is important because one of the well-known concerns relating to gene editing with Cas9 is potential for off-target effects, whereas Cas12i appears to offer reduced off-target activities.[93]

In January 2019, Vertex entered into a deal with Arbor for access to these novel endonucleases.[94] Notably, Arbor and Vertex are examples of companies looking to "sidestep the complex IP landscape surrounding the more commonly used CRISPR-Cas9."[95] This is likely to become a trend, whereby young biotechnology companies looking to bring new Cas effectors to market are not shackled by the existing Cas9 IP landscape.

IV. Infringement

a. Primer on Infringement

In thinking about patent infringement but without delving into the basic patent doctrines in-depth, one ought to briefly revisit the presumption of patent validity, patent claims delineating the boundaries of patent protection for a limited period of time, and territoriality of patent protection.

First, a patent enjoys the presumption of validity under 35 U.S. Code § 282.[96] Specifically, each of the claims is presumed to be valid independent of other claims in the patent.[97] Because of this presumption, "[t]he burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity."[98]

Second, 35 U.S. Code § 271(a) provides that whoever practices (makes, uses, offers to sell, or sells) a patented invention infringes a patent.[99] In turn, patent owners are entitled to exclude others from practicing their patented invention, the boundaries of which are delineated by the claims.[100] The claims are what "provide the measure of the patentee's right to exclude."[101] The scope of the claims in any infringement suit are first construed during a *Markman* hearing, named after a Supreme Court case that charged judges with the

interpretation of patent claims as a matter of law.[102] However, the Court was silent on what procedures judges should follow when engaging in such claim construction, thus, leaving the door open for local patent rules.[103] In interpreting the claims, judges seek to determine what each of the words in the claim mean in light of the specification, drawings, and any prosecution history in order to determine the so-called 'metes and bounds' of the claimed invention.[104] This remains a herculean task for U.S. District Court judges as evidenced by the relatively high reversal rate.[105] The task may be simply insurmountable for generalist judges, or potentially the Federal Circuit prefers to write on a clean slate. Although the percentage of cases with at least one construed claim reversed on appeal declined from around 40.6% pre-*Phillips* to around 29.5% post-*Philips* (after 2005), it still remains much higher than the most recent average reversal rate of around 11% for U.S. Court of Appeals for the Federal Circuit.[106] Some have suggested that the drop in reversal rates may be due to different appellate panels being more or less friendly to construction based on "intrinsic evidence [such as] the claim themselves, the specification, and the prosecution history" as compared to extrinsic evidence such as "dictionaries, encyclopedias, and treatises; expert testimony; inventor testimony; and evidence of industry practice and norms."[107] Despite a drop in reversal rates, with such variation among different appellate panels as discussed above, "the problems of *de novo* review" by the Federal Circuit remain.[108]

Often, claim construction can be outcome determinative by pressing the parties to settle once the district court defines the parameters of the patent claims.[109] At this juncture, one might be tempted to move along to the CAFC merely because of the high reversal rates and potentially get a second bite at the apple. However, despite the high reversal rates relative to the average reversal rates, about 70% of cases still are not reversed. In turn, assuming that the parties do not settle, the next step in infringement determination is for the jury to compare

the accused process or device to each element of each construed claim to determine if there is literal infringement under 271(a).[110] If at least one element is missing, there can be no literal infringement.[111] However, there may still be a finding of infringement under the doctrine of equivalents "if two devices do the same work in substantially the same way, and accomplish substantially the same result" because "they are the same, even though they differ in name, form or shape."[112]

At first blush, patent protection is defined by the concrete boundaries of strict territoriality and the claimed elements, the latter of which has a somewhat longer history. However, over the recent years the boundaries relating to territoriality have morphed from a rigid picket fence to something akin to a permeable membrane.[113] The first such permeable area, assuming there is a finding of infringement under 271(a), is liability under secondary infringement.[114] Such expansion beyond literal infringement includes Section 271(b), which prescribes that an entity may be liable for patent infringement if it "actively induces infringement" by another party.[115] The patentee must, however, show that there was actual infringement along with knowledge of the patent and knowledge that the defendant's acts will infringe on the patent.[116] Such infringement by inducement can be drawn to situations where the patented technology has multiple uses, one of which happens to be infringing.[117] One example is the *Lucent Technologies* case where the court found infringement when, despite the "entire software package ha[ving] substantial non-infringing uses[,]" the Microsoft Outlook date-picker tool "was 'especially made or especially adapted for' practicing the claimed method."[118] The Federal Circuit in *Global-Tech* elucidated the fact that both knowledge and intent are required to be found liable for induced infringement.[119] The requisite knowledge may come from actual knowledge or even willful blindness (defined

as a deliberate action to avoid confirming high probability of liability) while intent is interpreted as an actual desire to cause infringement.[120]

Contributory infringement under 271(c) is another expansion beyond the rigid literal infringement boundaries.[121] Contributory infringement occurs when an entity supplies components of a patent invention that can only be used in that patented invention.[122] If the supplied component is a staple article or has non-trivial alternative uses that are plausibly non-infringing, then the alleged infringer cannot be liable for contributory infringement.[123] Similar to induced infringement, the knowledge and intent requirements apply equally to contributory infringement as well.[124] These secondary infringement doctrines loosen the boundaries of patent protection to encompass additional potentially infringing acts.[125] However, one important limitation remains with respect to 271(b) and 271(c)—infringement acts must occur in the United States.[126] A strategic infringer might then opt to practice part of the patented invention outside the U.S. to circumvent these provisions, but not so fast. The terrain is far more complex.

Now that we have briefly reviewed doctrines underlying domestic patent infringement, we will turn our attention to its extraterritorial counterparts: Sections 271(f)(1) and 271(f)(2).

b. Extraterritoriality

Historically, a concrete pillar of patent law has been territoriality. Patents are generally understood to be creatures of national laws or of multi-national and international agreements that are transposed into domestic law.[127] The basic premise of patent law rests on the notion of territoriality through conferring exclusionary rights to the patentee within the

geographical bounds where any such patent issued—"within the United States."[128] As Justice Ginsburg noted in the 2017 *Lexmark* case, "[p]atent law is territorial. When an inventor receives a U.S. patent, that patent provides no protection abroad."[129]

The Supreme Court first discussed the extraterritorial reach (or lack thereof) of patent law in 1972's *Deepsouth Packing Co. v. Laitram Corp.*[130] In *Deepsouth*, the Court explicitly noted that "[o]ur patent system makes no claim to extraterritorial effect."[131] As a result of this case, for many years a loophole existed in the patent system for savvy infringers to exploit.[132] In *Deepsouth*, a multi-component shrimp deveining machine was patented in the United States.[133] If an identical machine was assembled or used in the US, it would literally infringe on a patent; however, what would happen if each of the patented components of the machine were to be made in the US and then merely shipped abroad to be assembled into the final patented product? According to the Court in *Deepsouth*, because US laws do not apply extraterritorially, there is no infringement regardless of the eventual shipping of those patented US-made components abroad, assembly of those components into a complete machine in about an hour, and the eventual use of the patented machine.[134] To a modern patent reader, this seems unpalatable because this permits a potential infringer to avoid patent infringement by assembling the US-patented invention outside the US.[135]

In 1984, Congress moved to correct this loophole by passing Section 271(f), which in part provides that patent infringement includes "supply[ing] in or from the United States all or a substantial portion of the components of a patented invention, where such components are uncombined in whole or in part, in such manner as to actively induce the combination of such components outside the United States."[136] The second paragraph of 271(f) addresses the export of any component of a patented invention "that is especially made or especially adapted for use in the invention and not a staple article or commodity of commerce suitable

for substantial noninfringing use."[137] The 271(f)(1) and 271(f)(2) are extraterritorial counterparts of 271(b) and 271(c) that regulate the import and export of components for patented inventions that now establish a path to potential infringement liability ex-US.

c. Modern Interpretations of 271

Recent case law, however, has buttressed the presumption against extraterritoriality of patent protection and only pushed itself as far as the statute in 271(f) prescribes.[138] The basic premise that US laws should only govern activities within the US remains strong. Importantly, 271(f) is limited to the movement of patented *components* across the US border. In turn, if something is determined to not be a component, 271(f) does not apply.

Legal discussions relating to 271(f) increased after 2004, starting with the *Pelligrini* case.[139] In *Pellegrini*, the court found that 271(f) liability does not exist where only the instructions for making a component of a patented invention were supplied from the US, not the physical component.[140] In other words, if a component is not physically present in the US and then exported to form the patented invention abroad, 271(f) does not attach.[141] In the gene editing context, there appears to be a loophole—supplying a genetic sequence that happens to encode for gRNAs (provide "instructions"). These instructions may come in the shape of a letter code sequence of an RNA guide or a nucleic acid encoding the RNA guide or even "[r]eady-to-use gRNAs in a purified RNA format suitable for microinjection or cell culture," which can be sequenced in a routine way to arrive at a code sequence.[142] For example, a gRNA to be used in the patented CRISPR-Cas complex abroad would not trigger 271(f). In turn, if the courts follow *Pelligrini* and interpret that a component may only be a physical component such as the above mentioned ready-to-use gRNA, but not be the coding

sequences (which are the instructions to produce the gRNA via routine laboratory steps), then potential infringers in the biotech space may be uniquely positioned to circumvent 271(f) liability.

The next year, the Federal Circuit in *Eolas Techs., Inc. v. Microsoft Corp.* set out to address whether software code created in the US and then exported in identical form on a golden master disk to be integrated "as an operating element of the ultimate device" could trigger Section 271(f) liability.[143] Here, Eolas claimed that Microsoft's Internet Explorer browser infringed on Eolas' patent claims because Microsoft shipped golden master disks with Windows OS that included the allegedly infringing browser abroad.[144] Said another way, in this case Microsoft appears to have duplicated allegedly infringing browser software (as part of an operating system) onto disks and exported those disks, not the intangible software itself in isolation, abroad. On the surface, this implicates 271(f)(1); which, in short, provides an avenue for a patentee to hold an infringer liable for exporting a part or a component of the patent invention.[145] The court elucidated that a "component" within the meaning of 271(f) is not limited to physical parts and can also include intangible patented inventions such as software code on golden master disks because the plain language of 271(f) does not include a tangibility requirement.[146]

The same year, the Federal Circuit in *Microsoft v. AT&T* addressed whether an intangible software code itself is a "component" within the meaning of the statute.[147] It found that software code itself is not a component of a patented invention because it is not a tangible object; thus, generating software code in the US for installation abroad does not trigger infringement liability.[148] However, if the code is fixed or embodied in a physical form in the US and later used ex-US to be installed using that physical medium, then the software code becomes a "component" for purposes of the statute.[149]

In the 2017 *AT&T* case, the Supreme Court held that "Microsoft did not supply combinable components of a patented invention when it shipped master disks abroad to be copied."[150] The Court viewed that "any software detached from an activating medium … remains uncombinable."[151] The nuanced logic of the Court, which appears to draw from copyright-like thinking, rests on the distinction between the software copy embodied on the master disk and the copies subsequently installed on computers. In turn, without a computer—an activating medium—software alone cannot be combined because it is just information, which cannot be treated as a component.

Moreover, because copies of Windows were made and then installed abroad, supplying of the "component" was not *from* the US but foreign countries and, thus, there was no 271(f) liability.[152] The takeaway from this decision is that information itself is not a component for purposes of 271(f). However, if a component of a patented invention is information-based and happens to be exported from the US in a tangible physical form in order to arrive at the patented invention abroad, 271(f) infringement liability may attach.

A decade later in *Life Techs. Corp. v. Promega Corp.*, the Federal Circuit addressed whether supplying just one component of a multi-component invention can trigger liability under Section 271(f)(1) (which specifies "all or a substantial portion of the components").[153] This case involved a patent on a genetic testing kit that was made up of five components, wherein four of these components were manufactured in the UK and the fifth was made in the US and shipped to the UK for assembly there.[154] The Court held "that a single component does not constitute a substantial portion of the components that can give rise to liability under § 271(f)(1)."[155] In doing so, the Court declined to give credence to the importance of a single, vital in making the entire patented invention function.[156] In short, for an infringer to trigger 271(f)(1) liability, the infringer would need to export more than one component of a multi-

component patented invention, but it remains to be seen how much more would be required.[157] That said, one may envision some clever claim-drafting to circumvent the Court's formalistic quantitative approach.

Now that we have toured some of the relevant precedent, we will explore what a component may be in the CRISPR-Cas space.

d. What is a "Component" in CRISPR-Cas?

Precedent discussed above reveals that applicability of 271(f) liability to a certain patented invention turns on what the court views as a "component." I propose that coding sequences for novel gRNAs and Cas proteins (if patented) should constitute a component and, if supplied from the US, should trigger 271(f) liability.

Notably, CRISPR-Cas is likely not going to be an exception in that the definition of a "component" will still likely be outcome-determinative. Biotechnology and gene editing in particular are complex fields, so determining what a component may be is not as simple as defining whether, for example, a catalyst in a reaction is a component or pinpointing whether a chemical moiety has been supplied from the US. I begin with the basic building blocks of nucleotides and amino acids, moving up to protein domains, and ending at a high level of Cas proteins and gRNAs themselves.

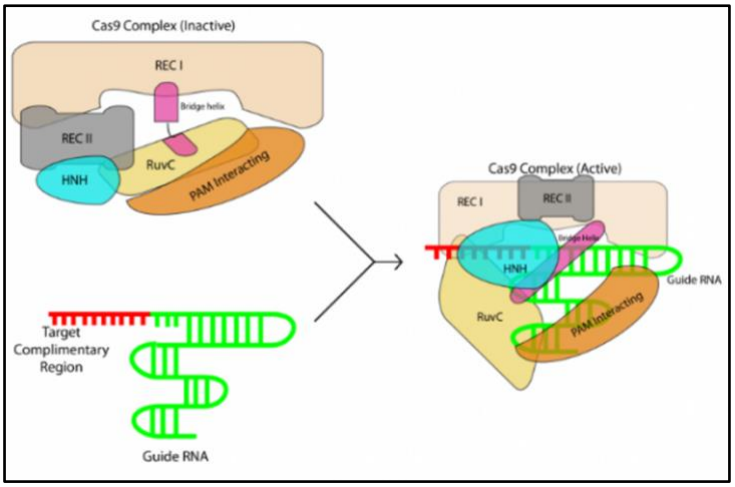
In order to ascertain the potential areas that the courts might review when determining what a component is in CRISPR-Cas space, below reproduced is a picture claim 15 from the first patent issued to Broad (US8697359B1).[158]

> 15. An engineered, programmable, non-naturally occurring Type II *CRISPR-Cas system* comprising a *Cas9 protein* and at least one *guide RNA* that targets and *hybridizes* to a target sequence of a *DNA molecule* in a eukaryotic cell, wherein the DNA molecule encodes and the eukaryotic cell expresses at least one *gene product*

> and the *Cas9 protein cleaves* the DNA molecules, whereby *expression of the at least one gene product is altered*; and, wherein the Cas9 protein and the guide RNA do not naturally occur together.[159]

At first glance, a Cas9 protein and a guide RNA are the two elements prominently featured in this sample claim. Let us take the Cas9 protein first: at a high level, Cas9 (or another effector protein in question) may be considered a "component" of the CRISPR-Cas complex. Cas9 protein is made up of numerous domains, as shown in the image below.[160] Domains are "distinct functional and/or structural units in a protein" that are "responsible for a particular function or interaction[,]" thereby together enabling the protein to perform a particular overall role.[161] In this case, the Cas9 protein includes RuvC, REC I and II, HNH, and PAM Interacting domains.[162] In turn, these domains could arguably be considered components of the patented invention for 271(f) purposes.

The image below highlights another important aspect of proteins: the difference in protein structure between its inactive form and its active form.[163] Briefly, the top left of the image below shows an inactive Cas9 structure while the right depicts how it changes in the presence of a guide RNA. Specifically, the REC II and HNH domains fold up on REC I domain while RuvC domain folds into the REC II/HNH domain space thereby allowing for Cas9 to interact with the gRNA.[164]



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Thus, the question becomes whether the Cas9 effector protein in its native inactive form or in its active form in the presence of a gRNA is a component of a patented invention. In turn, would supplying from the US an isolated Cas9 protein constitute supplying a component of a patented CRISPR-Cas invention under 271(f)? Also, would supplying a Cas9 protein with a modified PAM domain avoid liability even if it still accomplishes the goal of altering the gene target of interest? I propose to consider that amino acid changes to domains are not only possible but commonplace, and so a savvy infringer might elect to export a Cas9 protein with a modified PAM or modified HNH domains so the domain could be modified again abroad to be combined into a patented invention. Generally proteins have four levels of organization, which at a first level includes polypeptide chains made up of amino acids.[166] If a savvy infringer, using routine methods, alters the amino acid sequence thereby modifying a specific domain as mentioned above, this would likely not trigger 271(f) liability under the current state of affairs (as interpreted in *Life Technologies* most recently) because the exact component technically was not supplied *from* the US.

Now consider the gRNAs that are essentially sequences of nucleotides, pre-generated in the laboratory to target a specific gene of interest. Genes consist of specific arrangements

of nucleotides at specific locations that encode for proteins and RNA molecules.[167] Broadly, there are three types of nucleotide sequences: exons (coding sequences), introns (non-coding sequences), and regulatory sequences.[168] In some sense, nucleotide sequences themselves may be considered a component for 271(f) liability purposes. That is because in CRISPR-Cas related patents such sequences are often specifically claimed. Take for example a filing by Arbor Biotechnologies that features claims to particular gRNA sequences (US20190002875A1):

> 1. An engineered, non-naturally occurring Clustered Regularly Interspaced Short Palindromic Repeat *(CRISPR)-associated (Cas) system* comprising:
>
> an *RNA guide* or a nucleic acid encoding the RNA guide, wherein the RNA guide comprises a *direct repeat sequence and a spacer sequence* capable of hybridizing to a target nucleic acid, wherein the direct repeat sequence comprises 5′-X1X2X3X4TX5TX6AAAC-3′ (SEQ ID NO: 151) at the 3′ terminal end of the RNA guide, and wherein X1 is A or C or G, X2 is G or T, X3 is A or G, X4 is C or G or T, X5 is C or T, and X6 is A or G; and
>
> a *Type VI-D CRISPR-Cas effector protein* or a nucleic acid encoding the effector protein, wherein the effector protein is *capable of binding to the RNA guide and of targeting the target nucleic acid sequence* complementary to the spacer sequence, and wherein the target nucleic acid is an RNA.[169]

In this sample claim, an RNA guide or gRNA is defined with a certain level of particularity. In turn, such gRNA of SEQ ID. NO. 151 with modification within the provided parameters may be considered a component which if supplied from the US to practice such patented invention may trigger 271(f) liability.

In *Bristol-Myers Squibb*, the Federal Circuit employed the viewpoint of one having ordinary skill in the art (PHOSITA) of chemistry to delineate what a substantial portion of the components was.[170] From that standpoint, the court declined to extend 271(f)(1) liability because only a single side chain of the compound at issue had been supplied from the US.[171] This case holds-up post *Life Technologies* because a single side chain in a chemical drug compound invention does not constitute substantially all components for liability under

271(f)(1). It may be tempting to extend the same approach of utilizing the viewpoint of PHOSITA to determine what a component is in gene editing space; however, a problem is the art being so immensely complex may be a hurdle.[172]

In the CRISPR-Cas area, parallels are visible in interpretations between the *AT&T* and *Pelligrini* cases. Specifically, the courts interpreted software code on a disk as a component but not the code itself and distinguished between exporting instructions as opposed to exporting the ultimate product that will come into being if such instructions are followed. As discussed earlier, one of the parts of CRISPR-Cas complex is a gRNA, which is essentially a set of instructions or a code that the cell reads to guide the Cas protein to the right place in the genome to make a cut. Is that like copying software from a disk to a computer for it to operate where "informational precursors that do not physically become part of a final product and are thus 'intangible' in the same manner as software code?"[173] According to *Pellegrini*, providing instructions to arrive at a component of a patented invention was not considered a component itself. Thus, looking at it from the genetics perspective wherein sequence information is actually information that provides the parameters of what a protein or an RNA molecule is going to become, then perhaps sequences should not be viewed as components for 271(f) purposes. However, this interpretation exposes an obvious loophole because, for example, protein "production was once the domain of experts, but the development of simple, commercially available systems has made the technology more widespread."[174] In turn, because it is routine to arrive at a certain protein based on a specific sequence, such interpretation opens a clear loophole. Similarly, designing a gRNA library for genome editing with CRISPR or simply ordering validated gRNAs based on the target sequence of interest from suppliers such as Addgene is readily accomplished.[175] Addgene notes that "[a]s you develop and confirm new gRNAs, please consider submitting

their sequences … so that this shared resource can continue to grow."[176] Thus, I would argue that, for example, a coding sequence for any such new gRNA (if patented) does constitute a component and if supplied from the US should trigger 271(f) liability. If that is not the case, potential savvy infringers would send a sequence of proteins or RNA molecules instead of a physical vial with the already produced protein or gRNA thereby avoiding 271(f) liability.

If the current interpretations of the doctrine are strictly followed, sequences that encode, for example, a certain gRNA would not be considered a component for purposes of 271(f). However, one important distinction that is crucial between software code and genetic sequences is that genetic sequences are made up of nucleotides in the case of an RNA and of amino acids in the case of a protein. For example, a certain larger region of any such amino acid sequence when viewed collectively is known as a domain, which is a component of a protein and could arguably be considered a component of the patented invention for 271(f) purposes.[177] With respect to RNAs, equivalent to protein domains are segments of nucleotide sequences that make up functional units such as exons which code for proteins or non-coding regions such as introns and regulatory sequences.[178] In turn, it becomes apparent that, unlike software which, as elucidated by the Supreme Court, starts and ends with the code for purposes of determining what a component is, in the biotechnology world, the options range from sequences themselves to regions of sequences (domains in proteins or exons in RNAs), to proteins (in active or inactive configurations), and to gRNAs. In short, genetic sequences and software code differ in legally meaningful ways. In my view, the courts should consider all such options when determining what a component may be with respect to CRISPR-Cas because the alternative of ignoring sequences and domains or exons leaves only the final Cas protein and gRNAs as options for components. This, in turn, creates a loophole for a savvy infringer to take advantage of considering how standard it is to arrive at a protein or an RNA

from respective sequence information. In other words, a component for purposes of 271(f) in the CRISPR-Cas inventions should not merely be the obvious final product in a laboratory vial such as a Cas protein or a gRNA, but instead the courts should analyze the novel underlying sequences of any such patented final products. Although this may seem an arbitrary proposition, the alternative is closer to the CAFC claim construction thinking of the legal field-transcendent "I know it when I see it."[179]

e. Novel Cas Effectors- Percent Similarity to Cas9

As noted above, today the field has moved beyond the so called original Cas9 effector protein into other types and subtypes of CRISPR-Cas complexes. Some of these effectors can be 30%-40% identical in sequence to the patented Cas9 effector. Does that in turn mean that supplying any such novel Cas effector protein may still trigger 271(f) liability because it could be considered a "substantial portion" per 271(f)(1)? The statutory language of 271(f)(1) requires a supplying of "all or a substantial portion of the components."[180] Based on the precedent in *Life Technologies*, a single component cannot constitute a substantial portion of the multi-part patented invention. However, what if the patented invention, on its surface, has only two parts to it, and 40% of one of those parts is supplied from the US? This entirely plausible scenario again invites the courts to analyze infringement at a sequence level by looking beyond the quantity of parts in a multi-part invention and beyond the final product only as a component of a patented invention.

Section 271(f)(2) requires supplying any component that is especially made for use in a patented invention. The question then becomes whether a library of gRNAs that has been generated to specifically target a genetic location would be considered "especially made."[181]

Alternatively, would such library of gRNAs be actually considered a "commodity of commerce suitable for substantial non-infringing use" in that the same gRNAs could theoretically be used to target the same gene location but not necessarily for use with CRISPR-Cas.[182] I would propose that such analysis also rests upon whether sequences of any sort may constitute a component of a patented invention. If so, then other sequences with a high percentage of identity, even if titled something other than, for example, the effector protein in the patented invention, may potentially trigger 271(f) liability. Although at first blush it may seem that this would require a fair amount of expert information to analyze, determining percent identity between sequences, albeit tedious, can be readily done on various sites including NIH's BLAST tool.[183] This, in turn, may satisfy the court's desire, made apparent in *Life Technologies*, for a quantitative answer in determining 271(f) liability.

f. What About Method Patents?

In 2009, the Federal Circuit in *Cardiac Pacemakers, Inc. v. St. Jude Medical, Inc.*, held that a device made in the US and exported for practicing a patented method abroad does not trigger 271(f) liability.[184] In doing so, the court overruled its decision in *Union Carbide* where the Federal Circuit had previously held that method claims are within the purview of 271(f).[185] In short, 271(f) does not apply to method patents because, according to the court, it is not possible to supply method steps for them to act as a "component" under 271(f).[186] In other words, if a potential infringer supplies from the US a device that can then be used to perform a patented process abroad, no 271(f) liability attaches.[187] For purposes of illustration, reproduced below is claim 15 from one of UC's earliest patents (US10428352B2):

> 15. A *method of cleaving a target DNA* in a prokaryotic cell, the method comprising: contacting the target DNA inside of the prokaryotic cell with:

> (a) a *Cas9* protein; and
> (b) a single molecule *DNA-targeting RNA* comprising, in 5′ to 3′ order:
> (i) a targeter-RNA comprising a nucleotide sequence that is complementary to, and hybridizes with, a target sequence of the target DNA; and
> (ii) an activator-RNA that hybridizes with the targeter-RNA to form a double-stranded RNA duplex,
> wherein (i) and (ii) are covalently linked by intervening nucleotides,
> wherein said contacting *results in cleavage of the target DNA.* [188]

An interesting aspect is that some of the CRISPR-Cas patents include method claims similar to the one above. The court has held that 271(f) does not apply to such method or process claims (based on *Cardiac Pacemaker*). Thus, it would follow that claims such as the one above directed to methods for modifying a genome using CRISPR-Cas by cleaving a target DNA may fall outside of the 271(f) scope. If viewed in isolation of any other pertinent CRISPR-Cas patents and further considering that this particular UC patent is limited to method claims only, it would seem that an infringer would be free to export from the US, for example, "a single molecule DNA-targeting RNA" comprising the elements in the claim without the fear of 271(f) liability attaching. From a patent practice perspective, it would thus seem that including both method and composition claims (as practitioners often do anyway) would remain the best practice in this underexplored area of the patent doctrine.

g. Damages

Assuming the court determines a CRISPR-Cas patented invention does, in fact, trigger potential 271(f) liability, recovery of lost foreign profits is yet another interesting consideration. Review of this issue raises a palpable tension to the surface—that is "first, that owners are, in general, entitled to full compensation for their losses; and second, that patent rights are territorial, that is, unenforceable against conduct occurring outside a nation's

borders."[189] In *WesternGeco LLC v. ION Geophysical Corp.*, the Supreme Court provided guidance in a situation where components of a patented invention were made in the US but assembled ex-US, a 271(f)(2) scenario.[190] The court acknowledged the dogmatic presumption against extraterritoriality in patent law and went on to "announce[] a two-step framework."[191] According to the Court, the first step in the analysis is to determine whether 271(f) offers a "clear indication of an extraterritorial application."[192] If the answer to the first query is in the negative, then the second step would be to determine if the issue at hand "involves a domestic application of the statute."[193] Interestingly, after setting up a two-step framework, the Court stepped over the first part of the analysis, citing the excuse that it would not have been outcome determinative, and moved straight to the second step of the analysis.[194] Starting with Section 284, which prescribes that damages awarded should be "adequate to compensate for the infringement,"[195] the Court focused on the mindset of fully compensating the patentee for any infringing acts under 271(f)(2).[196] The Court focused on ION's US activity of supplying components "in or from the United States" via exporting parts of the competing system for surveying the ocean floor that were sold from the US to be assembled abroad.[197] Thus, the Court concluded that, because ION's acts fall squarely within the 271(f)(2) language, the "award of lost-profits damages in this case was a domestic application of § 284."[198] This means that once infringement under 271(f) is established, lost-foreign profits can be recovered for exporting components of a patented invention even if it is to be assembled abroad.[199] Although the Court in *WesternGeco* noted the narrow applicability of its decision, if 271(f) liability attached in the CRISPR-Cas space, then lost-foreign profits could similarly be recovered. However, what may be complex is ascertaining those lost foreign profits based on what the courts settle on as a component for 271(f) liability purposes. That is because, in multi-component products (such as the CRISPR-Cas system

would be), "courts seek to compensate patent owners for the value of the patented improvement" only.[200] In turn, it may prove to be challenging to "determine the value attributable to a subcomponent instead of the whole product, especially when there is no established market for just the infringing subcomponent" and even more so when foreign activities for lost foreign profits are factored in.[201] Thus, the reach of *WesternGeco* in the gene editing space remains to be seen.

V. Conclusion

This Note has explored two thorny problems—the technology of CRISPR-Cas, which has been a hotbed of patent issues, and the doctrinal question in the understudied area of patent law that is 271(f). Briefly, CRISPR along with CRISPR-associated Cas protein (a Cas9 initially and now many others) is a broadly used gene editing technology in the biotech space. It is used to effectuate a targeted modification in a selected genome target to, for example, correct a genetic disease such as sickle cell disease. A second aspect of this Note was a review of the reach of US patent law-based infringement liability doctrine abroad. Although there is a presumption against extraterritorial patent protection, if an actor exports a component created in the US that, when combined outside the country, will infringe a patented invention, that actor may be liable for infringement under 35 U.S.C. 271(f). In the backdrop of CRISPR-Cas technology, if a party supplies a library of patented gRNAs for export to be combined with a Cas9 effector in order to practice a patented CRISPR-Cas invention as a whole, there may be 271(f) liability. Notably, the crux of the puzzle rests on the analysis of what a component is in such gene editing inventions as discussed above. Courts may have options of viewing amino acid sequences, protein domains, Cas effectors themselves, nucleotide sequences, exons, or gRNA molecules themselves as components. Each choice brings on its

own nuances in terms of opening up opportunities for loopholes. In this Note, I proposed that to provide the most robust infringement protection ex-US, sequences that encode the Cas effector proteins and sequences that encode the gRNAs should be considered components for 271(f) liability purposes. That is because, if the courts interpret that a component may only be a physical component but not the coding sequences which are the instructions to produce the gRNA via routine laboratory steps, then that opens up a loophole uniquely positioning potential infringers in the biotech space to circumvent 271(f) liability. In other words, a component for purposes of 271(f) liability in the CRISPR-Cas inventions should not merely be the obvious final product in a laboratory vial such as a Cas protein or a gRNA, but instead the courts should dig down to the novel underlying sequences for any such patented final products.

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