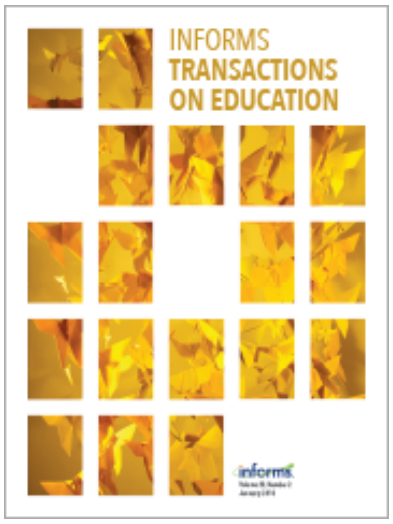

INFORMS Transactions on Education

Publication details, including instructions for authors and subscription information:
http://pubsonline.informs.org

Case—Idiopathic Pulmonary Fibrosis

David P. Kopcso, Howard Simon, Annie Gao

To cite this article:
David P. Kopcso, Howard Simon, Annie Gao (2016) Case—Idiopathic Pulmonary Fibrosis. INFORMS Transactions on Education 16(3):107-109. https://doi.org/10.1287/ited.2016.0155cs

Vol. 16, No. 3, May 2016, pp. 107–109
ISSN 1532-0545 (online)
INFORMS Transactions on Education

http://dx.doi.org/10.1287/ited.2016.0155cs

Case

Idiopathic Pulmonary Fibrosis

David P. Kopcso, Howard Simon, Annie Gao
Babson College, Wellesley, Massachusetts 02457
{kopcso@babson.edu, hsimon46@gmail.com, agao4@gsmtp.babson.edu}

Keywords: cases; teaching decision analysis; visualization; teaching modeling; decision trees; sensitivity analysis.
History: Received: January 2015; accepted: December 2015.

The Executive VP of Scientific and Medical Affairs looked up at the clock on the wall; it read 5:38 P.M. Another glance, down this time, revealed a stack of empty coffee cups and a pile of peppermint candy wrappers decorating the coffee table. He and InterMune's CFO had been locked up in the VP's office since the morning discussing the next strategic move for the company to expand its pulmonary drug portfolio.

InterMune was founded in 1998 by W. Scott Harkonen, M.D., as InterMune Pharmaceuticals, Inc. Originally a wholly-owned subsidiary of Connetics Corporation in Burlingame, California, the company was reincorporated at the time it went public in 2000 as InterMune, Inc.[1]

InterMune's initial intent was to develop pharmaceutical products to treat a wide range of pulmonary and infectious diseases such as cystic fibrosis, pulmonary fibrosis, tuberculosis and hepatitis C, as well as certain cancers, such as ovarian cancer. InterMune's business model was to license existing drugs and proteins from large, established pharmaceutical suppliers and to expand the use of those compounds into new therapeutic areas through traditional clinical development activities.

After the first few years, InterMune's management found that reorganization was needed—the company had to narrow its focus if it was to achieve profitability. Approved products were divested and clinical trials abandoned in order to focus the company's development activities specifically on pulmonology (dealing with diseases of the lungs) and hepatology (dealing with diseases of the liver, gallbladder, biliary tree and pancreas). Eventually, InterMune concentrated all its resources on developing treatments for idiopathic pulmonary fibrosis (IPF).

Idiopathic Pulmonary Fibrosis

IPF is a severe, progressive disease that destroys the lungs within five years of onset. Currently, there are approximately 100,000 patients in the United States, and 135,000 in the European Union (EU), diagnosed with IPF, with about 30,000 new diagnoses per year in each region. IPF is invariably fatal, with median survival ranging from two to five years from diagnosis. The cause of IPF is unknown (the word "idiopathic" means "of unknown origin"), and during the time of the events in this case, there was no FDA- (U.S. Food and Drug Administration) or EMA- (European Medicines Agency) approved therapy. The EMA is the EU agency for the evaluation of medicinal products that roughly parallels the FDA in the United States. However, with a U.S. patient population under 200,000 and an incidence level of fewer than five cases in 10,000 persons in the European Uion, drugs to treat IPF are eligible for designation by the FDA and the EMA as "Orphan Drugs"[2] and consequently can be marketed exclusively for seven years in the United States and for ten years in the European Uion after registration.

[1] http://www.intermune.com.

[2] http://www.ncbi.nlm.nih.gov/books/NBK50974/ and http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp&.

Pirfenidone

Pirfenidone, an orally-administered non-steroidal drug with anti-inflammatory and anti-fibrotic properties, was a product at which InterMune had been looking closely as a potentially promising new treatment for IPF. Marnac, Inc., founded in 1990 by Dr. Solomon Margolin, held the rights to pirfenidone in the United States while KDL GmbH held the European rights.

Solomon Margolin

Solomon Margolin was an inventor, but not the kind of inventor who discovered new types of light bulbs or trash compactors that can recycle. He earned a Ph.D. from Rutgers and held over 40 U.S. and foreign patents, including patents pertaining to medicines. Some of his more well-known over-the-counter drugs include Dimetapp® and Coricidin®. Dr. Margolin's biopharmaceutical company, Marnac, focused on the discovery and development of drugs to treat autoimmune, inflammatory and fibrotic disorders such as multiple sclerosis. (Marnac became inactive after Dr. Margolin's death in 2008, some years after the events described in this section of the case.) By 1999, Marnac had several drugs in the pipeline with potential efficacy for IPF.

As a small company, Marnac was concerned about stretching its limited resources too far by attempting to undergo the FDA approval process for multiple drugs. Two of Marnac's key drugs under development for IPF, an anti-inflammatory steroid and the non-steroid pirfenidone, were being considered. Marnac had the resources to pursue only one of them, but which one?

Based on prior experience, Marnac estimated that the steroid had an 11% chance of FDA approval and, if approved, would yield $1,251 M. (This case begins in 2000 and as such all dollar values have been prorated to year 2000 values to keep financial information on a standard ruler.) Since that time, pirfenidone has been approved for use in IPF in the European Union and currently is on the market in a number of European countries. As of early 2014, however, pirfenidone remained in clinical trials pending approval for sale in the United States. To advance the steroid through the FDA approval process would cost Marnac a total of $125.1 M. To advance pirfenidone through the approval process would cost the company a total of $247.5 M. Marnac estimated that pirfenidone had a 14.85% chance of FDA approval, and if approved would generate $1,762.5 M. (NPV of total revenue stream over the lifetime.) Because the steroid had already been FDA-approved and marketed for many other conditions, Marnac would not be required to generate as much safety data for the steroid as it would have to generate for pirfenidone, a new compound not yet approved for any disease; hence pirfenidone's higher development cost.

Although Marnac had experienced considerable success with FDA approval of over-the-counter drugs (OTCs), the FDA approval process is different (and far more difficult) for prescription drugs.[3] Still, Margolin decided to pursue pirfenidone.

Drug Development and the FDA Approval Process

The standard pharmaceutical industry joke about the cost of getting a new drug to market goes something like this: "The first pill costs a billion dollars to make. Everything after that is pure profit." It would seem that any firm trying to develop new drugs needs to have deep pockets and a high tolerance for risk. In fact, although estimates vary, it is generally recognized that the chance a new compound will eventually obtain FDA approval is in the neighborhood of one to five in a thousand!

U.S. drug patents last for 20 years. But often the patents are applied for long before the drug is approved and hence the patent protection may be effective for as little as half that time once the drug is on the market. Other protection may be available in the form of "exclusivity" which, depending on the type of exclusivity, can last for six months to seven years and goes into effect only after the drug has been FDA-approved.

The FDA review site[4] cites DiMasi et al. (2003), who summarized the stages of the drug-approval process along with the average cost, time commitments, and probabilities by stage. A subset of that information has been used to create Table 1. Additionally, Dimasi et al. suggest that the chance of the initial Investigational New Drug Application (the "IND") being approved—which is the required first step *before* Phase I clinical trials can begin—is 40%, while the development expenses through IND approval are approximately 30% of the total approval cost. On the brighter side, the chance of approval of the New Drug Application ("NDA"), which is the final request submitted to the FDA after all three clinical trial phases have been completed, is 90%.

Since Marnac didn't have the in-house expertise to feel confident in estimating the individual costs and likelihood of passing the various stages of FDA approval, Marnac relied on the literature, in particular on the work cited above of DiMasi et al. (2003) to

[3] http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/over-the-counterdrugs/default.htm.

[4] http://www.fdareview.org/approval_process.shtml.

Table 1 An Overview of the Drug Development Process

Testing phase	Phase I	Phase II	Phase III
Objectives	Safety	Safety, dosage, efficacy	Safety, efficacy, side effects
Mean cost (discounted Million $)	15.2	23.4	86.5
Duration (Months)	21.6	25.7	30.5
Conditional probability of reaching the next stage (%)	75	48	64

expand and revise its estimates in the FDA approval process. Marnac eventually passed Phase I and after reviewing its options, Margolin decided to open discussions with InterMune concerning pirfenidone.

InterMune and Pirfenidone

After discussions with Marnac, Inc. and co-licenser KDL GmbH over licensing pirfenidone for clinical development, InterMune had to weigh the expected costs and benefits to decide whether to conclude the agreement and take the license.

For InterMune to license pirfenidone, it would have to pay Marnac and KDL an upfront payment of $18.8 M and an additional $14.5 M for each successful clinical milestone as it occurred. InterMune would pick up the clinical trial process at Phase II, which would cost $52.5 M (author's estimate) to conduct and likely take three years to yield results. Analysts suggest only a 33%[5] probability that pirfenidone will pass Phase II trials. In the event Phase II results are insufficient to lead to FDA approval, it is possible to alter dosage and endpoint variables (i.e., the preselected measures of clinical success, aka "response variables"), and to repeat Phase II, at a cost of an additional $52.5 M. The re-trial would have a somewhat higher probability of success.

If pirfenidone reaches Phase III, InterMune then would conduct independent Phase III trials in both the United States and Europe. Total cost of testing would reach $195 M, and the results likely would take five more years to become available. The probability of FDA approval of pirfenidone for use only in the United States is estimated at 20%. The probability of EMA approval for use of pirfenidone only in Europe is estimated at 20%, while the probability of approval for use in both United States and Europe is estimated at 45%. Expected revenues of the three successful outcomes are $825 M (U.S. approval only), $1,113.75 M (EU approval only), and $1,762.5 M (US and EU approval).

Reference

DiMasi JA, Hansen RW, Grabowski HG (2003) The price of innovation: New estimates of drug development costs. *J. Health Econom.* 22(2):151–185.

[5] http://cureresearch4type1diabetes.blogspot.com/2011/02/chance-of-fda-approval.html.