Overpatented, Overpriced

Keytruda's Patent Wall

ISSUE: Given that many of today's best-selling drugs are biologics, there is a need to better understand the patent strategies used by drugmakers to protect them. Biologic drugs are a category of pharmaceutical products such as therapeutic proteins and monoclonal antibodies derived from living cells.

GOAL: Investigate the patent strategy for the cancer drug Keytruda in order to better comprehend how "patent walls" for biologic drugs are constructed, and how these strategies might differ from those used for small molecule drugs.

METHODS: Identify all patents related to Keytruda and analyze each one to determine the types of patents filed and how the filing pattern impacted the length of time the drug would be protected by patents. Patent and market data are as of June 2020.

KEY FINDINGS:

- Keytruda has **129 patent applications;** to date, 53 patents have been granted.
- **50%** of the patent applications on Keytruda were filed **after its first FDA approval.**
- **74%** of patent applications cover the different indications and formulations of the drug and **not the key antibody**.
- The estimated purchasing cost of branded Keytruda during the eight years of extended exclusivity without competition is **at least $137 billion.**

CONCLUSION: Because of the nature of biologic drugs, there appear to be more opportunities to file patents in each patent type than for small molecule drugs. Given the particular methods and regulations required to manufacture biologic drugs, method of production and process patents take on more significance than for small molecule drugs. There also appears to be a greater potential for filing more method of treatment patents for a biologic drug like Keytruda. These patent types are key to extending the period of protection. This raises the question of whether there are more defensive patenting strategies for a biologic drug like Keytruda in order to extend protection while also serving to erect barriers for biosimilar competitors.

May 2021

Results

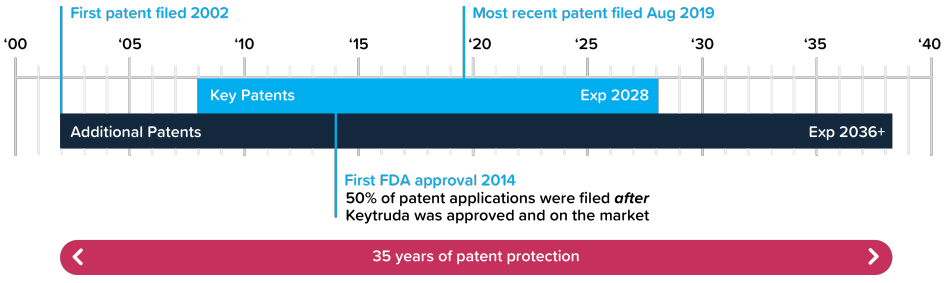
Half of Keytruda's patents were filed after the drug entered the market

The first application on Keytruda was filed in March 2002 and the most recent one was filed over 17 years later, in August 2019. Keytruda's patent wall — the portfolio of patents relating to a single drug — currently consists of 129 patent applications. 26% of patent applications were abandoned[5] after filing and 33% are still under examination and pending a decision. Currently, 41% of patent applications have been granted.

Our analysis identified key patents specifically covering the anti-PD-1 antibody, pembrolizumab (the non-proprietary name for Keytruda), and its formulation. These patents were filed in 2008 and are set to expire in 2028. Although patents relevant to the anti-PD-1 antibody were filed as early as 2002, the key patents filed in 2008 are what would be classified as the active ingredient in a small molecule drug.

Out of the 129 patent applications that currently make up Keytruda's patent wall, 50% were filed *after* 2014, when the drug received its first FDA approval for treating melanoma cancer. The most recent patents that have been granted are set to expire in 2036. This gives Merck a total period of 34.6 years of patent protection for Keytruda.

Figure 1: **Keytruda's Patent Lifecycle, 35 years of patent protection**



[1] Based on a per-dose Wholesale Acquisition Cost (WAC) of $9,724, assuming 17 doses annually for 200mg dose every 3weeks. Note, total price remains unchanged with April 2020 approval of 400mg dose every 6weeks. **https://www.keytruda.com/financial-support**

[2] From analysis of IQVIA invoice-based National Sales Perspective (NSP) pricing from Sept 2014 through Dec 2019.

[3] From an analysis of Merck's annual reports from 2014-2020.

[4] EvaluatePharma World Preview Report. Table 14: Top 10 Selling Products in the USA in 2024. May, 2019.

[5] Abandoned applications are patent applications that are voluntarily discontinued by an applicant. For a more detailed definition see our report Imbruvica's Patent Wall available at **i-mak.org/imbruvica**

Key facts about Keytruda

Classification: Keytruda belongs to a class of drugs known as immune checkpoint inhibitors used for cancer immunotherapy. It is a humanized antibody that binds to human PD-1 receptors to help activate the body's own immune response to fight cancer.

History: Initially discovered by Dutch drugmaker Akzo Nobel, which was acquired in 2007 by Schering-Plough. In 2009, Schering-Plough was acquired by Merck for $41 billion. Keytruda is now Merck's top-grossing product of all time.

FDA Approval & Indications: First approved in September 2014 for melanoma. Keytruda has 26 separate approvals for 18 different types of cancer.

Price: Current non-discounted annual price is $165,308.[1] The price has increased 147% in the 5 years since Keytruda was launched.[2]

Spending: Total net US sales of Keytruda between 2014 and 2020 is $21.7 billion, with average annual growth of 90% over the past five years.[3]

Forecast: Projected to become the top grossing drug in the world by 2024. Annual global revenues are estimated at $26 billion, accounting for half of Merck's total revenue.[4]

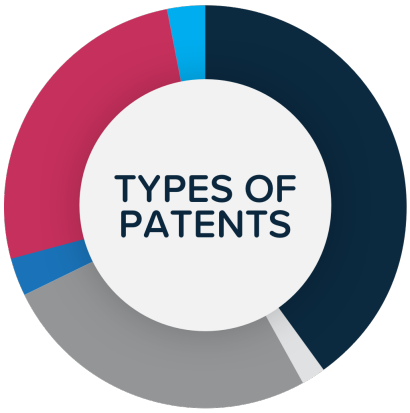
Method of production patents are the largest single category of patents in Keytruda's portfolio

Figure 2 provides a breakdown of the different patent types that make up Keytruda's patent wall.

Patents relating to the antibody pembrolizumab make up 26% of all patent applications filed to date. For the purpose of this report, we classify these types of patents as "product patents". Product patents are considered "primary patents" because they are akin to the active ingredient in terms of protecting the antibody and main mechanism of action that creates the immune response.

The remaining 95 patent applications in Keytruda's patent wall are secondary patents. Secondary patents cover many different features of a biologic drug beyond the antibody itself.

Figure 2:
The types of patents in Keytruda's patent wall



Primary Patents

- **Product (26%):** Covers the antibody, antibody fusion proteins, and vectors for delivery to the relevant site in the human body.

Secondary Patents

- **Biomarker (3%):** Method to measure the actions of a biologic drug.
- **Formulation (2%):** Pharmaceutical preparations, including ingredients, to help deliver the drug into the human body.
- **Method of Diagnosis (3%):** Method to identify which patients are most likely to respond to treatment.
- **Method of Production / Process (40%):** Manufacturing process for engineering the checkpoint molecule.
- **Method of Treatment (26%):** Specific indications (diseases) that can be treated with the checkpoint molecule alone or in combination with another checkpoint molecule(s) and or small molecule(s) (organic compounds).

40% of patent applications on Keytruda cover various methods of production and processes that can be used to manufacture the drug. This patent type represents the largest single category for Keytruda. **Compared to the number of methods of production and process patents typically found in a patent wall for a small molecule drug, this is a far higher percentage and indicates the strategic importance of such patents for biologic drugs.[6] Patents covering processes of production are more important for biologics than for small molecules, since this class of drugs is at least in part defined by the process used for production. This can have regulatory implications that make it difficult or even impossible for biosimilar competitors to get around process patents after the primary patents expire.**

26% of patent applications are for methods of treatment, covering the 18 different cancer types for which Keytruda has obtained regulatory approval. These patents also cover the use of Keytruda in combination with either other biologics and/or small molecule drugs.

Patents on biomarkers (3%) and methods of diagnosis (3%) are patents covering testing methods or kits that are used to measure the actions of the biologic drugs and to test patients to identify which are responding

[6] For example, method of production and process patents only made up 1% of Imbruvica's overall patent wall. See **i-mak.org/imbruvica**

or are most likely to respond to treatment. These patent types represent a new opportunity to add more patents to the patent wall of a drug.

Formulation patents (2%) cover the inactive ingredients and processes of combining them with the antibody pembrolizumab to help deliver the product into the human body. These inactive ingredients that are used for formulating the drug help to maintain the product's stability and efficacy and may be considered more routine in their level of inventiveness.

Overall, secondary patents make up a total of 74% of Keytruda's patent wall.

Patents covering Keytruda's indications and manufacturing processes are being filed later in the drugs lifecycle

As Figure 3 provides a timeline of how the different patent types making up Keytruda's patent wall have been filed over the course of the drug's life.

As mentioned above, methods of production and process patents represent 40% of Keytruda's patent wall. As seen in Figure 3, patent applications falling into this category have been filed as early as 2003, with the most recent in 2019. This is despite Keytruda already receiving FDA approval and being sold on the market since 2014.

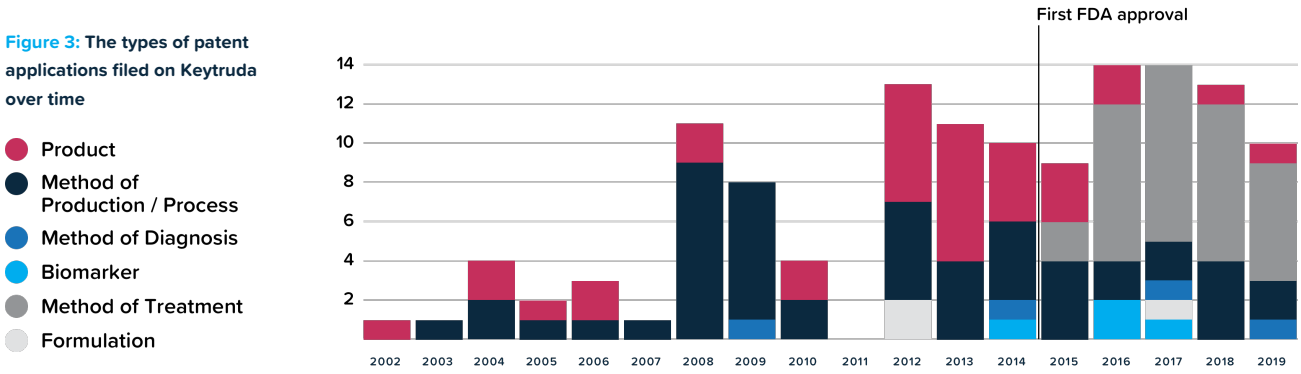
Unlike small molecule drugs where it is generally easier for generics to come up with alternative ways to work around methods of production and process patents, it is more difficult for biologic drugs. This is because manufacturing biologic drugs require very specific conditions to yield safe, pure and reliable production given the nature of substances involved. As such, working around or invalidating methods of production and process patents can be more difficult.[7] The continued filing of method of production and process patents after FDA approval raises the question of whether a number of these patent applications are for defensive purposes in order to delay biosimilar competitors, as opposed to what is actually used to manufacture the product itself. These patents may also have been filed years after they were implemented for production, thus representing another strategy to hinder competitors.

Specific method of treatment patents were also filed only after the first FDA approval. These patents have all been filed after the first approval for Keytruda and relate to the many subsequent FDA approvals for various other cancer indications. This filing pattern suggests that once the mechanism of action of a biologic is known for the first indication, testing the drug in clinical trials for other similar indications is an obvious step. As a result, this becomes an opportunity to obtain further method of treatment patents for other indications and extend the patent protection and commercial exclusivity.

[7]Aydin Harston, A Rare Successful Challenge of a Patent for a Method of Manufacturing Biologic Drugs, Rothwell Figg https://www.biosimilarsip.com/2018/03/12/a-rare-successful-challenge-of-a-patent-for-a-method-of-manufacturing-biologic-drugs/
See also W. Nicholson Price and Arti K Rai, Manufacturing Barriers to Biologics Competition and Innovation, Iowa Law Review, Vol 101.1023, 2016

It is noticeable that we see some product patents still being filed after first FDA approval. These patents claim aspects of the earlier product patents in a more narrow manner and appear to have been filed for defensive purposes to delay biosimilar competitors. This is similar to the drip feed patenting strategy we saw in Imbruvica.[8]

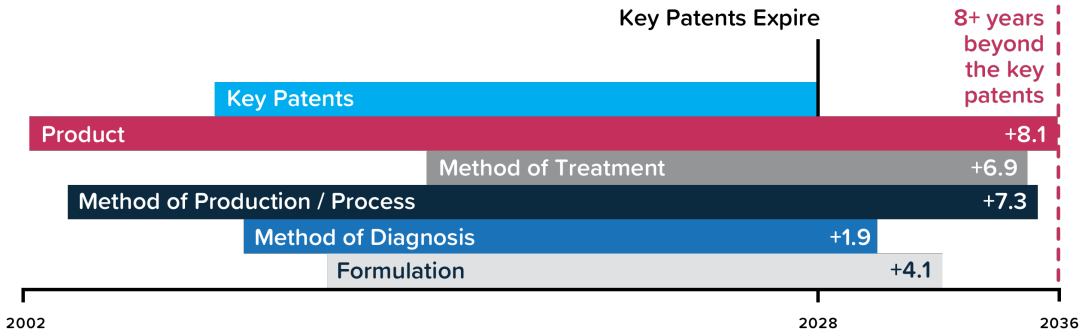
Figure 3: The types of patent applications filed on Keytruda over time



Patents on Keytruda could extend its monopoly term by at least 8 years, costing Americans an estimated $137 billion

Patent applications have been filed on Keytruda for the past 17 years. Patents filed and granted after the first FDA approval for Keytruda add a further 8 years of patent protection and potential commercial exclusivity beyond the key patents we identified. During that extended period of time (2028-2036), we conservatively estimate Americans will spend $137 billion on branded Keytruda[9]. Additionally, we anticipate that more patents will be filed and granted on this drug as it obtains regulatory approval for a growing number of indications. This could further extend the monopoly on Keytruda and cost Americans more.

Figure 4: How the types of granted patents extend the patent term on Keytruda



[8] https://www.i-mak.org/imbruvica

[9] Based on an I-MAK model of estimated total U.S. revenue/spending for Keytruda in the eight-year period from mid-2028 (the expiration dates of Merck's two key antibody and formulation patents) to Sep 2036 (the latest expiry of a currently granted patent). It assumes the annual growth in product revenue peaks in 2020 and steadily decreases from 15% to 1% annual growth from 2021 to 2028. From 2028 onward, the analysis conservatively assumes annual growth is only 1% through 2036, corresponding to annual revenue of approximately $25 billion. There is no assumption of a biosimilar product entering the market in this time period.

Conclusion

The goal of this report was to provide a more in-depth look into the patenting strategies for a biologic product. Our analysis of the Keytruda patent portfolio identified key patenting strategies that could help extend the period of protection for Keytruda while delaying biosimilar competition.

First, given the nature of biologic drugs and the particular methods required to manufacture them, method of production and process patents take on more significance than for small molecule drugs. This patent type represents the biggest share of patent applications in Keytruda's patent wall. Our analysis of these patents and their timing in the Keytruda patent lifecycle, particularly those filed after first FDA approval, raises the question of whether many of these later patents are for defensive purposes. For example, by filing these patents, Merck could be seeking to block off alternative methods of production that any biosimilar competitor may seek to use.

Closely connected to method of production and process patents and the fact that biologic drugs are more complex to replicate, we found that patent applications that fall into the product category are still being filed - most recently in 2019, five years after the first FDA approval for Keytruda. These patents claim aspects of the earlier product patents in a narrower manner, which could make it more difficult for biosimilar entrants to work around.

Second, method of treatment patents are also key to extending the period of protection for Keytruda. While this is a patenting strategy that is also commonly found for small molecule drugs[10], there appears to be a greater potential for filing more method of treatment patents for a biologic drug like Keytruda. This is because it has already been approved for 18 indications and several clinical trials for other indications are currently underway. Once the mechanism of action is known for a biologic drug like Keytruda, the possibility of extending it to other indications that are in the same disease area becomes more likely. As a result, under current patent laws, there is ample opportunity for Merck to file additional method of treatment patents in order to extend the potential period of exclusivity on Keytruda.

Finally, a strategy that is becoming more common to biologic drugs - and of commercial importance - is filing patents for biomarkers and methods of diagnosis. While these patent types may not always meet the current legal requirements of what is considered patent eligible subject matter, if granted, they can form another barrier for competitors. Any competitors seeking to enter with a biosimilar product will have to show a test for a biomarker in order to get marketing authorization of a biosimilar version for an indication. As such, patents on biomarkers and methods of diagnosis can be filed defensively in order to make it more difficult for biosimilar versions to be approved without infringing them.

[10] https://www.i-mak.org/imbruvica/

What is clear is from our analysis of Keytruda's patent landscape is that given the nature of biologic drugs, there are more opportunities to file different patents in each patent type identified than for small molecule drugs. This allows for greater defensive patenting strategies in order to extend protection while also serving to erect barriers for biosimilar competitors. This is especially the case when it comes to methods of production and process patents.

Supplementary material for this report is available at i-mak.org/keytruda