**Celgene: Revlimid's Longevity Beyond 2019 is Largely Dependent on the Polymorph Patent, Expiring in 2026; Biggest Risk Lies in Generics Practicing the '517 Patent**

The key to Revlimid's longevity beyond 2019 is the drug's polymorph patent (US# 7,465,800) expiring in 2026. Should this patent succeed in keeping generics at bay, Celgene would enjoy Revlimid exclusivity for 16 years, creating a very different outlook for the company. Our diligence indicates Revlimid's polymorph patent is free of any obvious flaws and has a good chance of maintaining franchise exclusivity. Although we anticipate the '800 patent will be challenged and expect that the investment community will never gain 100% confidence in the patent's ability to thwart generic competition, our research has increased our confidence in Revlimid's longevity.

Revlimid (lenalidomide) is small molecule organic compound derived from thalidomide. The drug's composition is claimed in U.S. patent # 5,635,517 expiring in October 2019. The '517 patent also covers methods for using lenalidomide to reduce undesirable levels of TNF alpha. Although we expect Revlimid's '517 composition of matter patent could be challenged (nearly all small molecule patents are) there is little debate that the patent will protect Revlimid's U.S. exclusivity into 2019. In Europe, Revlimid's composition of matter patent expires in 2022, and the franchise is likely to go generic soon thereafter,

In addition to Revlimid's '517 composition of matter patent, there are 11 FDA Orange-book listed patents covering various Revlimid-associated inventions.

**REVLIMID PATENT EXCLUSIVITY ESTATE**

| Patent Number | Date of Expiration | Description |
|---|---|---|
| 6,555,554 | 07/24/16 | Composition of Imid derivatives |
| 7,119,106 | 07/24/16 | Composition of Imid derivatives |
| 6,281,230 | 07/24/16 | Method of use for decreasing TNF-alpha production |
| 6,045,501 | 08/28/18 | Risk management program |
| 6,561,976 | 08/28/18 | Risk management program |
| 6,908,432 | 08/28/18 | Risk management program |
| 5,635,517 | 10/04/19 | Composition/method claims on a class of compounds, including lenalidomide |
| 6,315,720 | 10/23/20 | Risk management program |
| 6,561,977 | 10/23/20 | Risk management program |
| 6,755,784 | 10/23/20 | Risk management program |
| 7,189,740 | 04/11/23 | Method of use to treat cancers |
| 7,465,800 | 04/22/26 | A Form B polymorph (hemihydrate) of lenalidomide |

Source: FDA, Cowen and Company

Of these, the patent that is most critical to Celgene is U.S. patent 7,465,800 covering the marketed polymorph of Revlimid. Celgene management has expressed a high degree of confidence in this patent and believes it will maintain the drug's exclusivity until 2026. It is worth noting that **Celgene is also in litigation with the USPTO to extend the term of the '800 patent by 300+ days into 2027**. Our consultants lack confidence in the other Orange book-listed patents. They believe there is a high likelihood that patents covering the risk management program will be declared invalid. Hence franchise exclusivity beyond 2019 is likely to rest largely upon the strength of the .800 polymorph patent.

Our consultant can think of only a couple ways in which the '800 patent might be invalidated: 1) by identifying prior art disclosures that were overlooked by the USPTO, or 2) by obtaining lenalidomide material produced to support the '517 composition of matter patent and showing that this original material contains the Form B polymorph.

**Reasons To Believe The '800 Patent Is Valid**

1. The patent examiner's search found essentially no prior art on polymorphic forms of lenalidomide
2. Lenalidomide's original '517 composition of matter patent does not provide any physical or chemical characterization of drug substance, including any information on polymorphic form or melting temperature
3. The '800 patent describes recrystallization conditions that a very different from those in the '517 patent
4. The '800 patent sailed through USPTO review with essentially no fundamental objections

Source: Cowen and Company

**According to consultants the biggest risk to Celgene's patent extension strategy lies in the ability of generic companies to practice the teachings of the '517 patent following its expiry in 2019.** Recall that this composition of matter patent discloses one set of conditions for synthesizing and purifying lenalidomide. Although the '517 patent is vague in its description of the reaction conditions employed to produce lenalidomide, consultants believe that a generic

company would have freedom to practice these conditions, and that any product produced would likely be deemed not to infringe Celgene's subsequent polymorph patents (rules don't allow patenting the same material twice).

What is unclear is what type of lenalidomide material might result from practicing the teachings of the '517 patent. If the Form B hemihydrate is readily produced, this could be used to invalidate the claims of the '800 patent. However, there is good reason to think this will not be the case. The two solvents described in the '517 patent (dioxane and ethyl acetate) are anhydrous (free of water) and it is difficult to see how Form B (a hemihydrate that includes water molecules) could have been obtained under these reaction conditions. Hence, according to consultants, the key technical question is likely to be whether whatever one produces from practicing the teachings of the '517 patent is equivalent (by FDA standards) to Revlimid. Only time will tell if generic companies are successful using the teachings of the '517 patent to create an acceptable formulation of lenalidomide.

**Source:** Cowen and Company/Schmidt, June 15, 2010
**Oncology Indication:** Hematologic
**Keyword:** Policy/Legal