



IP Challenges with Combination Drug Patents in Pharmaceuticals: A Critical Analysis

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The article critically examines the intellectual property (IP) challenges of combination drug patents in the pharmaceutical industry. Although combination therapies are critical in treating complex diseases, patenting them involves significant hurdles due to stringent requirements for novelty and non-obviousness. The discussion raises ethical concerns regarding incremental innovation, where patents may protect combinations that offer limited clinical advancements, thereby restricting competition and delaying generic drug entry. The example of pembrolizumab (Keytruda) underscores the complexities involved in patenting combination therapies and suggests the need for reform in patent law such as revising non-obviousness criteria and strengthening compulsory licensing to align innovation with public health goals.

Keywords: Combination Drug Therapy, Intellectual Property (IP), Pharmaceutical Patents, Non-Obviousness, Incremental Innovation, Patentability Criteria, Market Exclusivity, Generic Drug Access, Compulsory Licensing, Regulatory Framework, Access to Medicines, Patent Law Reform, Healthcare Costs

The pharmaceutical industry increasingly values combination therapies for their ability to tackle challenging diseases, particularly in oncology, infectious diseases, and chronic conditions. These combinations optimize treatment efficacy and minimize drug resistance, offering substantial patient benefits. However, the patenting of combination therapies presents both regulatory and ethical dilemmas. This article critically assesses these complexities within the IP landscape, exploring how current legal standards create barriers for combination drug patentability and how these standards affect competition, market dynamics, and patient access to essential medications. The article argues for specific reforms to the IP framework that could better accommodate the realities of combination therapies without sacrificing competitive markets or affordable access.

The Patentability Landscape for Combination Drugs

Combination therapies often draw from known pharmaceutical compounds, making it difficult for them to meet traditional patent standards, particularly in novelty and non-obviousness. Traditional patent systems, designed primarily for single-drug inventions, require each invention to represent a

distinctly novel or non-obvious advancement. However, combination therapies rarely meet this criterion since each drug is often well-documented. Consequently, pharmaceutical companies must demonstrate that the synergy achieved in their combination is not obvious to an industry expert. This requirement for novelty can create an “innovation bottleneck,” dissuading companies from pursuing combination therapies that may lack strong IP protection.

The article underscores the need for a patent framework that better reflects the complexities of combination therapies. Current standards may overlook the clinical significance of combination therapies, potentially slowing down the development of critical treatments. Yet, balancing flexibility with rigorous standards remains challenging, as overly lenient criteria could encourage “patent stacking,” where minor modifications become an IP shield against competition. Thus, policymakers should consider nuanced criteria that reward genuine synergy while guarding against monopolistic practices that only marginally benefit patient outcomes.

Critical Examination of the Non-Obviousness Requirement

One of the most challenging hurdles for combination therapy patents is the non-obviousness

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criterion, which demands that the therapeutic benefits be both novel and inventive beyond what an expert might reasonably predict. This requirement intensifies the burden on pharmaceutical companies to produce clear evidence of “unexpected” synergistic effects. However, in practice, demonstrating such effects is far from straightforward, as the pharmacodynamics of combinations may be predictable, particularly if scientific reasoning supports their efficacy.

The non-obviousness criterion, as it currently stands, may inadequately reflect the unique attributes of combination drugs. For example, if a patent examiner deems the combination of two well-known chemotherapy agents as offering predictable benefits, this may preclude patent eligibility even if the therapy’s effectiveness in a clinical setting is profound. As a result, companies may face significant legal costs in attempting to argue for the inventive step of these combinations, potentially stifling innovation in therapeutic areas that depend on such drug pairings. This rigidity calls for more tailored IP standards that consider the distinct value propositions of combination therapies, emphasizing unexpected clinical outcomes rather than hypothetical expectations of obviousness.

Incremental Innovation v Genuine Therapeutic Advancements

The concept of “incremental innovation” in combination therapy patents invites ethical scrutiny. Many pharmaceutical companies patent combinations that provide limited improvements over existing treatments. This practice, often labeled “evergreening,” may extend patent exclusivity without substantially enhancing clinical value. The ethical question centers on whether such combinations justify prolonged exclusivity if their benefits to patient outcomes are minimal.

The article calls for stringent criteria to distinguish between substantial advancements and minor modifications that do not genuinely contribute to patient care. Granting patents for incremental changes, while profitable for IP holders, ultimately restricts generic competition and delays access to affordable medication. The debate over evergreening highlights the need for a reform that considers whether combination patents substantively improve treatment efficacy or serve primarily as a mechanism for market control. This distinction is crucial, as it directly affects patient access to affordable therapies and the competitive landscape within the pharmaceutical sector.

Economic and Market Implications of Combination Drug Patents

The economic implications of combination drug patents extend beyond the legal realm, impacting market dynamics and competition. Pharmaceutical companies, by securing combination patents, may extend exclusivity beyond the original lifespan of individual drug patents. This prolongs monopolies, allowing firms to set higher prices without competition. Patients, especially those in low- and middle-income countries, bear the brunt of these high prices, facing restricted access to essential medications due to high costs.

The pharmaceutical industry’s defensive strategies, including litigation against generic manufacturers, further extend market control. Legal tactics that delay generic competition represent a barrier to affordable alternatives. This lack of competition stymies price reductions, placing a strain on healthcare budgets globally. Thus, policymakers should consider reforms that facilitate earlier generic entry, potentially through provisions like patent term adjustments and clearer pathways for generic approval.

Case Study: Pembrolizumab (Keytruda) and Combination Patent Complexities

The combination patent challenges surrounding pembrolizumab (Keytruda) exemplify the intricate issues in this space. Approved by the FDA in 2014 for melanoma, pembrolizumab quickly became foundational in oncology treatments. Pharmaceutical companies then pursued combinations of pembrolizumab with chemotherapy agents, which presented nuanced patent challenges. For example, these combinations encountered scrutiny regarding non-obviousness, given the well-documented effects of the individual drugs. Nevertheless, some combinations of pembrolizumab exhibited therapeutic benefits, though debates persist over whether these effects justify standalone IP protection.

The pembrolizumab case underscores the difficulty in distinguishing between valuable combinations and marginal enhancements, a line that remains blurred in current patent law. Moreover, market exclusivity for these combinations delayed the availability of generic versions, increasing healthcare costs and limiting accessibility. This case study illustrates the need for a refined IP approach that incentivizes substantial therapeutic advancements without stifling competition or limiting patient access.

Recommendations for Reform

The complexities inherent in combination drug patents necessitate a comprehensive IP reform strategy to ensure that innovation aligns with public health objectives. Several recommendations can help create a more balanced framework:

Revise Patentability Criteria

Current Issue: The patent criteria for combination therapies currently follow the same stringent standards as those for single drug patents, focusing heavily on novelty and non-obviousness. This presents a challenge for companies seeking patents for combination drugs, as they must meet a high bar to demonstrate that the combination provides something "unexpected" or not obvious to someone skilled in the field. This approach often overlooks the unique, synergistic benefits that combination therapies can offer, especially in terms of clinical outcomes.

Combination drugs, which combine multiple active ingredients to enhance efficacy or reduce side effects, often provide therapeutic advantages that single-drug treatments cannot match. However, under the current system, proving that a combination therapy is "non-obvious" can be exceptionally difficult, even if the combination leads to improved clinical results. As a result, many companies struggle to obtain patents for combination therapies, despite the potential benefits they offer to patients.

The high patent bar also creates challenges for healthcare systems and patients, as the inability to secure patents may discourage innovation in combination therapies, limiting access to potentially more effective or safer treatment options. Additionally, some combination therapies may face patentability issues even when they demonstrate real-world therapeutic advantages, such as better patient outcomes, fewer side effects, or improved treatment regimens.

Suggested Reform: To address these challenges and better recognize the unique benefits of combination therapies, patent offices could adopt more flexible and nuanced criteria for patenting these drugs. The reform would focus on the real-world clinical benefits of combination therapies, rather than adhering strictly to traditional standards of "novelty" and "non-obviousness." The key elements of this proposed reform are as follows:

- (i) **Recognizing Synergistic Effects and Clinical Outcomes:** Patent offices should develop criteria that consider the synergistic

effects of drug combinations and their real-world clinical benefits. While the traditional patent system emphasizes novelty and non-obviousness, it does not adequately account for the unique ways in which combination drugs can work together to improve therapeutic outcomes. For instance, combinations of existing drugs may lead to enhanced efficacy or reduced side effects, which should be viewed as valuable therapeutic innovations. Regulators could refine patent standards to focus on these real-world benefits, ensuring that combinations with clinically proven advantages are not unduly restricted by rigid patent criteria.

- (ii) **Flexible Standards for Non-Obviousness:** The concept of "non-obviousness" traditionally requires that a combination of known compounds or treatments must provide an unexpected or non-trivial improvement. However, combination therapies often deliver value in ways that may be predictable based on the properties of the individual drugs, but still result in new and significant therapeutic benefits when combined. Patent offices could adopt a more flexible approach to assessing non-obviousness, considering the combined effect as a whole and how the combination therapy addresses unmet medical needs, rather than applying overly strict standards based on isolated components.

- (iii) **Emphasis on Real-World Value over Hypothetical Claims:** The evaluation of patentability for combination therapies should be grounded in real-world clinical data rather than hypothetical predictions. Patents could be granted based on evidence from clinical trials or real-world evidence that shows the combination therapy provides a tangible therapeutic advantage, such as improved patient outcomes, increased adherence, or reduced side effects. This would allow combination therapies that offer clear, measurable benefits to patients to be patented more easily.

- (iv) **Preventing "Evergreening" with Safeguards:** While adjusting the criteria to recognize the therapeutic value of combination therapies, it is crucial to avoid

"evergreening"—a practice where drug companies make minor modifications or combinations of existing drugs to extend patent exclusivity unfairly. Patent offices could incorporate safeguards to ensure that only genuinely innovative combination therapies are granted patents, rather than trivial modifications or combinations that do not provide significant new therapeutic value. This could involve closer scrutiny of the underlying scientific evidence and more rigorous checks to ensure that the combination represents a true innovation in therapeutic terms, not just a marketing strategy.

- (v) **Incentivizing Combination Therapies for Unmet Needs:** By creating a more flexible patenting framework, regulators could incentivize the development of combination therapies that target unmet medical needs, particularly in areas where current treatment options are limited or ineffective. This approach would encourage pharmaceutical companies to focus on combinations that address complex diseases, such as cancer, HIV, or multi-drug resistant infections, where combination therapies are often the key to improving patient outcomes.

Impact of the Suggested Reform

- (i) **Encouraging Innovation in Combination Therapies:** By adopting more flexible and realistic criteria for patenting, the reform would foster greater innovation in the development of combination therapies. Companies would be more likely to invest in researching and developing combinations that can offer significant therapeutic benefits, knowing that their intellectual property would be better protected.
- (ii) **Improved Access to Effective Treatments:** Recognizing the unique value of combination therapies could result in more treatment options becoming available to patients, especially for complex or multi-faceted health conditions. This would expand access to better and more effective therapies, improving patient outcomes across a range of diseases.
- (iii) **Reduced Barriers to Market Entry for Meaningful Combinations:** By easing patent

requirements for combinations that show clear clinical benefits, the reform would reduce unnecessary barriers to market entry. This would encourage the development of combination drugs that can offer patients better health outcomes, without being hampered by overly stringent patent criteria that focus too heavily on novelty and non-obviousness.

- (iv) **Balanced Intellectual Property Protection:** The reform would ensure that while combination therapies are protected from unjustified competition through patents, the system also prevents abuses of the patent system, such as evergreening. The adoption of flexible standards would strike a balance between protecting innovation and promoting competition and access to affordable medicines.

Strengthen Compulsory Licensing Provisions

Current Issue: Compulsory licensing allows governments to permit generic production without the patent holder's consent, often used to ensure access to essential drugs. However, these provisions are rarely applied, particularly for combination therapies, where the need for broader access may be significant but hindered by lengthy exclusivity periods.

Suggested Reform: Expanding compulsory licensing mechanisms specifically for combination therapies that treat critical or life-threatening conditions could help balance IP protection with public health needs. This would allow countries, particularly those with limited healthcare budgets, to provide affordable, life-saving therapies more quickly. Strengthening these provisions would incentivize companies to develop combination therapies with genuine therapeutic impact while ensuring that high prices do not block access to essential medications.

Encourage Transparent Pricing Models

Current Issue: The pricing of patented combination drugs often presents a significant challenge to healthcare systems and patients. Many combination drugs involve the merging of existing medications or active ingredients, and the resulting price is frequently not aligned with the added therapeutic value or benefits of the combination. This misalignment can lead to inflated prices, placing an unnecessary financial burden on patients and

healthcare systems, especially when the combination does not offer substantial improvement over the individual components.

A lack of transparency in pricing practices further exacerbates the issue. Patients, healthcare providers, and even policymakers often have little insight into how prices are determined, making it difficult to evaluate whether the costs are justified by the clinical benefits or if they are driven by market monopolies or lack of competition. This lack of clarity may hinder the adoption of more affordable alternatives or prevent the rational allocation of limited healthcare resources.

Suggested Reform: To address the issue of unjustifiable pricing for combination drugs, a transparent and value-based pricing model could be implemented. This system would aim to set drug prices based on their therapeutic value, clinical outcomes, cost-effectiveness, and health benefits. By tying the price of drugs more directly to their proven effectiveness and value to patients, it would help create a fairer pricing structure that aligns with public health goals. The key elements of this reform would include:

- (i) **Pricing Based on Therapeutic Value:** Pharmaceutical companies should set prices for combination drugs based on their added therapeutic value over existing treatments. This would require evidence-based assessment to determine whether the combination offers significant clinical improvements compared to individual drugs or generic alternatives. If the combination drug offers limited added benefits, its price should reflect that, rather than being set at a premium simply because it is a new formulation.
- (ii) **Independent Pricing Frameworks:** To ensure fairness and transparency, an independent body or government regulator could be tasked with setting and reviewing drug prices. This regulator could assess the clinical effectiveness, cost-effectiveness, and overall health benefits of a drug to establish a justified price range. Such frameworks would help mitigate the influence of market monopolies and ensure that prices are not arbitrarily set.
- (iii) **Public Access to Pricing Information:** Transparency in how drug prices are

determined would allow patients, healthcare providers, and policymakers to better understand the rationale behind pricing decisions. If drug prices are tied to clear metrics such as clinical efficacy and cost-effectiveness, stakeholders can make more informed choices about treatment options and healthcare budgeting. Public access to this information can also build trust in the pharmaceutical industry, which may help reduce skepticism around drug costs.

- (iv) **Cost-Effectiveness and Health Outcomes Assessment:** An integral part of transparent pricing would involve conducting and publicly sharing cost-effectiveness studies. These studies assess whether the benefits of a drug justify its cost relative to alternative treatments. For combination drugs, this would include determining whether the new formulation offers enough improvement in terms of health outcomes to justify a higher price.
- (v) **Incentivizing Innovation, Not Just Market Power:** Pharmaceutical companies would benefit from a pricing system that rewards genuine innovation rather than market power or monopolistic strategies. Transparent pricing would enable the industry to focus on creating drugs with real therapeutic advancements rather than relying on tactics like patent stacking or incremental modifications to drive up prices.

Impact of the Suggested Reform

- (i) **Fairer Drug Prices:** By linking drug prices to their therapeutic value and clinical outcomes, patients and healthcare systems would face more predictable and justifiable costs. This would prevent the price inflation often seen with combination drugs that do not provide meaningful clinical improvements over existing treatments.
- (ii) **Improved Access to Medicines:** More transparent and affordable pricing would make it easier for patients to access necessary medications, particularly in low- and middle-income countries. This could help reduce health disparities and improve overall public health outcomes by making essential treatments more accessible.

- (iii) **Strengthened Trust in Pharmaceutical Industry:** A clear, evidence-based pricing system could help rebuild public trust in the pharmaceutical industry, which has sometimes been criticized for opaque pricing strategies. By showing that the prices are aligned with real health benefits, the industry would be seen as more accountable to the public and healthcare providers.
- (iv) **Encouragement of Genuine Innovation:** This system would prioritize the development of truly innovative therapies, rewarding companies that create drugs that offer significant health benefits, rather than those that simply make incremental changes to existing treatments.

Prioritize Generic Market Entry Post-Patent Expiration

Current Issue: Patent holders often employ strategies to delay the introduction of generic versions of their drugs even after the expiration of their original patents. One of the most common tactics is "patent stacking," where patent holders file additional patents for minor modifications, such as new formulations, combinations, or delivery methods. These strategies allow them to extend their market exclusivity beyond the original patent period, preventing generic manufacturers from entering the market.

The result is that generic alternatives, which are usually more affordable, are kept out of the market for a longer period. This tactic keeps drug prices high and restricts access to life-saving medications for patients, particularly in developing countries and underserved populations.

Suggested Reform: To address this issue and promote broader access to affordable medicines, regulatory agencies could implement reforms that streamline the approval process for generics following the expiration of combination drug patents. Specifically, regulatory bodies should focus on:

- (i) **Accelerated Generic Approval Pathways:** After the expiration of a combination drug patent, regulators could establish clearer and more efficient pathways for approving generic drugs. This would involve simplifying the regulatory requirements for generics based on the expiration of combination patents, ensuring that generics

are not subject to the same delays caused by minor patent modifications.

- (ii) **Review and Tighten Patent Scrutiny:** Regulatory agencies could introduce more stringent criteria for granting patents, particularly for incremental changes or modifications that do not offer significant innovation. By ensuring that only truly novel inventions are granted patents, it would limit the potential for "patent stacking."
- (iii) **Encourage Transparency in Patent Litigations:** Transparent and accessible information regarding the status of drug patents and patent disputes would enable generic manufacturers to plan their entry into the market. Regulatory agencies could require regular updates on patent expirations and litigation outcomes, fostering a more predictable environment for generics to enter the market.
- (iv) **Incentivize Generic Manufacturers:** Governments could provide incentives to generic manufacturers to produce and bring affordable alternatives to market once the patent for combination drugs expires. This could include offering fast-track approval processes or offering fee reductions for generics that meet specific affordability criteria.

Impact of the Suggested Reform

- (i) **Lower Healthcare Costs:** By reducing barriers to the entry of affordable generic medicines, the cost of essential drugs would decrease significantly. This would make healthcare more affordable for individuals and healthcare systems, especially in countries with limited access to patented medications.
- (ii) **Wider Patient Access:** The availability of generics would expand access to life-saving drugs, especially for underserved populations and those in low- and middle-income countries, where the cost of patented drugs is often prohibitive.
- (iii) **Enhanced Market Competition:** The entry of generics into the market would increase competition, driving down prices and improving the quality of medicines available to patients. This competition can spur innovation

within the pharmaceutical industry as companies would need to focus on real innovation to stand out in a competitive market.

- (iv) **Support for Public Health Systems:** Affordable generics would ease the financial burden on public health systems, enabling them to allocate resources more efficiently and invest in other critical areas, such as preventive care or expanding access to health services.

Conclusion

The IP landscape for combination drug therapies requires thoughtful reform to support innovation without compromising competition or accessibility. This article argues that regulatory bodies should recalibrate patent criteria and strengthen licensing mechanisms to balance pharmaceutical incentives with broader health objectives. By doing so, stakeholders can ensure that combination therapies reach patients who need them most without inflating costs or restricting competition. Ultimately, a more equitable patent system for combination drugs would foster genuine innovation while safeguarding public health interests.

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