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NOTE

PATENT TERM EXTENSION AND THE ACTIVE INGREDIENT PROBLEM

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Patent term extension (PTE) is a statutorily-based mechanism to compensate inventors for patent term loss due to regulatory delay during the drug approval process at the United States Food and Drug Administration (FDA). In the context of pharmaceutical products, PTE is only available for the active ingredient of a drug formulation. Case law and interpretation of the relevant statutory text have clearly delineated the boundaries of what qualifies as an active ingredient in a chemical formulation for purposes of PTE. As therapeutics expand beyond simple chemical formulations into cell-based and gene therapy-based formulations, where a chemical compound is not the active ingredient, an interpretation of active ingredient for purposes of PTE is lacking. I term this shortcoming "the active ingredient problem." In the absence of applicable case law, it has become increasingly important to review FDA guidance and recommendations. Furthermore, the United States Patent and Trademark Office (USPTO) has offered limited indications of how it may interpret active ingredients in these scenarios. Moving forward, it will be essential for inventors to understand how these cutting-edge therapeutics will be protected and how their efforts will be compensated as a result of delays associated with the regulatory approval process. In this paper, I advocate the adoption of "treatment complex protocols" or TCPs, a novel framework for PTE for cellular and gene-based therapeutics. This framework

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moves away from considerations of an active ingredient and instead embraces the complexities of the production and development of cellular and gene-based therapies. Under this framework, PTE would be granted to a TCP, which is a complete protocol-based description of the inputs, modifications, and outputs required to develop these complex and clinically important therapeutics. Although TCPs are necessarily more complex than determinations of active ingredients for chemically based therapeutics, they have the potential to clarify this increasingly murky, yet clinically relevant, area of the law.

INTRODUCTION

The twenty-year patent term serves as a means of incentivizing inventors to create and innovate in exchange for a grant of a period of exclusivity during which they hold exclusive rights to exclude others from practicing the invention. The twenty-year term, however, often implies that the inventor can begin practicing her invention (and begin excluding others) as soon as the patent is granted. This is frequently not the case, especially for patents covering therapeutics that cannot be fully practiced (i.e., marketed and sold) until they have gone through a required regulatory approval process. In the United States, this approval is completed by the United States Food and Drug Administration (FDA). In cases where the invention could be practiced (i.e., marketed as a drug) but-for this delay, it seems sensible that the inventor should not bear the burden of the "lost" time of protection of the patent term. Patent term extension (PTE) is a statutory mechanism to deal with this precise issue: it permits the inventor to recoup at least a portion of the time that was spent approving the product and that resulted in a delay in commercial exploitation of the product.

PTE exists as a regulatory mechanism to compensate inventors for patent term loss due to unfair regulatory delay during the drug approval process by the FDA.[1] To ensure that inventors are not inappropriately recovering lost patent terms, PTE is only available for the active ingredient, which is, generally speaking, the component of the drug that is responsible for providing its pharmacological activity. Traditionally, this has been defined as a chemical compound in the drug formulation that, when administered to a patient, results in the drug's beneficial effects.[2] Case law and interpretation of the relevant statutory text have clearly delineated the boundaries of what qualifies as an active ingredient in a chemical formulation for PTE well beyond the traditional FDA definition. As therapeutics expand beyond simple chemical formulations into cell-based and gene therapy-based formulations (i.e., where the treatment is not comprised of a chemical compound), and a chemical compound is thus not the active ingredient, it is less clear precisely what the "active ingredient" is. An applicable interpretation of the active ingredient in complex therapeutics like cellular and gene-based therapies is lacking for purposes of PTE. Furthermore, the shortcomings of the PTE statute will not easily be ameliorated by

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[1] *See* 35 U.S.C. § 156 (2018); *see, e.g.*, Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661, 663 (1990) ("The [Patent] Act was designed to remedy . . . distortions," for instance when "the patentee would as a practical matter not be able to reap any financial rewards during the early years of the term while he was engaged in seeking [regulatory] approval.").

[2] *Active Ingredient*, FDA, https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-glossary-terms (last visited Apr. 6, 2020).

amending the statute or adding simple additional language. As I argue in this Note, simply amending the statute or modifying the statutory definitions almost certainly would not resolve what I described as "the active ingredient problem," and the question "what is an active ingredient in a cell-based or gene therapy-based formulation?" remains open and unanswered.

In the absence of extensive, applicable case law, it has become increasingly relevant to review FDA guidance and recommendations. Furthermore, the United States Patent and Trademark Office (USPTO) has offered limited insight with regards to the interpretation of active ingredients in cell-based therapeutics. Although the USPTO will likely not be granted any agency deference by courts,[3] this still provides an important step forward in understanding how these cutting-edge therapeutics will be protected and how inventors' innovations will be compensated as a result of delays associated with the regulatory approval process. In the meantime, appropriate claim construction that reflects the active ingredient contained in the FDA regulatory filing may alleviate some of the uncertainty while ensuring protection extensions for inventors.

In this paper, I argue that the statutory definition of "active ingredient" fails to work effectively in the context of novel therapeutics and, as a result, there exists a need for a novel framework. As a result, the concept of active ingredient for PTE should be revamped entirely with respect to novel therapeutics. In its place, I propose "treatment complex protocols," or "TCPs" which are a protocol-based collection of information that would include a holistic review of the treatment, its components, and input and output information related to the production of the clinical therapeutic. Although extending the active ingredient analysis may be cumbersome, the current

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[3] Courts have not yet recognized a basis for *Chevron* deference for the USPTO. *See, e.g.*, John M. Golden, *Working Without Chevron: The PTO as Prime Mover*, 65 DUKE L.J. 1657, 1659 (2016). The United States Court of Appeals for the Federal Circuit has held that "Congress has not vested the [USPTO] Commissioner with any general substantive rulemaking power." Merck & Co. v. Kessler, 80 F.3d 1543, 1550 (Fed. Cir. 1996). The United States Supreme Court has stated that *Chevron* only applies where Congress has delegated relevant authority (e.g., substantive rulemaking authority) and when the agency interpretation seeking deference was promulgated under that authority. United States v. Mead Corp., 533 U.S. 218, 226–27 (2001). The bid for adjudicatory deference is constantly being litigated: as recently as March 18, 2020, the Federal Circuit held that "even if § 315(c) [of the Patent Act] were ambiguous—which it is not—we would conclude in the alternative that on appeal the PTO's interpretation . . . is not deserving either of Chevron or Skidmore deference," reaffirming that Congress did not delegate substantive rulemaking authority to the agency. Facebook, Inc. v. Windy City Innovations, LLC, 2020 U.S. App. LEXIS 8522, at *67 (Fed. Cir. Mar. 18, 2020).

statutory definition of active ingredient fails to capture the complexities and nuances incident to novel therapeutics.

This paper begins with Section I introducing patent term extension, the FDA regulatory approval process, and the interplay between the two. Section II explores the current, albeit limited, case law and interpretation of the relevant statutory provisions pertaining to patent term extension and active ingredients for purposes of PTE. Section III describes in detail the paradigmatic shift we are observing in the types of therapeutics that have been approved by the FDA. This section will also describe how this shift will impact our understanding of incentivizing innovation, in addition to how it will impact regulatory procedures surrounding PTE. Section IV addresses suggestions for updating the current patent term extension and active ingredient framework, while also suggesting how inventors and patent drafters can operate in the current case law and statutory structure before concluding.

I
THE TUG-OF-WAR: PATENT TERM EXTENSION (PTE) AND THE UNITED STATES FOOD AND DRUG ADMINISTRATION (FDA) APPROVAL PROCESS

Patent term extension (PTE) is a means for an inventor to recover the portion of her patent term during the regulatory review process when she could not effectively practice her invention. Before describing PTE and the FDA regulatory process in more detail, it is important to remember an essential factor of the interplay between drug approval and patent term: it can take several years for a drug to be approved and to reach market, yet the patent protecting the drug or therapeutic may have been filed years earlier. The patent may have been filed at a time when the drug was still being developed, but before it was tested and approved and, thus, before it was ready to enter the market. As a result, the proverbial patent term clock would have been ticking well before the drug or therapeutic could be approved and, thus, enter the market.

A. Patent Term Extension and 35 U.S.C. § 156

The provisions governing patent term restoration/extension are found in 35 U.S.C. § 156 (Extension of patent term) of the Drug Price Competition and Patent Term Restoration Act ("Hatch-Waxman").[4] Patent term extension does not apply broadly for all types of all patents: it only applies to patents covering human drug products, medical devices, food additives, color additives, and animal drug

[4] 35 U.S.C. § 156 (2018).

products.[5] A patent in one of the prescribed areas of protection, regardless of whether it claims a product, method, or method of manufacture, according to the statute, "shall" receive an extension on its term provided that 1) the patent term has not expired prior to the application for extension having been submitted,[6] 2) the patent term has not been extended previously,[7] and 3) the application is submitted in accordance with several additional procedural requirements.[8] These requirements include the identity of the approved product and the federal statute under which regulatory review occurred,[9] the identity of the patent for which extension is being sought,[10] a brief description of activities undertaken by the applicant during the applicable regulatory review period,[11] and other information used for determining the eligibility of the patent for extension[12] or that the Director may require.[13]

The option to extend a patent term is not *carte blanche* for the inventor to unfairly extend her patent term indefinitely. Section 156 contains provisions on calculating periods of regulatory review[14] for products that are new drugs, antibiotics, or human biological products;[15] food additives and color additives;[16] medical devices;[17] animal drugs;[18] and veterinary biological products.[19] In each of these situations, the total period of extension may not exceed five years.[20]

Furthermore, § 156(c)(3) states an important exception to term extension: the total patent term cannot exceed 14 years after the product's approval date, and if it does, that product is not eligible for patent term extension.[21] This is a statutory

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[5] *Id.* §§ 156(a), (f).
[6] *Id.* § 156(a)(1).
[7] *Id.* § 156(a)(2).
[8] *Id.* § 156(a)(3).
[9] *Id.* § 156(d)(1)(A).
[10] *Id.* § 156(d)(1)(B).
[11] *Id.* § 156(d)(1)(D).
[12] *Id.* § 156(d)(1)(E).
[13] *Id.*
[14] *Id.* § 156(g).
[15] *Id.* § 156(g)(1).
[16] *Id.* § 156(g)(2).
[17] *Id.* § 156(g)(3).
[18] *Id.* § 156(g)(4).
[19] *Id.* § 156(g)(5); Note that each of the foregoing, with the exception of the provision in § 156(g)(1), lies beyond the scope of clinical therapeutics and will not be covered further in this Note.
[20] *Id.* § 156(g)(6)(A)–(B).
[21] *Id.* § 156(c)(3); *Small Business Assistance: Frequently Asked Questions on the Patent Term Restoration Program*, FDA, https://www.fda.gov/drugs/cder-small-business-industry-assistance-

protection to ensure that the inventor is not extending her term well beyond the normal twenty-year term of protection. It is important to note that both the 14 year total and the five-year cap apply together: that is, if 14 years from the approval date is a shorter period than a five-year period added after the patent expires, the earlier of the two dates, here the 14 years from the approval date, is the maximum extension permitted. This also applies if the five-year total cap ends earlier than 14 years after the approval date.[22]

Taken together, the determination that a patent is eligible for extension may be made by the Director solely by what is contained in the application for extension.[23] If the application is eligible under § 156(a)(1) and compliant with the application content requirements found in §156(d)(1)–(4), then the extension shall be granted for a term prescribed in § 156(c).[24] Section 156(b) governs rights derived from extended patents and will be addressed fully in Section II.

B. The Patent Term Extension Regulations: 37 C.F.R., Subpart F and "Active Ingredients"

The relevant regulations interpreting the patent term extension statute can be found in 37 C.F.R., Subpart F—Adjustment and Extension of Patent Term, sections 1.710–1.791.[25] Many of the regulations in this section cover important procedural requirements related to a PTE application, including its contents (section 1.740) and the duty of disclosure in patent term extension proceedings (section 1.765). The regulations in sections 1.775–1.779 cover how to calculate the term extension for all products covered by PTE (including human drugs, antibiotic drugs, or human biological products;[26] food additives or color additives;[27] medical devices;[28] animal drug products;[29] and veterinary biological products[30]).

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sbia/small-business-assistance-frequently-asked-questions-patent-term-restoration-program (last visited Mar. 15, 2020).

[22] § 156(c); *Frequently Asked Questions*, *supra* note 21.

[23] 35 U.S.C. § 156(e)(1).

[24] *Id.*

[25] 37 C.F.R. §§ 1.701–1.791 (2020). Note that §§ 1.701–1.705 covers patent term adjustment (PTA), which deals with delay during examination at the USPTO. PTA is covered by 35 U.S.C. § 154. Together PTA and PTE are the two mechanisms for recovering term time that may be "lost" due to either agency or regulatory delay.

[26] *Id.* § 1.775.

[27] *Id.* § 1.776.

[28] *Id.* § 1.777.

[29] *Id.* § 1.778.

[30] *Id.* § 1.779.

Section 1.710—Patents Subject to the Extension of Patent Term includes two important and relevant provisions. The first, section 1.710(b), sets forth the language in § 156(f)(2) defining the term "active ingredient."[31] The second, section 1.710(a), states that "[a] patent is eligible for extension of the patent term if the patent claims a product as defined in paragraph (b) of this section, either alone or in combination with other ingredients that read on a composition that received permission for commercial marketing or use, or a method of using such a product, or a method of manufacturing such a product . . ."[32] There are two important requirements included in this subsection: 1) the patent must claim the product (i.e., the "active ingredient" as defined in § 156(f)(2) and section 1.170(b)); and 2) that claimed product must read on a composition that received permission for commercial marketing or use. Taken together, the two subparts of the regulation mean that a patent is eligible for extension if it claims a product (i.e., "active ingredient") that has received permission for commercial marketing or use (i.e., FDA approval).

Section 1.720 also provides an essential interpretation of the statute, setting forth the conditions for extension of the patent term.[33] First, the patent must claim a product or method of using or manufacturing the product as defined in section 1.710.[34] Second, the term of the patent must not have been previously extended (except for an extension issued pursuant to sections 1.701, 1.760, or 1.790).[35] Third, an application must be submitted in compliance with section 1.740.[36] Fourth and finally, the product must have been subject to a regulatory review period prior to its commercial marketing or use,[37] and the product must have actually received permission for commercial marketing or use.[38] Importantly, the permission for the commercial marketing or use of the product must be the *first* received permission for the commercial marketing or use under the provision of law that the regulatory review occurred.[39] No other patent term can have been extended for the same

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[31] 35 U.S.C. § 156(f)(2); 37 C.F.R. § 1.710(b).
[32] 37 C.F.R. § 1.710(a).
[33] *Id.* § 1.720.
[34] *Id.* § 1.720(a).
[35] *Id.* § 1.720(b).
[36] *Id.* § 1.720(c).
[37] *Id.* § 1.720(d).
[38] *Id.* § 1.720(e).
[39] *Id.* § 1.720(e)(1).

regulatory review period for the product.[40] There are also additional procedural requirements.[41]

C. A Brief Primer on the United States Food and Drug Administration (FDA) Regulatory Approval Process

The United States Food and Drug Administration (FDA) describes a five-step Drug Development Process that begins with Discovery and Development (Step 1), where research for new drugs begins in the laboratory setting.[42] During this stage, basic research is performed, compounds are identified, and potential future clinical applications may begin to take shape.[43] This represents the earliest stages of research, and many of the potentially interesting therapeutics that are studied do not make it past this stage.

Step 2 focuses on preclinical research. At this point, potential drugs undergo testing, both in the laboratory and in animal models, with the aim of elucidating information about the safety of the compounds; if the compound has high levels of toxicity, for example, it will not be a viable lead compound for further development into a potential therapeutic.[44] This stage is also the point when researchers submit an Investigational New Drug (IND) application to the FDA, which includes important information regarding testing in humans, the hallmark of Step 3.[45]

Step 3 focuses on clinical research. During this stage, drugs are tested on actual persons, and the outputs are safety and efficacy.[46] In other words, the clinical research has to show that the candidate therapeutic is safe and that it works in the way it is supposed to work. The clinical testing phase includes Phase I trials, which are studies of approximately 20–80 healthy volunteers focusing on the safety and

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[40] *Id.* § 1.720(h).

[41] *See id.* § 1.720(f)–(g). For further information on additional procedural requirements, as well as relevant case law for many of the rules and regulations surrounding patent term extension, see MPEP, Chapter 2700 (9th ed. Jan. 2018).

[42] *The Drug Development Process*, FDA, https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process (last visited Mar. 15, 2020); *U.S. Food and Drug Administration Drug Approval Process*, FDA, https://www.fda.gov/media/82381/download (last visited Mar. 15, 2020).

[43] *Step 1: Discovery and Development*, FDA, https://www.fda.gov/patients/drug-development-process/step-1-discovery-and-development (last visited Mar. 15, 2020).

[44] *Step 2: Preclinical Research*, FDA, https://www.fda.gov/patients/drug-development-process/step-2-preclinical-research (last visited Mar. 15, 2020).

[45] *Id.*

[46] *Step 3: Clinical Research*, FDA, https://www.fda.gov/patients/drug-development-process/step-3-clinical-research (last visited Mar. 15, 2020).

side effects of the compound of interest.[47] Phase II trials are larger and focus instead on efficacy.[48] The main goal of a Phase II study is to collect data to determine whether there is a difference in the treatment of affected individuals given the treatment and affected individuals who are administered a placebo.[49] Phase III studies are even larger than Phase II trials, often containing thousands of patients.[50] These studies focus on understanding safety and efficacy in more detail while studying different populations (e.g., different ages) and appropriate dosages.[51]

Once the data are collected, the process moves onto Stage 4, which is FDA review.[52] During this phase, the New Drug Application (NDA), containing all the data collected from the animal and human testing, pharmacological information, and manufacturing information, is filed by the investigators and reviewed by the FDA. The FDA considers information pertaining to proper labeling and inspects drug manufacturing facilities during this stage. Importantly, it is at this point where "regulatory delay" becomes an important factor relative to patent term and where inventors can "lose" part of their patent term. At this point, the application can be approved, or a response letter may be issued requesting more information or changes to the application. The IND and NDA periods, together, comprise the "regulatory review period" that the patent term extension statute uses as the basis for calculating the length of the extension of the patent term.[53] Finally, during Step 5: post-

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[47] *Id.*

[48] *Id.*

[49] *Id.*

[50] *Id.*

[51] *Id.*

[52] *Step 4: FDA Drug Review*, FDA, https://www.fda.gov/patients/drug-development-process/step-4-fda-drug-review (last visited Mar. 15, 2020).

[53] 35 U.S.C. § 156(g); Note that multiple INDs and NDAs can serve as the basis for multiple PTE applications. Although this lies outside the scope of this Note, this is an important practical consideration for applications for and grants of patent term extension. In short, if more than one NDA is approved on the same day, it appears that there may be more than one first received permission for commercial marketing under section 156(a)(5)(A). Often a product is covered by more than one patent, and INDs and NDAs can also cover more than one patent. As a result, the possibility emerges where an applicant can mix-and-match regulatory review periods for a particular product or patent. For example, if a product is covered by three patents and those patents are covered by two INDs (A and B) and two NDAs (C and D), it could be possible for the applicant to allege four regulatory review periods, as long as C and D were approved on the same day. The result is period 1: AC, period 2: AD, period 3: BC, and period 4: BD. Although an inventor cannot receive more than one extension on the same patent, § 156 (a)(2), there is nothing in the statute about more than one PTE per *product*. Furthermore, the regulations envision such a setup in 37 C.F.R. section 1.785 (Multiple applications for extension of term of the same patent or of different patents for the same regulatory review period for a product). Importantly, the regulation sets forth

marketing safety monitoring, all drugs and devices are regularly monitored by the FDA for safety.[54] This monitoring usually takes place through the submission of safety reports from drug manufacturers to the FDA.

In summary, and for the purposes of this paper, there are two important takeaways with regards to the FDA approval process. First, the process for approval by the FDA is neither quick nor speedy; in fact, the average time to receive approval for a new drug is twelve years.[55] This fact alone underscores why inventors feel PTE is an essential incentive to continue innovating in the space of therapeutics that require regulatory approval. Second, the drug development process clearly illustrates the tension between the patent system and the regulatory approval process, which will be explored further in the following subsection.

D. The Intersection (and Challenges) Between the Patent System and FDA Regulatory Approval

Generally speaking, a drug producer will be unable to market her drug until it is approved, which comes at the end of Step 4, described in the previous subsection. The important, innovative, and influential work that inventors will want to protect with a patent, however, begins much earlier, often even as early as Step 1. The time from the filing of the patent until the end of Step 4, then, represents a time when the inventor is unable to market her drug. This is the precise time that PTE aims to recover.[56]

A hypothetical example clearly illustrates the concept, and it is not difficult to see that the extension of the term may not (and in fact, almost certainly *will* not) recover all of the time lost to regulatory review. Suppose that an inventor files a patent two years after discovering a potential compound, but immediately before entering Step 2 of the drug development stage, which focuses on preclinical research (see Figure 1). The patent clock begins to run, and the twenty-year term has begun, even though the inventor cannot yet begin to practice (i.e., market) her invention as a clinical therapeutic. At this stage, all the inventor can do is exclude others from

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procedural requirements for selecting the final patent to receive the PTE grant, but it does not discuss the possibility of having more than one first permitted commercial marketing and *different* regulatory review periods for the same patent or product.

[54] *FDA Post-Market Drug Safety Monitoring*, FDA, https://www.fda.gov/patients/drug-development-process/step-5-fda-post-market-drug-safety-monitoring (last visited Mar. 15, 2020).

[55] Gail A. van Norman, *Drugs, Devices, and the FDA: Part I: An Overview of Approval Process for Drugs*, 1 JACC: BASIC TO TRANSLATIONAL SCI. 170, 170 (Apr. 2016).

[56] Note that PTE does not recover the Step 1–Step 4 time, but just the time lost to regulatory delay, per section 156 and the promulgated regulations.

practicing the invention, but she can neither sell nor market the drug. Suppose, again, that the regulatory review period takes twelve years, and that the inventor, as a result, is unable to practice her invention for 14 years after the patent term has begun (that is, Steps 2 through 4 in the FDA approval process take 14 years total). The inventor has a remaining six years on her patent term. This hardly seems a fair compensation in light of the twenty-year patent term that an inventor may expect at the outset of filing a patent. Even in this situation, though, the inventor can only recover up to the shorter of five years total extension or 14 years after the approval date of the therapeutic.[57]

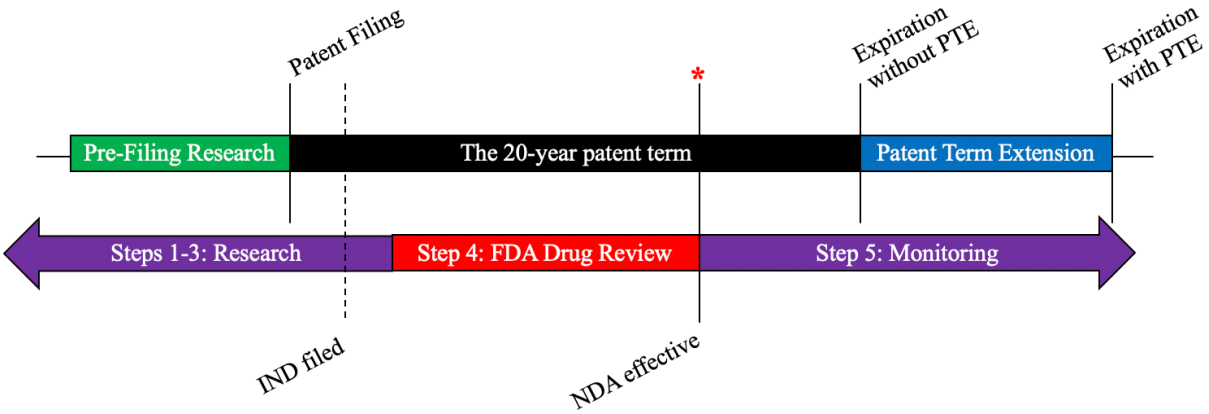

FIGURE 1: A Comparison of the Patent Term and the FDA Drug Approval Process. This example illustrates how the FDA approval process of a drug affects the patent term. In this example, the inventor cannot market her drug until the NDA is effective, which is marked by a red asterisk. The inventor may have filed the patent many years before (at some stage during the research process); this filing will have started the 20-year patent term clock. Patent term extension serves as a way to recover a portion of the term when the inventor could not market her invention because it was not yet approved. In particular, the period of recovery is based on the regulatory review period, or the period from when the IND is effective until the NDA is approved. Note: the times here are approximate and are not drawn to scale, particularly with regards to Steps 1–3, which can last many years before FDA drug review (Step 4) begins. The top bar represents the patent term, and the bottom bar represents the FDA regulatory process.

The statutory framework, interpreted in the context of the FDA approvals process, sheds important light on the balance at play between the goals of patent law (i.e., promoting, and then protecting, innovation) and the mandates and goals of regulatory approvals (i.e., promotion of public health and safety and ensuring that pharmaceutical products are safe and effective before being marketed and sold). It is not clear that the incentives on either side win: although the full patent term may be truncated as a result of the regulatory review process, the patent term extension statute allows for the recovery of only some of that term. On the other hand, the

[57] 35 U.S.C. § 156(g)(6).

regulatory process is allowed to proceed without external pressure from inventors who, in the absence of the statute, may otherwise feel that there is little reason to innovate in this particular space because of the perceived decreased in patent term.

II
PHARMACEUTICAL ACTIVE INGREDIENTS, *PFIZER V. DR. REDDY'S*, AND 35 U.S.C. § 156

Section 156(f)(2) defines a "drug product" as the "active ingredient of . . . a new drug, antibiotic drug, or human biological product . . . or a new animal drug or veterinary biological product . . . including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient."[58] The importance

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[58] *Id.* §§ 156(f)(2)(A)–(B). It should be noted that the terms "drug," "antibiotic drug," and "human biological product" are used as defined in the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 301, *et seq.*) and in the Public Health Service Act (42 U.S.C. § 201, *et seq.*).

The term "drug" is defined in 21 U.S.C. § 321(g)(1) as follows:

> (1) The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C). A food or dietary supplement for which a claim, subject to sections 343(r)(1)(B) and 343(r)(3) of this title or sections 343(r)(1)(B) and 343(r)(5)(D) of this title, is made in accordance with the requirements of section 343(r) of this title is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 343(r)(6) of this title is not a drug under clause (C) solely because the label or the labeling contains such a statement.

The term "antibiotic drug" is defined in 21 U.S.C. § 321(jj) as follows:

> The term "antibiotic drug" means any drug (except drugs for use in animals other than humans) composed wholly or partly of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other drug intended for human use containing any quantity of any chemical substance which is produced by a micro-organism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including a chemically synthesized equivalent of any such substance) or any derivative thereof.

The term "biological product" is defined in 42 U.S.C. § 262(i)(1) as follows:

> (1) The term "biological product" means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic

and relative limitations of this definition become apparent when considering the limited applicable case law in this area, § 156(b) of the PTE statute, and the changing nature of therapeutics (See Section III).

Under § 156(b), patent rights during the extended period apply, in the case of product patents, to any use approved for the product,[59] for method patents, only to any use claimed by the patent and approved for the product,[60] and for method of manufacture patents, only to the method of manufacturing as used to make the approved product.[61] Of particular interest to active ingredients and novel therapeutics is § 156(b)(1), pertaining to product patents, which includes extension for only the approved product.[62] An analysis of the statute shows that the approved product, under § 156(f)(1)(A) is defined, for purposes of the statute, as a "drug product."[63] Under § 156(f)(2), a "drug product" is "the active ingredient of . . . a new drug, antibiotic drug, or human biological product . . . or a new animal drug or veterinary biological product . . . including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient."[64] Therefore, patent term extension for a drug product only covers the approved active ingredient. Although "active ingredient" is not directly defined, the fact that it "includ[es] any salt or ester,"[65] implies that the statutory framework is constructed primarily for application to chemical compounds and active ingredients that are chemically based. As clinical therapeutics evolve and cell-based and gene therapy-based therapeutics continue to play an increasingly important role in clinical treatment, the definition of "active ingredient" will need to be expanded, or at the very least, adjusted. Right now, the statutory definition that focuses on chemical formulations simply does not provide enough definitional coverage to clearly elucidate what is or will be considered an "active ingredient" for purposes of patent term extension.

Interpretations of the statute in case law have provided limited guidance in terms of applying this framework outside of the context of chemical compounds. A leading case in the area of patent term extension and active ingredient interpretation

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compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

[59] 35 U.S.C. § 156(b)(1).

[60] *Id.* § 156(b)(2).

[61] *Id.* § 156(b)(3)(A); § 156(b)(3)(B) includes a separate requirement that the product must have been subject to a regulatory review period as described in § 156(g)(1), (4), and (5).

[62] *Id.* §156(b)(1).

[63] *Id.* § 156(f)(1)(A).

[64] *Id.* § 156(f)(2).

[65] *Id.* § 156(f).

is *Pfizer, Inc. v. Dr. Reddy's Laboratories, Ltd*.[66] In this case, the United States Court of Appeals for the Federal Circuit asked whether patent term extension applies to all salts of a molecule covered by the patent or only to the particular salt covered by the patent. The majority held that PTE applies to all salts because of the provision in § 156(f) that states that the active ingredient, "includ[es] any salt . . . of the active ingredient."[67]

Pfizer held a patent (Patent No. 4,572,909; the '909 patent) claiming "certain dihydropyridine compounds and their acid additional salts," including amlodipine and its salts.[68] Importantly, Pfizer had obtained federal registration on a drug product with amlodipine (a dihydropyridine compound) as the active ingredient, but only as the besylate salt formulation.[69] Dr. Reddy's Laboratories, a producer of generics, filed a new drug application that would permit them to market the amlodipine maleate formulation of the drug.[70] Interestingly, Dr. Reddy's conceded that the '909 patent covered both amlodipine besylate and amlodipine maleate, but argued that the patent term extension only covered amlodipine besylate because that was what Pfizer had pursued in its regulatory proceedings due to the ease of tableting that particular formulation.[71]

The Court determined that the active ingredient for purposes of patent term extension was amlodipine, and therefore, it did not matter whether it was administered as the besylate or maleate salt,[72] particularly in light of the provision in § 156(f) that states that active ingredients include salts and esters of the active ingredient. As a result, the term extension for the '909 patent could not be limited only to the besylate formulation, and Dr. Reddy's could not produce the maleate version of the drug during the extended period of protection.[73] However, in a dissenting opinion, Judge Mayer emphasized that the majority inappropriately excluded § 156(a)(4) from its interpretation, which provides that eligibility for patent term extension requires that the product must "ha[ve] been subject to a regulatory review period before its commercial marketing or use."[74] In the dissent's view, this means that the only product eligible for patent term extension was amlodipine

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[66] Pfizer, Inc. v. Dr. Reddy's Labs., Ltd., 359 F.3d 1361 (Fed. Cir. 2004).
[67] *Id.* at 1366–67; 35 U.S.C. § 156(f).
[68] *Pfizer*, 359 F.3d at 1363.
[69] *Id.*
[70] *Id.* at 1364.
[71] *Id.* at 1363–64.
[72] *Id.* at 1366.
[73] *See id.* at 1366–67.
[74] *Id.* at 1367 (Mayer, J., dissenting); 35 U.S.C. § 156(a)(4).

besylate and neither amlodipine alone nor amlodipine maleate; after all, neither amlodipine alone nor amlodipine maleate were subject to regulatory review. The dissent would have Dr. Reddy's Laboratories beginning to produce amlodipine maleate during the extension that Pfizer had received and would consider the extension as covering amlodipine besylate alone.

The debate between the majority and dissenting opinions in this case illustrates the potential real-world and market effects of defining an active ingredient in one way or another. Although there may be no difference in treatment, efficacy, administration, or formulation with differing active ingredient salts (in *Dr. Reddy's*, between amlodipine maleate and amlodipine besylate), restricting the active ingredient definition would permit competitors to potentially alter (and impinge upon) the inventor's ability to exclude. Under the dissent's approach, incentives for drug development could begin to suffer. Inventors could be placed in a squeeze between losing portions of the patent term to regulatory review when they cannot market their yet-to-be approved drug, and having their term extension eroded by competitors who are able to begin production and marketing on an equivalent—albeit slightly different—formulation before the full extended term has elapsed. The majority opinion, on the other hand, is more patentee-friendly in that it permits a patent holder to claim exclusivity, in some way, over variants of the same active ingredient, rather than in only one specified chemical compound.

Dr. Reddy's has played an important role in interpreting the active ingredient provision of § 156, and the case remains good law, but its interpretation remains limited to therapeutics that are comprised of chemical compounds. In addition to *Dr. Reddy's*, there has been a string of other cases that are relevant to the interpretation of "product" and "active ingredient" for purposes of PTE. In *Ortho-McNeil Pharmaceutical v. Lupin Pharmaceuticals*,[75] the Federal Circuit held that the approval of an enantiomer[76] qualifies as the first permitted commercial marketing or

[75] Ortho-McNeil Pharm. v. Lupin Pharms., 603 F.3d 1377 (Fed. Cir. 2010).

[76] Enantiomers are pairs of molecules that are mirror images of each other. The traditional example to explain enantiomers are left and right hands—they are mirror images of each other and cannot be superimposed. Different enantiomers of the same molecule can have vastly different clinical effects. Thalidomide, a drug that was used to treat morning sickness in pregnant women, resulted in 10,000 infants born with limb malformation. *See generally Molecule of the Week Archive: Thalidomide*, AM. CHEMICAL SOC'Y (Sept. 1, 2014), https://www.acs.org/content/acs/en/molecule-of-the-week/archive/t/thalidomide.html. The culprit was determined to be only one of the two enantiomers. Blaschke, Kraft, Fickentscher & Köhler, *Chromatographic Separation of Racemic Thalidomide and Teratogenic Activity of Its Enantiomers*, 29 ARZNEIMITTELFORSCHUNG 1640 (1979). Additional research has come out that illustrates that the enantiomers interconvert in vivo, suggesting that the enantiomeric explanation

use of the product when the racemate[77] had been previously approved. The underlying rationale is that the enantiomer is a different drug product than the racemic mixture and, thus, it required its own regulatory approval before marketing and use.[78] In *Hoechst-Roussel Pharmaceuticals, Inc. v. Lehman*,[79] the Federal Circuit held that claims to a metabolite were not eligible for patent term extension because the metabolite was not part of the active ingredient that is present in the formulation administered to the patient.[80] Taken together, these cases illustrate that a salt or ester of an active ingredient is eligible for patent term extension, a metabolite is not, and an enantiomer is, at least in cases where the racemic mixture has already received approval. While these are all important developments in the law, none provides instructive guidance for dealing with therapeutics that are not chemically based.

An additional case, *PhotoCure ASA v. Kappos*[81] may, however, be of limited instructive value in considering how to deal with the active ingredient problem. The Federal Circuit held that "product," for purposes of patent term extension, means the product subject to regulatory approval, not the active ingredient of the formulation.[82] Under this approach, then, it may be important to understand the approved product rather than what may be an "active ingredient." Interestingly, the approved product often *is* the active ingredient, and even in cases of complex therapeutics that are not chemically based, this distinction may still prove insufficient. Taken together with the previously discussed case law, however, the application to and coverage of these cases do not cover novel therapeutics that are not comprised of chemical compounds.

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for limb malformation is possibly more complex than previously thought. Etsuko Tokunaga, Takeshi Yamamoto, Emi Ito & Norio Shibata, *Understanding the Thalidomide Chirality in Biological Processes by the Self-Disproportionation of Enantiomers*, 8 NATURE SCI. REPS., Article Number 17131 (2018).

[77] A racemate is a mixture that contains both enantiomers, or mirror-image, non-superimposable molecules. To continue the "hand example," a racemic mixture of hands would contain both right hands and left hands. *See supra* note 76.

[78] *Ortho-McNeil Pharm.*, 603 F.3d 1381.

[79] Hoechst-Roussel Pharms., Inc. v. Lehman, 109 F.3d 756 (Fed. Cir. 1997).

[80] *Id.* at 759 n.3 (stating that the patent term extension defines "product" as "active ingredient" of a drug that receives FDA approval, and that for purposes of patent term extension, this particular active ingredient must be present in the drug when it is administered to the patient).

[81] PhotoCure ASA v. Kappos, 603 F.3d 1372 (Fed. Cir. 2010).

[82] *Id.* at 1376–77.

The developed caselaw thus ultimately remains limited at best and inapplicable at worst.[83]

III
CHANGING THERAPEUTICS

As Section II described and established, the current case law and statutory interpretation frameworks do not factor in the myriad advances in technology and therapeutics that have been developed in recent years. In short, the current framework for determining the active ingredient of a pharmaceutical or therapeutic product for purposes of patent term extension is not easily applied beyond chemical compounds and salt formulations. Yet, there are many novel, exciting, and valuable therapies focused on cellular and gene therapy-based products that involve genetic engineering and patient-tailored formulations.[84]

A. Active Ingredients in Currently Approved Cellular and Gene-Based Therapeutics

To begin to understand how patent term extension can be calculated for "active ingredients" of cellular and gene-based therapies, it is first important to ask what the active ingredients of those treatments are according to the FDA and those marketing these products. In other words, why does the current framework not apply to these therapeutics, and how *might* it apply? It is only then that we can begin to understand how to develop a more applicable framework.

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[83] There is an additional case in this area of jurisprudence that tackles similar themes, although it was issued prior to any of the cases discussed in text. In *Glaxo Operations UK Ltd. v. Quigg*, the Court held that a patentee was entitled to a grant of patent term extension for an ester of a compound which was therapeutically active and effective when orally administered even though two of the salt formulations of the compound had already been approved by the FDA. Glaxo Operations UK Ltd. v. Quigg, 894 F.2d 392 (Fed. Cir. 1990). Relying on the plain language of the statute, the Court focused on the fact that the formulation in question was an ester, and "product"/"active ingredient" in § 156 of the statute includes esters.

[84] Personalized medicine is a growing area of clinical therapeutics. Sunil Mathur & Joseph Sutton, *Personalized Medicine Could Transform Healthcare*, 7 BIOMEDICAL REPS., 3, 3 (2017). In some sense, personalized medicine is fueling (or at least contributing to) the active ingredient problem—as treatments for individual patients become more patient-specific and patient-tailored, a treatment for the same disease or condition can take on different genetic, molecular, and compositional characteristics that make them harder to define as a homogenous genus.

The FDA currently has seventeen approved cellular and gene therapy-based products,[85] which pales in comparison to the 20,000+ FDA products approved for marketing, nearly all of which contain chemical compounds as active ingredients.[86] Remarkably, eight of the sixteen approved cellular and gene-therapy based products are for cord blood.[87] Cord blood, or blood that has been isolated from an umbilical cord, is a rich source of stem cells. Stem cells have a high degree of plasticity, meaning that, under appropriate conditions, they can be transformed into many types of cells in the body and thus, have a high potential for reparative and therapeutic benefit. In particular, cord blood is especially valuable for patients suffering from various types of blood cancers.[88] Cord blood can be used for "immunologic reconstitution," which is the establishment of a new population of healthy and non-cancerous blood cells and blood components in the previously affected patient.

In the particular case of the cord blood products, the active ingredient of the formulation is listed as hematopoietic progenitor cells expressing CD34 (CD34+ cells).[89] In other words, the active ingredient is a stem cell (i.e., a full cell) that expresses a particular protein on its surface. Although this may sound specific to the non-specialist, there is an important consideration to be made regarding CD34: it is found on *all* hematopoietic stem cells,[90] meaning that it is not as specific an identifier as one may perhaps expect. At this point, a comparison to a chemical compound is in order: for chemically based therapeutics, the active ingredient is comprised of a homogenous mixture of synthesized or isolated compound. There is, or should be, nothing more, and nothing less. In the case of cellular therapeutics, this is not the

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[85] *Approved Cellular and Gene Therapy Products*, FDA, https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products (last visited Mar. 16, 2020).

[86] *Id.*; *Fact Sheet: FDA at a Glance*, FDA, https://www.fda.gov/about-fda/fda-basics/fact-sheet-fda-glance (last visited Mar. 16, 2020).

[87] *Approved Cellular and Gene Therapy Products*, *supra* note 85.

[88] *See, e.g.*, Justyna Ogonek, Mateja Kralj Juric, Sakhila Ghimire, Pavankumar Reddy Varanasi, Ernst Holler, Hildegard Greinix & Eva Weissinger, *Immune Reconstitution after Allogenic Hematopoietic Stem Cell Transplantation*, 7 FRONTIERS IN IMMUNOLOGY, 1 (2016).

[89] FDA-approved products in this group are Allocord, Ducord, Clevecord, Hemacord, Cord Blood (Clinimmune Labs), Lifesouth Cord Blood, and Bloodworks Cord Blood. *Approved Cellular and Gene Therapy Products*, *supra* note 85.

[90] CD34 is a glycophosphoprotein that is expressed on the surface of early-stage developmental cells (i.e., stem cells) that will develop and differentiate into the various types of cells that comprise blood. It is unsurprising, then, that it is found in cord blood, since cord blood is rich in stem cells that are capable of constituting the entire complement of blood (e.g., red blood cells, white blood cells, etc.); *see, e.g.*, D.S. Krause, M.J. Fackler, C.I. Civin & W.S. May, *CD34: Structure, Biology, and Clinical Utility*, 87 BLOOD, 1 (1996).

case. In fact, some of the therapeutics are comprised of complex, heterogeneous mixtures, or are comprised of more than one "active ingredient" or component, which will be illustrated in the following discussion.

1. Autologous and Allogenic Cell-Based Therapeutics

The remaining seventeen FDA approved cellular and gene therapy-based products can be grouped into several classes. The first class contains products with listed active ingredients that contain autologous cells, or cells that have been harvested from the patient and will be readministered to the same patient after undergoing some modification or reprogramming. Interestingly, and in almost all cases, the FDA-listed active ingredients are *lists* rather than *individual components*. As the examples will illustrate, this immediately calls into question the applicability of the "active ingredient" definition in § 156 to these types of therapies.

Matrix-applied characterized autologous cultured chondrocytes (MACI)[91] have been approved for cartilage repairs and defects of the knee. The active ingredient is listed as 1) autologous cultured chondrocytes (collagen-producing cells harvested from, and then readministered to, the patient), and 2) porcine (i.e., derived from a pig) Type I/III collagen. The patient's own cells are embedded on a collagen matrix (the porcine collagen), which is then implanted into the patient's knee.[92] The patient's cartilage cells regenerate on the matrix and repair tissue that may have been damaged by injury or another condition.[93]

Also belonging to this class is Laviv (Azficel-T), which has been approved for the improvement of the appearance of moderate to severe nasolabial fold wrinkles (i.e., the wrinkles/folds that extend from the bottom of the nose to the corners of the mouth, commonly referred to as smile lines) in adults, and interestingly, an active ingredient is not listed.[94] Instead, the FDA filing notes that it includes autologous skin cells.[95] This class also contains Provenge, a treatment for prostate cancer. The active ingredient of Provenge is autologous peripheral blood

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[91] *See The MACI Story*, MACI, https://www.maci.com/healthcare-professionals/the-maci-story/index.html (last visited Mar. 16, 2020).

[92] *How MACI Works*, MACI, https://www.maci.com/patients/how-maci-works/the-maci-procedure.html?gclid=EAIaIQobChMIgLCfn9765wIVAT0MCh0CBQWZEAAYASABEgJdxPD_BwE (last visited Mar. 16, 2020).

[93] *Id.*

[94] *Approved Cellular and Gene Therapy Products*, *supra* note 85.

[95] *Id.*

cells,[96] including a particular class of immune cells, called antigen presenting cells, as well as an immune cell activator.

A subset of this class includes Gintuit, a topical scaffold application for use in mucogingival (i.e., oral) wound treatment. The active ingredient is listed as allogenic keratinocytes, allogenic dermal fibroblasts, and bovine Type I collagen. Although the cells in this formulation are allogenic, meaning that they are isolated from a compatible donor, instead of autologous, meaning they are isolated from the patient directly, Gintuit still falls into the class of cell-based therapeutics.

This class also contains Yescarta® and Kymriah™, the two chimeric antigen receptor T- cell (CAR T-cells) treatments. T-cells are a particular type of immune cell that are primarily responsible for mediating our bodies' responses against foreign "invaders," including bacteria, viruses, and even self-cells that have begun to exhibit signs and patterns of becoming pre-cancerous. CAR T-cell treatments involve isolating a particular set of T-cells from a cancer patient, reprogramming the cells to target the cancerous cells, and then reintroducing the cells to the patient in the hopes that the reprogrammed cells specifically target the cancerous cells while leaving non-cancerous cells intact.[97]

The goal of CAR T-cell therapy is to treat cancer using a patient's own immune system.[98] Interestingly, both Yescarta® and Kymriah™ list an engineered T-cell as the active ingredient (axicabtagene ciloleucel for Yescarta® and

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[96] Peripheral blood is blood that is circulating through a living organism and that is not sequestered in the lymphatic system, spleen, liver, bone marrow, or other organ.

[97] *See, e.g.*, Androulla N. Miliotou & Lefkothea C. Papadopoulou, *CAR T-cell Therapy: A New Era in Cancer Immunotherapy*, 19 CURRENT PHARM. BIOTECHNOLOGY, 5 (2018).

[98] Some have described CAR T-cell therapies as heralding a "new era" of cancer treatments. *See, e.g.*, *id.*; Rimjhim Mohanty, Chitran Roy Chowdhury, Soloman Arega, Prakriti Sen, Pooja Ganguly & Niladri Ganguly, *CAR T Cell Therapy: A New Era for Cancer Treatment*, 42 ONCOLOGY REPS., 2183, 2183 (2019). In a CAR T-cell therapy, a patient's T lymphocytes, a class of immune cells (e.g., white blood cells) that are responsible for detecting and destroying foreign invaders, are reprogramed to target cancerous cells. Interestingly, T-cells can also play a role in detecting internal invaders (i.e., cells that are no longer growing and dividing properly—cancer cells). In a CAR T-cell therapy, T-cells are engineered to express a chimeric antigen receptor (CAR). A CAR is a surface receptor that has been engineered to recognize and target the previously described "internal invaders" (i.e., cancer cells), while leaving normally growing and reproducing cells intact. The process involves isolating the cells from the patient, reprogramming them, growing them in cell culture in the lab, and readministering them to the patient. *NCI Dictionary of Cancer Terms: CAR T-cell Therapy*, NAT'L CANCER INST., https://www.cancer.gov/publications/dictionaries/cancer-terms/def/car-t-cell-therapy (last visited Mar. 16, 2020).

tisagenlecleucel for Kymriah™). Personalized treatments such as this are interesting to explore when considering active ingredients and patent term extension: if one developed ten CAR T-cell treatments for ten different patients, the cells in each of the ten treatments would be individualized to each patient and thus different from the other nine. How, then, can a treatment that is personalized to each patient have a consistent active ingredient? The patent term extension application for Yescarta® highlights this issue and provides an important case study in this area, emphasizing the need for the law to catch up quickly. Since the application has introduced particularly interesting issues with regards to active ingredients in the context of patent term extension, and given the importance of and recent attention given to CAR T-cell therapies, I will return to the Yescarta® patent term extension application and subsequent follow up as a case study in subsection III.C.

2. Gene Therapy-Based Therapeutics

Another class of approved therapeutics are gene therapy-based therapeutics. Gene therapy is any treatment that seeks to modify the recipient's DNA with the aim of ameliorating a genetic mutation or defect.[99] To more fully understand gene therapies, it is important to first understand the central dogma of molecular biology, which, in brief, states that the DNA in our cells contains information that is translated into a functional protein through an intermediate molecule called mRNA.[100] If there is a problem with the source material (the DNA), then there will likely be a problem with the functional protein. Gene therapy aims to correct this type of underlying issue by replacing the non-functional or malfunctioning DNA with the correct information.

This class of FDA approved products includes Imlygic and Andexxa. Imlygic, which lists talimogene laherparpvec (genetically modified attenuated Herpes

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[99] *What is Gene Therapy?*, NIH, https://ghr.nlm.nih.gov/primer/therapy/genetherapy (last visited Mar. 16, 2020).

[100] The central dogma of molecular biology, in its simplest formulation, describes information flow in a living organism. In the central dogma, DNA can be thought of as a blueprint that contains all the information required for an organism to grow, develop, and maintain itself. The information in DNA encodes proteins, which are the actual cellular components that carry out biochemical processes encoded in DNA. RNA acts as an intermediary molecule between DNA and proteins. The central dogma describes the flow of information from DNA to RNA to protein. It also states that information cannot be transferred from one protein to another protein or from a protein to DNA or RNA. This is (more or less and for purposes of this discussion) a one-way street. *See, e.g.*, Francis Crick, *Central Dogma of Molecular Biology*, 227 NATURE 561 (1970). The actual situation is far more complex than described here, but the central dogma represents a central tenet of molecular biology and information flow and transfer in living systems.

Simplex Virus-1) as its active ingredient, is an oncolytic viral therapy.[101] This means it uses tumor-targeted viruses to fight cancer. Andexxa, which lists its active ingredient as a genetically modified variant of human factor Xa, is a coagulation factor, which can be used in patients with blood-clotting disorders.[102] Interestingly, Luxturna, an adeno-associated virus (AAV) vector-based gene therapy used in the treatment of Leber congenital amaurosis,[103] does not have any listed active ingredient.

Gene therapy-based therapeutics are also beginning to test the applicability of our current active ingredient framework in ways different from cell-based therapeutics. An important factor with regards to gene therapies are their composition: a gene-based therapeutic must contain the genetic material that is to be delivered to the recipient as well as a vector, or carrier. In the case of gene therapies, the carrier is a viral capsid[104] which encapsulates the genetic material to be delivered to the recipient patient. As a result, an emerging question in this area is whether the active ingredient is or should be considered the genetic information alone or the genetic information coupled with the viral vector, which could be considered part of the delivery or drug formulation. Including the vector as part of the formulation, instead of as part of the active ingredient, could prevent controversy in terms of infringement, given that similar or identical vectors are often used for the administration of vastly different therapeutics with varying targets.[105]

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[101] Oncolytic viral therapies use lytic viruses that are targeted to tumors. Lytic viruses have the ability to lyse, or destroy, particular cells. *See, e.g.*, *Oncolytic Virus Therapy: Using Tumor-Targeting Viruses to Treat Cancer*, NAT'L CANCER INST., https://www.cancer.gov/news-events/cancer-currents-blog/2018/oncolytic-viruses-to-treat-cancer (last visited Mar. 16, 2020).

[102] *Approved Cellular and Gene Therapy Products*, *supra* note 85.

[103] Leber congenital amaurosis is an eye disorder that results in severe visual impairment from infancy. In addition to vision problems, patients with the disorder may have other vision problems including sensitivity to light, involuntary movement of the eyes, and extreme farsightedness. *Leber Congenital Amaurosis*, NIH, https://ghr.nlm.nih.gov/condition/leber-congenital-amaurosis (last visited Mar. 16, 2020).

[104] A viral capsid can be thought of as a shell comprised of proteins that surround and protect the viral genetic material. *See, e.g.*, W.H. Roos, I.L. Ivanovska, A. Evilevitch & G.J.L. Wuite, *Viral Capsids: Mechanical Characteristics, Genome Packing and Delivery Mechanisms*, 64 CELLULAR AND MOLECULAR LIFE SCIS. 1484, 1484 (2007).

[105] In January 2020, the FDA issued Draft Guidance for Industry entitled, *Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations*. In the guidance, the FDA proposes the following. First, two gene therapy products expressing different transgenes and having or using different vectors will be considered different drugs. Next, two gene therapy products expressing different transgenes but having or using the same vector will also be considered different drugs. Finally, gene therapy products having or using vectors from different

B. Defining the Active Ingredient Problem in Light of Current Therapeutics

The awkwardness and cumbersome nature of describing active ingredients as "engineered T-cells" or "allogenic keratinocytes, allogenic dermal fibroblasts, and bovine Type I collagen" suggests that the basic approach to identifying active ingredients in pharmaceutical formulations has already begun to show cracks. How can a full cell, which is far more complex than an individual chemical compound, and of which there is a great degree of cell-to-cell variability, be considered an "active ingredient"? In fact, a major benefit of chemical compound-based therapeutics is that, with appropriate manufacture, testing, and monitoring, patients can be certain that the active ingredient they receive when taking a particular therapeutic is identical from dose to dose: there is not, and in fact, *must* not be any variability from dose to dose or manufacture to manufacture. In other words, all patients receive the same exact treatment.

In cell-based therapies, however, this framework breaks down, and new approaches are needed. Many cell-based therapies are *centered* on the fact that each patient can be treated individually with the hopes of being able to specifically use the patient's reprogrammed cells to better combat the patient's ailment with decreased chances of negative side effects, tissue rejection, or unsuccessful treatment. CAR T-cell therapies, for example, operate under the assumption that the engineered T-cell will be *specific* to each patient and that these patient-specific cells will be reprogrammed in a particular way that results in a patient-targeted therapy. Thus, when describing active ingredients in cell-based therapeutics, a major difference is that the active ingredient will, at some level, *differ* from patient to patient. How then can an active ingredient be adequately described in light of this therapeutic heterogeneity?

This development in clinical therapeutics, broadly speaking, represents a paradigmatic shift in terms of how treatments are developed, administered, and considered successful; the shift does not, however, only affect clinicians and patients, but also inventors, regulators, manufacturers, and distributors.

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viral classes will be considered different drugs, even if they include the same transgene. Determinations of whether two vectors are the same will be made on a case-by-case basis, and minor differences in transgenes and vectors will not count as actual differences between two transgenes or two vectors. The FDA will receive comments on this proposed Guidance until July 28, 2020. *Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations*, FDA, (Jan. 2020) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/interpreting-sameness-gene-therapy-products-under-orphan-drug-regulations (last visited May 17, 2020).

C. The Yescarta® CAR T-Cell Therapy Case Study

The active ingredient problem is not imaginary; in fact, we are already seeing the challenges of active ingredient determinations in novel therapeutics. Recent PTE applications have revealed the challenges surrounding active ingredients in cell-based therapeutics and emphasize the need for a clearer framework as we move forward.

Yescarta®, a CAR T-cell cancer therapy used to treat B-cell lymphoma, is a prime example that illustrates the difficulties surrounding the definition of "active ingredient" in light of these novel cell-based therapies. The 2017 10-K SEC filing for Gilead, the parent company that produces Yescarta®,[106] included information that it had a pending patent term extension application for United States Patent Number 7,741,465 (the '465 Patent) filed to recover part of the patent term for Yescarta® that had been lost as a result of the regulatory review period.[107] A further investigation revealed that a patent term extension application for the '465 patent had initially been filed on December 14, 2017,[108] and the USPTO issued a "Requirement for Information" on April 3, 2018[109] requesting a further elaboration of the active ingredient of the CAR T-cell therapy. The letter also stated that an active ingredient had not yet been disclosed:

> Clearly, the lymphocytes differ from patient to patient since the drug is designed for each particular patient. Each patient will have its own unique lymphocyte cells therefore the active ingrediant [sic] cannot be the cells obtained from the patient. The antibody that is expressed on the cell surface is also not an active ingrediant [sic] because it has not been defined in the Application as filed.[110]

Although a Request for Information is not a binding regulation from the USPTO, it suggests that patent examiners are already struggling with exactly how

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[106] Gilead exclusively licenses a patent from Cabaret for Yescarta® in the oncology field. *Cabaret Biotech Files Lawsuit Against Gilead Over Yescarta Drug*, BLOOMBERGLAW (Sept. 16, 2019, 4:45 PM) https://news.bloomberglaw.com/pharma-and-life-sciences/cabaret-biotech-files-lawsuit-against-gilead-over-yescarta-drug.

[107] Gilead, Annual Report (Form 10-K), available at https://www.sec.gov/Archives/edgar/data/882095/000088209518000008/a2017form10-k.htm (2017).

[108] Application for Patent Term Extension, U.S. Patent No. 7,741,465 (filed Dec. 15, 2017).

[109] Requirement for information sent under 37 C.F.R. 1.750, U.S. Patent No. 7,741,465 (Apr. 3, 2018).

[110] *Id.*

to evaluate what active ingredients are or should be in the context of cellular therapeutics. Interestingly, this PTO communication also emphasizes two important concerns, one of which has been previously highlighted in this Note: 1) many of these therapeutics are not as homogenous in their composition as chemical-based therapeutics are, and the heterogeneous solution cannot be an active ingredient, and 2) additional aspects of the drug formulation that are not defined in the regulatory filings cannot be considered the active ingredient.

In a letter from the USPTO to the FDA dated August 7, 2018,[111] the USPTO further stated the challenge they faced:

> Applicant is seeking to extend [the '465 Patent] based on the regulatory review and approval of YESCARTA® (axicabtagene ciloleucel), where the product is comprised of non-disclosed components of lymphocytes, differs from patient to patient, and is produced with a non-disclosed vector type expressing non-disclosed chimeric DNA. Applicant has failed to provide a sufficient detailed disclosure of the product such that the Office can determine compliance with the eligibility requirements of 35 U.S.C. § 156, because no specific elements which form the product are disclosed. It is therefore concluded, in order to determine the rights that will be derived from the extension . . .
>
> [that] the information provided is not adequate for the Office to determine eligibility of YESCARTA® (axicabtagene ciloleucel).[112]

Despite the FDA's and applicant's response on June 19, 2018,[113] the USPTO remained unconvinced. In a seemingly unconventional response, the USPTO presented the FDA with information gathered "through its own diligence,"[114] including "the sequence and chemical identity of YESCARTA®" obtained "through information submitted to the World Health Organization to establish a generic name for YESCARTA® (axicabtagene ciloleucel) under the International Nonproprietary Name (INN) conventions . . ."[115] In short, the USPTO "requested that FDA confirm

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[111] Second letter to regulating agency to determine regulatory review period, U.S. Patent No. 7,741,465 (Aug. 7, 2018).

[112] *Id.*

[113] Transaction for FDA Determination of Regulatory Review Period, U.S. Patent No. 7,741,465 (June 19, 2019).

[114] Second letter to regulating agency, *supra* note 111.

[115] *Id.*; International Nonproprietary Name (INN) conventions are rules that, according to the World Health Organization (WHO), "facilitate the identification of pharmaceutical substances or

that the vector and sequence disclosed in the attached information from the World Health Organization does describe the approved YESCARTA® (axicabtagene ciloleucel) product."[116]

The FDA accepted this information and moved forward with its determination of the regulatory review period as required by § 156(d)(2)(A),[117] making a final regulatory review period determination, pursuant to notice and comment procedures,[118] on December 26, 2019.[119] As of May 17, 2020, no PTE had been granted for Yescarta®, but the process was fully underway, even despite its unconventional history and the novel situation it presented. In some sense, it appears that the question of a homogenous active ingredient was skirted in the communications between the USPTO and the FDA, as the USPTO provided to the FDA what it would consider appropriate for furthering the inter-agency communications for determining patent term extension. Although the situation has not been resolved (i.e., the PTE has not yet been granted), the above process provides important information on what concerns the USPTO has and how they may be overcome.

IV
POTENTIAL SOLUTIONS

Although the USPTO may have shed some light on what it accepts as appropriate information for fulfilling the requirements of 35 U.S.C. § 156, there are two important lessons to acknowledge. First, the Yescarta® case study represents a single data point, and further efforts to obtain PTE on cellular and gene-based therapeutics may be instructive in elucidating how the USPTO and the FDA may continue to navigate this new terrain. Second, just because the USPTO has provided a way forward, it does not preclude the possibility of additional, less challenging and novel paths forward for PTE on these novel classes of therapeutics. The remainder of this Note explores some of these potential paths forward, addressing the benefits and potential drawbacks associated with each.

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active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property. A nonproprietary name is also known as a generic name." *Essential Medicines and Health Products: International Nonproprietary Names*, WHO, https://www.who.int/medicines/services/inn/en/ (last visited Mar. 16, 2020).

[116] Second letter to regulating agency, *supra* note 111.

[117] *Id.*; 35 U.S.C. § 156(d)(2)(A).

[118] Transaction for FDA Determination, *supra* note 113; Determination of Regulatory Review Period for Purposes of Patent Extension; YESCARTA, 84 Fed. Reg. 18,055 (Apr. 29, 2019).

[119] FDA Final Eligibility Letter, U.S. Patent No. 7,741,465 (Dec. 26, 2019).

A. Monoclonal Antibody-Based Therapeutics and the Sameness Analysis

Monoclonal antibody-based therapeutics are affected by many of the same challenges that affect cellular and gene-based therapies. For example, antibodies are more analogous to cellular and gene-therapies, in that they are, at least on a molecular scale, large and complex.[120] Furthermore, there have been challenges with defining the active ingredient[121] and how to determine whether such complex molecules are the "same" or "different."[122] Finally, clinical formulations may exhibit non-clinically relevant batch-to-batch variation that results in a slightly different antibody composition, but that, importantly, does not affect drug function or efficacy. A central question surrounding antibody-based treatments is what precisely counts as the "same" given the inherent variability between production batches and the lack of homogeneity within production batches.

In April 2014, the FDA issued a Guidance for Industry, entitled *Interpreting Sameness of Monoclonal Antibody Products Under the Orphan Drug Regulations*.[123] In its Guidance, the FDA turned to the "sameness" analysis found in the FDA Orphan Drug regulations.[124] Under these regulations, an antibody-containing drug is the same as another antibody-containing drug if it "contains the same principal molecular structural features (but not necessarily all of the same structural features) and is intended for the same use as a previously approved drug . . . ."[125] An antibody-containing therapeutic is "different" from an approved antibody-containing therapeutic if it is either demonstrated that 1) it is chemically or structurally distinct from an approved orphan drug, or 2) it is "clinically superior" to the approved orphan

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[120] It is important to note an essential difference between antibodies and cellular and gene-based therapeutics: while antibodies are macromolecules, neither cellular therapeutics nor gene-based therapeutics are.

[121] *See* Malgotzata Kesik-Brodacka, *Progress in Biopharmaceutical Development*, 63 BIOTECHNOLOGY AND APPLIED BIOCHEMISTRY, 306, 306–07 (2018).

[122] *See id.*

[123] *Interpreting Sameness of Monoclonal Antibody Products Under the Orphan Drug Regulations*, FDA (Apr. 2014) https://www.fda.gov/files/vaccines,%20blood%20&%20biologics/published/Interpreting-Sameness-of-Monoclonal-Antibody-Products-Under-the-Orphan-Drug-Regulations.pdf (last visited Mar. 16, 2020).

[124] *See Orphan Drug Regulations: Regulatory History*, FDA, https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-regulations-regulatory-history (last visited Mar. 16, 2020).

[125] 21 C.F.R § 316.3(b)(14)(ii).

drug.[126] The sameness analysis focuses on two separate aspects of the therapeutic that are directly relevant to antibody-based therapeutics: structure and efficacy.

In its Guidance, the FDA acknowledges "diversity" that results from the antibody production process—something which is also seen particularly in cellular therapeutics—and states that, "[b]ecause of the many processes involved in generating antibody diversity, it is unlikely that independently derived monoclonal antibodies with the same antigen specificity will have identical . . . sequences."[127]

Currently, there is a "sameness analysis" for other types of drugs that is used for purposes of determining whether a drug is different from an approved orphan drug.[128]

- Two protein drugs are considered the same if the differences are due to post-translational events or minor differences in amino acid sequences (antibodies fit in this bin).
- Two polysaccharide drugs are considered the same if they have identical saccharide repeating units, even if there are a different number of repeating units.
- Two polynucleotide drugs are considered the same if they contain identical sequences of purine and pyrimidine bases bound to an identical sugar backbone.
- Vaccines for the same indication are considered the same unless the subsequent drug is clinically superior.

These classes illustrate an important point: none of them relies on the determination of an active ingredient that is chemically based. It then seems reasonable to consider developing a sameness analysis for cellular and gene-based therapies. For example, two CAR T-cell therapies could be considered the same because they are defined as an autologous treatment aimed at treating a particular

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[126] An orphan drug is a pharmaceutical that is commercially underdeveloped because it has limited potential for profitability. These drugs are often used for treatment in rare diseases. *See, e.g.*, *Designating an Orphan Product: Drugs and Biological Products*, FDA, https://www.fda.gov/industry/developing-products-rare-diseases-conditions/designating-orphan-product-drugs-and-biological-products (last visited Mar. 16, 2020); *NCI Dictionary of Cancer Terms: Orphan Drug*, NAT'L CANCER INST., https://www.cancer.gov/publications/dictionaries/cancer-terms/def/orphan-drug (last visited Mar. 16, 2020). For more information on orphan drugs and their uses, see *List of FDA Orphan Drugs*, NIH, https://rarediseases.info.nih.gov/diseases/fda-orphan-drugs (last visited Mar. 16, 2020).

[127] *Interpreting Sameness of Monoclonal Antibody Products*, *supra* note 123, at 2–3.

[128] *Id.*

type of cancer. Another example could be that two cell-based therapies are considered the same because they contain the same types of cells targeted to fight the same disease, even if the cell has been programmed to be patient-specific. In the context of gene therapies, two therapeutics could be considered the same if they contain the same genetic material, targeting the same disease, enclosed in the same capsid. Or perhaps two gene therapies could be considered the same if they contain the same capsid and target the same underlying genetic condition.[129] What is important is not that a sameness analysis be developed here; in fact, developing a sameness analysis would require investigations and efforts that lie beyond the scope of this Note. Furthermore, just because two cells do the same thing does not necessarily mean they should be clinically defined as the "same." What should be the focus, however, is that a sameness analysis *could* be developed for cellular and gene therapies, and this could potentially help to solve the active ingredient problem.

B. FDA Guidance on Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use

A second FDA guidance, entitled *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use*,[130] issued in 2017, may also be relevant in solving the active ingredient problem. This Guidance focuses on the regulation and proper use of human cells and tissues, and it focuses on two standards: minimal manipulation and homologous use.

The concept of minimal manipulation will likely fail to be applicable in the current framework, since minimal manipulation has been defined to include various types of processing that do "not alter the relevant biological characteristics of cells or tissues."[131] That is precisely what is being done, to the benefit of the patient, in something like a CAR T-cell therapy or in any of the approved allogenic therapies.[132]

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[129] See *Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations*, *supra* note 105.

[130] *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use*, FDA (2017), https://www.fda.gov/media/124138/download (last visited Mar. 16, 2020).

[131] *Id.*

[132] Kazuo Yano, Alessondra T. Speidel & Masayuki Yamato, *Four Food and Drug Administration Draft Guidance Documents and the REGROW Act: A Litmus Test for Future Changes in Human Cell- and Tissue-Based Products Regulatory Policy in the United States?*, 12 J. TISSUE ENGINEERING & REGENERATIVE MED., 1579, 1581 (2018).

The concept of homologous use, however, could be extremely helpful. Homologous use for tissue products requires that the product repairs, reconstructs, replaces, or supplements the recipient's cells or tissues with tissue product that performs "*the same basic function or functions in the recipient as in the donor*"[133] (or presumably in the case of an autologous treatment, the same basic function or functions in the recipient after reintroduction of the modified tissue or cell). This standard, endorsed by the FDA in its guidance, could be particularly instrumental in ameliorating the active ingredient problem. A "homologous use" approach could be used, under which two cellular-based or gene-based therapeutics are the same if each "repair[s], reconstruct[s], replace[s], [or] supplement[s] . . . a recipient's cells or tissues . . . with [cells] that perform[] *the same basic function or functions in the recipient as in the donor*." [134] This overcomes the issue of defining the active ingredient for purposes of PTE; instead, the inquiry relies on whether two compared therapies perform the same basic function before and after donation or before and after isolation, modification, and reintroduction (in the case of autologous treatments).

There are, however, drawbacks to importing a "homologous use" standard from the FDA Guidance, because vastly different products could be used for similar treatments. This could lead to a definition that casts too broad a net and that ensnares too many unrelated products for purposes of PTE. This could confound some of the clear delineations that already exist surrounding various types of therapeutics and their clinical applications.

C. Proposed Statutory Changes

At the very least, § 156's definition of active ingredients is currently too narrow, only focusing on chemical compositions and salts and esters of those compositions. An additional mechanism for solving the active ingredient problem, and one that could incorporate some of the above-discussed solutions, is amending the statute to more clearly define "active ingredient" in light of the discussed novel cellular and gene-based therapeutics. "Amendment" in and of itself should not be viewed as a monolithic change to the statute; in fact, there are many paths the amendment could take, several of which are addressed below.

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[133] *Id.* at 1584 (emphasis added).
[134] *Id.* (emphasis added).

1. A New Framework for Cellular Therapeutics and Gene Therapies

First, the statute could be amended to adopt a novel definition or standard for active ingredients that applies to all novel cellular therapeutics and gene therapies. This amendment could incorporate the homologous use standard or a therapeutic-specific sameness analysis. Assuming that this approach to amending the statute keeps the current framework in place for chemically based compounds, clear lines of delineation could help direct particular therapies into particular bins. A caveat of this approach is that if different therapeutics have different treatments (real or perceived) of PTE, it could skew how a PTE applicant seeks to define her drug, and, in particularly extreme circumstances, could negatively affect particular areas of innovation. A more easily extended patent term for a cellular therapeutic could, for example, push innovation further into this realm, but there is also the concern that it could stifle innovation by increasing patent term unfairly for innovators. Determining the true effect would require an empirical analysis, but it is at least clear that the lever works both ways: if there is a particular innovative space that Congress feels *should* be incentivized, building in these sorts of incentives could lead to desired outcomes (e.g., more innovation surrounding novel cellular therapeutics as a result of favorable PTE treatment for these inventions).

2. Fixing the Problem Once and For All? Abolishing the Active Ingredient Approach for Novel Therapeutics

To this point, I have advocated what may seem like deliberate and careful changes to the statute and its interpretation that could help to ameliorate the active ingredient problem. The final suggestion is the most drastic, but, perhaps also the most promising in fixing the active ingredient problem—abolishing the concept of active ingredient altogether with regards to more complex, non-chemical-compound-based therapeutics. Here I advocate an entirely novel framework that leaves intact the current PTE structure for chemically based therapeutics but that introduces a completely separate and novel approach for cellular and gene therapy-based products.

I propose using "treatment complex protocols" instead of "active ingredients" for purposes of defining what is protected by PTE for cellular and gene-based therapeutics. A treatment complex protocol, or TCP, would be a complete compilation of the input (e.g., cells isolated from a patient), the precise modification or reprogramming that is performed (e.g., laboratory and clinical procedures), and the output (e.g., the reprogrammed autologous cells that are introduced back into the patient, and perhaps even the method of reintroduction). Instead of focusing on an active ingredient, the analysis would focus on a holistic review of what the treatment

is and how it is developed for the particular patient. Two products would then be the same if they had the same input, the same modifications, and the same output, while not being concerned with the heterologous nature of the actual therapeutic contents, or with the result of treatment (since clinical results cannot always be anticipated in all patients *a priori*).

The applicability of this framework is broad and alleviates challenges related to the definition of active ingredient for complex, non-chemically based pharmacological products. Not only would it apply to cellular-based therapeutics, but it would also apply to gene therapies, with a slight tweak: input of the TCP could be considered a combination of the DNA, the capsid carrier, and the target of treatment (i.e., the disease).

The concept of TCPs are beneficial for another reason: it seems that the current system largely works for chemically based therapeutics, but does not for more molecularly complex products. Considering TCPs only for these more complex products will allow the current setup to remain for chemical formulations; after all, there is little reason to reinvent the wheel, at least in circumstances where the wheel functions sufficiently well.

One potential challenge to TCPs relates to the administrability of a fairly complex system such as this. That is, how would inputs, modifications, and outputs be defined? Although fully fleshing out definitions would be the work of the legislature, the FDA, and USPTO, I make the following recommendations:

- Inputs should be defined as the starting material used in the treatment. For example, in MACI, described in Section III, the input would be chondrocytes isolated from the patient and the porcine collagen matrix.
- Modifications should be defined as what happens to the input in order to take that starting material and transform it into the clinical therapeutic (i.e., the output). In the case of MACI, the modifications would, generally speaking, be the specific conditions of culturing the chondrocytes and the procedure that incorporates them into the matrix that will eventually be implanted in the patient's knee.
- Outputs should be defined as the modified input (i.e., what will be used in the clinical treatment and what will be administered to the patient). In the case of MACI, the output would be the matrix-applied cultured chondrocytes that could be reintroduced into the patient for repairing cartilaginous injuries or defects of the knee. It is also possible to consider the method of administration of treatment as part of the output

(e.g., arthroscopic surgery to implant matrix-applied autologous cultured chondrocytes).

TCPs would solve the active ingredient problem of PTE in at least three major ways. First, TCPs completely do away with having to consider what the active ingredient of a complex formulation is while providing a useful comparative mechanism to describe the product. Since determining the active ingredient of a complex therapeutic could be unworkable, this is an attractive benefit of TCPs and could lessen the administrative burden attached to deciphering what the active ingredient is in a cellular or gene therapy formulation and what precisely is protected for purposes of PTE.

Second, TCPs are better tailored to the complexities of cellular and gene-based therapeutics. As I argue above, the current PTE active ingredient determination falls immensely short with cellular and gene therapy-based products. With this change, PTE would not be granted on an "active ingredient" but on a "TCP," which represents the input, modification, and output. Admittedly, a TCP, in practice, could be a lengthy written document that could invite questions of similarities and differences between TCPs in later litigation, but, at least as a first pass, it would be a better way of handling complex therapeutics for purposes of PTE. Concerns of additional paperwork and related administrative challenges could be addressed through instituting procedural requirements (for example, TCPs cannot be longer than 1,500 words).

Finally, TCPs could have an effect on encouraging innovation in the area of complex therapeutics. Although there does not seem to be any shortage of innovation in this space at this time, it is possible that uncertainties surrounding PTE for cell-based and gene-based therapies could chill innovation: if an inventor is not sure whether she can capitalize on that extension without immense administrative burdens, she may decide it is not worth it at all to develop a therapeutic that may only have five years of protection after the product is approved and can enter the market.

In summary, it seems as though a bifurcated approach to PTE may have arrived with the advent of non-chemically based therapeutics. TCPs could represent the way forward and could provide for a smoother path to PTE for cell-based and gene-based therapies.

D. Patent Claim Drafting

Statutory changes require immense effort on the part of advocates, buy-in from Congressional representatives and senators, and sufficient political will and

motivation to make the change. As a result, these changes happen slowly and (perhaps) methodically. In the meantime, what can inventors and PTE applicants do to ensure they capture the extended term with relative ease, similar to their peers developing chemically based drugs?

The answer may lie in patent claim drafting. Accurate description of an active ingredient in both a patent application and a regulatory filing is extremely important. In fact, under 37 C.F.R. Section 1.710, a patent up for PTE must claim the product/active ingredient, and the claimed product must read on a composition that received permission for commercial marketing or use.[135] As a result, careful claim drafting may clear the path for PTE in what may be an otherwise challenging landscape. Unfortunately, however, this still does not solve the core problem of what precisely the active ingredient is in a cell-based or gene therapy-based formulation. In fact, the Yescarta® case study suggests that even careful claim drafting can still lead to inter-agency strife as each party attempts to parse out precisely what the active ingredient is in a complex formulation. Interestingly, TCPs would help to overcome this challenge, in addition to those spelled out in the previous subsection.

In short, legislative change takes time and immense effort, but sometimes technology cannot wait for the law to change. Thus, careful claiming of the approved (or more likely, to-be-approved product) could increase the likelihood of a patent term extension grant because patent term extension only extends to approved products (i.e., the active ingredient), and approved uses of the product that must be claimed in the patent under the statute and regulations.

CONCLUSION

We are currently experiencing an immense growth in the types and number of novel therapeutics that are available, and the legal framework that describes drug products as compound-based is beginning to show cracks. Cellular and gene therapy-based therapeutics are changing the clinical landscape and are playing an increased role in treatment and management of diseases.

In short, a new framework, i.e., one that is not rooted in the world of chemical-based therapeutics, is needed to ensure adequate patent term protection and to appropriately incentivize innovation. The regulatory process is an essential part of developing and approving a drug, but if we are not careful, the measures put in place for safety and efficacy may erode the very incentives that encourage innovation in the first instance.

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[135] 37 C.F.R. §§ 1.710, 1.720.