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Overlapping Method of Use Patents to Prevent Generic Entry

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Abstract

Brand-name pharmaceutical firms increasingly use method of use patents and associated Orange Book "use codes" to delay generic entry, complicating the skinny labeling pathway that permits low-cost generics to omit patented indications from their labels and market their products for unpatented uses. Recent litigation, however, shows how overlapping use codes — targeting patient subgroups or biomarker thresholds rather than distinct conditions — can obstruct the skinny labeling pathway. Case studies of icosapent ethyl (Vascepa) and sacubitril-valsartan (Entresto) illustrate how overlapping use codes delay generic entry, inflate costs, and limit patient access. Reforms are needed to improve FDA and USPTO oversight of use code assignments and clarify legal standards for induced infringement, which would preserve the balance between rewarding innovation and ensuring timely access to affordable medicines.

Keywords: patent; Orange Book; Food and drug law; method of use; skinny label

About This Column: Aaron Kesselheim serves as the editor for Health Policy Portal. Dr. Kesselheim is the JLME editor-in-chief and director of the Program On Regulation, Therapeutics, And Law at Brigham and Women's Hospital/Harvard Medical School. This column features timely analyses and perspectives on issues at the intersection of medicine, law, and health policy that are directly relevant to patient care. If you would like to submit to this section of JLME, please contact Dr. Kesselheim at akesselheim@bwh.harvard.edu.

After a new brand-name drug is approved for one indication, it may be tested successfully for other indications as well. A few drugs, like the cancer drug pembrolizumab (Keytruda), can even acquire dozens of new indications over the course of their time on the market. To secure Food and Drug Administration (FDA) approval, each new indication must be backed by evidence from expensive clinical trials. To protect their investments, drug manufacturers often obtain "method of use" patents lasting 20 years on these new uses from the US Patent and Trademark Office (USPTO). For small molecule drugs, relevant method of use patents are listed on the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) along with a "use code."[1] In this article, we will describe the role that use codes can play in blocking generic entry through a special regulatory pathway called skinny labeling created by Congress over four decades ago.

Individual use codes describe the treatment indications that correspond to method of use patents. Use codes are created and self-designated by the manufacturer, and neither the FDA nor the USPTO evaluates or confirms the patent's relevance to the FDA-approved indication. A drug can be associated with multiple use codes that may have only loose connections to the drug's FDA-approved indication. Indeed, pharmaceutical firms can create use code thickets, or multiple use codes directed to the same drug. Competitors must either wait for the relevant patents on a brand-name drug — and their associated use codes — to expire or contest their validity or infringement in court before selling an FDA-approved generic drug for the new indication.

However, such a system could allow drug manufacturers to extend market exclusivities for their products by filing serial patent applications to slightly different "new" indications. To prevent this scenario, Congress in the Hatch-Waxman Act of 1984 created the "skinny label" generic entry pathway to incentivize the pursuit of new indications while allowing competitors to enter the market for indications related to previously expired or invalidated method of use patents. The skinny label pathway allows generic manufacturers to sell their drugs for non-patent-protected FDA-approved indications of existing drugs. The generic manufacturer, however, must carve out any unexpired patented indication from its drug's labeling. The outcome is a generic product with a skinny label, permitting the sale of a generic version for the non-patented indication. This regulatory pathway is colloquially called skinny labeling because the generic drug's label does not include the full list of all approved indications, but only indications that are not protected by patents and described in use codes.

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Since the Hatch-Waxman Act, manufacturers have vigorously pursued supplemental indications for their new products, while the skinny-labeling pathway has led to billions of dollars in savings by enabling the market entry of generic drugs sooner than if the generic had to wait for the expiration of patents on all the FDA-approved indications. From 2015 to 2019, 43% of new generic drugs came onto the market with skinny labels.[2] Similarly, from 2015 to 2021, 67% (22/33) of biosimilars entered the market with a skinny label.[3]

In recent years, brand-name manufacturers have used the skinny-labeling pathway to obtain and list patents for multiple uses that overlap in complex ways with prior uses.[1] These patents typically cover a new patient population that intersects with a prior (now unpatented) patient population. The skinny label pathway was created to allow manufacturers to seek genuine label expansion of their brand-name products to new indications, while encouraging generic entry for the older indication. Consider the example of thalidomide (Thalomid), which was originally approved in 1998 for leprosy and then later found to be effective in multiple myeloma and FDA approved in 2006 for that indication.

However, firms are now subverting this system by obtaining patents within previously-approved patient populations that make it difficult to use the skinny label pathway. For example, in the case *Amarin v. Hikma*, Amarin (a brand-name drug manufacturer) marketed the prescription fish oil product icosapent ethyl (Vascepa), which was initially FDA approved in 2012 for severe hypertriglyceridemia (triglyceride levels ≥ 500mg/dL), a now-unpatented indication. Icosapent ethyl was subsequently FDA approved in 2019 to reduce cardiovascular risk in patients with triglyceride levels ≥150 mg/dL, an indication protected by different method of use patents lasting until 2033. The problem for generic manufacturers seeking to sell a skinny-labeled product before 2033 is that the new patented indication overlaps with the old unpatented indication. Thus, it is challenging for generics to carve out the patented cardiovascular risk (triglyceride ≥ 150 mg/dL) indication while describing in the drug labels the severe hypertriglyceridemia (triglyceride ≥ 500 mg/dL) indication.

Box 1. Comparison of 2015 and 2021 Relevant Labeling for Entresto Indications

Entresto 2015 Label

ENTRESTO is…indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and *reduced ejection fraction.*

Entresto 2021 Label

ENTRESTO is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure.

As of 2024, Amarin owned 67 issued patents associated with 39 distinct use codes covering numerous aspects of Vascepa, including its use to treat patients with various diseases. These patents covered multiple indications, some still undergoing clinical trials, including: hypertriglyceridemia, heart disease, diabetes mellitus, and coronary angioplasty status.[4] However, many of these new patented uses are not directed to expanded disease indications — the purpose of the skinny-labeling pathway — but are directed to patient populations, disease severity measures, and laboratory values. Ideally, these four indications, represented by the use codes for each distinct disease indication, should not overlap, because patents are intended to protect only new and non-obvious methods (see Figure 1). The case is currently being appealed to the Supreme Court.

Other examples have since surfaced of brand-name drugs with similarly overlapping use codes. For example, Novartis recently sued a generic manufacturer of its heart failure-treating combination drug sacubitril-valsartan (Entresto). Entresto was originally approved in 2015 to reduce the risk of cardiovascular death in patients with chronic heart failure and *reduced* ejection fraction. In 2021, Entresto's approval was expanded to include chronic heart failure patients with *preserved* ejection fraction. The generic manufacturer sought to market only the non-patent protected "chronic heart failure and reduced ejection fraction" indication by carving

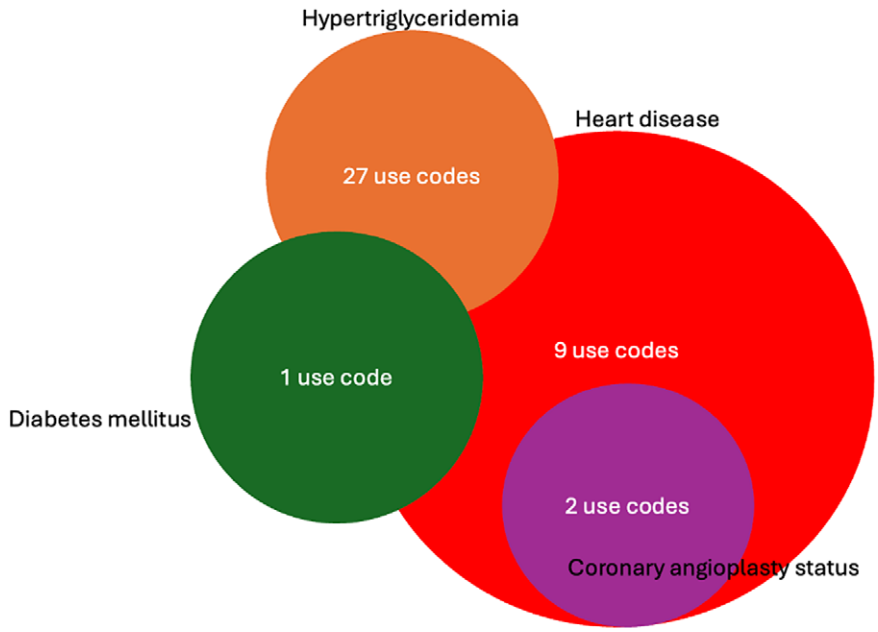


Figure 1. Indications Associated with Amarin's Icosapent Ethyl (Vascepa) Use Code Patents.
Note: National prevalence of indications claimed by Amarin's use code patents on icosapent ethyl (Vascepa). The extent of the overlap between each indication is proportional to the extent of co-occurrence between each indication claimed by the use codes. Data source: Centers for Disease Control and Prevention. International Classification of Diseases, Tenth Revision codes were used to categorize the indications claimed by each use code.

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out the larger patent-protected "chronic heart failure" indication (see Box 1). Novartis argued that the FDA could only "delete words" from the label and not add words back. The district court rejected this argument and agreed with the FDA that an "omission" under the regulation must turn on the "substance of the information that is omitted — not whether that substantive omission is accomplished by adding words or deleting them." The decision is currently being appealed.

The initial order to dismiss the *Amarin v. Hikma* suit has been reversed by the federal circuit and the Entresto case is still awaiting final disposition on appeal, meaning that the legal status of the skinny-labeling pathway remains uncertain. The skinny-labeling pathway was created as a way to balance access to affordable generic medicines and pharmaceutical innovation related to supplemental uses of existing FDA-approved products. This balance is jeopardized if brand-name manufacturers are allowed to retain market exclusivity by serial filings of overlapping method of use patents.

There are several steps that the FDA and USPTO could implement to forestall this type of litigation and provide clarity for generic and brand-name drug manufacturers alike.

Currently, drug manufacturers independently create use codes, with the FDA taking a purely "ministerial" role.[5] This allows brand manufacturers to manipulate use codes in a way that hinders generic entry. To curb such practices, the FDA and USPTO should collaborate to play a more active role in managing the use codes associated with patents. They should ensure use code patents are associated with their corresponding FDA-approved indication and assign use codes based on these indications.[6]

Additionally, use code descriptions can be expanded beyond the current limit of 250 words. Use code descriptions are currently restricted to 250 words, partly due to limitations in the FDA's database system, which was created in the 1980s.[7] Shorter use code descriptions allow for broader FDA protection, even if the patented indication is much narrower. Directly linking the use code to the FDA-approved indication, rather than the manufacture's self-described use, would allow the listed patent to more accurately reflect the scope of FDA protection.

Congress could also intervene by clarifying which actions are excluded from patent infringement based on labeling. Recent efforts such as the bipartisan *Skinny Labels, Big Savings Act of 2025* (S. 43) are promising first steps, but additional measures are likely needed to fully safeguard generic entry. For example, the bill creates a narrow safe harbor from patent infringement for specific actions, such as promoting the drug using language from its FDA-approved labeling. Thus, if a hypothetical generic drug manufacturer makes statements such as that the drug is "generic" or "therapeutically equivalent to" the reference drug or describes the use of the drug consistent with the FDA-approved indication, those actions should be excluded from infringement. Accordingly, while the bill marks an important first step, because it offers only limited protection, as it does not cover all conduct related to generic marketing of the unpatented indication, more is required. Finally, Congress should clarify the scope of "induced infringement" in pharmaceutical cases to prevent courts from equating generic drug labels with direct instructions to infringe the patented indication (as recent Federal Circuit decisions have done).[8]

The existing arrangement weakens the skinny-label pathway, departs from the traditional inducement infringement doctrine, undermines the Hatch-Waxman Act's carve-out provisions, and ignores real-world physician behavior. As the US continues to struggle with high drug costs, Congress and regulatory agencies should intervene to restore certainty in the skinny-labeling pathway and reestablish the critical balance between exclusivity and competition in the prescription drug market.

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