To Carve Out or Not to Carve Out – That is the Question

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In April, this column talked about Orange Book use codes in the wake of *Caraco v. Novo Nordisk*, 132 S.Ct. 1670 (2012) and how overbroad use codes may now be challenged by ANDA applicants as unlawful under the Hatch-Waxman Act. In particular, the article examined the use code drafter’s dilemma: too broad a use code and the brand could find itself the target of an antitrust suit; while too narrow a use code and the ANDA avoids the patent via the section viii “carve out” statute. It also offered advice on how to overlay patent claims on drug label language to ensure that the use code does not, in the words of the Supreme Court, “preclude generic marketing of non-infringing uses of the brand drug.”

This article looks at a slightly different use code issue, that being, when a use code cannot be carved out because it would leave the generic drug less safe or effective than the brand for the remaining non-protected conditions of use. 21 C.F.R. §314.127(a)(7). The FDA has been formally asked to address this issue more than a dozen times and only once has found for the brand. Although the “less safe or effective” standard is a demanding one it is not insurmountable. The way the FDA has implemented the use code carve out process is as follows: first, all of the use code language is scrubbed from the generic label to make sure there is no overlap between the two; second, the FDA analyzes whether the remaining “conditions of use” on the generic label are less safe or effective than those same conditions on the brand label, considering that brand still contains the use code language; and third, if the generic is found to be as safe and effective as the brand for the remaining (non-protected) conditions of use the section viii carve out will be allowed. Even if the carved out use is foreseeable and the generic is unsafely labeled for such use it will still be allowed. In this respect, the FDA has been steadfast in applying the “safe and effective” test only to the “on label” non-protected conditions of use.

A question that still arises from time to time is what exactly is a “condition of use.” How the FDA answers this question can mean the difference between a “skinny labeled generic” being approved under a section viii or kept off the market until the use patent expires. Here are some examples to illustrate this point.

Example 1: A drug is approved to treat patients suffering from renal impairment with a separate dosing requirement depending on whether the patient’s condition is mild, moderate or severe. A patent claims dosing for severely impaired patients only and a use code with that limitation is listed in the Orange Book. A generic applicant files a section viii statement, requesting FDA permission to carve out the use code. If the FDA considers the treatment of renal impairment to be a single condition of use – as it is indicated on the label – the use code might not be eligible for carve out because the generic would be less safe or effective than the brand for treating patients suffering renal impairment, a non-protected condition of use. In other words, the brand would be labeled to treat all renal patient populations whereas a carved out generic would be labeled only to treat mild and moderate sufferers, leaving severely impaired patients in a potentially unsafe condition. On the other hand, if the FDA viewed the drug as being approved to treat three conditions of use, the use code for severely impaired patients would be eligible for carve out because its removal would not leave the generic less safe or effective than the brand.
for the remaining two non-protected conditions of use.

However, it should be noted that the only carve out decision to be decided in favor of the brands involved Rapamune (sirolimus) an organ rejection drug that was labeled for low, medium and high risk patients. Although only the low and medium risk patients were protected by exclusivity, the FDA refused to allow a generic carve out because a drug labeled only for high risk patients could lead to confusion by physicians and “unsafe conditions” should a high risk patient move to the medium or low risk populations.

Example 2: A drug is approved to treat a particular disease as a monotherapy and in combination with another drug. The label contains evidence of clinical studies that show the combination therapy to be more effective in a significant percentage of patients with the disease. A patent claiming the combination use is listed in the Orange Book. Here again, the key question is whether the drug has been approved for one condition of use (the disease) or two (the methods of treatment). If the FDA considers the treatment of the disease (albeit in multiple ways) to be the drug’s single condition of use, no use carve out would be allowed because the combination therapy has been shown to be more effective than the monotherapy. A generic without the combination information on the label would be less effective than the brand for treating the disease – i.e. the remaining non-protected condition of use. However, if the FDA were to view the drug as being approved for two conditions of use, a carve out of the combination therapy patent would be allowed because it would not render the generic less safe or effective than the brand for treating the disease with the non-protected monotherapy.

As the foregoing examples illustrate, a “condition of use” can be an amorphous concept in the context of patents, use codes, and drug labels. Despite such uncertainty, a careful review of the FDA rulings going back to 2002 may provide useful guidance for brand manufacturers struggling to understand how the carve out rules may be applied. Here are some broad principles that may help:

- If a use code claims a new indication that is not “intertwined” with other (non-protected) indications on the label, generic “carve outs” will generally be allowed.

- If a use code claims dosing, drug administration, warnings, etc., for a new patient population, generic “carve outs” will generally be allowed.

- If a use code is related to safety or efficacy for a non-protected patient population, generic “carve outs” will generally not be allowed.

- If the use code relates to safety or efficacy for a patient population that an existing (non-protected) patient population could reasonably become, generic “carve outs” will generally not be allowed.