Elixir of the afterlife

Predicting post-exclusivity market situations for medicines past midpoint of the product lifecycle

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Executive summary

There is no such thing as eternal exclusivity for medicines. All medicines eventually lose exclusivity and become open to competition from generic or biosimilar alternatives. Loss of exclusivity (LOE) occurs when the period of patent protection and any prohibiting instruments are no longer in effect. The post-LOE market can be tranquil, choppy, or stormy for proprietary medicines.

To gauge what the future holds after LOE, pharmaceutical companies must carry out a market prediction using the post-LOE market prediction model. Foreknowledge of the post-LOE market will enable the proprietary firm to determine what LOE strategy to pursue to maximize value from the medication.

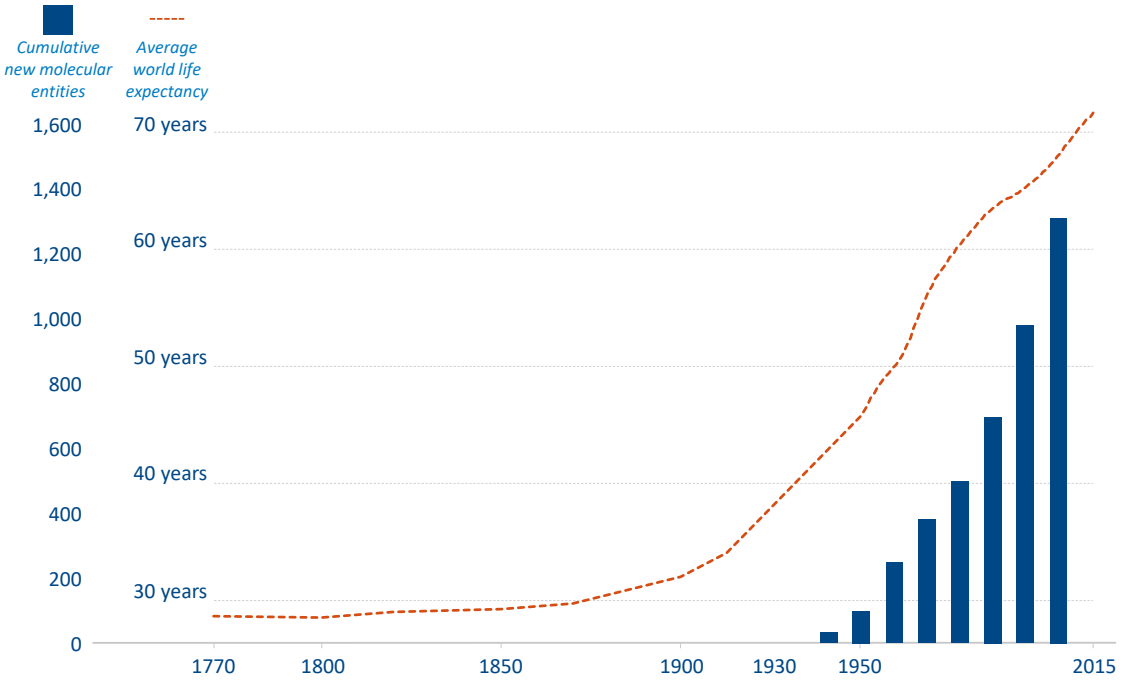
1. All medicines eventually lose exclusivity

Alchemists across cultures and through the ages have sought to identify formulae for potions to provide eternal life or eternal youth. These are often referred to as "elixirs of life." Although immortality has not yet been achieved through medicine, the increased availability of innovative medicines to prevent and treat diseases has contributed to global improvements in health and longevity (see Figure 1). Even in areas of medicine where non-pharmacological interventions play a significant role (e.g., in the treatment of mental illnesses), pharmacological interventions remain central to the improvement of health.[1]

Developing new medicines

The pharmaceutical industry continues to be the main vehicle of innovation in drug development. There is a high risk as well as high cost in successfully delivering a medicine from bench to patient. The failure rate in drug development has been estimated to be over 96%,[2] while the average cost of a successful drug, albeit a matter of disagreement, is generally accepted to be more than US $1 billion.[3] Medicines that successfully come to market are therefore considered to be important assets to pharmaceutical companies, and their commercial exclusivity

Figure 1: Life expectancy and medicine innovation



Source: Roser, Max, Esteban Ortiz-Ospina, and Hannah Ritchie. "Life Expectancy." OurWorldInData.org, 2013.

1 Source: Barnes, Thomas R., et al. "Evidence-Based Guidelines for the Pharmacological Treatment of Schizophrenia: Updated Recommendations from the British Association for Psychopharmacology." ***Journal of Psychopharmacology***, Vol. 34, No. 1, January 2020.

2 Source: Hingorani, Aroon D., et al. "Improving the Odds of Drug Development Success Through Human Genomics: Modeling Study." ***Scientific Reports***, Vol. 9, No. 1, 11 December 2019.

3 Source: "Average Cost of Developing a New Drug Could Be Up to $1.5 Billion Less than Pharmaceutical Industry Claims." London School of Hygiene & Tropical Medicine, 4 March 2020.

(which is time limited) provides the opportunity for these companies to recoup the investments they made to develop and commercialize the medicine. This money is usually reinvested into further research and development to ensure that there always is a pipeline of new drugs. LOE can have a significant financial impact on a company (see Figure 2).

Figure 2: Impact of LOE

Company	Percentage of revenue loss solely due to patent expiry (2010-2012)
Pfizer	41%
AstraZeneca	38%
Sanofi	34%
Bristol Myers Squibb	30%
GSK	23%
Eli Lilly	22%
Merck	22%
Novartis	14%

Source: Taylor, David. "The Pharmaceutical Industry and the Future of Drug Development." *Pharmaceuticals in the Environment*, 2015.

Loss of exclusivity

When the period of patent protection, exclusivity, and any prohibiting instruments are no longer in effect (i.e., after LOE), interested parties have the opportunity to commercialize a generic (for small molecules) or biosimilar (for large molecules) version of the proprietary medicine. The LOE of a medicine provides upsides and downsides to stakeholders in the health system.

On the positive side, with the LOE of a medicine, innovative companies can be motivated to find another successful medicine and bring incremental innovation to the therapy area. Generic and biosimilar companies can provide a comparable medicine at a lower price, while payers, providers, and patients can continue to enjoy the improved health outcomes that they have become accustomed to at a lower price. On the downside, the innovator company may experience a (sometimes very sharp) drop in revenue from the medicine.

In either case, medicines come into the market with protected exclusivity for the proprietor company and lose that exclusivity at a point in time later down the road, usually with some financial impact on the proprietor company.

2. Mitigate the LOE impact

To mitigate the impact of LOE, companies usually pursue either a traditional or aspirational LOE mitigation approach (see Figure 3).

Traditional LOE mitigation

Traditional LOE mitigation usually assumes that the entry of generics into the market is inevitable and the impact will be wholly negative (i.e., rapid loss of revenues). Therefore, the commercial objective is usually to reduce the speed of revenue and profit decline. The strategies pursued to achieve this objective can include:

- **Prevention.** Employ means to legally delay or temporarily deter generic entrants (e.g., secure a pediatric license extension).
- **Innovation.** Create or develop something that can be protected by patent (e.g., extend the product line – usually an incremental innovation on the soon-to-be generic drug).
- **Extraction.** Extract the most value from the product before generics enter the market (e.g., intensify promotion for a short period of time).
- **Adaptation.** Enter the generics market (e.g., offer a generic version through a subsidiary).

Aspirational LOE mitigation

Aspirational LOE mitigation usually expects generics to enter the market at some point post-LOE but it does not assume a wholly negative impact. There is the expectation instead that generic entry may herald a decline in revenues but may also bring some positives, such as an increase in prescribing of the medicine.

This view of generic entry can motivate proprietary companies to take a more aspirational position and consider how to take advantage of the potential benefits of generic entry into the market. Thus the commercial objective of mitigation can be to achieve a longer-term increase in revenue and profit after a short-term dip. The strategies pursued to achieve this commercial objective are usually bespoke to the product and the therapy area and are based on certain key principles, one of which is harnessing the changes that generic entry into the market will bring. The full details of the principles and framework for aspirational LOE strategies can be found in the ADL Report titled "The BIG patent expiry question: Why sink when you can sail?"[4]

Figure 3: Traditional and aspirational LOE mitigation approaches

Strategy selection process	Key differences in the process of LOE strategy selection	
	Traditional strategy	Aspirational strategy
***Perception** of generic entry into the market*	■ Generic entry seen as wholly negative ■ Revenues and profits expected to diminish rapidly	■ Generic entry seen as partly positive and a potential opportunity ■ Revenues and profits may be impacted negatively in the short term but can certainly benefit in the longer term
*LOE **commercial objective***	■ Slow down the decline of revenue and profit from the product	■ Grow revenue and profit from the product
***Strategy** to achieve LOE objective*	■ Traditional strategy – Prevention – Innovation – Extraction – Adaptation	■ Aspirational strategy – Bespoke to product and therapy area – Designed using aspirational strategy framework

Source: Arthur D. Little analysis

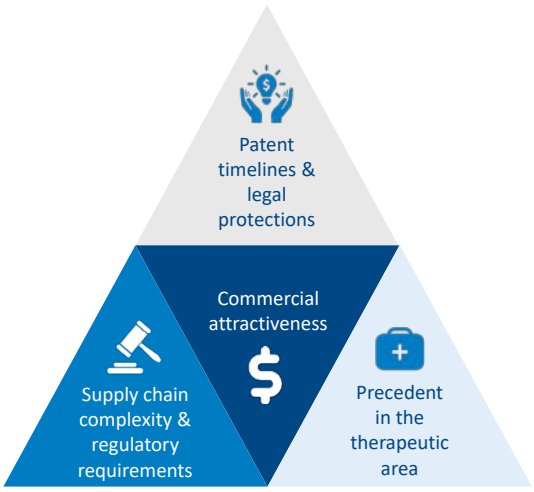
4 Source: Aisabokhae, Emmanuel, and Ben Enejo. "The BIG Patent Expiry Question: Why Sink When You Can Sail?" Arthur D. Little, June 2018.

3. Make effective post-LOE predictions

To select the right LOE mitigation strategy, pharmaceutical companies need to understand what the post-LOE landscape will look like. They must make predictions of the likelihood that generics or biosimilars will enter the market and the timing of their entry into the market to inform the selection of the appropriate LOE mitigation strategy. The post-LOE market prediction model shown in Figure 4 provides a framework that uses data about the medicine to predict generic/biosimilar entry likelihood and timing. The model has four parts:

1. Commercial attractiveness
2. Patents and legal protections
3. Supply chain complexity and regulatory requirements
4. Precedent in the therapy area

Figure 4: Post-LOE market prediction model



Source: Arthur D. Little analysis

Commercial attractiveness

The commercial attractiveness of a medicine is influenced by a number of factors including the market share, price, annual revenue, profits, and market growth. Also important are the market dynamics and competitive landscape in the medicine's therapeutic class. A medicine could be seen as attractive if it has a high market share, a high enough price to allow a generic to come in at a significant discount and still be profitable, high annual revenues and profit, a market that is set to grow in the future, few or no existing comparable alternatives, and few or no comparable alternatives on the horizon.

Patents and legal protection

The patents and legal protection of a medicine cover a number of important aspects of that medicine. Companies must carefully study – with legal assistance – the details of the patents to assess the likelihood and timing of potential generic/biosimilar entry. Medicines usually have core patent(s) that provide standard legal protection and commercial exclusivity. There can also be associated patents that cover things like manufacturing methods and proprietary excipients. Not all patents have the same level of strength and enforceability, but they all must be considered in the assessment of the post-LOE market situation.

Supply chain complexity and regulatory requirements

Medicines have different supply chain complexities and regulatory requirements, and these have a bearing on how they are perceived by firms interested in developing generic or biosimilar equivalents. Medicines that have many expensive and complex steps (requiring unique know-how) in the supply chain and where the final output has to navigate many challenges and carries a significant risk of not achieving the minimum quality assurance standards may not be considered to be attractive from a generic/biosimilar perspective. Another consideration is the post-marketing requirements of the medication (e.g., real-world evidence, high demands on the risk management plan, extensive patient monitoring). These will need to be part of the assessment of the post-LOE market situation.

Precedent in the therapy area

The history and dynamics in a therapy area are influential in the assessment of generic or biosimilar entry. A therapy area with historically low investment suggests that it may not be attractive even for generic entrants. Also, there may be cases where there is a high use of off-label or off-license medicines in the therapy area, making the true available market for a generic entrant difficult to determine. There are other factors to consider as well, such as the presence of patient access schemes or even events in adjacent therapy areas that may have a bearing on the therapy

area of focus. For example, based on historical precedence, occurrences in the treatment of depression may have an impact on the dynamics of the treatment of schizophrenia and/or bipolar disorder, as these are adjacent therapy areas.

Tranquil, choppy, or stormy waters?

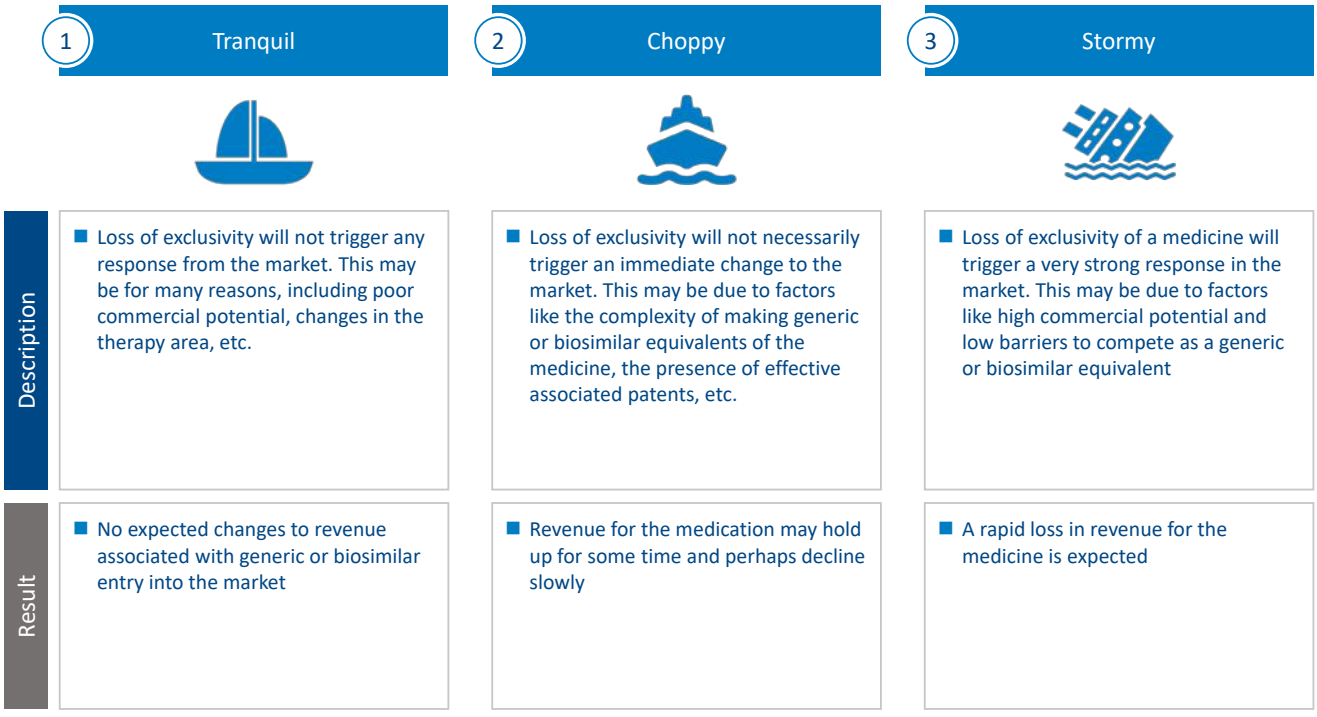
The post-LOE market prediction model is able to predict whether the post-LOE market situation will be tranquil, choppy, or stormy (see Figure 5). A prediction of "tranquil" refers to a situation where the loss of exclusivity will not trigger any response from the market. This may be for many reasons, including poor commercial potential, changes in the way patients are treated, and so on. No material changes to revenue due to LOE are expected in this scenario.

A "choppy" scenario refers to a situation where there may be new entrants into the market after LOE, but their entry may not necessarily trigger a sharp response in the market. This may be due to factors like non-interchangeability between the proprietary and generic or biosimilar medicines due to observed differences in patient outcomes. In this scenario, revenue for the proprietary medication may show some resilience as it declines slowly over time.

A "stormy" scenario is one in which the LOE of a medicine will trigger a very strong response in the market. This may be due to factors like high commercial potential and low barriers to competition as a generic or biosimilar equivalent. In this scenario, a rapid loss in revenue for the medicine is expected.

The post-LOE market prediction model requires both quantitative and qualitative data to make a prediction. It also requires collaboration between different disciplines in the medicine value chain. Ultimately, informed expert judgment will have to be made about what is likely to happen in the future, and there is always a risk associated with such decisions. However, the model provides a framework for companies to use to make an educated prediction so that they can select an appropriate mitigation strategy.

Figure 5: Post-LOE market scenarios



Source: Arthur D. Little analysis

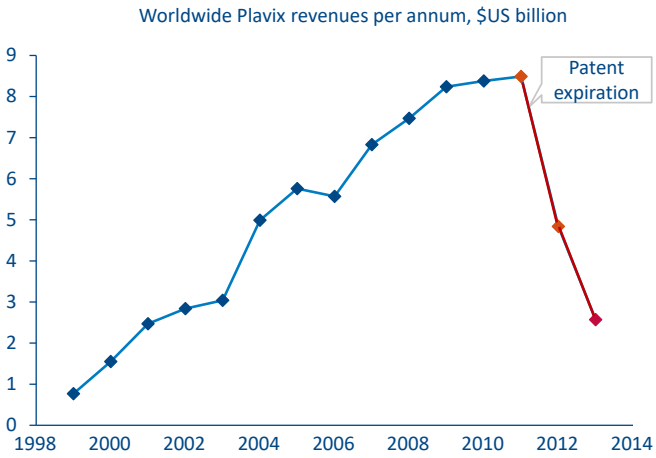
4. Case studies – Validating the post-LOE market prediction model

Using the post-LOE market prediction model can assist pharmaceutical companies in determining the post-LOE market situation for their medicines. We illustrate the potential here in two case studies.

Case study 1: Plavix

Plavix (clopidogrel) is an antiplatelet medication used to reduce the risk of heart disease and stroke in those at high risk. It is also used together with aspirin in heart attacks and following the placement of a coronary artery stent. Plavix was approved for medical use in the US in 1997 and became a great success, with sales for Bristol Myers Squibb and Sanofi of more than $8 billion in 2011. At the end of its exclusivity period in 2012, generic versions became available in the market, and Plavix experienced a sharp decline in revenue (see Figure 6).

Figure 6: Plavix revenue



Source: Arthur D. Little analysis

Commercial attractiveness

In the three consecutive years before LOE, Plavix had achieved sales of over $8 billion in each year. Although a second-generation medication (in the thienopyridine family), Plavix had a significant share of the market as it was considered to be safer than the first-generation thienopyridine ticlopidine. There was no sign of slowing down in the use of Plavix to address heart disease and strokes both as a preventative measure and in an acute/post-acute situation. Therefore, the market looked attractive.

Patent timelines and legal protections

The date for the expiry of the patent for Plavix in the US was known to be 17 May 2012. Bristol Myers Squibb had explained that it would not hold on to the drug beyond the exclusivity expiry date and was preparing for life after Plavix.[5] The data exclusivity period in the EU had expired in July 2008. There was some legal protection for the bisulphate form of clopidogrel in the EU that was due to last into 2013, but this did not prohibit the availability of alternative salt forms of clopidogrel.

Supply chain complexity and regulatory requirements

Plavix is a film-coated tablet with a list of regular excipients. It did not present as particularly challenging to manufacture, and there were no onerous demands in terms of the post-production supply chain (e.g., the requirement for cold storage). There were no unusual post-approval regulatory or patient-monitoring requirements.

Precedent in the therapy area

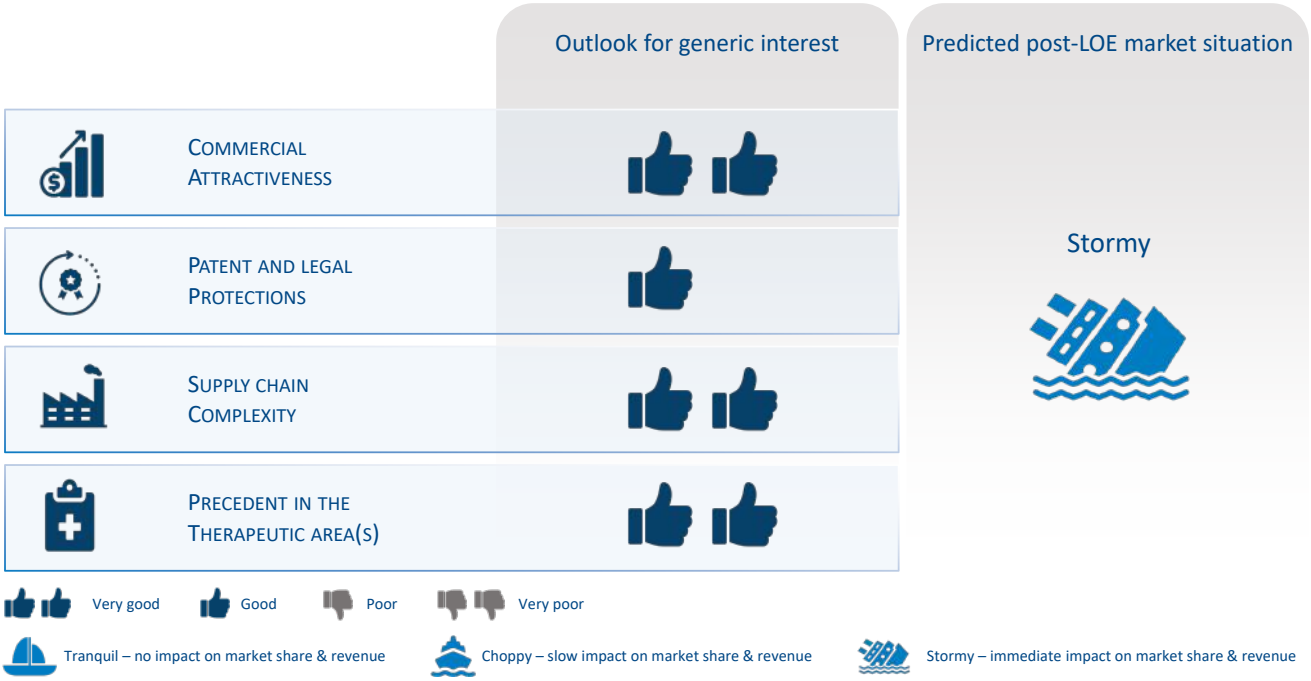
In the cardiology therapy area, prescribers used aspirin to prevent strokes and blood clots before Plavix became available. After Plavix became available, the two medicines were used together in some cases. With aspirin long available as a generic drug, clinicians had demonstrated that they were not averse to prescribing generic antiplatelets for their patients. The high volume of patients on Plavix also meant that payers would be looking to reduce medication costs where possible.

Post-LOE market prediction for Plavix

With a very high commercial attractiveness, relatively uncomplicated legal protection, relatively simple supply chain, and clear precedent of generic prescribing in the therapy area, the post-LOE market prediction model would have predicted a very high likelihood that Plavix would experience strong generic competition as soon as its exclusivity protection was no longer effective (see Figure 7).

5 Source: Thomas, Katie. "Plavix Set to Lose Patent Protection." *The New York Times*, 16 May 2012.

Figure 7: Post-LOE retrospective analysis for Plavix

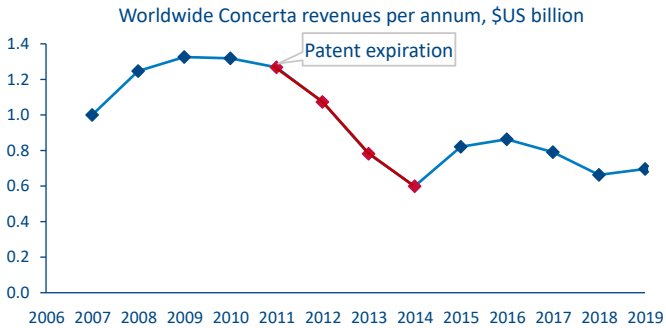


Source: Arthur D. Little analysis

Case study 2: Concerta

Concerta (methylphenidate) is a tablet used for the management of attention-deficit/hyperactivity disorder (ADHD). It is based on the methylphenidate drug delivered via an OROS osmotic pump. The biphasic nature of the release of the drug during the day provides treatment over a 12-hour period. Concerta achieved over $1 billion in sales for several years before the first generic entry into the US market in 2011 (see Figure 8). With the market entry of the generic version of Concerta, the revenue for Concerta did not experience a sharp decline. Instead, global revenues in 2012 declined somewhat but still exceeded $1 billion.

Figure 8: Revenue for Concerta



Source: Johnson & Johnson, Arthur D. Little analysis

Commercial attractiveness

At the time of Concerta's LOE, ADHD was considered to be the most commonly diagnosed behavioral disorder in children, and the market was growing. In addition, about 75%-80% of children diagnosed with ADHD were treated with psychostimulant drugs like Concerta.[6] Concerta also had a significant share of the market, with an earlier source putting the market share at over 25%.[7]

Patent timelines and legal protections

Concerta had different LOE dates in different geographies, with the US LOE date in 2011.[8] This date was different from the date of an associated patent related to the OROS technology, which has a significant influence on the characteristic and performance of Concerta as a medicine. The associated patent was still effective at the time of the core patent expiry.

6 Source: Bokhari, Farasat, and Gary Fournier. "Entry in the ADHD Drugs Market: Welfare Impact of Generics and Me-Toos." *The Journal of Industrial Economics*, Vol. 61, No. 2, June 2013.
7 Source: Connor, Daniel F., and Ronald J. Steingard. "New Formulations of Stimulants for Attention-Deficit Hyperactivity Disorder." *CNS Drugs*, Vol. 18, No. 14, December 2004.
8 Source: "UPDATE 1-Watson Pharma Signs Generic Drug Deal with JNJ Unit." Reuters, 2 November 2010.

Supply chain complexity and regulatory requirements

Concerta is a sophisticated tablet that releases the drug in a very defined way using the OROS osmotic pump. It therefore requires a more complex production methodology than would be expected for a regular medicine that comes in a solid tablet dosage form. In addition, the tablet releases 22% of the medicine in the first hour and then 78% over the next 10 hours,[9] creating a unique pharmacokinetic profile that is linked to patient outcomes.

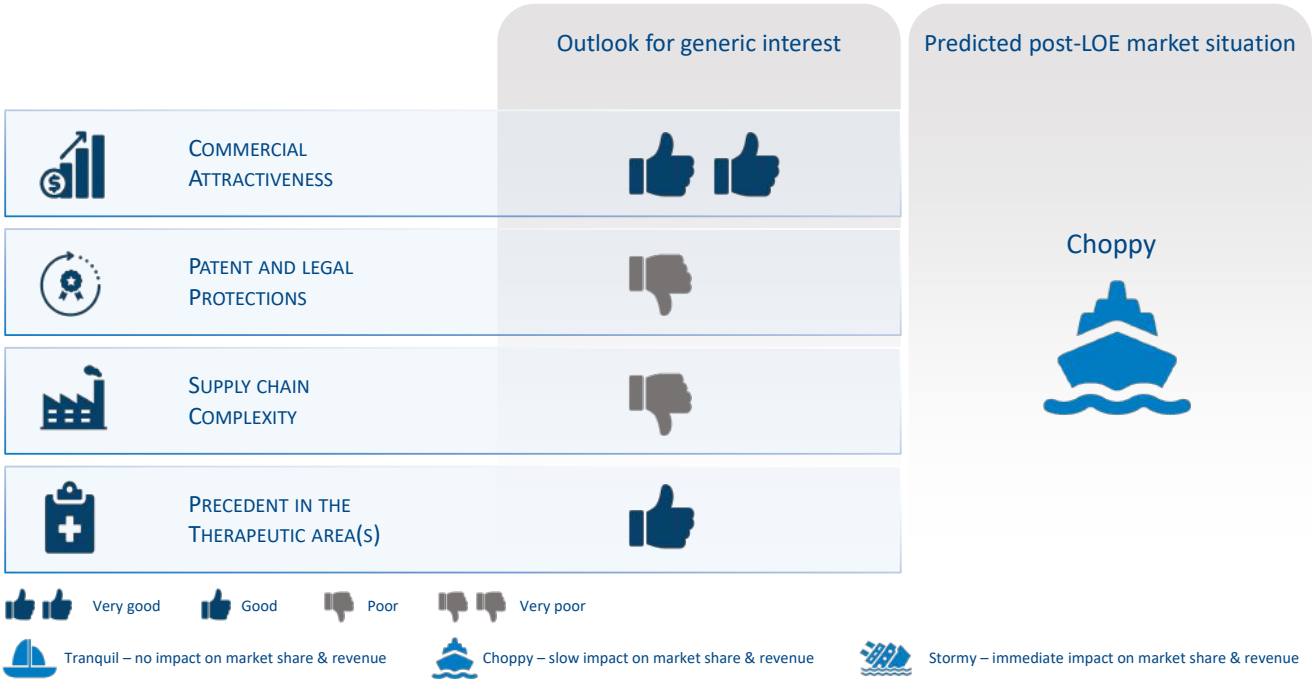
Precedent in the therapy area

ADHD is a condition that affects mainly children and is therefore a very sensitive treatment area. Once a child is stabilized on a medication, there may be real hesitation to change the drug and put the child's therapeutic stability at risk. In addition, there were other formulations of methylphenidate in the market that released the drug over a period of time but were not the medication of choice for prescribers and hence did not have the market share that Concerta had.

Post-LOE market prediction for Concerta

The commercial attractiveness of Concerta was high as a candidate for generic replication; however, at the time of LOE the patent for the OROS technology was still effective. Therefore, it would have been a challenge to develop a generic version of a sophisticated medicine like Concerta to an equivalent pharmacokinetic profile without employing the same OROS technology. Furthermore, prescribers had chosen Concerta over alternatives (both immediate and extended/slow-release alternatives), giving the impression of prescriber confidence. The post-LOE market prediction model would have predicted a slow decline of revenue for Concerta, with the market share holding up for a period soon after LOE (see Figure 9).

Figure 9: Post-LOE retrospective analysis for Concerta



Source: Arthur D. Little analysis

9 Source: Connor, Daniel F., and Ronald J. Steingard. "New Formulations of Stimulants for Attention-Deficit Hyperactivity Disorder." *CNS Drugs*, Vol. 18, No. 14, December 2004.

5. Initiate post-LOE market prediction to maximize value

All medicines will eventually lose their exclusivity and face the prospect of competing with generic or biosimilar alternatives. Before pulling the trigger on LOE strategies for the post-LOE life of a medicine, it is imperative that biopharmaceutical companies first carry out a prediction of what the post-LOE market situation will look like. By carrying out this analysis, it will become much clearer what the options are for the appropriate mitigation approach.

For example, in a case where the post-LOE situation will be "tranquil" or "choppy" and the medicine will remain the choice for prescribers for some time, it will be appropriate to continue to support prescribers and to ensure that they are able to help their patients achieve expected health outcomes.

Elixir of the afterlife

Failing to carry out a post-LOE market prediction may mean the selection of the wrong post-LOE strategy (e.g., resources could be withdrawn prematurely from supporting the use of the medication). A post-LOE market prediction assessment is the diagnosis needed to ensure a medication's elixir of the afterlife is correctly chosen. This diagnosis and subsequent action enables a medicine to remain commercially vital post-LOE for as long as possible. A post-LOE market prediction assessment should therefore become a top priority for any medicine past the midpoint of the product lifecycle and should be done well in advance of the year of LOE.

Notes

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Elixir of the afterlife

Predicting post-exclusivity market situations for medicines past midpoint of the product lifecycle

Arthur D. Little

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